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Ioan Opris
Manuel F. Casanova *Editors*

The Physics of the Mind and Brain Disorders

Integrated Neural Circuits Supporting the Emergence of Mind

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In memory of my beloved mother
Ileana Opris

Preface

This volume endeavors to articulate recent advances that have been made toward the understanding of brain structure, functionality, and cognitive disorders based on fundamental principles of physics. A broad range of physical phenomena arise within the brain circuits that are encompassing perception, cognition, emotion, and action, being under investigation in this book. Novel insights into devastating cognitive disorders are revealed, such as schizophrenia, dementia, autism, aging, or addictions, as well as new and conceptual strategies for the potential mapping and repair of the brain.

Further, this text surveys the least-probed domain of physics-related scientific resources, as applied to the multitude of aspects of the brain and its devastating disorders. An insight is provided to show how much physics may contribute to the imaging, diagnosis, treatment, and monitoring of the human mind/brain and to discuss brain repair strategies and the augmentation of brain functions. The crystalline structure of the brain, which consists of cortical layers, minicolumns, and microcircuits that operate concurrently with nanometric neurobiophysics, provides a foundation for understanding the myriad of functional disorders of the brain. This book will assist with enhancing the reader's appreciation of how the brain is so intricately and elegantly interconnected to facilitate the processing of information while articulating the deleterious consequences that ensue when brain microcircuits become improperly wired.

Why the Physics of the Mind?

1. The brain comprises a biophysical system that consists of hundreds of billions of elements (neurons) that are interconnected to form the connectome, neural states, or neural fields within which a voltage distribution varies across the system. The system is anatomically organized via a hierarchical architecture of cortical modules (layers and minicolumns->microcircuits), subcortical nuclei (basal ganglia, thalamus->cortical-subcortical loops), brainstem (midbrain, pons,

medulla->cortical-brainstem networks), and low-level (sensory (visual, auditory, touch, smell, and taste) and motor (eye, hand, limb, and pupil dilation)) and high-level cognitive functionality (perception, awareness, memory, decision, reasoning, and language).
2. The fundamental laws of physics (e.g., symmetry and conservation) are involved in the emergence of the mind.
3. The mind is a highly complex system with minimum entropy, which operates under the principles of organized hierarchical brain dynamics.
4. The fine and highly complex hierarchical architectures of the brain/dynamics of the mind are subject to vulnerabilities that can lead to dysfunctional and debilitating disorders.
5. Brain/mind dysfunction is exorbitantly costly, both economically and sociologically.
6. New brain diagnostics and therapeutics based on physics are emerging.
7. The complete elucidation of brain/mind functionality comprises the greatest challenge in science.

What Is the Book Bringing New to the Field?

The book is presenting an overarching integrated articulation of higher brain functions from combined physical and neuroscience fields, as well as from normal vs. brain disorders perspectives.

What Do the Chapters of the Book Describe?

The book is organized into 34 chapters that address not only the physical foundations and the neuroscientific aspects of the mind, but also their connection to other scientific disciplines. The book is structured in five parts, being opened in Part I by Jon H. Kaas and Suzana Herculano-Houzel's chapter, illustrating the key features of the mind that makes the human brain special, and is followed by a formal biophysical introduction of concepts by Aurel I. Popescu and Ioan Opris.

Part II entitled "Microcircuits and the Emergence of Mind" begins with Chap. 3 on systems approach to the emergent properties of the nervous system by Casanova and colleagues. Chapter 4 by Opris and collaborators deals with the integrated neural circuits supporting the emergence of the mind. Next, Chap. 5 presents the hierarchical circuit for executive control of movement by Brian R. Noga and Ioan Opris. In Chap. 6, Liviu Bilteanu reminds us about the fundamental property of symmetry and the Noether theorem that is extended to the brain microcircuits. The breaking of the symmetry is shown for locomotion by Brian Noga and Ioan Opris in Chap. 7. In Chap. 8, Ioan Opris, Brian Noga, Liviu Bilteanu, and Manuel Casanova

are showing how perturbation of symmetry breaking occurs in cognitive disorders like Alzheimer's disease, autism, or schizophrenia. In Chap. 9, Karl Friston's team extends theoretical physics concepts like "gauge fields" to the central nervous system. Chapter 10 by Alistair and Moira Steyn-Ross simulates a nonlinear dynamics aspect of the brain regulating sleep at the edge of chaos. In Chap. 11, Shigeyoshi Fujisawa provides insight into the slow oscillation mechanism of prefrontal cortex underlying local computations. Chapters 12 and 13 show two aspects of memory: the integration and selection processes over space and time in temporal cortical microcircuits by Masaki Takeda and a holographic model of information processing of neuronal microcircuits by Alexey Redozubov, respectively. Chapter 14 by Florin Dolcos and his team presents some opposing effects of emotion on cognition (perception and memory).

Part III entitled "Disorders of the Mind" deals with mind disorders. Chapter 15 by Andrea Cavanna presents the neural correlates of normal and impaired consciousness. An interesting scenario for assessing consciousness after rebooting from coma is discussed by Mihai Moldovan's team in Chap. 16. In Chap. 17, Oleg Favorov and colleagues discuss the role of feedforward inhibition in neocortical information processing and the implications for neurological disorders. Chapter 18 by Steven Chance provides insight into some fundamental aspects like lateralization, aging, and disruption across the lifespan in cortical microstructures. Chapter 19 by Maria Luiza Flonta presents the building elements of the adaptive and pathological pain neural networks. The insightful concepts of connectomics are applied by Cristian Donos and collaborators in Chap. 20 to patients with temporal lobe epilepsy. Chapter 21 by Cosmin Sonea and collaborators provides insights into the nutrition and addiction facets of the brain.

Part IV entitled "Computational Approaches and Neurointerfaces" deals with the modeling, implementation, and neuro-engineering facets of the mind and brain. Chapter 22 by Diana Deca provides a model for grid cell data acquisition to hardware implementation. Chapter 23 by Yoshio Sakurai and his team discusses the multipotentiality of the brain to be revisited repeatedly. Chapter 24 by Dong Song and Ted Berger shows an insightful characterization of complex brain functions with sparse nonlinear dynamical modeling. Chapter 25 by Mehdi Ordikhani-Seyedlar and Mikhail Lebedev illustrates how attention is controlled with neurofeedback. Chapter 26 by Marius Leordeanu and Rahul Sukthankar illustrates the use of multiple views for object recognition at different levels of spatiotemporal context.

Part V is entitled "Beyond the Mind's Barriers". Chapter 27 contributed by Jonathan Tsou discusses the pharmacology of the mind. Chapter 28 by Tatiana Popovitchenko and Mladen-Roko Rasin discusses the genetics of the mind and brain disorders. Chapter 29 by Andrew Newberg provides information on the spiritual brain: science and religious experience. Chapter 30 by Diana Stanciu discusses the neurobiology of moral decision-making and embodied cognition. Chapter 31 by Gabriel Predoi and his team provides insights into the animal's mind. Chapter 32 by Leon Zagrean's team discusses the blood-brain barrier and the mind. Chapter 33

by Angela Domschke and Frank Boehm describes the application of a nanomedical vascular scanning nanodevice to the mapping of the human brain. Chapter 34 by Iype Cherian and Margarita Beltran describes a unified physical theory for CSF circulation and cooling and cleaning of the brain in degenerative cognitive disorders.

Who Is the Book for?

It is for anyone interested in the workings of the brain/mind, how it gives rise to our cognitive faculties, and how it translates to human behaviors and mental disorders. The book is aimed at basic researchers spanning the fields of neuroscience, physics, and biophysics and clinicians in the fields of neurology, neurosurgery, psychology, and psychiatry.

Miami, FL, USA — Ioan Opris
Greenville, SC, USA — Manuel F. Casanova

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Contents

Part I
Introduction

Chapter 1
What Makes the Human Brain Special: Key Features of Brain and Neocortex

Jon H. Kaas and Suzana Herculano-Houzel

Abstract Humans have the largest brain of any primate. While it seems logical to assume that overall size is very important for generating complex behaviours, brain size relative to body size has been considered to be a major factor in predicting overall brain capacity. It turns out, however, that the absolute number of neurons in the cerebral cortex, regardless of body mass, may be a more relevant factor. Here we review the ways in which brains have increased in size, why absolute brain size is sometimes important, and why the size of the human brain allowed us to have cognitive abilities that exceed those of other primates. We suggest that cognitive functions are largely mediated by the neocortex, and because the human brain scales like a typical primate brain, the large neocortex of humans contains more neurons than any other mammal, even those with larger brains such as elephants. Further, as neurons in primary sensory cortex increase in numbers with brain size at a greater rate than the increase in the number of neurons in thalamic relay nuclei, primates with larger brains and more neocortex also have more neurons to analyze these sensory inputs. As numbers of neurons increase, individual neurons are free to specialize in different ways, generating increasing variability in cell size, shape, dendritic arborization and other features. In addition, an expanded cortical sheet contains more cortical areas, thereby increasing the number of computational levels involved in information processing, decision-making, and information storage. Having more cortical areas allows any given area to become more specialized in terms of laminar and sub-laminar organization, modular organization, connectivity and function. Increases in cortical field number also allow for greater variation in the sizes of areas, and thereby different types of functional specializations. Finally, large brains have more areas that are removed from primary sensory inputs and capable of hemispheric specialization. Of course, the costs of a large brain are considerable in terms of gestation time, postnatal vulnerability, and metabolic costs. Thus, it is not surprising that most mammals have relatively small brains that are constrained

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in their processing capacity, but are more metabolically efficient, and mature rapidly allowing for early reproduction.

Keywords Areas • Columns • Neurons

1.1 Introduction

Human perceptual and cognitive abilities are so profound that no other species comes close to matching them. Modern humans left Africa more than once, but with a major success only 60,000 years ago as they spread out to dominate most of the world, while two competing hominids, the Neanderthals and the Demisovans, died out after limited admixture. With tools and fire, and sometimes boats or rafts to cover water, early *Homo sapiens* were able to spread out from tropical to temperate to even artic zones and prosper (Fan et al. 2016; Timmermann and Friedrich 2016). Their abilities to learn from each other and pass on cultural innovations, including the domestication of plants and animals, allowed population densities to increase, the advent of cities, the beginning of science and modern medicine. Our various cultures have produced remarkable individuals in many fields, including, art, music, and sport. Modern human created the technology to place humans on the moon, and instruments on Mars. We have also been involved in multiple wars and produced horrible weapons of mass destruction. Our impact on the Earth has been so great that many now consider us to be in a geological epoch called the anthropocene, the epoch remarkably changed by humans.

Why have we been so capable of dominating the Earth and all competing species? Surely there are a number of reasons, starting with the first bipedal steps of our early ancestors as they diverged from the ancestors of present-day chimps and bonobos some five to seven million years ago (mya), with which brains that were no larger than present day chimps. Thus, early evolution was not marked by significant changes in brain structure, but rather the use and specialization of our forelimbs and hands in new ways, allowing advances in tool manufacture and use, and the making of fire. However, we had already inherited a brain from early primate ancestors that had more densely packed neurons than other lines of mammalian evolution (Herculano-Houzel 2016), and this likely favored further dependence on the brain, and ultimately, the evolution of the modern human brain. All of our behavioral and cultural advances depend on our brain. How is our brain different from those of other mammals? This is not fully known, but we are beginning to see some of the ways our brains differ from those of our early ancestors. Here, we briefly review current understanding of how human brains are different, and what the differences mean. Much of our comparisons will be of anatomical features of the brain, as these can be more reliably and productively identified and measured across species. As anatomical features have functional implications, understanding these features also leads to a better understanding of our minds and how they work. We start with something that is easy to measure, brain size, and then consider other features such

as neuron numbers, neuron distributions and size across brains, brain parts, numbers and types of cortical areas, and laminar and modular specializations of cortical areas.

1.1.1 The Importance of Brain Size

As brains are the source of mental abilities, it seems reasonable to assume that the bigger the brain the better. Thus, it is comforting to know that human brains are the biggest of any primates. Primates vary greatly in brain and body size, with the smallest primates, mouse lemurs of 30 g, having brains of 1.5 g, and the largest of primates, 170 kg gorillas, having brains of 535 g. Because body size is easy to measure, there is a long tradition of relating brain size to body size (e.g., Jerison 1973), but the relationship is only approximate (Herculano-Houzel 2016). Within each mammalian clade, larger animals do tend to have larger brains, although the exact relationship is specific to each clade, such that mammals with similar body sizes may have different brain masses (Herculano-Houzel 2017). The reasons for this trend for larger species to have larger brains are not very clear, but one proposed factor is that a larger body surface requires more somatosensory inputs to the brain, leading to a larger brain (see Kaas 2000). Yet, such an increase in sensory input would seem to impact on only a small part of the brain, the sensory representations, and constitute only a minor factor in adapting brains to a larger body. Indeed, brains gain neurons much more slowly than they gain mass, and clade-specific relationships are particularly clear between body mass and number of neurons in the brainstem structures that interact more closely with the body, which argues that body mass is not a universal determinant of numbers of neurons in the brain (Herculano-Houzel 2017). Similarly, there is only a modest increase in numbers of motor neurons with increasing body mass across both primate and marsupial species, which led to the proposition that larger bodies might allow the survival of larger numbers of neurons during development, rather than require a larger number of neurons to operate larger bodies (Watson et al. 2012).

An alternative view is that, as larger bodies take longer to mature and this delays sexual reproduction, there may have been more selection pressure in larger mammals for those cognitive brain functions that increase life expectancy, thus leading to larger brains (see Allman et al. 1993). In support of this premise, domestic mammals generally have proportionately smaller brains than their wild ancestors (Kruska 2007), suggesting that they have been spared the need for some of the brain functions related to finding food and mates, and avoiding danger. It remains possible, however, that the effect of domestication on the relative size of the brain is rather an indirect consequence of increased body mass, exactly because of the increased abundance of food that comes with domestication.

Overall, there is experimental support for the view that absolute brain sizes across mammalian species is related to abilities we associate with intelligence (Byrne and Corp 2004; Dunbar 1998; Barrickman et al. 2008; Deaner et al. 2007; Lefebvre et al. 2004; MacLean et al. 2014). Another possible reason why larger mammals evolve

with larger brains is that, compared to the small early mammals, the metabolic costs of a larger brain can be more easily met by a larger body (Herculano-Houzel 2015). There is also evidence for development constrains on how brain parts enlarge as brains get bigger, so that the increases in neocortex is greater than other parts of the brain (Finlay and Darlington 1995). These authors suggest that adaptive pressure for an increase in any part of the brain would provoke a coordinated enlargement of other parts of the brain as well. However, there is also clear evidence that adaptive increases in specific sensory representations occur without coordinated increases in other sensory representations (e.g., Krubitzer et al. 2011, 1995; Collins et al. 2005), which is referred to as "mosaic evolution" in contrast to the "concerted evolution" view that all brain structures scale together (Barton and Harvey 2000).

It is in this context that the size of the human brain seems at odds with the size of the human body: human brains vary around 1400 g, nearly three times that of male gorillas, while our body size of around 70 kg is considerably less. Our early Australopithecus ancestors had brains the size of present day chimps. About 2 million years ago (mya), hominids from *Homo habilis* to *Homo erectus* to archaic *Homo sapiens* had increasingly larger brains, showing an overall increase of about three times until reaching modern levels. Although the large size of the human brain relative to the human body was long hailed as the main explanation for our cognitive superiority (Jerison 1973), a simple alternative is that great apes, whose relative brain size is much smaller than that of other primates, cannot afford enough energy to support the larger numbers of neurons (and therefore the larger brains) that they would be expected to have. This metabolic constraint, which must have already applied to our last shared ancestors, was possibly lifted in the human lineage with the advent of tools for modifying foods, that is, cooking (Fonseca-Azevedo and Herculano-Houzel 2012; Herculano-Houzel 2016). Once the constraint that continues to apply to other primates was lifted, the human brain, and it alone amongst primates, quickly evolved to its modern size, with more neurons than any other primate brain.

Yet, brain size clearly is not everything. Brain size in normally functioning humans varies considerably, (Mc Henry 1994; Azevedo et al. 2009). Human females tend to have both smaller bodies and smaller brains than males, while modern academic records suggest that their brains function at least as well as in males, despite long held assumptions (Gould 1981). More to the point, humans do not have the largest of mammalian brains, and yet dominate the planet. African elephants have 5000 g brains, roughly three times larger than ours, and sperm whales have 9000 g brains that are over six times larger than ours (Herculano-Houzel 2016). Obviously, we need to consider other factors than brain size.

1.1.2 The Importance of Neuron Numbers

It came as a great surprise when it turned out that across mammalian taxa, brains of nearly the same size vary greatly in numbers of neurons (Herculano-Houzel 2016).

Thus, the 16 g brains of a small monkey has 1.5 billion neurons while the 18 g brain of an agouti, a large rodent, has only 0.9 billion neurons (Herculano-Houzel et al. 2006, 2007). Larger primate brains are composed of proportionately larger numbers of neurons, while rodent brains gain mass faster than they gain neurons; this seems to result from an increase in average neuronal cell size in non-primate species, whereas primate neurons maintain a fairly constant average cell size (Herculano-Houzel et al. 2014a). Thus, primates have an advantage over rodents and other mammals in that the former fit larger numbers of neurons in the brain, and the larger the brain, the larger the numeric advantage of primates – to the point where the human brain has ca. 7 times as many neurons than would be expected in a non primate brain of similar mass (Herculano-Houzel 2009). In primates, neuron packing densities remain fairly constant across brain sizes, while they decrease in rodents and other mammals with brain size – an indication that average neuronal cell size increases with brain size in rodents and other mammals, while remaining the same in primates (Mota and Herculano-Houzel 2014).

Because precise but different relationships between brain mass and numbers of neurons apply for primates and rodents, predictions of number of neurons from brain endocasts in extinct rodents and hominids are possible. Thus, the largest rodent that ever lived, at 700 kg, had a brain just over half the size of a human brain, but presumably with less than one tenth the number of neurons. While brain sizes in *Homo erectus* varied, over one million years of evolution, a 963 g brain would have 63 billion neurons, compared to a modern human brain of 1400 g and 86 billion neurons (Herculano-Houzel and Kaas 2011; Herculano-Houzel 2016). Still the, number of neurons in brains as a whole cannot be the only factor. The larger African elephant brain has three times the number of neurons in a human brain, 257 million against our 86 billion neurons (Herculano-Houzel et al. 2014b). However, 98% of neurons in the African elephant brain are found in the cerebellum, which is even more than the typical 80% of all brain neurons found in the cerebellum of other mammals, primates (and humans) included. The cerebellum and cerebral cortex typically gain neurons in tandem, maintaining a fairly fixed average proportion of four neurons in the cerebellum to every neuron in the cortex (Herculano-Houzel et al. 2014a), and the preponderance of neurons in the cerebellum over the cerebral cortex might be a simple consequence of densely packed very small neurons, the granule cells (Herculano-Houzel 2010). Although the cerebellum has traditionally been assigned important functions in motor predictions and error compensation (Stein and Glickstein 1992; Thach et al. 1992), recent models of brain function acknowledge that cerebellum and cerebral cortex work in conjunction (Leiner et al. 1989; Ramnani 2006). Accordingly, there has been a concerted increase in size of the prefrontal cerebral cortex, in prefrontal inputs to the cortico-pontine system, and in prefrontal-projecting cerebellar lobules in primates (Ramnani et al. 2006; Balsters et al. 2010). Thus, while cognitive and perceptual functions and consciousness are traditionally considered to depend on neocortex (e.g., Delacour 1997), it seems that cerebral cortex and cerebellum operate together, and typically gain neurons together (Herculano-Houzel et al. 2014a). The deviation of the elephant cerebellum from the patterned of coordinated scaling of numbers of neurons in the cerebral cortex and

cerebellum might be associated with massive addition of supernumerary neurons to the elephant cerebellum that are related not to cerebral cortical processing, but to processing of afferent information from the brainstem, possibly related to the trunk or to infrasound communication (Herculano-Houzel et al. 2014a).

The smaller human cerebral cortex has about three times as many neurons (16 billion compared to 5.6 billion) as the twice larger cerebral cortex of the African elephant (2.8 kg compared to 1.2 kg; Azevedo et al. 2009; Herculano-Houzel et al. 2014a). Because it scales as other primate cortices do, the human cerebral cortex is predicted to have more neurons than the cerebral cortex of even the much larger brains of the largest whales (Herculano-Houzel 2016). It seems safe to presume that humans have the most neurons in the cerebral cortex of any species. Thus, although the cerebral cortex generally gains neurons proportionately with the cerebellum, we have proposed that the large number of neurons in the human cerebral cortex is the simplest correlate of our superior cognitive capabilities.

While the cerebral cortex and cerebellum gain neurons proportionately across most species, both gain neurons faster than the remaining brain areas (Herculano-Houzel et al. 2014a). As proportionally more neurons are found in neocortex over the non-cerebellar rest of brain in larger primate brains, the proportional role that neocortex (together with the cerebellum) has in modulating brain functions, including behavior, increases. Early investigators noted that behavioral impairments were greater in humans than in smaller brained mammals after cortical lesions, and called this the "corticalization of function" (e.g., Brodal 1981). For this reason, the subsequent sections of this paper focus on the cerebral cortex.

1.1.3 Cortical Fissures Are of Limited Significance

The human brain has more of neocortex hidden in fissures than any other primate – although less than larger brains, such as elephant and cetacean brains. For animal researchers and neurosurgeons, fissures are often useful landmarks that indicate roughly where cortical areas of interest are located. Of course, cortical fissures have no brain functions, but their existence could be due to some functional advantage imparted by folding. For example, across the crests of folds on the surface of cortex, the gyri, cortex on both sides of the folds of the gyri is interconnected over shorter pathways, increasing the speed of their interactions (Van Essen 1997). In general, the folding of cortex increases with the size of neocortex both across species and during development. There have been a number of explanations of folding patterns, including both functional and mechanical theories, but we now know that only two physical features of neocortex are necessary to account for over 99% of the variation in the amount of folding. In a study across a large sample of mammalian species, Mota and Herculano-Houzel (2015) convincingly demonstrated that cortical folding scales universally with cortical surface area and cortical thickness. Thin cortex folds more easily than thick cortex, and a large cortical sheet tends to have more folds than a small cortical sheet – but the exact degree of folding depends on the product of

these two variables. Below a certain size, cortex does not fold. The reason for this universal relationship seems to be that the cortex settles into the most energetically favorable conformation as it develops under push-pull tensions, and the degree of folding that imparts the most favorable conformation depends on the combination of surface area and thickness. Local differences within a same cortex also appear to be related to variation in thickness and local surface area. For example, the part of V1 or striate cortex that represents peripheral vision is thinner in primates than the part that represents central vision, and that is where the fissure in V1 of all primates, the calcarine fissure occurs. Additionally, the overall pattern of local connections within a cortical area, or even between areas, is expected to contribute to local variations in push-pull tension that may determine where the first, and therefore main, folds are placed, and thus influence the spatial pattern of folding. In primary somatosensory cortex, for example, there are few local connections between adjoining representations of the face and hand (e.g., Liao et al. 2016; see Welker 1990; Radinsky 1976). As a result, a narrow cell-poor septal zone exists between the representations where a fissure sometimes emerges. Thus, small differences in histological structure and tangential connections do exit and thus they appear to influence the locations of cortical fissures.

1.1.4 The Importance of the Areal Organization of Neocortex

There are four aspects of neocortical organization that are functionally important as we consider human capabilities: the numbers and kinds of cortical areas, laminar and sub-laminar specialization, modular subdivisions, and connection patterns. We start with cortical areas.

By the time Brodmann (1909) published his well known comparative study of areal organization of neocortex of various mammals, the beginnings of understandings of how the cortical sheet is divided into numbers of functionally distinct regions or areas was well underway. For Brodmann, cortical areas were the "organs of the brain", functionally specialized patches of cortex that were specialized like the heart, liver, and lungs of the body. The basic premise of his investigations was that functional specializations are reflected in anatomical specializations, including the ways neurons were arranged and packed into layers and sub-layers of cortex. Differences in the laminar appearance led to the identification of just over 50 proposed areas of the human brain, some of which are well supported, such as area 17 for primary visual cortex, and area 3b for primary somatosensory cortex. But even these areas were not consistently identified across species by Brodmann (1909), largely because laminar differences are not very pronounced for many areas, and for especially some species. Currently, cortical areas are most reliably identified by multiple criteria, including various histological features, patterns of connections, and the physiological properties of neurons. Sometimes, alterations in behavior after the deactivation or lesions of an area provide findings that suggest the main functions of an area, as do behaviors influenced by electrical stimulation of neurons

in an area. Often, the functions of an area are not totally apparent, as areas are parts of networks of areas and nuclei that function together. More abstractly, one can say that the function of an area is to transform inputs into altered outputs. Thus, revealing this process tells the function or functions (as areas have several types of outputs) of an area. The most easily identified areas are those that systematically represent a sensory surface, the retina, skin or cochlea, or provide a systematic body movement map when micro-stimulated throughout. In general, portrayals of full sets of cortical areas for any mammal are estimates largely based on architectonic evidence, supplemented by various amounts of supportive evidence.

Although the exact numbers of cortical areas in any mammal remain uncertain, major species differences are obvious. Current estimates of the number of cortical areas in the human cortex (one hemisphere) vary (e.g. Kaas 2006), and the most recent estimate is 180 (Glasser et al. 2016). All estimates put the human brain well over the estimates for other primates, and probably all other mammals, including elephants and whales with more neocortex. This is obviously uncertain, given the limited studies on neocortex of most mammals. However, there is great evidence that primate brains with more cortex have more functional areas, while such differences with more cortex appear to be less marked in rodent and brains (Krubitzer et al. 2011; Kaas and Preuss 2014). Early mammals likely had about 20 cortical areas (Kaas 2007), while early primates had nearly 50 areas (Wong and Kaas 2010).

The sizes of cortical areas are typically larger in mammals with more neocortex, which restricts the potential increase in number of areas. Thus, primary visual cortex, V1 or area 17, is only about 4.5 mm^2 in a mouse, but 1200 mm^2 in a macaque monkey, and perhaps 3000 mm^2 in a human (Kaas 2000). However, a chimpanzee has an area 17 of about the same size as in human, although the cortical sheet is over three times as large in a human. As the retinotopic map in V1 contains the information used to locate and identify objects in space, this map is obviously very crude in a mouse, and very precise in a human, although not notably different than in a chimpanzee. This observation suggests that a further increase in the map size in humans would not be that useful, as the resolution limit is set by the eye. However, V1 in humans, as in other primates, has a modular organization that allows an increase in functions that cannot be afforded a mouse. A much smaller V1 than that in a mouse would no longer be capable of retaining an image (Cooper et al. 1993).

The main advantage that comes with increasing the number of cortical areas is that serial processing can produce fantastic outcomes out of a number of simple computational iterations. Each cortical area modifies inputs to create different outputs, but the transformations may be rather slight. It is the number of transformations across numbers of cortical areas that produce astonishing outcomes, and it is the creation of multiple processing networks made possible by large number of cortical areas that makes multiple outcomes possible (Pinker 1997).

1.1.5 *The Importance of Laminar, Sub-laminar, and the Cellular Organization of Neocortex*

The neocortex of mammals evolved out of the therapsid cortex, which presumably was something like the dorsal cortex of modern non-avian reptiles (Kaas and Preuss 2014; Kaas 2017). The basics of laminar and cellular organization are similar across most mammals. Like the dorsal cortex of modern non-avian reptiles and possibly of early amniotes, neurons in neocortex consist of pyramidal neurons and star-shaped inhibitory neurons, although some excitatory pyramidal neurons have become modified by losing their apical dendrite and becoming star-shaped stellate or granule cells (Fournier et al. 2015). Instead of having a single row of pyramidal cells as in dorsal cortex, the thicker neocortex is packed with many neurons that are traditionally divided into six layers, and variously into sub-layers. Layer 1 resembles the superficial layer of axons and dendrites in the dorsal cortex of reptiles in that it continues to get widespread axons from subcortical neurons that connect the apical dendrites of many deeper pyramidal cells with a weak, modulating influence. In primary sensory areas, layer 4 is the new target of activating sensory inputs from the dorsal thalamus. Layer 4 is characterized by excitatory stellate neurons or even smaller granular neurons that are often densely packed. Higher order sensory and other areas receive activating inputs from primary sensory areas or earlier areas in processing hierarchies (Felleman and Van Essen 1991). Layer 3 provides feed-forward projections to other cortical areas, while layer 6 provides feedback connections to the thalamus or to other cortical areas. Layer 5 provides most of the projection to subcortical structures in the thalamus, basal ganglia, midbrain, brainstem, and spinal cord. These different connections and functional roles result in various laminar and sub-laminar specializations of neurons (Kaas 2010).

A major type of specialization is in neuron size. Small neurons, especially the tiny granular neurons of layer 4 in primary sensory areas, have small dendritic arbors, and are activated by dense synaptic inputs by only a few axons of thalamic or cortical neurons. Thus, layer 4 neurons sum only a few "driving" inputs, and their response properties clearly reflect those of these inputs. Put in another way, layer 4 neurons largely preserve rather than integrate information. In contrast, the large pyramidal neurons of layer 5 have large dendritic arbors and sum the inputs of many axons. Their outputs do not clearly reflect individual inputs, but rather the computational result of many inputs from other areas and subcortical sources, other layers, and local layer 5 influences. Smaller pyramidal neurons likely reflect aspects of these two roles of preserving information, or integrating it, as the result of the summing process to produce an altered output. Thus, different functional roles of cortical layers are reflected in the sizes of neurons in those layers. The smallest neurons are in layer 4, which preserves information for distributions locally to neurons vertically aligned above and below the layer 4 neurons. Layer 3 neurons include the smaller pyramidal neurons that integrate limited local inputs in various ways to provide altered outputs to other cortical areas. Layer 6 neurons integrate local influences with some direct feedforward inputs to provide feedback to the

input to the thalamic nucleus or cortical area that provides the feedforward input. These anatomical features of neurons in layers and sublayers of cortex are more pronounced in some cortical areas and in some mammals than others, as part of the great diversity of cortical organization that is associated with variations in cortical function. In general, small brained mammals with short life spans have less pronounced laminar and areal specialization, and laminar and areal features are less distinct. As a result, identification of cortical areas in such mammals on the basis of cytoarchitecture can be difficult. With fewer cortical areas and fewer neurons, areas and neurons in these mammals must have general purpose functions and not be anatomically specialized. In mammals with larger brains and more cortical areas, more pronounced specializations of individual neurons may occur sometimes in the same layer. For example, a few very large pyramidal neurons of layer 5 of primary visual cortex of primates are more widely spaced than the adjoining smaller layer 5 pyramidal neurons. These larger neurons sum more inputs as reflected by their larger receptive fields, and they project to visual area MT, part of the visual pulvinar, and the superior colliculus (Fries et al. 1985). Thus, neurons may have different anatomical and functional roles within a cortical layer, and this is another variable across species.

If one considers the differences in neuron packing densities across the cortical sheet, they vary across functional areas in the brains of mice (Herculano-Houzel et al. 2013), and perhaps more so in primates, and especially in primates with more cortex (Collins et al. 2016: Turner et al. 2016; Young et al. 2013). As expected from histological appearance, primary visual cortex (V1, area 17) has neuron packing densities two to four times higher than most cortical areas. This is mainly due to the dense packing of the very small granule neurons in layer 4 (Brodmann 1909), although layer 3 has smaller pyramidal cells that are more densely packed than other cortical areas. The high density of small neurons with small dendritic arbors in V1 the largest of cortical areas in primates is the anatomical framework for an extremely detailed retinotopic map of the visual hemifield. It also allows for the creation of five distinctly different parallel projections from V1 to other visual areas (see following section). It is not known yet if the V1 representation in humans is much different from that in chimpanzees, but the sub-laminar organization of V1 has laminar specializations that may promote detection of visual motion in dim light or other functions (Preuss et al. 1999; Preuss and Coleman 2002).

In addition to V1, areas V2 and V3, and adjacent visual areas also have high neuron packing densities in primates, and this is especially the case in chimpanzees and likely humans. High densities also occur in primary somatosensory cortex, area 3b, and primary auditory cortex. Another region of high packing densities is in dorsomedial prefrontal cortex, a region important in working memory (Goldman-Rakic 1996). The smaller neurons with smaller dendritic fields that reflect this packing density may be important for retaining the details of the retained information. Only primates have a region of frontal granular cortex (Preuss 1995), and we recently found that neuronal densities in frontal cortical areas can be as high as in occipital cortex (Gabi et al. 2016). Other neurons in prefrontal cortex, the layer 3 pyramidal neurons, may have large dendritic arbors comparable with many synaptic inputs

and proposed executive functions (Elston et al. 2006). As expected, primary motor cortex (M1) and premotor cortex (PM) areas with a very thin or unclear layer 4 (agranular and dysgranular cortex) have large neurons with large dendritic arbors that both sum larger amounts of information, but also have large axons to conduct outputs rapidly to the brainstem and spinal cords. Motor and premotor cortex have larger neurons of lower packing density in primates (Young et al. 2013).

One of the benefits of having a large brain, with a large number of neurons and cortical areas, is that all neurons and areas do not need to have general purpose or broad range functions. This allows some areas and neurons to specialize morphologically and functionally. The study of these specializations in the early stages of development, but relevant observations are accumulating. As an interesting example, spindle cells, named for their spindle shaped cell bodies, are found in anterior cingulate cortex and the anterior insular of human brains (Nimchinsky et al. 1999). Fewer numbers of these neurons, also called von Economo cells, have been found in chimpanzees. There have been various speculations about the functions of spindle cells (see Allman et al. 2005), but functional studies of the cellular level have not been possible. Other differences in the distributions of neuron cell types that favor human brains have been described elsewhere (Spocter et al. 2015: Casanova and Opris 2015).

1.1.6 The Roles of Cortical Columns, Modules, and Domains

Cortical areas have functional subdivisions, in addition to layers and sublayers that have been variously identified as mini-columns, columns, modules, and domains (Kaas 2012; Kaas and Balaram 2015). One of the universal features of neocortex is that narrow, vertical arrays of neurons from surface to white matter are highly interconnected. As a consequence of these restricted vertical connections, the responses of all neurons within the array reflect the information that is sent to layer 4 neurons (or layer 3 in the absence of layer 4), although this information is modified differently in the layers and sublayers. The arrays of the densely interconnected neurons, on the order of 30–50 μm in diameter, are called minicolumns (Mountcastle 1957; Opris et al. 2015). They are sometimes clearly separated from each other by neuropil, and they can be expected to be larger in portions of cortex with larger neurons.

Human minicolumns in many parts of cortex appear to be larger, with more neurons and neuropil, than in other primates (Buxhoeveden et al. 2001; Spocter et al. 2015). In addition, minicolumns are expected to be specialized in different ways, according to the laminar and connectional specializations of cortical areas. The larger cortical sheets of humans provide an advantage in having more minicolumns, and having more functional types of minicolumns.

The classical columns of Mountcastle (1957) are another feature of neocortex that is probably universal. Classical columns of two or more types subdivide areas with repeating sets of modules that have neurons with distinctly different response

properties (see Kaas 2012 for examples). In effect, they allow individual cortical areas to have patchworks of neurons of two or more related, but different functions. For example, the cytochrome oxidase blob and non-blob modules of primary visual cortex of primates divide V1 into regions that process inputs to extract stimulus orientation or color and brightness (Livingstone and Hubel 1988). In a similar manner, cytochrome oxidase dense bands of two types divided by cytochrome oxidase light bands of two types from repeating sets of four different classes of modules in V2 of anthropoid primates, allowing V2 to function as four closely interacting areas (Felleman et al. 2015). The advantage of the human brain with a V2 at least as large as in chimpanzees is that the human V2 has as many or more sets of these modules as any other primate. As many or most cortical areas, especially the larger ones, likely have some type of modular organization that subdivides their functions, and humans have more cortical areas, and some of the largest of cortical area, the subdivision of areas into modules of differing functions likely has the greatest impact in human brains.

Another type of cortical subdivision is one we called domains (Kaas 2012; Kaas and Stepniewska 2016). Domains are functional subdivisions of cortex that are larger and more complex than columns, but still parts of areas. They have many of the characteristics of areas, and can easily be confused with them. Likely, arrangements of columns within an area evolve sometimes into domains, and domains into areas. There has not been much effort to distinguish domains from areas, but the clearest example is in primary motor cortex of primates. M1 has long been recognized as a single area, as it forms a single, crude representation of the movements of parts of the contralateral half of the body. Stimulating with a brief sequence of electrical pulses via microelectrodes at near threshold values evokes different movements from toes to trunk to fingers to face and then tongue in a medial to lateral sequence across M1. However, at a local level, adjacent stimulation sites after evoke different movements, with a site for a wrist movement next to a site for a finger movement for example, and finger, wrist, and arm movement sites repeated and mixed with each other. Thus, M1 has a “mosaic” or “fractured” internal organization of mixed micro-columns rather than a faithful somatotopic map of body parts (see Gould et al. 1986 for early evidence). At a larger scale, a number of these differing micro columns form a larger unit that mediates a specific behavior, such as reaching, grasping, threating, defending, or running. These functional domains were first studied systematically by Graziano and coworkers (see Graziano 2009). The exact number of domains is not yet clear, but for most or all primates it is likely eight or more. Our studies indicate that these M1 domains exist in a wide range of primate species, and there is evidence for them in human M1 (Desmurget et al. 2014), and for a smaller number in rodents (e.g. Brown and Teskey 2014). The main conclusion is that M1 is subdivided with a small number of domains for different behaviorally relevant complex movement. As parts of M1, the domains interact, in often a competitive way, but also cooperate to create more complex movements such as reaching to grasp and retrieve food to the mouth. Thus, M1 is subdivided into domains that mediate different movement goals.

Matching domains in terms of evoked behaviors are found in premotor cortex (PMC) and in a part of posterior parietal cortex. Depending on the types of movements, domains are either in ventral premotor cortex or dorsal premotor cortex, suggesting that these two "areas" might between considered to be a single area. Likewise, the domains and associated cortex in a portion of posterior parietal cortex, such as previously defined anterior, posterior and medial intraparietal areas (AIP, LIP, and MIP), might be considered as functional divisions within a single area for grasping, looking, reaching, and other behaviors (Kaas and Stepniewska 2016).

The sequence of the three processing stations of posterior parietal cortex (PPC), premotor cortex, and M1 are all parts of a so called dorsal stream of sensorimotor processing (see Ungerleider and Haxby 1994; Goodale and Milner 1992). The domains at all three levels are involved in a decision process that results in a specific type of action over others. As the inputs to PPC are mainly from higher-order sensory areas, mostly visual and somatosensory, and variable across domains, the dominance of one domain over others depends on the mixture and content of ongoing perception. At the next level, premotor cortex domains are under the influence of inputs from the motor thalamus, other motor areas, and prefrontal cortex, so the dominance in the array of the motor domains may change from that in PPC. Likewise, M1 domains are under a different set of thalamic and cortical influences, and the final outcome will largely depend on domain selection process in M1 (Kaas and Stepniewska 2016). Of course, the dominant domain in PPC would selectively activate the functionally matched domains in PMC and M1, and the dominant domain in PMC would selectively activate the matching domain M1.

In the non-primate relatives of primates, rodents and tree shrews, M1 appears to have only a few action specific domains (Baldwin et al. 2016), premotor cortex is poorly developed, and there is little cortex that could be considered to be posterior parietal cortex. Thus, M1 outputs depend on more direct sensory and other inputs. As a result, primates have the advantage over these non-primates of having a large region of PPC, where at least eight sub-regions or domains are specialized for specific behaviors, and other parts of posterior parietal cortex are large and participate in further levels of processing sensory information. Additionally, more motor and premotor cortex domains exist, and especially premotor cortex is more developed. All these motor regions are larger in human brains, and posterior parietal cortex is larger in proportion to the rest of cortex (Hill et al. 2010). Most importantly for human brains, additional domains have evolved within the domain structure of PPC. Thus, the contribution of auditory input to the dorsal stream of sensorimotor processing in PPC of primates has resulted in the differentiation of a language production module as domain in PPC of humans (Rauchecker and Scott 2009; Tremblay and Dick 2016). There is also evidence that the domain for grasping and manipulation of PPC in primates has enlarged and differentiated into regions for specialized for tool use in humans (Frey 2008).

1.1.7 Cortical Asymmetries and the Human Brain

Mammalian brains have two hemispheres that are highly symmetrical in organization. Thus, cortex of the right cerebral hemisphere represents the sensory inputs of the left body surface and the left visual hemifield, and the left ear is more dominant, while motor outputs of the right hemisphere largely control the muscles of the left side of the body. The left hemisphere mirrors this organization. Overall, this appears to be a bad design. As brains get bigger, the connecting axons between the hemispheres get longer, and distance is time in the nervous system. The innovation of the corpus callosum with the advent of placental mammals shortened this pathway and the conduction times, but not enough. The usual way of reducing conduction times is to increase the diameters of axons (Kaas 2000). However, this can be costly in that long, thick axons tend to bulk up the brain so much that after a certain size, one greater than for the brains of present day mammals, a theoretical limit is reached that means that nothing computationally is gained by a further increase in brain size (Cherniak 1990). Another advantage of thick axons is that they are capable of maintaining higher firing rates, and thus a greater rate information transfer (Perge et al. 2012). Yet, the corpus callosum has few large diameter axons, presumably due to space constraints. In macaque monkeys, the largest 15% of axons in the corpus callosum occupies more than half of the cross-sectional area of the callosum. In humans, the corpus callosum has about 300 million axons, most of them small and slowly conducting. Across primates with different sizes of brains, the conduction times for the fastest neurons with the largest axons increases with brain size, indicating that the compensation for the larger conduction distances is not complete (Phillips et al. 2015; Caminiti et al. 2009). There is practically no change in axon diameter in the corpus callosum between humans and chimpanzees with much smaller brains. The large, fast axons connect sensory and motor areas, where the speed of transmission is likely to be the most critical, but the human brain also compensates by having important functions mediated within a single hemisphere (Ringo et al. 1994). Thus, much of language is mediated in the left hemisphere, and manual motor skills are most frequently more effectively mediated in the left hemisphere. While there are functional and structural differences between the two hemispheres in apes, they are much more prominent in humans, where marked cognitive differences in the abilities of the two hemispheres have been revealed in patients with section of the corpus callosum, or with lesions of one hemisphere or the other (e.g. Gazzaniga 2000). Primate brains, and especially larger primate brains, have reduced the need for corpus callosum connections by eliminating the connections from parts of primary somatosensory cortex (area 3b) and most of primary visual cortex (Cusick and Kaas 1986; Doty 2007). Larger primate cortices have a decreasing fraction of their neurons connected through the white matter, with an increasing fraction of their neurons connected within the gray matter (Herculano-Houzel et al. 2010); in contrast, the fraction of neurons connected through the white matter remains constant across rodent species (Ventura-Antunes et al. 2013). The decrease in proportion of long-range connections probably contributes to keeping

primate cortices small as they gain neurons, compared to non-primate cortices. But the evolution of hemispheric specializations for human mental functions removed some of the constraints of the need to closely tie the two hemispheres, and allowed human brains to expand by three times, while having colossal connections much like those of a chimpanzee. The major cognitive role of the left hemisphere in humans as the interpreter of one's behavior (Gazzaniga 2000) allows the speaking left hemisphere to feel quite normal in split-brain patients.

1.1.8 The Corticalization of Function

The "corticalization of function" refers to an old concept in neurobiology that reflects the common observation that cortical lesions that appear to be functionally equivalent in humans and other mammals, especially those with small brains, have much greater functional impact in humans (Brodal 1981). Most notably, lesions of the motor cortex in non-primate mammals often did not cause lasting behavioral deficits (Creutzfeldt 1993).

While interpretations of ablation behavioral results across species has been complex and difficult, a "corticalization of function" may in large part be the consequence of the great increase in cortical neurons in comparison with subcortical neurons as cortex disproportionately expands relative to the brain stem and spinal cord with increases in brain size, especially in primates, but also in other mammals. Thus, in a study of primate species, Herculano-Houzel et al. (2016) describe a "cortical takeover of spinal motor control with increasing brain size in primates". These authors propose that cortical and non-cortical motor projections to the spinal cord compete for functional connections on the bases of activity and relative numbers of inputs, so that as cortical inputs become more and more dominant, their loss has more and more impact. Similar consequences likely follow the great increases in numbers of cortical neurons and their descending projections of other cortical areas as a consequence of increasing brain size. Thus, across primates of different brain sizes, primary auditory cortex gains neurons faster than subcortical auditory structures (Wong et al. 2013). This results in proportionately more cortical feedback to subcortical auditory and other structures in primates with bigger brains, increasing the functional dominance of cortex. Similar findings were reported for visual cortex, where primary visual cortex, V1, gains neurons with brain size faster than the superior colliculus and the dorsal lateral geniculate nucleus (Collins et al. 2013). These results suggest that with increasing brain size, and numbers of V1 neurons, V1 gains more control over the sensory and motor functions of the superior colliculus, and more dominating feedback modulation of the lateral geniculate neurons projecting to V1. Faster scaling of cortical than non-cortical neurons for all or nearly all cortical areas is expected, given the results and the finding that cortex overall increases in neuron number with brain size faster than the subcortical brainstem and spinal cord. Thus, the corticalization of function should

occur for nearly all cortical areas across taxa with increases in brain size, especially in primates, and corticalization of function should be most pronounced in humans.

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Chapter 2
Introduction: From Neurons to the Mind

Aurel I. Popescu and Ioan Opris

Keywords Biophysics • neuron • resting potential • action potential • excitable membrane • ionic channel • synapse • spine • plasticity • mind

2.1 Introductory Biophysics Concepts

We begin with the introduction of the general biophysics relevant concepts for the nervous system that will be discussed in more detail in the next chapters of the book. The *first step* deals with the neuron: the fundamental morphological and functional unit of the human nervous system (HNS). It is known that HNS (i.e., central nervous system, CNS and peripheral nervous system, PNS) consist of about 86 billion neurons (Azevedo et al. 2009; Herculano-Houzel 2009) without taking into account the glial cells that outnumber neurons by tenfold, and astrocytes. However, it is interesting to note that astronomers estimate the number of stars in the Milky Way as being about 400 billion, that is, only five times the number of HNS neurons! It seems that glia has only the role to insulate, support, and nourish the neighbor neurons, construct axon myelin, repair brain injury, although this simple view merely reflects our ignorance about glial function (Bear et al. 2001).

It is important to emphasize that neurons are not at all identical but, on the contrary, present a very large variety: the brain is not an organ such as the liver, which consists of a stereotyped population of cells (Nicholls et al. 2001). The number of neurons within the CNS is quite impressive but more challenging and

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intriguing is the number of the inter-neuronal contacts (i.e., synapses) which is two orders of magnitude higher than that of neurons. The role of synapses in complex functioning of CNS seems to be even more important than that of the neurons themselves. Therefore, *the second step* in this chapter is to describe the morphology and operation modality of the synapses which also, present a great morphological and functional variety.

It is known that CNS has many characteristic features like high reliability, versatility and plasticity endowed with an associative and distributed memory, to integrate the organism in its environment by receiving and processing information from stimuli, and making adequate decisions. What is even more important to emphasize, is that CNS is not only capable of storing in memory facts and events, but also to learn strategies, solve problems and control organism's behavior, to think and predict future events and to confer self-conscience to its possessor. Indeed, the CNS is the most unique system in the known Universe that is capable to study other systems while itself is being studied and analyzed.

Human CNS has the great advantage of being built according to the very economical, space-saving scaling rules that apply to other primate brains. Therefore, among the economically built primate brains, it is the largest, thus containing the greatest number of neurons (Herculano-Houzel 2009). The astronomic numbers of neurons and synapses are not only the responsible features for the high performance of the CNS. What adds a supplementary value to the CNS is the rigorous hierarchical topological organization of the neuronal populations. *The third* and *fourth steps* in this chapter will be dedicated to the associations of neurons in interconnected neuronal clusters (i.e., microcircuits and neural networks), each capable to accomplish a specific task, but altogether to assure a coherent integration of the whole organism in its ever-changing environment.

2.2 Neurons, the Basic Units of the CNS

As it is already well known, the neurons of the CNS present a great diversity in their morphology (e.g., dimension) and function (e.g., sensitive/motor neurons). For instance, the human neurons can be as small as 10 μm (e.g., granule cells) or as big as 100 μm (e.g., Betz cells) (Purves et al. 2008). In spite of the great morphological and functional diversity, all neurons manifest common traits, so that one can speak of a generic or "standard" neuron whose main properties will be presented below.

2.2.1 Neuronal Morphology

As it is well known, the neuronal cell is composed of three important parts: *soma*, *dendrites,* and *axon*. Soma is the cell body in the cytosol of which the nucleus and other cellular organelles (e.g., mitochondria) are embedded (Fig. 2.1).

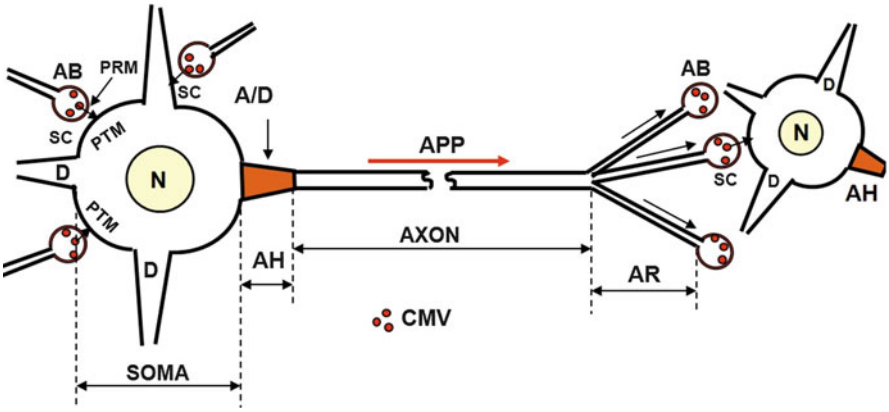

Fig. 2.1 The schematic neuronal morphology and its synaptic connections. *N* nucleus, *PRM* presynaptic membrane, *PTM* postsynaptic membrane, *CMV* chemical messenger vesicles, *SC* synaptic contact (synapse), *D* dendrite, *AB* axonal button, *AH* axonal hillock, *A/D* analog-digital conversion block, *APP* direction of action potential propagation, *AR* axonal ramifications (With permission from Popescu 2016)

The role of the dendrites (i.e., soma ramifications) is to collect signals from the neuron's exterior, acting like a reception antenna of a radio station. The axon, the unique long ramification of the soma, is somehow spatially opposed to the dendrite tree, presenting several branches terminated by small swollen regions called *axonal buttons* (Fig. 2.1) at its distal part. One can say that the axon, with its branches terminated in axonal buttons, behaves like the emission antenna of a radio station, sending signals to the neuron exterior or, recurrently, to itself. Below, we make a classification of neurons taking into account different criteria, in order to emphasize the great diversity of CNS units.

- Taking as a criterion the number, n, of dendrites, the following classes of neurons are encountered in CNF (Fig. 2.2): (1) *(pseudo)unipolar neurons*, when $n = 0$ (found, for instance, in the sensory ganglia of cranial nerves V, VII, IX, and X); (2) *bipolar neurons*, when $n = 1$ (e.g., retinal bipolar cells); and *multipolar neurons*, when $n \geq 2$ (e.g., ganglion cells of retina), the champion being the *Purkinje neuron* of the cerebellum which is very rich in dendrites and involved in about 200,000 synapses.
- Another nomenclature takes into account the form of soma, according to which there are the following categories of neurons (Fig. 2.3): (1) *pyramidal neurons* (with pyramid-shaped cell body) and (2) *stellate* (with star-shaped cell body).
- Another criterion to classify neurons is whether their dendrites and axons present spines. According to this criterion, there are *spiny neurons* and *aspinous neurons*. In cerebral cortex, all pyramidal neurons are spiny, while stellate neurons could be either spiny or aspinous (Bear et al. 2001). The average number of spines on a pyramidal neuron dendrites is about 6000 (Laberge and Kasevich 2007).
- According to the axonal length, the neurons are (1) *Golgi type I neurons* (or *projection neurons*) that extend from one part to remote parts of the brain (e.g.,

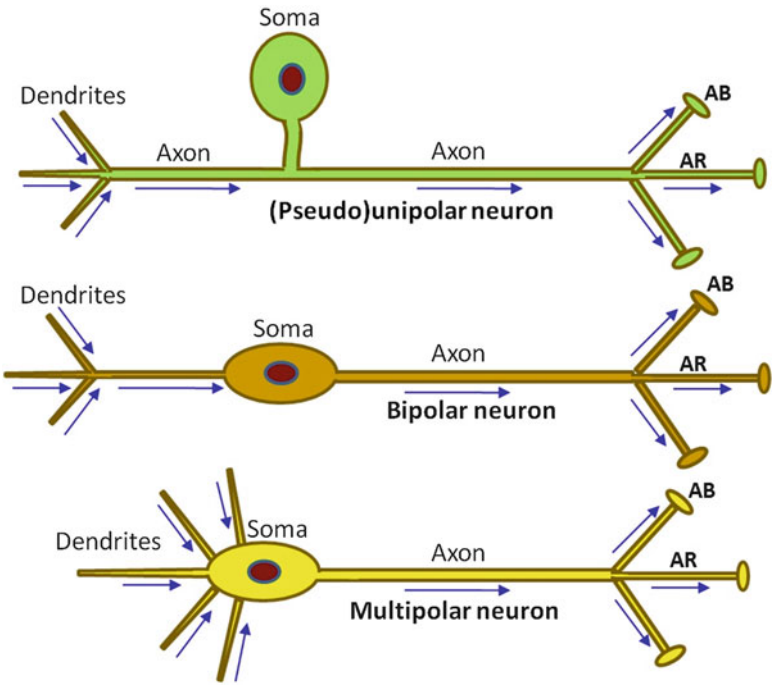

Fig. 2.2 Classification of neurons based on the number of dendrites. *AR* axonal ramification, *AB* axonal button

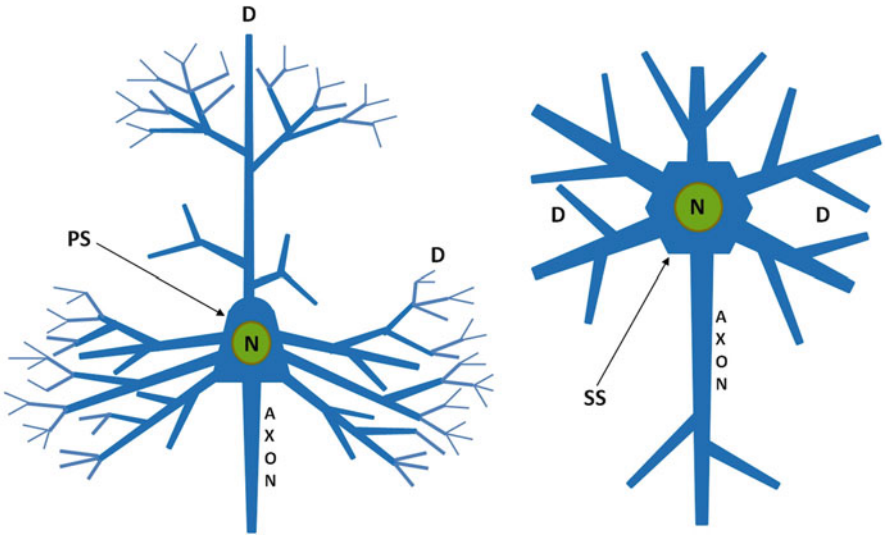

Fig. 2.3 Schematic representations of the cortical pyramidal neuron (*left*) and stellate neuron (*right*). *PS* pyramidal soma, *SS* stellate soma, *N* nucleus, *D* dendrite. A confocal microscopy image of a pyramidal neuron of the human cingulate cortex is presented in Fig. 2.13 (*vide infra*)

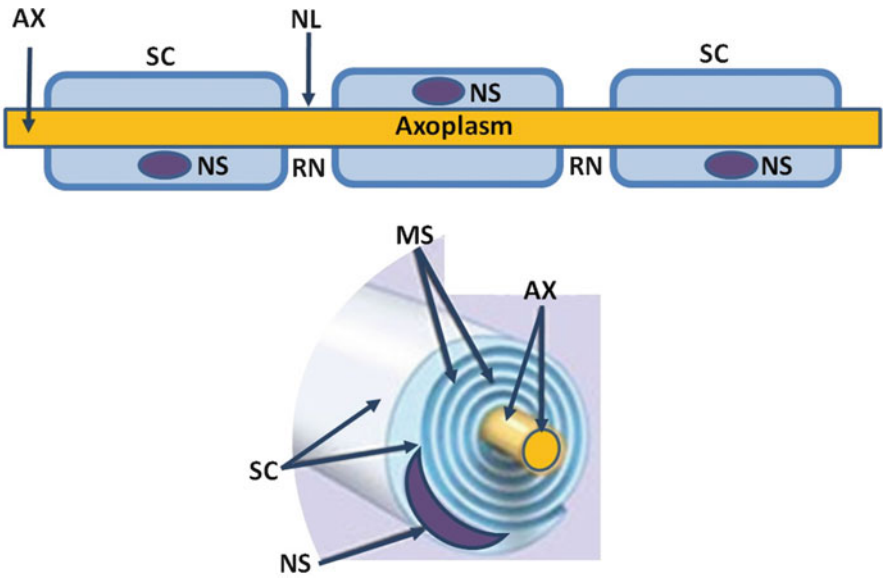

Fig. 2.4 Schematic representation of myelinated axon: longitudinal section (*up*) and transversal section (*down*). *AX* axon, *SC* Schwann cell, *NL* neurolemma, *NS* nucleus of Schwann cell, *MS* myelin sheath, *RN* Ranvier node

pyramidal cells of the cortex) and (2) *Golgi type II neurons* with short axons that never extend beyond the cerebral cortex (e.g., stellate cells).

- Taking into account the axonal morphology, one can encounter, on the one hand, the *myelinated* (Fig. 2.4) and *unmyelinated* axons and, on the other hand, short, medium and long axons.
- After the position in the nervous system, neurons are classified as: (1) *primary sensory neurons* (of first order, I) in direct interaction with the stimulus source (e.g., cone and rod retinal cells); (2) *interneurons* (secondary, tertiary, etc. neurons) that receive signals from other neurons and convey it to others, including the terminal ones located in CNS; and (3) *motor neurons* which are receiving signals from the internal neurons of CNS and convey it to the *effectors* (i.e., muscles, glands).
- Based on the neurotransmitter used in their *axonal buttons*, the neurons are: (1) *cholinergic* liberating acetylcholine (the case of motor neurons); (2) (*nor*)*adrenergic* liberating *adrenaline, noradrenaline* or *dopamine* as neurotransmitters (the case of the secondary neurons of the sympathetic nervous system); (3) *GABAergic neurons* which generate *gamma aminobutyric acid* (GABA), one of the two inhibitory neurotransmitters in CNS; (4) *glycinergic* which produce *glycine*, a major inhibitory transmitter in the mammalian CNS; (5) *glutamatergic* which liberate *glutamate*, one of the most common excitatory neurotransmitters in CNS; and (6) *serotonergic* which synthesize the neurotransmitter *serotonin* (5-HT), found in CNS.

This summary classification, which does not exhaust the criteria taken into account, provides evidence of the great diversity of neurons composing CNS. It is this diversity which, together with other structural features, gives CNS the great variety of its complex functions.

2.2.2 *Neuronal Resting Potential*

The membranes of all neurons are electrically polarized, the potential difference (the resting membrane potential), $\Delta\Phi_{\mathrm{RM}}$, between the interior cellular potential, Φ_{i}, and the exterior cellular potential, Φ_{e}, being of the order of tens of mV:

$$\Delta\Phi_{\mathrm{RM}} = \Phi_{\mathrm{i}} - \Phi_{\mathrm{e}} \approx -60 \ \ldots \ -90\mathrm{mV} \tag{2.1}$$

The potential difference is the result of the highly asymmetric of Na, K, and Cl ionic distribution across the neuronal membrane (Fig. 2.5) as the Goldman-Hodgkin-Katz formula states:

$$\Delta\Phi_{\mathrm{RM}} = -\frac{RT}{F}\ln\frac{P_{Na}\left[\mathrm{Na}^{+}\right]_i + P_K\left[\mathrm{K}^{+}\right]_i + P_{Cl}[\mathrm{Cl}^{-}]_e}{P_{Na}\left[\mathrm{Na}^{+}\right]_e + P_K[\mathrm{K}^{+}]_e + P_{Cl}[\mathrm{Cl}^{-}]_i} \tag{2.2}$$

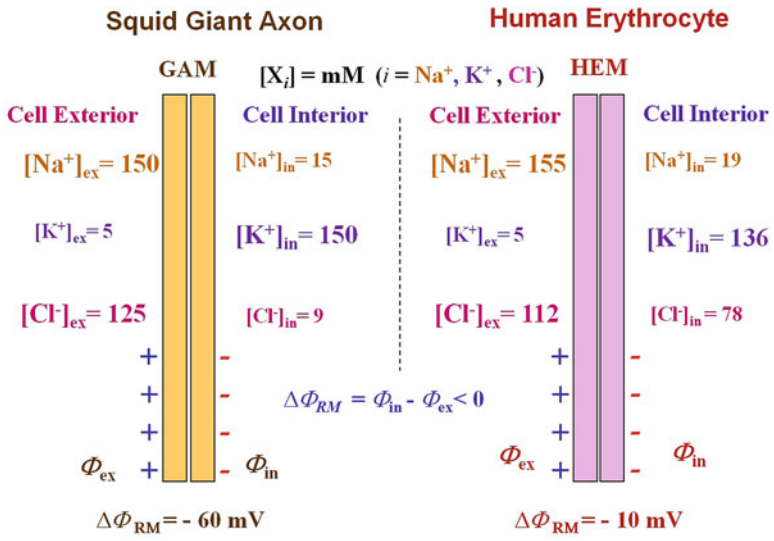

Fig. 2.5 The Na^{+}, K^{+}, and Cl^{-} concentrations across the giant axon membrane (*GAM*) of squid and of human erythrocyte membrane (*HEM*); $\Delta\Phi_{\mathrm{RM}}$ = resting membrane potential difference (With permission from Popescu 2016)

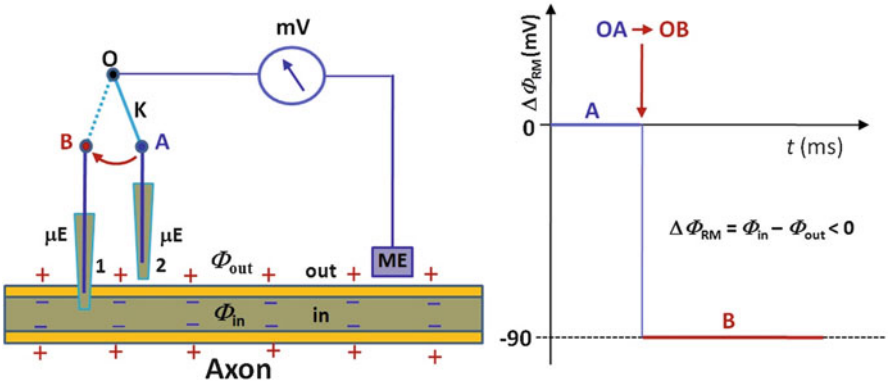

Fig. 2.6 The scheme of axon's resting potential measurement. Φ_{in}, Φ_{out} = internal respectively, external electric potential, *ME* exterior macroelectrode; μE glass microelctrode; the microelectrode 1 (μE) is inserted into the axon; the microelectrode 2 (μE) is placed outside the axon; *K* two position key, *mV* milivoltmeter

where P_{Na}, P_K, P_{Cl} are the ionic permeabilities, that is, the ratio between the diffusion coefficients and the membrane thickness, $[X]_i/[X]_e$ are the concentrations of the species X, inside/outside the neuron, R the universal gas constant, T the absolute temperature and F the Faraday number (96,500 C mol^{-1}).

The resting potential, $\Delta\Phi_{RM}$, can be measured with the aid of a microelectrode (μE) inserted into the cell through the membrane and a macroelectrode (ME), placed in the exterior cellular medium (Fig. 2.6). The resting potential has different values (of the order of tens of mV), depending on the cell types. For instance, in the case of the squid giant axon, it is of about −60 mV, while in the case of frog striated muscle fiber it is of −90 mV.

The primary sensory neurons can be excited only by their adequate stimuli (e.g., olfactory receptors by odorants, ciliated cells by mechanical stimuli, photoreceptors by light, etc.). These specific stimuli modify the membrane potential of the neurons, as a rule, provoking membrane depolarization (i.e., the decreasing the absolute value of resting potential).

For this reason, in biophysics laboratory experiments, the neurons are usually excited by electrical stimuli considered as universal, hence unspecific stimuli. Therefore, in order to study the behavior of the excitable cells to stimulation, one prefers to use experimental setups generating various types of electrical signals (more frequently, rectangular currents of different intensities, frequencies, and durations). From the electrical point of view, a very small unmyelinated membrane patch can be modelled by an elementary electrical circuit composed of: *sources*, *resistors*, and a *capacitance* (Fig. 2.7), while the whole membrane is considered as a set of elementary circuits connected in parallel. The representation of the electrical parameters of a membrane by distinct sources, resistors and capacitance, for each ionic species, is justified by the existence of *independent ionic channels* that can be selectively blocked by different inhibitors (e.g., the Na^+ channels by tetrodotoxin and K^+ channels by tetraethyl ammonium).

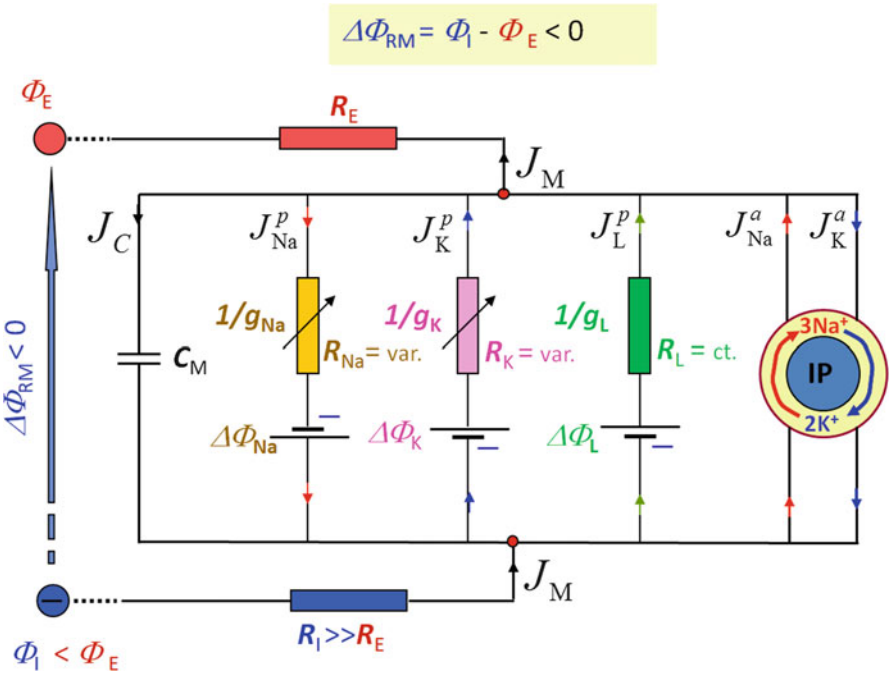

Fig. 2.7 Electrical model of an excitable membrane patch. $\Delta\Phi_{Na}$, $\Delta\Phi_K$, $\Delta\Phi_L$ = the equilibrium electrochemical potentials for the ions: Na^+, K^+, and the other ions, that is, the leakage ions. R_{Na}, R_K, R_L = the unit membrane area resistance; R_E, R_I = specific external and internal medium resistance; g_{Na}, g_K, g_L = membrane ionic conductivities; J^p_{Na}, J^p_K, J^p_L = ionic currents due to the passive transport; J_C capacitive current; *IP* ionic pump; J^a_{Na}, J^a_K = ionic currents due to the active transport; Φ_E, Φ_I = electrical potentials of the external and internal cellular medium; $\Delta\Phi_{RM}$ = resting potential difference (With permission from Popescu 2016)

2.2.3 *Neuronal Action Potential*

According to the *ionic theory of excitation*, the recorded experimental time course (Fig. 2.8) of AP can be understood if the microscopic passive and active movements of ions, across the specific Na^+ and K^+ channels of the excited membrane, are understood, too. The AP potential is elaborated if, and only if, the membrane depolarization attains a critical value named *threshold*, that is, AP is subjected to *all or none law* the stimuli over the threshold eliciting the same APs, irrespective of their amplitude, while those stimuli under the threshold are ignored.

The membrane depolarization, consecutive to cell excitation, firstly provokes the opening of Na^+ channels, which results in its much higher permeability to Na^+, as compared to the resting state. Then, a massive amount of Na^+ will diffuse into the cell, due to Na^+ concentration gradient across the cell membrane. This Na^+ influx into cell generates an *inward sodium current*, J_{Na}, which decreases in time, since an inactivation mechanism of the sodium channels comes into play (when the equilibrium Na^+ difference potential is attained).

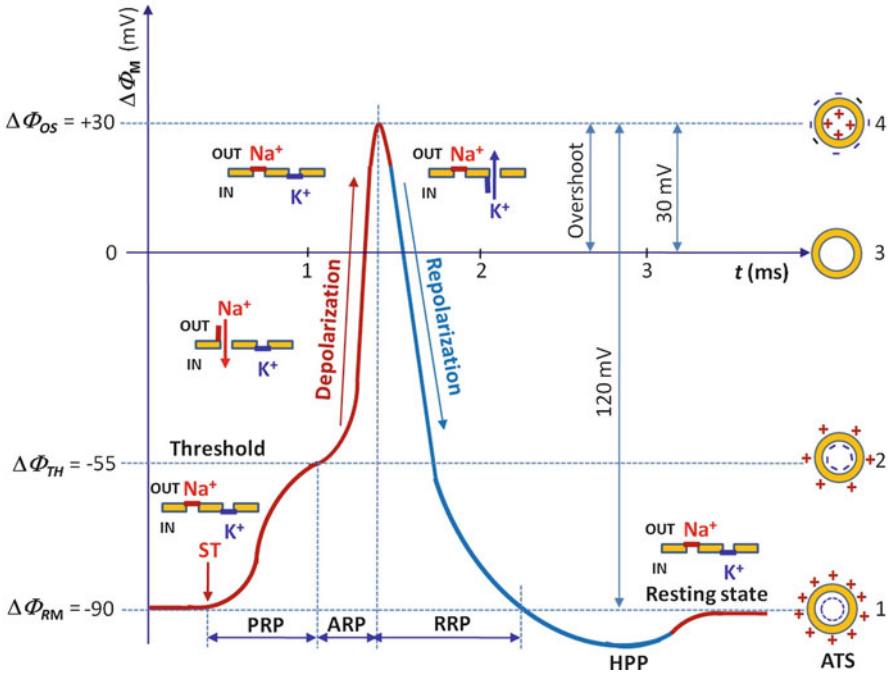

Fig. 2.8 The time course of action potential: $\Delta\Phi_M = f(t)$. $\Delta\Phi_{RM}$ = resting membrane potential; $\Delta\Phi_{TM}$ = threshold potential of the membrane; $\Delta\Phi_{RM}$ = action potential overshoot; *ST* stimulus, *PRP* prepotential; ARP = absolute refractory period; *RRP* relative refractory period, *HPP* membrane hyperpolarization; *1*, *2*, *3*, *4* = four axonal transversal sections presenting the successive electrical polarizations of the membrane (drawn in *yellow*). Five snapshots of the Na^+ and K^+ channel states are also presented

The inward sodium current is created at the moment in which the AP is almost elaborated. In this moment, a sudden decrease of membrane permeability to Na^+, takes place simultaneously with an increase of membrane permeability for K^+. This phenomenon will engender a passive diffusion of K^+ out of the cell, thus generating an *outward potassium current*, J_K, which will repolarize the membrane and even hyperpolarize it, before the resting membrane potential is attained. Therefore, the time course of the potassium ionic current is temporally delayed in comparison with the time course of sodium ionic current.

Moreover, due to the fact that the membrane itself is suffering depolarization followed by repolarization, a *capacitive current*, $J_C(t)$, is superimposed onto these two ionic currents. One must also take into account the global contributions, $J_L(t)$, of the leakage of the other ions (e.g., Cl ions) to the *total membrane current*, $J_M(t)$:

$$J_M(t) = C_M \frac{d(\Delta\Phi_M)}{dt} + J_{Na}(t) + J_K(t) + J_L(t) \tag{2.3}$$

Taking into account the time course of sodium and potassium transmembrane currents, Hodgkin and Huxley postulated that the ionic conductances (g_{Na}, g_{K}) depend on the transmembrane potential, $\Delta\Phi_{\mathrm{M}}$, and the time, t, in a complicated manner (Hodgkin and Huxley 1952; Hille 2001; Clay 2005) which will be presented below.

Using the mathematical dependence of g_{Na} and g_{K} conductances on probability of channel gate activation/inactivation and applying the *cable model* to the AP as a *propagating wave*, along a cylindrical axon, one obtains the differential equation describing the time course of an AP (i.e., $\Delta\Phi_{\mathrm{M}}$ dependence of time), at any given point of an axon (for details, see Raicu and Popescu 2008):

$$\frac{a}{2\rho_{in}v^2}\frac{d^2(\Delta\Phi_M)}{dt^2} = C_M\frac{d(\Delta\Phi_{\mathrm{M}})}{dt} + (\Delta\Phi_{\mathrm{M}} - \Delta\Phi_K)\, g_K^{\max}[n\,(\Delta\Phi_{\mathrm{M}}, t)]^4 + (\Delta\Phi_{\mathrm{M}} - \Delta\Phi_{Na})\, g_{Na}^{\max}[m\,(\Delta\Phi_{\mathrm{M}}, t)]^3 h\,(\Delta\Phi_{\mathrm{M}}, t) + (\Delta\Phi_{\mathrm{M}} - \Delta\Phi_L)\, g_L \tag{2.4}$$

where a is the axon radius, ρ_{in} the resistivity of the internal medium of axon, v the velocity of AP propagation along the axon; $0 \leq n \leq 1$ represents the probability that one K^+ gate (of four gates) to be activated (i.e., allows K ions to diffuse across the membrane); $0 \leq m \leq 1$ represents the probability that *three gates* of Na *to be activated*, and $0 \leq h \leq 1$ represents the probability that *one gate* of Na *to be inactivated* under the membrane depolarization.

The above differential equation may be numerically integrated to obtain the value of the action potential at any moment. Using this equation, Hodgkin and Huxley were able to fit the experimental time course of the AP in the squid unmyelinated axon. However, the small noticed discrepancy between the predicted and measured values of AP velocity required the necessity for improvement of the Hodgkin-Huxley model (HHM). In the meantime, several corrections have been applied to the model, but in all cases, the main features of HHM were preserved. For this outstanding achievement, Hodgkin and Huxley were awarded the Nobel Prize in Physiology or Medicine, in 1963.

2.2.4 Propagation of Action Potential Along the Axons

The action potential presents some characteristic features: it presents a *latency time* (i.e., a delay between the stimulus action and the AP outbreak) dependent of the stimulus intensity; it is a *very rapid response* of the excitable cell (it lasts a few ms); it obeys an *all or none law*, the time course being stereotyped, irrespective of the intensity of the stimulus above the threshold, although its frequency depends on stimulus intensity (Fig. 2.9); presents an *absolute refractory period* (when the neuron do not respond to any stimuli) and a *relative refractory period* when

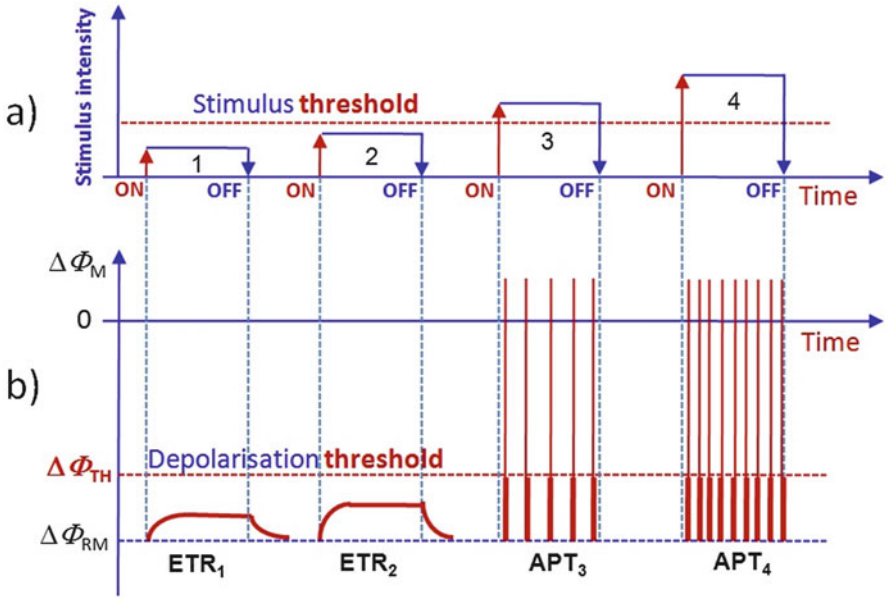

Fig. 2.9 Frequency coding of AP on the intensity (amplitude) of the stimulus. (**a**) Four *rectangular* stimuli of increasing intensities. (**b**) Responses of the neuron to stimuli of increasing intensities. ETR_i (i = 1, 2): electrotonic responses; APT_i (i = 3, 4): schematic presentation of action potential trains; $\Delta\Phi_{RM}$ = resting membrane potential difference; $\Delta\Phi_{TH}$ = threshold membrane potential difference; $\Delta\Phi_M$ = membrane potential difference

the neuron responds, but not optimally, to the stimuli; it is a *transitory* process, the neuron recovering its resting state after a very short time; it is delocalized, propagating *without decrement* over long distances.

APs propagate non-decrementally along the axonal membrane with velocities in the range, (1–100) m/s, depending on the morphology of axons, especially on the axon thickness. In the case of unmyelinated axons, the longitudinal ionic currents are generated by small local currents, called *Hermann currents*, which propagate with a relatively slow velocity (Fig. 2.10). Instead, in the case of myelinated nerve fiber, the ionic currents propagate in larger steps, from a Ranvier node to another, by the so called *saltatory currents*, therefore generating, longitudinal currents which propagate with a much higher velocity, $V >> v$. The most evident proof of saltatory propagation, in the case of myelinated neurons, is the blocking of AP propagation by *narcotization* (i.e., by applying a local anesthetic) of Ranvier node. On the contrary, by applying the same anaesthetic onto the myelin sheath, the AP propagation is not at all affected.

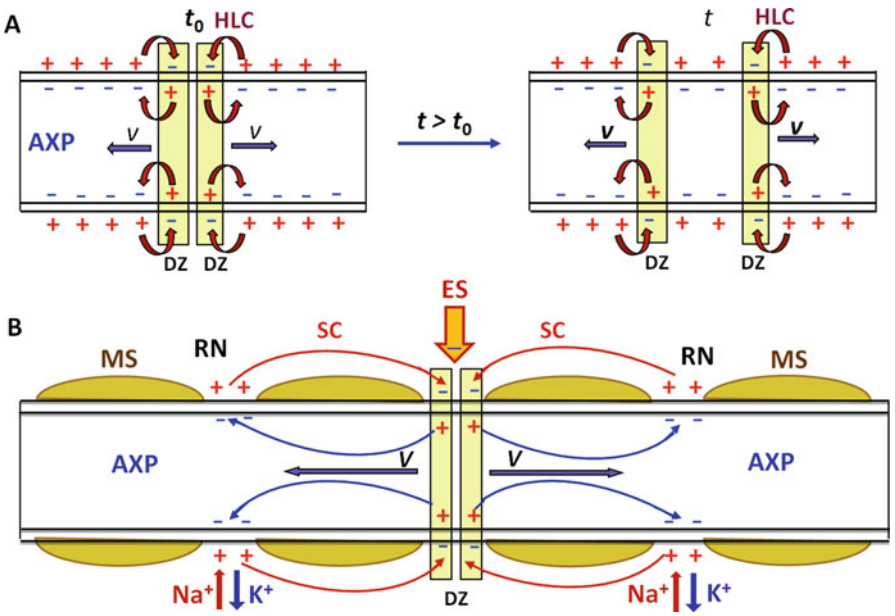

Fig. 2.10 Propagation of AP along: (**a**) unmyelinated nerve fibers (axons) and (**b**) myelinated axons. *ES* electrical stimulus. In *yellow rectangles*, the depolarization of the axonal membrane are presented; *DZ* depolarized zone, *HLC* Hermann local currents (*reddish curved arrows*), *SC* saltatory currents (*red* and *blue arrows*); *MS* myelin sheaths, *RN* Ranvier nodes, *AXP* axoplasm; *v* and *V* velocities of AP propagation in the two types of axons (With permission from Popescu 2016)

2.3 Synapses, the Omnipresent Inter-neuronal Junctions in CNS

The huge number of CNS units forms a complex spatial scaffold (sustained also by the glial cells) of interconnected neurons that permanently modify their states and process, receive, and exchange information through the myriad of synapses, ranging from 10^{14} to 5×10^{14} (Drachman 2005). A neuron can establish one or more synapses with one or more neurons, in some cases, with thousands of neurons (on average making 7000 synaptic connections to other neurons). As we already said, the robustness and versatility of CNS are, in a very great measure, the result of these multiple and subtle interneuronal connections.

- According to their morphology and their way of operation, there are two classes of synapses: *chemical* and *electrical*, the latter representing, however, a very small fraction of the total synapses in mammalian CNS.
- At the same time, it is important to mention that chemical synapses are of two kinds, according to their efferent effect: *excitatory* and *inhibitory synapses*. For instance, the ganglion cells receive both types of synapses and, depending on

whether their contribution to the membrane depolarization surpasses a threshold, they will elaborate action potentials.

- Based on electron microscopy images which emphasize the thickness of pre- and postsynaptic membranes, there are two categories of synapses: (1) *asymmetrical* (Gray's type I synapses) when the two membranes have different thicknesses, the postsynaptic membrane being thicker and (2) *symmetrical* (Gray's type II synapses) when the two membranes have the same thickness.
- Taking into account the parts involved in synaptic junctions, one can distinguish many types of synapses: (1) *axo-somatic*; (2) *axo-dendritic*, (3) *axo-axonal*; (4) *dendro-dendritic*; (5) *dendro-somatic*; (6) *somato-dendritic*; (7) *somato-somatic.*
- It is interesting to mention that there are two other types of synapses not encountered in CNS: *neuromuscular junctions* between a neuron and a muscle fiber and *neuroglandular synapses* between a neuron and a gland.

Understanding the AP propagation action from neuron to neuron, the action of psychoactive drugs, the causes of mental disorders, the bases of learning and memory is impossible without a deep knowledge of the AP synaptic transmission.

As a rule, in the physiological normal situation, APs (which are discrete electrical signals), propagate *orthodromically* in the neuron, that is, from dendrites, passing through soma and axon, toward the axonal ramifications. These APs are reaching the presynaptic membrane of an axonal button, part of the synaptic junction of the neuron with another neuron or with an effector. How will the APs be transmitted across the synapse, due to the neuronal morphological discontinuity (i.e., neuronal contiguity)? The answer will be given below for each type of synapses.

2.3.1 Chemical Synapses

In CNS, chemical synapses are present in a very great number, exceeding the number of electrical synapses.

A chemical synapse consists of the following parts: (1) *presynaptic space* (situated in the axonal button), (2) *presinaptic membrane* (PRSM), (3) *synaptic cleft* (a narrow space of about 20–50 nm, between the two opposing neuronal parts), and (4) the *postsynaptic membrane* (PTSM) (Fig. 2.11).

1. In the pre-synaptic space, there are dozens of *synaptic vesicles* (SV) of about 50 nm in diameter, filled with about 6000–7000 molecules of neurotransmitters (Kuffler and Yoshikami 1975; Nicholls et al. 2001). In the same space, there are also larger vesicles of more than 100 nm in diameter called *secretory granules* filled with *neuropeptides*. There are three classes of neurotransmitters: (a) *amino acids* or of amino acid types (e.g., Gly, Glu, and GABA); (b) *amines* (e.g., acethylcholine, adrenaline = epinephrine, noradrenaline = norepinephrine, histamine, dopamine, serotonin), and (c) *neuropeptides* (e.g., enkephalin, somatostatin, dynorphin, cholecystokinin, substance P, composed of 11 amino acids, neuropeptide Y, composed of 36 amino acids, etc.).

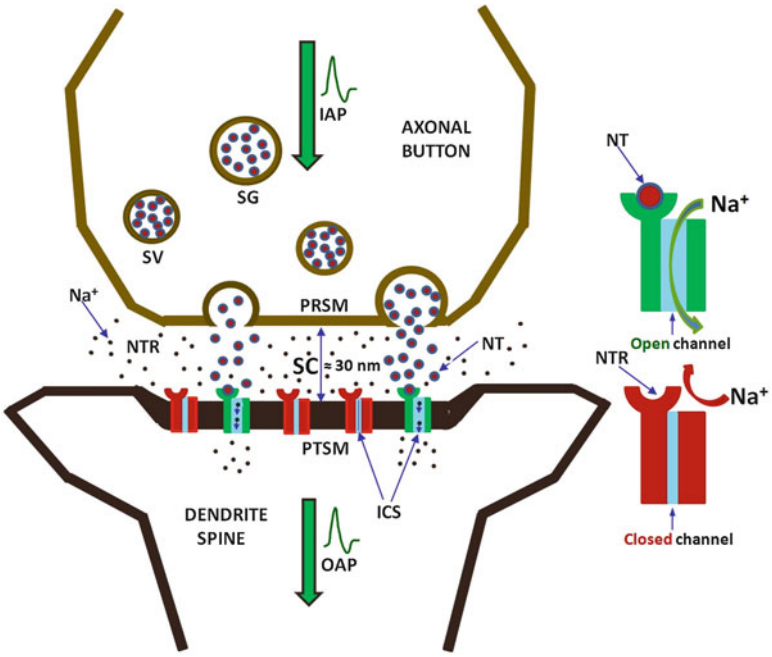

Fig. 2.11 Schematic morphology of an axo-dendritic chemical synapse. *PRSM* presynaptic membrane, *PTSM* postsynaptic membrane, *SC* synaptic cleft, *SV* synaptic vesicle, *SG* secretory granules, *NTR* neurotransmitter receptor, *ICS* ionic channels of the postsynaptic membrane, *IAP* incoming action potential, *OAP* outgoing action potential

2. The PRSM presents, toward the axonal button space, the so-called *active zones* formed by proteins which are the actual sites of neurotransmitter release.
3. The synaptic cleft (SC), the 20–50 nm wide space between the PRSM and PTSM, is filled with fibrous proteins contributing to the adherence of the two membranes in order to form a stable morphological structure.
4. The postsynaptic membrane presents a thick accumulation of proteins into it or just under it, forming the *postsynaptic density*. This structure contains *neurotransmitter receptors* (NTRs) which, binding coming neurotransmitters, modify the polarization state of the postsynaptic cell (exciting or inhibiting it).

If the Na^+ channels of PTSM are opened by the coupling of excitatory neurotransmitters to NTRs, the PTSM depolarization takes place and the synapse is of excitatory type, generating an *excitatory postsynaptic potential* (EPSP). Examples of excitatory neurotransmitters are: L-glutamate, serotonin, norepinephrine, epinephrine, and acetylcholine. If, on the contrary, the Cl^- channels of PTSM are opened by inhibitory neurotransmitters, the hyperpolarization of this membrane takes place and the synapse is of the inhibitory type generating an *inhibitory postsynaptic potential* (IPSP). Examples of inhibitory neurotransmitters are: Gly and GABA. It is interesting to note that dopamine can have both an excitatory and inhibitory effect.

The sequence of events that take place in synaptic transmission (lasting about 0.5–1.0 ms) from a presynaptic to a postsynaptic neuron are the following: (*i*) the *trafficking of SV components*, from the axonal ramifications toward the synaptic space by the kinesin motors, (*ii*) the arrival of electrochemical excitation wave (i.e., the action potential) at the PRSM, (*iii*) the depolarization of the PRSM causing the opening of the Ca^{2+} channels, (*iv*) the *diffusion* of Ca^{2+} through the PRSM, increasing the Ca^{2+} concentration into the axonal button, (*v*) the *activation* the Ca^{2+}-sensitive proteins attached to SVs loaded with neurotransmitters, (*vi*) the priming of SVs by formation of partially assembled SNARE complexes, prior to SV docking and fusion, induced by the activated sensitive proteins, with PRSM thereby opening the SVs and thus releasing their neurotransmitters into the synaptic cleft (SC), (*vii*) the *neurotransmitter diffusion* within the SC (some of them bind to the molecular receptors embedded into PTSM), (*viii*) the *specific binding* of neurotransmitters to NTRs from PTSM causing the activation of these receptors and inducing the *depolarization* or *hyperpolarization* of the PTSM (this process is the main step by which the presynaptic neuron influences the postsynaptic neuron), (*ix*) the *generation* of an AP (or a train of APs) if the depolarisation of the PTSM is beyond a threshold, (*x*) the *liberation* of neurotransmitters from the NTRs, due to thermal motion, and their away diffusion, and (*xi*) the *neurotransmitter reabsorption* by the presynaptic neuron or their enzymatic *breaking down* (e.g., the acetylcholine by acetylcholinesterase).

Chemical synapses, involved in the electrical transmission or blockade of neuronal signals, have a crucial role in information processing both in CNS and PNS. The inappropriate loss of synaptic number, microanatomy, biochemistry, and stability leads to the perturbation of neuronal circuits which causes the so-called *synaptopathies* like, for instance, some psychiatric and neurologic disorders: mental retardation (fragile X syndrome), Alzheimer's disease, schizophrenia, autism, addiction, etc. The chemical synapses are the site of action for many psychoactive drugs: cocaine, morphine, curare, strychnine, etc. The synapses constitute important targets for treatments to slow progression and preserve cognitive and functional abilities in the brain diseases (Spronsen and Hoogenraad 2010).

2.3.2 Electrical Synapses

Electrical synapses are simpler than chemical ones, allowing direct flow of ionic current from a neuron to another. These synapses are composed of interneuronal hydrophilic channels called *connexons* that assemble together to form the so-called *gap junctions*. Unlike chemical synapses, the synaptic cleft of electrical synapses is narrower, being of about 3 nm as compared with SC of chemical synapses large of 20–50 nm. Each connexon consists of six proteins (connexins) forming a relative large hydrophilic pore with a diameter of about 2 nm, thus allowing the free diffusion of ions and even of small molecules. The channel-connexons are bridging the SC connecting the cytosols of the two adjacent neurons (Fig. 2.12).

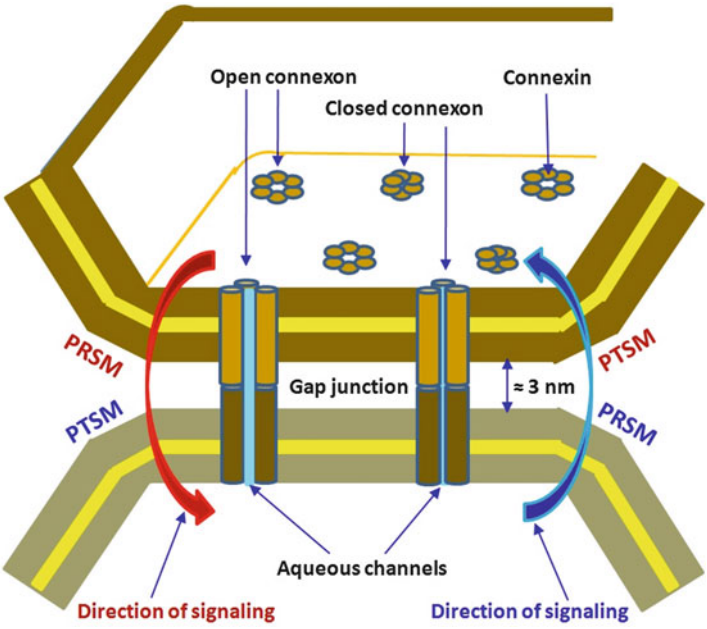

Fig. 2.12 Schema of an electrical synapse. *PRSM* presynaptic membrane, *PTSM* postsynaptic membrane. The directions of signaling are indicated, too, this type of synapse conducting bi-directionally

Due to this peculiar morphology, the AP transmission between the two neurons is much faster than in the case of chemical synapses which involve a *rate limiting step* due to neurotransmitter diffusion (a slow physical process). In the case of electrical synapses, an AP in the presynaptic neuron induces, almost instantaneously, an AP in the postsynaptic neuron. In the CNS of mammals, these types of synapses are encountered in specialized brain zones where the activity of neighboring neurons requires their high synchronization (Bear et al. 2001). In PNS, this type of synapses occurs, for instance, between retina cells.

It is also important to mention that, due to the rapid transfer of AP along the electrical synapses, these, practically, *present a very short synaptic delay* ($\approx$ 0.1 ms) as compared to chemical synapses ($\approx$ 0.5–5 ms). Besides, with a few exceptions [e.g., crayfish giant synapse (Nicholls et al. 2001)] electrical synapses *do not exhibit rectification*, conducting the AP in both directions very well, while chemical synapses are unidirectional.

Moreover, the excitation coming from the presynaptic neuron does not induce lasting modifications in the postsynaptic neuron as is the case of chemical synapses involved in synaptic plasticity (*vide infra*).

2.3.3 *Dendritic Spines*

A dendritic spine is a small "door knob" shaped extension from a neuron's dendrite that receives excitatory synaptic input from a single axon. Dendritic spines serve as memory storage sites for the synaptic strength and help transmit electrical signals to the neuron's cell body.

To illustrate the fine morphological details of the whole neuron we show in Fig. 2.13 confocal microscopy images of an intracellularly injected layer III pyramidal neuron (panel A) of the human cingulate cortex with its basal (panel B) and apical dendrites (panel C). The dendritic shafts and spine volume reconstruction (seen in panels D&E) obtained using semiautomatic software tools, and accurate representations of the fine morphological details of the whole neuron were analyzed and quantified using a method described in detail in Benavides-Piccione et al. (2013).

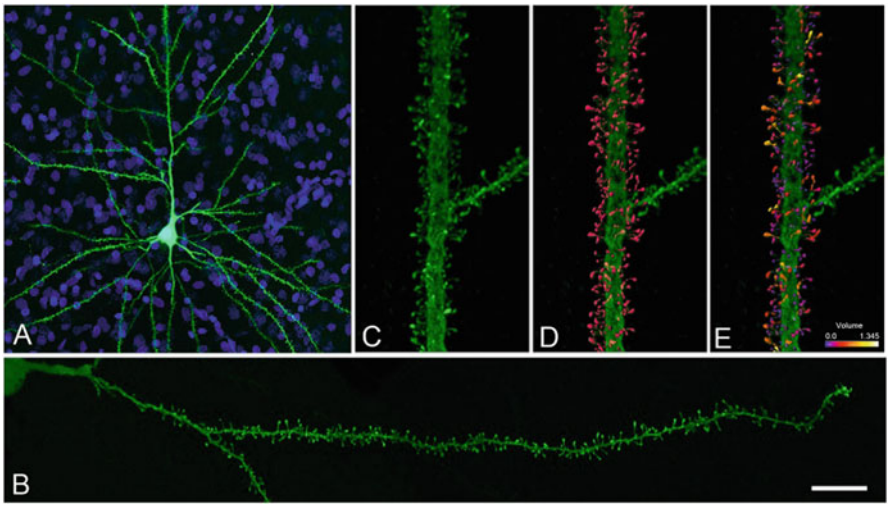

Fig. 2.13 Confocal microscopy and 3D reconstructions of injected cells. (**a**) Confocal microscopy image of an intracellularly injected layer III pyramidal neuron of the human cingulate cortex. DAPI staining in *blue*. (**b**) Lower magnification image shows a horizontally projecting basal dendrite, to illustrate the extent of the labeling. (**c**) Higher magnification image of an apical dendritic segment acquired at 100 μm distance from its soma. (**d**) Three-dimensional reconstruction of the complete morphology of each dendritic spine shown in (**c**, **e**). Estimation of the spine volume values shown in (**d**) by color codes (*blue-white*: 0.0–1.345 μm^3). Scale bar (in **b**): 40 μm in (**a**), 13 μm in (**b**), and 7 μm in (**c**–**e**) (With permission from Benavides-Piccione et al. (2013) and Merchán-Pérez et al. (2009) and with the courtesy of Professor Javier DeFelipe)

2.3.4 Synaptic Plasticity

A very important characteristic, especially of the chemical synapses, is their *plasticity*, that is, their high ability to permanently reshuffle and refresh under the influence of the signals traversing them, i.e., under the influence of the previously received signals. Such changes in response to signals can last for a very short time (ms, s) of or for a very long time (hours, days). This synaptic feature enables them with the specific property required for their implications, practically, in all the brain higher functions including learning and behavior. The modifiable synapses are also considered to be the brain main memory-storage elements.

According to the duration of the synaptic modification, the synaptic plasticity is of two types: short-term and long-term plasticity. The short-term plasticity consists in: (a) *facilitation* lasting 100 ms, (b) *augmentation* lasting 10 s, and (c) *post-tetanic potentiation* (PTP) lasting about 10 min.

The long-term changes consist in: (a) *long-term potentiation* (LTP) correlated with the increase of the size of postsynaptic response and (b) *long-term depression* (LTD), which is correlated with the decrease of this response, lasting from minutes to tens of hours.

There is experimental evidence that synaptic morphology and function are not fixed once forever, they changing after each apposing neuron's strong or weak interaction. The effectiveness of a synapse in generating an output from the postsynaptic neuron is characterized by the so called synonymous terms: *efficacy*, *strength*, or *weight*.

It was noticed that the correlated simultaneous activation of two neurons making a synapse is conducting to modification of the strengthening of their synapse (i.e., to the increase/decrease of the synaptic efficacy/strength/weight). This was already stated about 60 years ago by Hebb (1949): "whenever an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency as one of the cells firing B is increased".

From this *principle of Hebb*, it resulted one of the most popular unsupervised learning rule of the artificial neuronal networks (the Hebb's rule) which, in its original formulation, not being a quantitative law, explains its popularity (Ripley 1996). According to this rule, a synaptic weight, w_{ij}, between two neurons i and j is increased, *if and only if*, the two neurons are simultaneously activated (neurons that fire together, wire together) or decreased if their activities are not at all correlated (neurons that fire out of synchronization weaken their link).

For this reason, it was later suggested that the reinforcing, δw_{ij}, of the synaptic weight, w_{ij}, is proportional to the product of the simultaneous activities, s_i and s_j of neurons, N_i and N_j (Ripley 1996):

$$\delta\, w_{ij} = \varepsilon\, s_i s_j \tag{2.5}$$

where $0 < \varepsilon \ll 1$ is the intensity learning parameter.

In the case of a neural network storing p patterns of N bits each pattern $(s_i^1, \ldots, s_i^j, \ldots, s_i^p)$, $(i = 1, 2, \ldots N)$, the synaptic weights are chosen according to the mathematical rule (known as Hebb's rule, also):

$$\delta\, w_{ij} = \sum_{\mu=1}^{p} s_i^{\mu}\, s_j^{\mu}/N \tag{2.6}$$

There are two cases: (a) if $s_i^{\mu} = s_j^{\mu}$, then: $\delta\, w_{ij} > 0$, and the weight will increase, the synapse becoming *excitatory*, (b) if $s_i^{\mu} = -s_j^{\mu}$, then: $\delta\, w_{ij} < 0$, and the synaptic connection will become *inhibitory*.

It is important to note that synaptic plasticity is attenuated with age, being enhanced in early development and infancy (when gross rearrangements of the axonal arborizations takes place) and diminished in adult life (when only small local changes of the synaptic efficacies are taking place).

The perturbation of synaptic plasticity has been involved in several mental illnesses, such as depression, addiction, dementia and anxiety disorders (Lüscher and Isaac 2009).

2.4 The Associations of Neurons into Neuronal Networks

The neurons are not isolated entities, like the books in a library, but they are interconnected in great ensembles called *neuronal pools* (or neuronal circuits/pathways), consisting of thousands to millions excitatory and inhibitory neurons, which cooperate in order to fulfill various specific body functions (e.g., the control of the breathing rhythm, the rhythmical moving of the limbs during walking).

A neuronal pool (NP) has a number of input sources and of output destinations which can be other NPs, or effectors. For instance, an output of a NP can influence the state of another NP (exciting or inhibiting it) or can control the peripheral effectors (muscles and/or glands). NPs can be either localized in specific parts of the CNS or distributed over different zones of the CNS.

According to their topology and, especially, to their function, there are five types of neuronal pools (circuits/pathways): (1) convergent; (2) divergent; (3) reverberant; (4) serial; and (5) parallel (Fig. 2.14).

(a) In a *convergent neuronal pool*, the outputs of many neurons are funneled to one neuron and from the neurons of the same rank, like this one, to several others neurons and so on (Fig. 2.14a). It is the case, for instance, of receptive fields of the visual system where the outputs of many receptor retinal cells are funneled to a bipolar cell, the outputs of many bipolar cells are converging to a ganglion retinal cell, the outputs of many ganglion cells are projected to the same neuron pertaining to *lateral geniculate nuclei*, and so on.

(b) In a *divergent neuronal pool*, one axon of an "initial" neuron branches and makes synapses with many postsynaptic neurons which will, in their turn, make

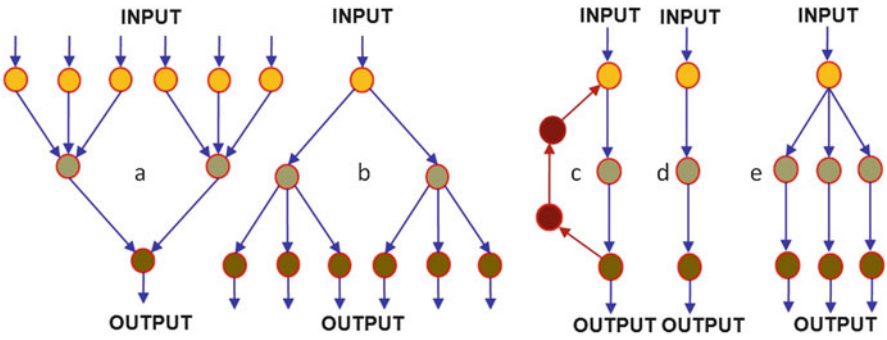

Fig. 2.14 The five types of neuronal pools: (**a**) convergent pool; (**b**) divergent pool; (**c**) reverberant pool; (**d**) serial pool; (**e**) parallel neuronal pool. Neuronal soma is represented by colored *circles*

synapse with many other neurons, so that the output of the initial neuron can ultimately excite a multitude of neurons or effector cells (Fig. 2.14b). It is, for instance, the case of a brain motor neuron that stimulates thousands of striated muscle fibers.

(c) In a *reverberant neuronal pool*, the neurons stimulate/inhibit each other being connected in a feedback loop (Fig. 2.14c). Such a pool generates prolonged or repetitive signals lasting until one neuron (or more neurons) in the loop fail to fire. An example of the reverberant pool is that which permanently sends repetitive signals to the diaphragm and inter-costal muscles, in order to maintain (by a negative feedback) the air ventilation in the lungs. Reverberant pools are involved in short-term memory and also in the uncontrolled excitation of neurons (by a positive feedback) during the paroxysmal epilepsy stroke.

(d) In a *serial neuronal pool*, there is a one-to-one neuron connection forming a shorter or longer neuronal chain (Fig. 2.14d). An example is the neuronal chain starting from cone receptors situated in *fovea centralis* of the retina and reaching the visual fields (17) in the brain's occipital lobe.

(e) In a *parallel neuronal pool*, an input neuron stimulates several chains of neurons (Fig. 2.14e). Since each pathway differs in the total number of successive synapses (each causing a delay) the signals arrive at the destination output neuron at different times. For this reason, this output neuron fire for some time after the initial input has already ceased, that is, an *after-discharge* takes place. This pool type explains, for instance, the post images of the very intense light sources, seen after the eye closing.

2.4.1 Minicolumns and Columns

The cortical *minicolumns* are basic components (i.e., the smallest modules) of brain organization.

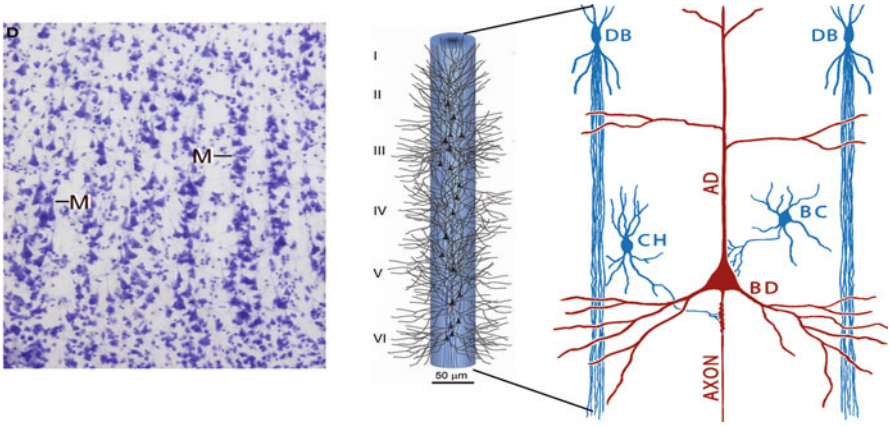

Fig. 2.15 Prefrontal cortical minicolumns (*left*). *M* minicolumn; columnar display of prefrontal cortical column in the human brain (*center*). I–VI = cortical layers; a prefrontal cortical minicolumn with all six layers (*middle*). *AD* apical dendrite, *BC* basket cell, *BD* branching dendrite, *CH* chandelier neuron, *DB* double bouquet interneuron, Pyramidal prefrontal cortical cell (*red*) surrounded by inhibitory interneurons forming a curtain of inhibition (*right*) (Adapted with permission from DeFelipe (2011) and Casanova (2013))

Vernon Mountcastle described, for the first time, the electrophysiological basis of the cortical minicolumn and suggested it as an elemental unit of information processing (Mountcastle et al. 1955; Mountcastle 1957, 1997). According to this view of cortical organization, neurons and their connections form a vertical "chain" that integrates the cells of each minicolumn (Fig. 2.15) into a coordinated "functional unit" (Mountcastle 1978, 1997). In this case, the smallest "unit of cortical organization" is the minicolumn, usually defined in Nissl stained sections by "a narrow radial array of pyramidal neurons" traversing laminae II–VI (Rakic 1988; Mountcastle 1997). Minicolumns are assembled in larger columns, also called macrocolumns (e.g., barrel somatosensory cortex of the rodent) "linked together" by short- range horizontal connections (Jones 2000; Zhang and Alloway 2006; Jones and Rakic 2010; DeFelipe et al. 2012). The different "echelons" are semi-independent of each other, having a limited number of information channels between them (Casanova 2005).

According to Buxhoeveden and Casanova (2002) and in agreement with Favorov and coworkers (Favorov et al. 1987; Favorov and Diamond 1990) and Mountcastle (1957, 1997), the estimated width of cortical macrocolumns is 350–600 μm. Hubel and Wiesel (1974) found that "optimal orientation tuning" changes systematically through 180° with an electrode advancing between 0.5 and 1.0 mm. The term hypercolumn refers to a complete rotation of columns (e.g., 0°, . . . , 180°; Wiesel and Hubel 1974). An interesting hypothesis by Rinkus (2010) posits that: (i) a macrocolumn's function is to "store sparse distributed representations of its inputs" and to "recognize" those inputs; and (ii) the generic function of the minicolumn is to "enforce macrocolumnar code sparseness". 4th ed., Sinauer Associates, pp. 432–434.

Such "distributed representations of inputs" flowing from visual to higher association areas in the prefrontal cortex (PFC) are part of "distributed networks", named "cognits" by Fuster and Bressler (2012). However, the specific role of prefrontal macrocolumns in "prospective coding and representation storage" is yet to be demonstrated (Bastos et al. 2012). A "sparse distributed representation" is one where items are encoded by activation of a "small set of the available representing units". "Sparse encoding" does not reduce to a straight "majority vote scheme". Anatomically, "sparse encoding" may be enforced by variability between minicolumns, which "suggest" differences in their "internal architecture" (Casanova et al. 2008; Rinkus 2010). This "variability" between components of a minicolumn may contribute to the "fault tolerance" of larger networks such as macrocolumns. McCulloch and Pitts (1943) have shown that when individual components fail (e.g., cell loss in initial stages of Alzheimer's disease) "redundant networks" of unstable nets could be designed for higher reliability than "redundant systems" of stable nets of the same size.

Cortical minicolumns unify cortex "horizontal" and "vertical" components within the same columnar space. Minicolumns are highly similar repetitive units. In spite of this apparent stereotype, they manifest considerable heterogeneity in different cortical areas and even within different brain *macrocolumns* (Casanova et al. 2015). Both the heterogeneity and the interaction between minicolumns assure the emergence of cerebral higher cognitive functions (Opris et al. 2011, 2012a, b, 2013; DeFelipe (2010)).

The disruption of these interactions is provoking a multitude of brain disorders such as autism, schizophrenia, Alzheimer, and drug addiction. The changes in characteristics at lower morphological levels have a substantial impact at superior levels of cortex organization and function (Opris and Casanova 2014).

2.4.2 Cortical Maps

Early studies by Mountcastle (1955, 1957, 1997) and Hubel and Wiesel (Hubel and Wiesel 1974; Wiesel and Hubel 1974; Gilbert and Wiesel 1989) showed that "neurons with similar response properties are grouped in vertical columns", having 0.5–1mm in diameter, with "each column oriented perpendicular to the surface of the cortex and spanning its thickness". Correspondingly, anatomical studies (using histological staining for the enzyme cytochrome oxidase) showed a "modular organization" in the primate visual cortex with "periodically spaced patches" 350 μm apart (Horton and Adams 2005; Opris and Casanova 2014). In the primate neocortex, the diameter of columns "varies between 300 and 500 μm", but it "does not differ significantly in size" between brains with over three orders of magnitude difference in volume (Bugbee and Goldman-Rakic 1983; Herculano-Houzel 2009).

This "common periodicity" means that any block of cortex, approximately the size of a single hypercolumn, contains "cells tuned to all values" of every receptive field variable (Swindale et al. 2000; Opris and Casanova 2014). Hubel (1982)

applied the term "module" to this tissue block comprising multiple, overlapping hypercolumns. On the other hand, Mountcastle (1997) has used the term "module" interchangeably with "column". The most "salient" feature of cortical organization is the presence of an orderly "topographic map of visual space" that is "remapped" sequentially as information flows from visual cortex to the prefrontal cortex (Salinas 2004). "The brain represents the external world as specific maps of activity created by networks of neurons" (Quast et al. 2016). Neighboring neurons "tend to have receptive fields in similar positions in visual space", and these positions change "predictably" as a function of cell's position on the cortex (Swindale et al. 2000). The "receptive fields" are large enough, so that the fields of adjacent neurons "overlap", but receptive fields of cells, separated by 1–2 mm, although near each other, will "not overlap". In addition, visual neurons vary in their preference with: i) the "orientation of bar" or edge stimuli, ii) the "direction of motion" of the oriented bar or edge, iii) stimuli delivered to one eye or the other ("ocular dominance"), and iv) low versus high "spatial frequencies" in the visual image (Swindale 1998). All of these features have been found to "vary" in an orderly way, so that a complete "set of values" occurs at least once every mm or so. An example of prefrontal cortical mapping relevant for learning in children is shown in Fig. 2.16.

2.4.3 Prefrontal Cortical Loops

Several lines of evidence indicate that the basal ganglia participate in multiple parallel segregated circuits or *thalamo-cortical loops* that make connections with

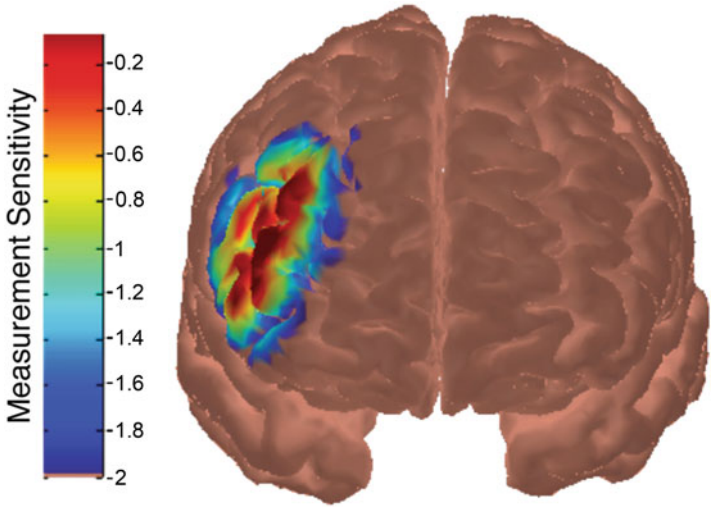

Fig. 2.16 Mapping key locations of the prefrontal cortex in children, including the right dorsolateral PFC that provides evidence for learning (With permission from Werchan et al. 2016)

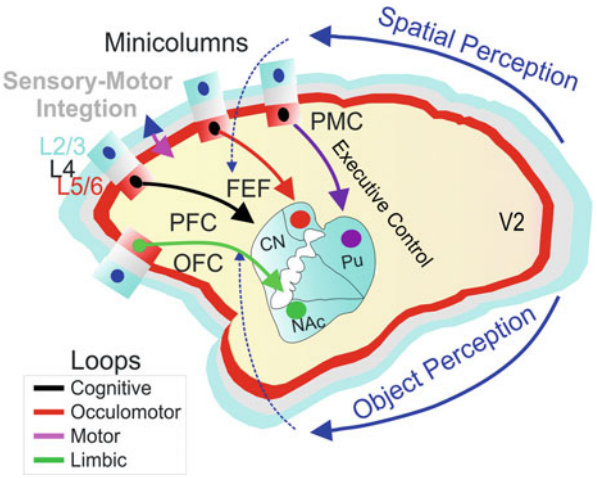

Fig. 2.17 Prefrontal cortical loops. *FEF* frontal eye field, *OFC* orbital frontal cortex, *PFC* prefrontal cortex, *PMC* premotor cortex, *CN* caudate nucleus, *NAc* nucleus accumbens, *Pu* putamen, V2 = Area BA18 of visual cortex; L_i (i = 2/3, 4, 5/6) = cortical layers (With permission from Opris et al. 2015a)

motor, sensory and cognitive areas of the cerebral cortex (Alexander et al. 1986). In Fig. 2.17 is drawn a diagram of the prefrontal cortical loops.

Prefrontal cortical areas seem to be the target of extensive, topographically organized outputs from the basal ganglia (Santos et al. 2014). Such thalamo-cortical projections from basal ganglia to the superficial and deep prefrontal cortical layers can directly activate specific inputs to the re-entrant loop (McFarland and Haber 2002; Opris and Casanova 2014; Swadlow et al. 2002; Takeuchi et al. 2011). Thus, the outputs from the inter-laminar microcircuits of prefrontal cortex are in ideal position to support the decision to act via the synchronous excitation of the circuit constellation in the executive hierarchy (Opris et al. 2013; Opris and Bruce 2005).

2.4.4 Neural Systems

The neural microcircuits and circuits in the brain are further organized into loops and large scale distributed networks. The main neural systems are: (a) sensory system-processing environmental stimuli, (b) motor system-processing all the movements performed by the body, (c) cognitive system-processing neural signals related to memory and executive control of behavior, and d) limbic system (including the reward system) processing emotional stimuli.

2.4.5 Connectome

The human brain is, as already said, a complex biophysical system consisting of 86 billions of neurons (Herculano-Houzel 2009), and each neuron makes tens of thousands of synapses (Andersen 1990), resulting over one hundred trillion synaptic

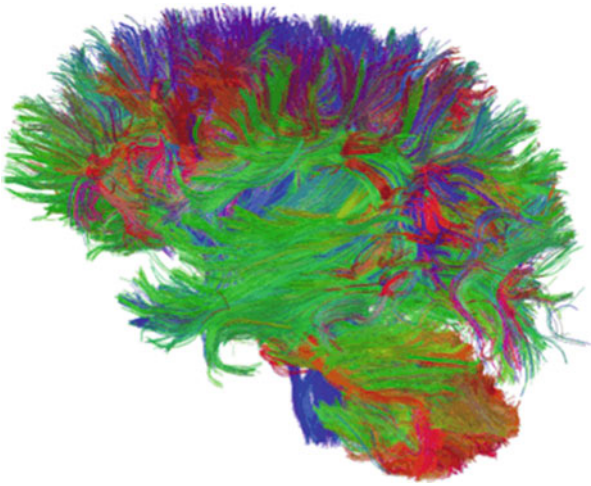

Fig. 2.18 The human connectome. Images show the fiber architecture of the human brain as revealed by diffusion imaging (With permission from Olaf Sporns 2016)

connections. The totality of these huge brain connections represents the so-called *connectome*. In Fig. 2.18 is shown a simplified image of these connections inside the CNS.

The connectome was examined using either traditional tracing methods or diffusion-based imaging in vivo (Shanahan 2012). The information extracted yields data for a connectivity matrix covering the major cortical areas of the animal's forebrain, or even the entire neocortex, namely the brain's structural connectome (Beul et al. 2015). The resulting connectivity matrix is then analyzed using advanced mathematical concepts for complex networks (i.e., graph theory), to reveal its large-scale interconnections. A number of topological features include the sparse network and the meso-level microcircuits defining the *cortical modularity* (Opris and Casanova 2014).

2.5 The Global Hierarchical Organization of the CNS

The hierarchical organization of brain functions was introduced by Joaquin Fuster based on Hughlings Jackson's assumption that the cortex is the highest level of the nervous system that controls (activates and/or inhibits) the functions of lower levels so that cortical disorders led to two sets of symptoms: 'negative' from loss of the controlling cortex and 'positive' from the emergence of the lower center (Fuster 1990, 2007; York and Steinberg 2011). This implies an anatomical and physiological hierarchy of higher and lower centers, with the higher ones suppressing the function of the lower ones (Fuster 1990; York and Steinberg 2011). The hierarchical architecture consists of cortical modules (layers and minicolumns-microcircuits), subcortical nuclei (basal ganglia, thalamus – cortical-subcortical loops), brainstem (midbrain, pons, medulla – cortical-brainstem networks), low level (sensory: visual,

auditory, touch, smell, and taste; and motor: eye, hand, limb, and pupil dilation), and high level cognitive functionality (perception, awareness, memory, decision, reasoning, and language). Our focus is to provide an overview on the hierarchy of neuronal circuitry of the executive control of behavior/memory that spans over frontal and parietal cortices, subcortical structures in basal ganglia and thalamus, brainstem, and spinal cord, from the biophysics level to the neuroscience systems level. The mind, after all, represents the integrated expression of the cognitive brain functions.

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Part II
Microcircuits and the Emergence of Mind

Chapter 3
Systems Theory, Emergent Properties, and the Organization of the Central Nervous System

Manuel F. Casanova, Ioan Opris, Estate Sokhadze, and Emily L. Casanova

Abstract The Central Nervous System can be understood as an organization whose levels have been established throughout evolution. In this organization, the cerebral hemispheres occupy the highest level of a hierarchical open system wherein the function of the brain is to match relationships among objects in the surrounding environment. The outer portion of the cerebral hemispheres is comprised of vertical arrays of cell bodies (minicolumns) whose close apposition provide for the cerebral cortex. Thalamic afferents terminate in the middle layers of the minicolumns and are integrated into microcircuits by vertical connections to more superficial and deeper layers. These repeating microcircuits comply with a definition for modules as weak linkages connecting elements within the module are more abundant than those between the modules. Electrophysiological studies with conformal multielectrode recording arrays have defined the transmission codes by which minicolumns give rise to executive functions, e.g., task-related selection. The emergence of minicolumnar functions appears to be prompted by physical constraints where laws of conservation guide the self-organization of minicolumns during brain development and ageing. The fact that minicolumns exhibit scalar properties relating pyramidal cell size and minicolumnar core size, rotational symmetry, and conservation of translational movements helps to conceptually organize the cytoarchitecture of the isocortex.

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Keywords Cerebral cortex • Minicolumns • Modules • System theory • Laws of conservation

3.1 Introduction

Systems Theory investigates those discernible regularities that help clarify how the different components work on a common goal within an organization. Systems Theory makes the complexity of an organization more understandable by giving them both a structure and a frame of reference. By better understanding the framework of an organization any problems that arise within the same can be solved from a holistic perspective.

Different types of Systems Theory have been reported each one providing a distinct conceptual framework to a specific discipline. In Systems Theory, the complexity of an organization is directly related to its integrative levels. Each one of these levels can be characterized by the emergence of qualities or unpredictable novelties. Arguably, knowledge of lower levels helps our understanding of higher levels. Systems can be classified according to whether or not they allow interaction of their internal elements with the environment.

Open systems interact with their environment and increase the likelihood of prosperity for the same. Systems that are closed, and thus isolated from their immediate environment, tend to involute and disappear. Systems Theory in this regard does not focus on individual functions; rather, it is a holistic view that seeks to explain the synergy and interdependence of elements within an organization while taking into account the potential effects of the environment.

In neuroscience, systems theory is usually applied to the study of neural circuits by analyzing different levels of complexity going from molecular mechanisms in single cells, to networks of neurons, and ultimately to behaviors. Neurons and networks of neurons, contrariwise to behaviors, can be distinguished by physical boundaries within a closed system. Behaviors, therefore, implement equifinality as they manifest within an environment and ultimately make of the central nervous system (CNS) an open system.

In neuroscience, Systems Theory emphasizes establishing correlations, a chain or hierarchy of influence, between the different levels of the CNS (Fig. 3.1). Thus far, research into System Theory and neuroscience has been biased in focusing on anatomical elements within a closed organization and have, to a large extent, bypassed direct correlations to behaviors.

3.2 Ideal Systems

In an ideal scenario, the organization of the CNS should have been flatter in order to avoid the “bureaucracy” or sluggishness that comes along with multilayering. Such an idealized system would still be feasible in nature and operationally viable but sluggish in implementing small-scale evolutionary changes.

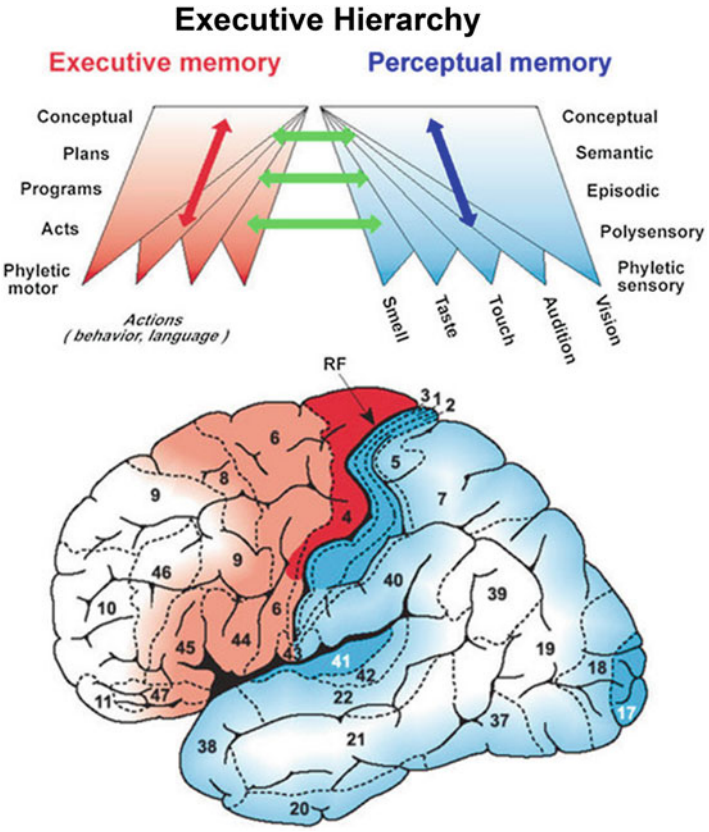

Fig. 3.1 Hierarchical organization of cognits in the cerebral cortex. Perceptual cognits are organized hierarchically between primary sensory areas (*blue*) and posterior association cortex (*white*) by order of category of perceptual memory, from phyletic sensory memory (sensory cortex) at the *bottom* to conceptual perceptual knowledge at the *top*. Executive cognits are organized hierarchically between primary motor cortex (*red*) and prefrontal cortex (*white*) by order of category of executive memories, from phyletic motor memory (motor cortex) at the bottom to conceptual executive knowledge at the *top*. (**a**) Schematic hierarchical order of perceptual and executive cognits. Bidirectional arrows indicate cortico-cortical connectivity: perceptual (*dark blue*), executive (*red*), and perceptual-executive (*green*). The inverted *triangles* symbolize the divergence of connections and increased the size of cognits with ascending hierarchical order. (**b**) Lateral view of the left hemisphere, areas numbered according to Brodmann's cytoarchitectonic map (*RF* Rolandic fissure) (Both panels adapted, with permission, from Fuster 2001. From Fuster and Bressler 2012)

In an organization, each layer provides for a potential bottleneck (Fig. 3.2). The finite capacity of an organization to process information provides a tradeoff between accuracy and complexity. Perceptual overload in the brain may require only one piece of information to be processed at any given time. This "filtering" of information and/or stimuli transforms the brain from a parallel processing machine to a less efficient serial processing computer. In psychology, this bottleneck effect is usually the explanation given for selective attention.

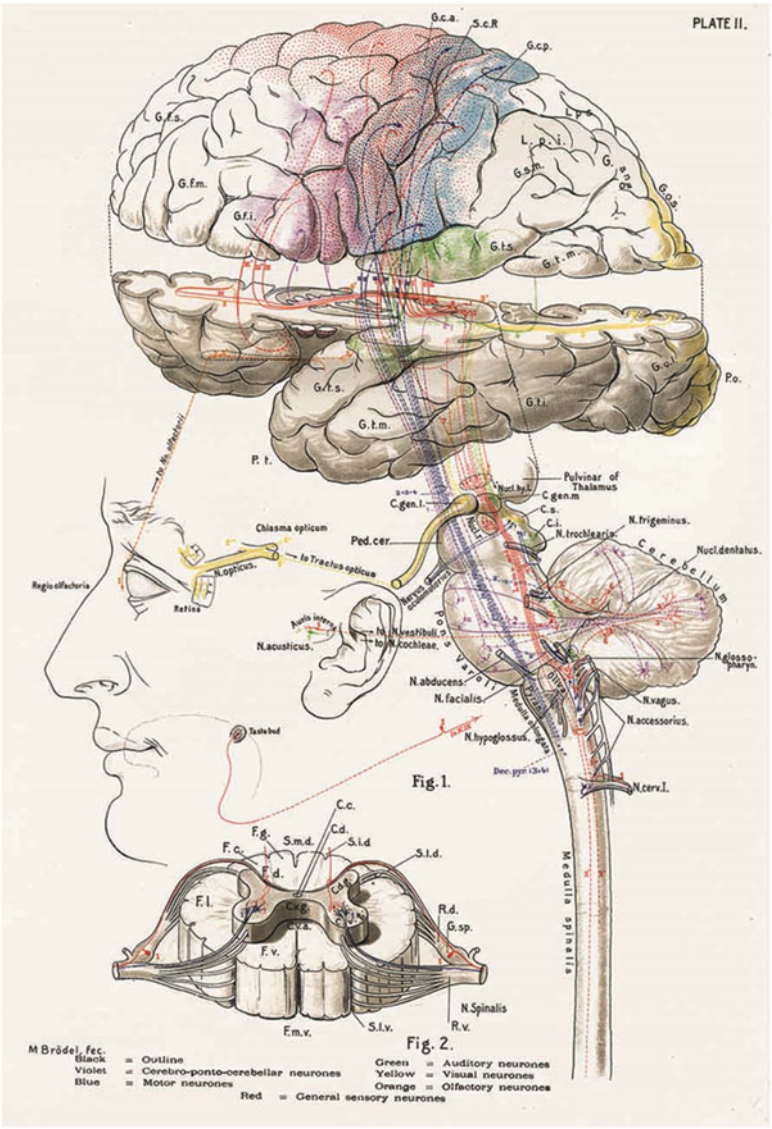

Fig. 3.2 The systems theory and the central nervous system. The central nervous system works as a whole. Schematic drawing by Barker (1899) to illustrate some of the multiple relationships between different parts of the central nervous system (Taken with permission from DeFelipe 2015)

The sluggishness of the CNS is exemplified by the glacially slow conduction speed of an axon as compared to the nanosecond rise time for pulsed signals in modern electronic equipment. The quickness of transmission is dependent on the type of stimuli and the type of task you are doing. Speed of processing also varies

with age and follows an inverted U type curve increasing from childhood to adolescence, plateauing in adulthood, and then steadily declining after our middle age.

In the CNS, information flows in a bottom-up fashion wherein innovation is often brought about by replacing components in such a way so as to add synergism to the organization as a whole. Indeed, the CNS is a hierarchical organization where change has been promoted by adding layers of complexity. In a famous essay in 1977 by Francois Jacob it was stated that "Nature is a tinkerer, not an inventor" (Jacob 1977). There is no master plan to the evolution of the brain but rather an imperfect patchwork of anatomical elements pieced together to allow different organisms to develop structural adaptations to similar environmental problems. The final result is a CNS that exhibits multiple redundancies and exaptations during evolution within and among species.

This bottom-up layering of the CNS is exemplified in Paul MacLean's proposed model for the evolution of the vertebrate forebrain. The model was explained at length in his voluminous work, *The Triune Brain in Evolution*. In this model, we see a staggered evolution where different structures are added upon preexisting ones: reptilian cortex → limbic system → neocortex. According to Jaak Panksepp, "There appears to have been relatively long periods of stability in vertebrate brain evolution, followed by bursts of expansion" (Panksepp 2004). The different evolutionary strata of the mammalian Triune Brain seem to reflect those periods of expansion.

The Triune Brain has drawn many criticisms from modern day comparative anatomists; however, rather than discarding Paul Maclean's model the same has been reinterpreted. Neuroanatomists now agree that there are subsystems in the CNS and that information is gathered from the environment and processed in a stepwise fashion until we form a perception or final cognition.

3.3 The Reductionistic Approach

From the time of Schleiden and Schwann and until the late 1800s, neuroscience engaged in a bottoms-up approach that focused on cells and their workings as the basis for explaining rather complex mental functions. This ontological approach is exemplified in the 1994 book "The Astonishing Hypothesis" where Francis Crick posited that "a person's mental activities are entirely due to the behavior of nerve cells, glial cells, and the atoms, ions, and molecules that make them up and influence them" (Crick 1995). Crick's argument emphasizes his belief that physical reality is the only truth of nature. His statement is a throwback to Niels Stensen reductionistic proclamation:

> There are two ways of coming to know a machine one is that the master who made it should show us its artifice; the other is to dismantle it and examine its most minute parts separately and as a combined unit . . . But since the brain is a machine we need not hope to discover its artifice by method other that than those that are used to find such for other machines. There remains to be done; therefore, only what would be done for all other machines. I mean dismantling of all of its components, piece by piece, and consideration of what they can do separately and as a whole. (Stensen 1669; Swanson 2003)

The reductionist agenda attempts to explain entire systems based on the mechanics or functions of their components. Reductionism is an infinite postponement at gaining understanding of a particular discipline. It claims that knowledge in one domain can be explained by knowledge at a different level of resolution thus opening the door to an infinite regress. Unfortunately, as in the literary allusion to a Mother Goose character, sometimes not even all of the king's horses and men can put Humpty Dumpty together again.

Contrary to the reductionistic approach the American philosopher of science and physicist, Thomas Kuhn, thought that fundamental changes to our basic concepts are provided by novel explanations; meaning, those that lie outside of prevailing explanatory frameworks. In this regard advances in science are provided by revolutions rather than by the piecemeal increase of a particular domain of knowledge. Without paradigmatic shifts, science has a tendency to become stagnated by subjective views.

3.4 The Neuron Doctrine

The upsurge of systems neuroscience has occurred *pari passu* to the gradual waning of the classic reductionist theory offered by the neuron doctrine. The founding father of neuroscience, Santiago Ramon y Cajal, provided a position statement that neurons were the cells that exemplified in their actions the holistic properties of the brain. In this regard the neuron doctrine recapitulated the ideas of Schwann and Schleiden that tissues are composed of representative cells and that variability in their size, shape or structure did not affect their functional specialization. According to this view hepatocytes are the cells that represent liver function just as neurons do the same for the brain. The final pillar for the cell theory came from Rudolf Virchow who popularized the idea that cells come from preexisting cells (Yandell 2013).

Traditionally neurons have been described as idealized anatomical elements which according to Shepherd and Koch served as models so, "... that they can be incorporated into more realistic simulations of the neural operations of those regions" (Shepherd and Koch 1998). The generalized neuron concept embodied neurons with three main components each containing specialized features: dendrites, cell body, and an axon. This current conception endows the generalized/canonical neuron with the following functional elements (Brown 2001):

- A receptive component for input to the neuron either from other neurons or for sensory signals,
- An impulse-initiating and impulse-propagating component which sends the impulse,
- A transmitter-releasing component.

All three of these components presumably act in a singular fashion. According to Ramon y Cajal's law of dynamic polarization the reception of impulses occurs in dendrites and are then transmitted via the axon. This, in essence, constitutes a unidirectionality in the fow of information.

It is now the prevailing view within neuroscience that variability in the shape, size or structure of neurons represents differences in kind rather than degrees. In the case of interneurons, the timing of onset during brain development, their position within the central nervous system, the anatomical structure of dendrites and axons, as well as their firing patterns, have provided for nomenclatures emphasizing the existence of different types of cells rather than a single representative cell.

Many neurons fail to adhere to the simplistic generalized neuron concept. Axons may bear receptive surfaces, dendrites may generate all or none impulses, and/or neurons may fail to adhere to Ramon y Cajal's Law of Dynamic polarization. As a matter of fact, in different parts of the nervous system information processing is mediated by electrical synapses in neural ensembles rather than individual neurons.

3.5 Modules

Alf Brodal in his acclaimed textbook *Neurological Anatomy in Relation to Clinical Medicine* claimed that a proper understanding of the field is prompted by three precepts (Brodal 1981):

1. There is an extremely high degree of order in the anatomical organization of the central nervous system.
2. The nervous system is composed of a multitude of minor units, each with its particular organization, specific as regards its finer intrinsic organization as well as with its connections with other units.
3. Investigation of the structure of the nervous system in all its detail is a prerequisite for progress in studies of its function.

A module (Latin *modus* or measure) is a conglomerate of independent self-contained units. Modularity to some extent describes the existence of components within a system that can be separated and/or recombined. Connectivity within these modules far outpaces connectivity between modules. Since interaction between modules are not necessarily linear, the resultant behaviors, although dependent on initial conditions, are difficult to predict.

There are suggestions within the literature that a reiterative process akin to signal processing would have propitiated a columnar organization within the cerebral cortex. A simplistic circuit could become more complex by the sequential addition of neurons in a columnar structure. Such an organization is deterministic in the sense that it does not depend on the resources of the environment. This view advocates for a rather flat circuit with closely adjacent/short connections far outstripping longer ones. The resultant circuit would have to exhibit the characteristics of weak linkages, providing for fast adaptations to the environment without a need for genetic change. Weak linkages would also promote the combination of different modules depending on any prevailing exigencies. This advantage of weak linkages would make them a conserved property.

There is some controversy as to what may be called modules within the cerebral cortex. For example, Calvin (1995) prefers using the terms "minicolumn" and "macrocolumn" instead of module. He believes that the term modules should be restricted to repeating units with an internally identical architecture. It should not apply, as the term is used in many fields, to something that is merely repeated, segmented, or grouped. In this regard modules differ from the definition offered in many dictionaries, making them separable and interchangeable components which accommodate into units of differing size, complexity or function.

According to Calvin (1996) columns provide a possible example of a self-organizing unit within the nervous system, "... if we go around wiretapping the individual neurons in the cerebral cortex, we discover that neurons with similar interests tend to be vertically arrayed there, forming cylinders known as cortical columns, which cut through most of the layers. It's almost like a club that self-organizes out of a crowd at a party, where people of similar interests tend to cluster together" (Calvin 1996). The genesis of minicolumns will be discussed in the next section, "Minicolumns".

3.6 Minicolumns

The existence of repetitive circuits or modules carrying generic types of operations within the cerebral cortex has been well discussed within the field of neuroanatomy. The nomenclature for this reiterative circuit has shifted through the decades being called either a basic, local or canonical circuit by different authorities (Shepherd 1974, 1978; Rakic 1975; Douglas and Martin 1991). Lorente de Nó was the first researcher to propose the existence of vertically oriented cellular elements within the cerebral cortex that conjointly acted as a circuit. Lorente de Nó described these vertically arranged cellular aggregates as follows: "All the elements of the cortex are represented in it, and therefore it may be called an elementary unit, in which, theoretically, the whole process of transmission of impulses from the afferent to the efferent axon may be accomplished" (Lorente de Nó 1938) (Fig. 3.3).

Mountcastle's work indicated the presence of vertically arranged cellular structures with similar electrophysiological properties in different parts of the brain (Casanova 2013) (see below). The findings suggested that the cerebral cortex was more homogeneous in its function than previously thought. According to Bach-y-Rita, this meant that, "... any part of the cortex should be able to process whatever electrical signals were sent to it, and that our brain modules were not so specialized after all" (Doidge 2007, p. 18). Otto Creutzfeld believed that these repetitive neocortical microcircuits processed information in similar manner with the resultant output depending on both the source of information and modulatory influences peculiar to each brain region (Creutzfeld 1917).

The discovery of "functional" cortical minicolumns was made by Mountcastle from recording in approximately 23 hundred neurons in the somatosensory cortex of cats and monkeys (Mountcastle 1957; Mountcastle et al. 1957; Powell and Mount-

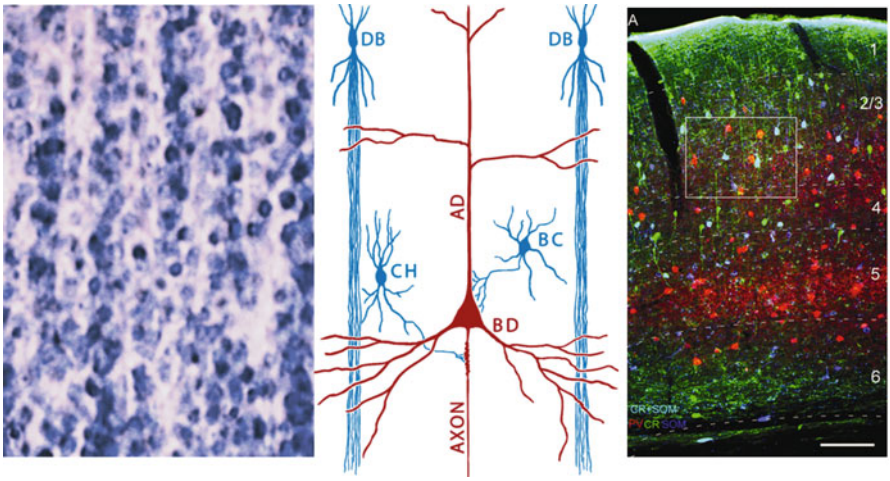

Fig. 3.3 Cortical minicolumns. *Left* Human brain tissue highlighting the cortical minicolumns in lamina III of the frontal cortex BA 9 (control specimen). *Center* Curtain of inhibition depicted by pyramidal cell surrounded by inhibitory double bouquet cells. *Right* Various inhibitory cells (depicted in colors) in regards to the minicolumn. Lamina are identified to the right of the figure with a *dashed line* indicating the divisions of the multiform layer (Front Neuroanatomy, 1:3, 2008)

castle 1959). The latency and spiking frequency of a large number of these were quantified and spiking response of each neuron analyzed in terms of its receptive field and modality. The columnar arrangement of these functional ensembles was confirmed from early studies where slanting penetrations were made at an angle of 45° to the tangential plane, demonstrating a change in modality as the microelectrode passed through adjoining regions from layer to layer (Mountcastle 1957).

The cell minicolumn consists of 60–100 neurons along with their afferent, efferent and interneuronal connections. Together the elements provide for a canonical circuit to the neocortex. Input is feed-forwarded through a short chain of two or three neurons within the same columns and then transmitted to other target areas. Anatomical cells are arranged along a radial scaffolding more noticeable in thick Nissl-stained slides. The juxtaposition of cells becomes less prominent with aging, providing a thickness dimension that is easily missed in thin paraffin sections (Buxhoeveden and Casanova 2002).

The genesis of the minicolumns occurs early in gestation when symmetrical divisions of periventricular germinal cells create their total number. After E40, both in macaque monkeys and humans, a subsequent series of asymmetrical divisions determines the cellular constituency of the minicolumn. This radial organization is thus preeminent to other organizations based on either synapses or layering. The addition of minicolumns accounts for the growth of the human neocortex as compared across species. It also helps explain why the human neocortex is 1000-fold larger than that of the mouse while only a two or threefold difference separates them according to their cortical widths. Numerous studies using C-2-deoxyglucose,

intrinsic optical signaling (IOS), nerve regeneration, and evoked potentials have established the minicolumn as a physiological unit of the brain (Casanova 2005). In addition, a recent study on the spatial characterization of neurons in 3D space using a cylindrical K-function has shown the non-random and columnar distribution of these anatomical elements without an a priori assumption as to the existence of minicolumns (Rafati et al. 2016).

Once neuroblasts reach the cerebral cortex working relationships are formed between those that migrated vertically (pyramidal cells) and those that migrated tangentially (interneurons). The resulting microcircuits circuit are unlikely to have developed together as it would have required the emergence of two simultaneous novelties. Indeed, although many interneurons form functional dyads with pyramidal cells, not all interneurons are constituents of arbitrarily defined anatomical units.

3.7 Emergence of Properties

Components of perception are processed in a distributed network that entail different patterns of minicolumnar activity. These are specialized to process information from afferents channeling information specific to various types of sensory receptors. These patterns are compounded into parallel cortical streams, each to some degree insulated from the rest and specialized for a specific functional aspect of the perceptual whole. There has been some preliminary success in functionally defining some of these patterns of activity in terms of operational transforms upon inputs to produce outputs (Fig. 3.4). The following list of some candidate cortical functions is adapted from Mountcastle (1998 and Casanova (2005):

Thresholding: a nonlinear relation between the level of presynaptic input and cortical neuronal discharge.

Amplification of inputs: as in the example of when a single impulse in a single myelinated fiber of a peripheral nerve in an attending human suffices to evoke a conscious perception.

Derivative function: cortical operations tend to accentuate and amplify transient inputs, adapt to constant ones.

Feature convergence: the creation of a neural representation of a complex feature or set of features by combining signals of two or more simpler ones.

The distribution function: some areas receive the neural signals of certain simpler features of sensory stimuli and distributed then separately to other cortical areas. Areas 3b and V1 in addition to having other functions, serve as distribution centers.

Coincidence detection: by convergence of excitation, linking together two events that occur closely in time.

Synchronization and coherence of activity in the different nodes of distributed system.

Pattern generation: creation of spatial and temporal patterns in output signals that are not present in inputs (e.g., induced rhythms).

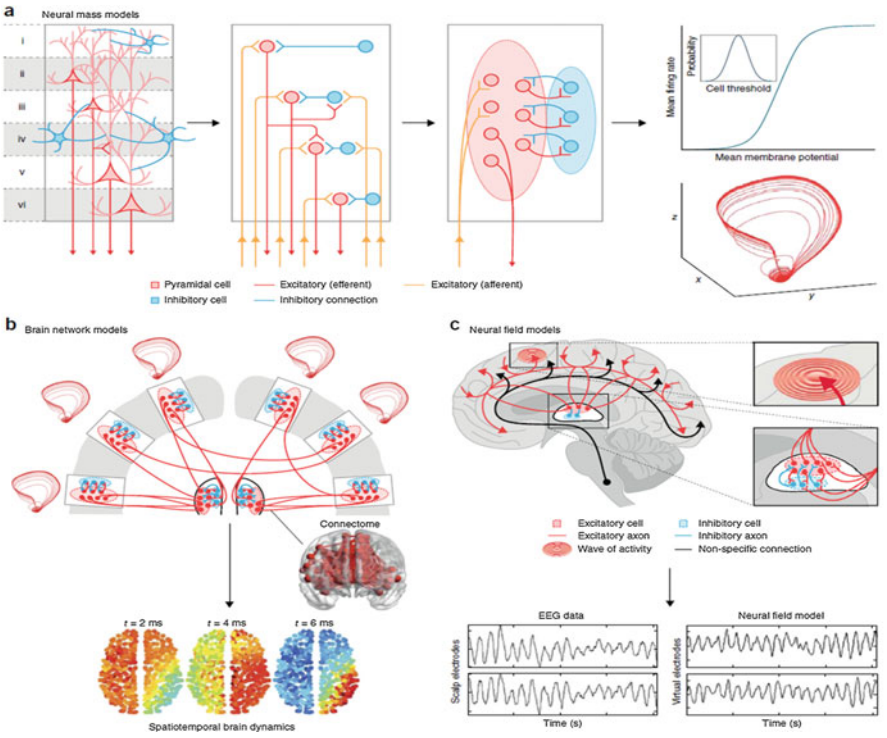

Fig. 3.4 Emergence of functional properties in the brain. Models of large-scale brain dynamics. (**a**) Neural mass models (*NMMs*) are obtained by taking the average states in all neurons of each class (pyramidal, inhibitory) in a local population, here a cortical column (*left*). Traditional spiking neural models treat each neuron as an idealized individual unit (*center*). NMMs go further, reducing the entire population dynamics to a low-dimensional differential equation representing the average states of local interacting neurons (*right*). The variability in the cell threshold (*inset*, *top right*) smooths the all-or-nothing action potential of each neuron into a smooth sigmoidal map between average membrane potential and average firing rate. Integrating this equation yields an attractor for the local dynamics (*bottom right*). (**b**) Brain network models (*BNMs*) are composed by coupling an ensemble of NMMs into a large-scale system (*top*), with connections informed by the connectome (Adapted from G. Roberts, A. Perry, A. Lord, A. Frankland, V. Leung et al. Mol. Psychiatry, in the press). Due to strong short-range connections, BNMs can yield wave patterns (*bottom*). This example shows a wave traveling diagonally to the *right*. (**c**) In a neural field model (*NFM*), the cortex is treated as a smooth sheet (*top*) that supports waves of propagating activity (*top inset*). Neural field models that include a neural mass in the thalamus (*bottom inset*) yield alpha oscillations with the same spectral properties as those observed in empirical data (*bottom*; adapted from Breakspear et al. (2006, 2017)

In recent years, Opris et al. (2012) implemented the use of a unique conformal multielectrode recording array to define the role of interlaminar circuitry within prefrontal cortex minicolumns in task-related target selection in nonhuman primates. Activation of innate prefrontal cortex minicolumns via the encoded interlaminar correlated firing sequences resulted in improved performance on trials where

specific information was required depending on context (Opris et al. 2013). The results indicate interlaminar correlated firing during the decision phase of target selection and provide a direct demonstration of real-time minicolumnar processing during an executive function task. Thus far, the minicolumn is the smallest unit of information processing where the emergence of executive functions has been demonstrated. It is therefore unsurprising that thinning of the minicolumn over the dorsolateral prefrontal cortex correlated to a declining IQ and an increase plaque load in Alzheimer's dementia (Van Veluw et al. 2012). For a review of minicolumns and cortical modularity in medical disorders see Casanova and Tillquist (2008) and Hutsler and Casanova (2016).

3.8 Laws of Conservation

As explained in the introduction to this chapter certain elements within the CNS are defined by anatomical boundaries which do not readily interact with the environment. This "isolation" defines properties of the system that are constant and therefore cannot change. They thus serve as constraints for the behavior of the CNS during its development and later maturation (ageing). These laws are usually expressed in terms of symmetry relationships that remain constant despite either a transformation or when looking at them from different perspectives. Knowledge of these laws can help simplify many problems. In this section, we will talk about some of the laws of conservation that may apply broadly to the cerebral cortex and hold at all points in space-time (for a review see Casanova et al. 2011).

Laws of conservation apply to the minicolumns of the cerebral cortex. The neuropil space acts in a permissive way to help conserve the symmetry of the minicolumn. We can apply transformative operations (e.g., translation, rotation) to the space coordinates of minicolumns or fragments of minicolumns and the final measurement will remain the same. A similar argument applies to the translation of pyramidal cells around the central axis of minicolumns. Early during brain development, the pyramidal cells arrange themselves in a rectilinear fashion. This linear aggregation is disturbed with aging causing the displacement of cells such as to blur the original minicolumnar design. Still, the vectorial sum of discrete or contiguous pyramidal cell translations around the central axis is zero regardless of brain parcellation or age. The resultant arrangement therefore links symmetry in space (i.e., translation of cells in different brain regions) with time (i.e., aging).

Another transformation is the preservation of the relative size of pyramidal cells when compared to the width of the minicolumn to which it belongs. This transformation or resizing is a conversion where objects become larger of smaller but leave unperturbed the content and relationship between its elements and module as a whole. This scalar relationship is obvious to microscopists who examine the cerebral cortex. The striatal cortex is the prototype of granular cortex and exhibits the smallest minicolumnar widths reported. By way of comparison, the motor cortex boasts of having the largest cortical neurons (Betz cells) and the widest minicolumns so far reported.

In a comparative anatomy study by our group done in primates we found that despite large changes in minicolumnar width across species, the core space of minicolumns remained the same (Casanova et al. 2009). The core compartment of minicolumns is composed primarily of pyramidal cells, apical dendritic and axonal bundles. These basic constituents of the minicolumn appear to be irreducible to some extent. Variability is most prominent within the peripheral neuropil space where many of the interneuronal elements and their projections are present.

In this chapter we have argued that the smallest unit of information processing for the cerebral cortex is the minicolumn rather than the neuron. It is the minicolumn that bears the holistic properties of the brain and provides for the emergence of properties not foretold by its constituent elements. The minicolumn arises by means of self-organization during brain development and its architecture is defined from local interactions guided by laws of conservation.

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Chapter 4
Prefrontal Cortical Microcircuits Support the Emergence of Mind

Ioan Opris, Manuel F. Casanova, Mikhail A. Lebedev, and Aurel I. Popescu

Keywords Mind • Prefrontal cortex • Cortical microcircuits • Macro-networks • Emergence of mind • Integration • Connectome • Hub • Executive functions • Intrusive thoughts

4.1 Introduction

This chapter dwells on the high-order neural processing that underlies the emergence of the mind. We discuss the operation of microcircuits, such as neurons in different laminae of cortical columns, modular networks composed of microcircuits, and the hubs of the brain's connectome (Beul et al. 2015). We show how the integration of information by distributed networks of neurons generates engrams, cognitive functions, and complex mental sequences, such as the *perception-to-action cycle*. The mind is considered to be the product of the integration of perceptual prefrontal cortical signals processed in supra-granular cortical layers, action-related information represented in infra-granular layers, and reward sig-

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nals originating in the midbrain. The cortical modules and their microcircuits are described as building blocks of this complex neural circuitry that performs hierarchical processing. We emphasize the importance of bidirectional information flow in cortico-cortical and thalamo-cortical loops, which integrate *bottom-up* and *top-down* communications between the brain areas.

Steven Pinker suggested that information and computation are the "soft" components of the mind that reside in the "patterns of data" (i.e. ensembles of firing patterns) and in the functional "relations of logic that are independent of the physical medium that carries them" (Pinker 1997). We agree with this statement, but focus on the real physical medium composed of neural circuits. Perhaps the studies of these circuits will help to build artificial carriers for the mind in the future that operate according to the discovered principles for the brain. One such principle is, for example, the neural operations described by Joe Tsien's group, which follow the *power of two permutation logic* (Xie et al. 2016).

Overall, determining the foundation of human cognition is a challenging task, but neuroscientists are advancing the understanding of neuronal mechanisms of knowledge, perception, and learning. Investigations of the relationship between the brain structure and cognitive functions are clearly bringing us closer to understanding the mind (Goldman-Rakic 1995, 1996; Mountcastle 1997; DeFelipe 2011; Arnsten 2013; Opris and Casanova 2014).

4.2 The Mind

The mind is the ability of human beings to reason and think. The necessary skill sets for these operations include perception, memory, judgment, thinking, volition, and language. The human mind can be described as a complex process utilizing reasoning, thoughts, imagination, and recognition to generate complex behaviors, actions, and subjective states, such as feelings and emotions. The mind encompasses myriads of neural processes whose details we cannot consciously monitor. Conscious mental processes emerge from this vast unconscious processing. In terms of localization, many authors consider the *prefrontal cortex* (PFC) to be the seat of the mind because of its representation of higher brain functions, including memory and cognition. For example, the paramount role of PFC in cognition was demonstrated by lesion studies in humans and monkeys (Bauer and Fuster 1976; Funahashi et al. 1989, 1993).

4.2.1 Anatomical Substrate of the Mind: From Microcircuitry to Macro-networks

The anatomical organization of the brain is the key to understanding the emergence of the mind, from the microscopic level (DeFelipe 2011) and up to the macroscopic, large-scale neuroanatomy.

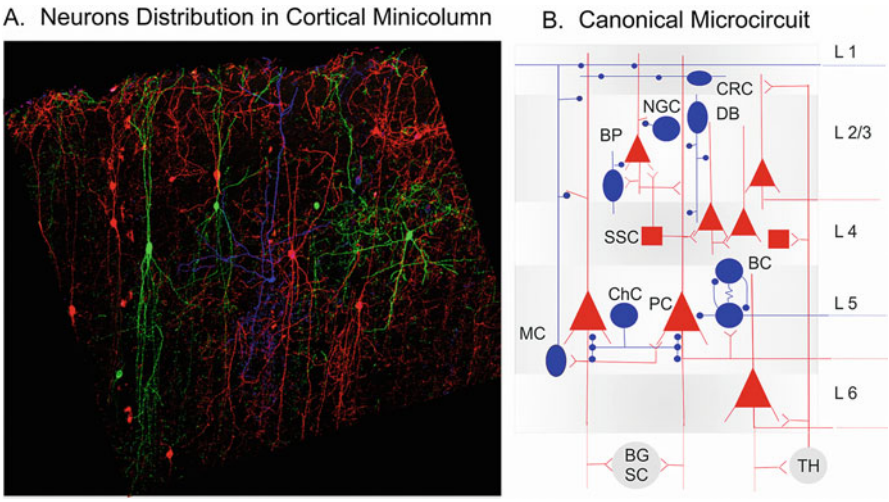

Fig. 4.1 Cortical microcircuits. (**a**) Distribution of neurons in cortical minicolumn. The image shows pyramidal cells, double bouquet neurons, basket cells, chandelier cell (With permission from He et al. 2016). (**b**) Canonical microcircuit diagram illustrating the connections between cells across the laminae. Cells in *red* denote excitatory activity while cells in *blue* indicate interneurons/inhibition. Symbols legend: CRC =, *PC* pyramidal cell, *SSC* stellate cell, *BC* basket cell, *BG* basal ganglia, *BP* bipolar cell, *DB* double bouquet interneuron, *ChC* chandelier interneuron, *MC* Martinotti cell, and *NGC* neuroglia cell, SG =, *TH* thalamus (Redrawn from Grillner et al. 2005)

Cortical Microcircuitry

Functional specialization of the brain starts with microcircuits that form modules. A modular network can be partitioned into subsets of nodes (modules) that are densely interconnected internally but only sparsely to other subsets (Chunga et al. 2016). In the cortex, modules are composed of "vertical arrangements" of cortical neurons, called *minicolumns* (Szentágothai and Arbib 1975; Mountcastle 1997) (Fig. 4.1). Within the minicolumns, cortical neurons are "wired into" six horizontal layers (or laminae): three supra-granular layers (L1–L3), a granular layer (L4) and two infra-granular layers (L5/L6) (Opris 2013).

The granular layer receives "sensory input via the thalamus" (Constantinople and Bruno 2013). The supra-granular layers "consist of" small pyramidal neurons that form "vertical connections" with the larger pyramidal neurons of the infra-granular layers that generate most of the output from cerebral cortex to other parts of the brain (Buxhoeveden and Casanova 2002). According to this "three-stratum functional module", infra-granular layers execute the "associative computations" elaborated in supra-granular layers (Buxhoeveden and Casanova 2002; Casanova et al. 2011). Interestingly, the PFC, that has a crucial role in cognition, has a thicker layer 2/3 than sensory and motor cortices.

Brain Connectome

As it was seen in the introductory chapter, the human brain is a complex biophysical system consisting of 86 billion neurons (Herculano-Houzel 2009), each one interconnected to others by thousands of synapses (Andersen 1990), resulting in over one hundred trillion synaptic connections. All connections of the brain are called the *connectome*. The connectome's pathways between forebrain and neocortex are referred to as a *connectivity matrix*. The connectome's structure and function can be analyzed using mathematical methods developed for complex networks, for example graph-theoretical methods. With these approaches, topological features of the connectome can be described, such as sparse networks and meso-level microcircuits that define cortical modularity (Opris and Casanova 2014). Within these topologies, dynamical neural states can be described as a spatial arrangement of electrical activity.

The main components of the hierarchical architecture of the brain include *cortical modules* (layers and minicolumns), subcortical nuclei (basal ganglia and thalamus) and brainstem structures (midbrain, pons, and medulla). These structures process sensory inputs, including vision, auditory information, touch, smell, and taste. The end results of neural processing are manifested as overt motor behaviors of different complexity, such as eye and limb movements, and speech and covert cognitive states, such as perception, awareness, memory, decision, and reasoning.

Functional Connectomics: Default Mode Networks vs. Executive Control Networks

In large-scale neuronal networks, electrical activity is spatially distributed across brain regions. Specific spatio-temporal neuronal patterns occur at rest and during cognitive tasks. The networks exhibiting patterns of activity at rest (in the absence of external task demands) are known as the *default mode network* (DMN), while the networks exhibiting patterns of activity during cognitive (executive control) tasks are known as the *executive control network* (ECN; Fig. 4.2).

DMN includes a set of midline and inferior parietal regions in the absence of most external task demands, but are associated with cognitive processes that require internally-directed or self-generated thoughts, such as mental simulation and perspective/future thinking (Young et al. 2016). ECN activation is shown within the lateral prefrontal cortex, a core hub of the executive control. ECN is engaged during cognitive tasks that require externally-directed attention, such as working memory, relational integration, response inhibition, and task-set switching. ECN brain networks are linked to the top-down control of attention and cognition. Cognitive functions, like *creative thinking*, recruits brain regions associated with both cognitive control and spontaneous imaginative processes (Young et al. 2016). These complex functions implicate regions within large-scale networks, including the ECN and the DMN. Despite their apparent cooperation, the DMN and ECN tend to act in opposition, the activation of one network typically corresponding to

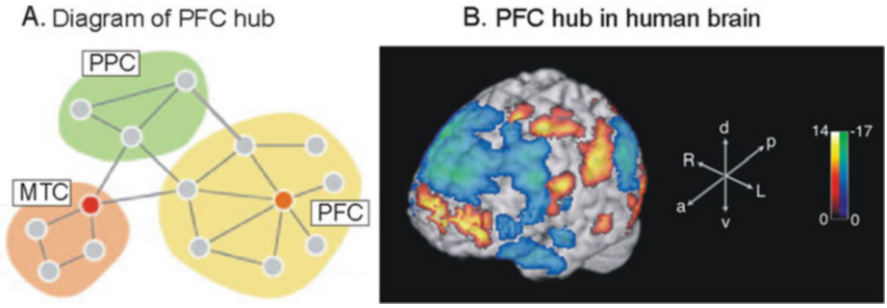

Fig. 4.2 The connectome and the prefrontal cortical hub. (**a**) Schematic diagram of a brain network consists of nodes and edges. *MTC* middle temporal cortex, *PFC* prefrontal cortex, *PPC* posterior parietal cortex. The node degree corresponds to the number of edges that are attached to each node. Networks can be decomposed into communities or modules. Connections (edges) are either linking nodes within modules or between modules. Highly connected nodes are hubs, and they either connect primarily with other nodes in the same community (provincial hub) or with nodes that belong to different communities (connector hub) (With permission from van den Heuvel and Sporns 2011). (**b**) Medial prefrontal cortex activation, dorsolateral prefrontal cortex deactivation, and sensorimotor activation can be seen in the 3-D surface projection of activations and deactivations associated with improvisation during the Jazz paradigm. The *scale bar* shows the range of t-scores; the axes demonstrate anatomic orientation. Abbreviations: *a* anterior, *p* posterior, *d* dorsal, *v* ventral, *R* right, *L* left (With permission from Limb and Braun 2008)

suppression of the other. This antagonistic relationship is thought to reflect opposing modes of attention, with ECN activity indicating focused external attention and DMN activity indicating spontaneous interoception.

4.2.2 Neurophysiological Substrate of the Mind: From Microcircuitry to Macro-networks

Modularity is a key characteristic of structural and functional brain circuits/networks across multiple domains of the connectome and scales (Murray 2012; Sporns and Betzel 2016). Anatomical modules generally reflect functional associations among neurons within cortical areas (microcircuit modularity) and between brain regions (network modularity). Structural modules are often spatially compact, whereas functional modules can be more widely distributed and fluctuate in relation to cognitive states. Modular organization may confer increased robustness and more flexible learning, help to conserve wiring cost, and promote functional specialization and complex brain dynamics. Clune et al. (2013) argue that modularity has evolved as a by-product of strong selection pressure on reducing the cost of connections in networks. Indeed, the notion that wiring cost is a major constraint on the layout of (structural) brain networks has a long history in neuroscience. In addition to the spatial layout of nodes and hubs, specific functional

constraints, such as network's processing efficiency, were found to be important in supporting the idea that brain network topology is shaped by a trade-off between spatial and functional factors (Bullmore and Sporns 2012).

Prefrontal Cortex Is an Integrative Hub over Multiple Domains of the Connectome

Prefrontal cortical connections: Distinct domains of the PFC in primates have a set of connections suggesting that they have different roles in cognition, memory, and emotion.

Next, we discuss, the prefrontal cortical hub-related edges: frontal pole, premotor, temporal, parietal, limbic, striatal, thalamic, brainstem, inter-hemispheric, etc. (Ramnani and Owen 2004a). Dense connections between the prefrontal cortical hub and other cortical/subcortical nodes may thus provide short communication relays, efficient neural communication, and robustness of inter-hub communication (Van der Heuvel and Sporns 2013) (Fig. 4.3).

Frontal Pole Cortex

The anterior-most part of the frontal lobe of each cerebral hemisphere of the primate brain are called the frontal poles. They correspond to Brodmann area 10 (BA10) (Semendeferi et al. 2001; Gilbert et al. 2006; Petrides and Pandya 2007; Wallis

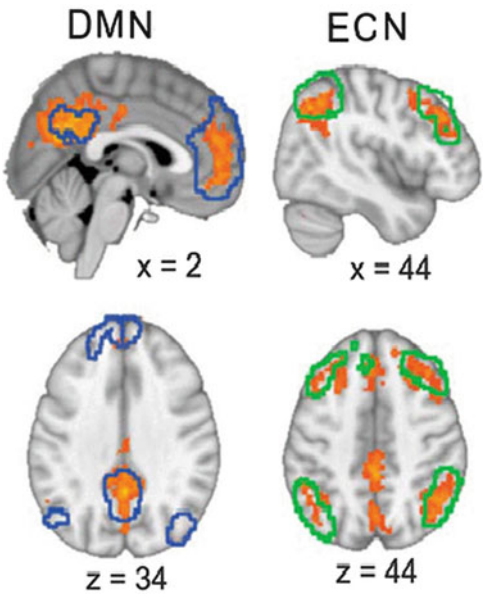

Fig. 4.3 Default mode network vs. executive control network. Validation of the executive control and default mode networks. Areas significantly correlated with the eigenvector describing the underlying temporal patterns of each network are shown. Results were thresholded using a Gaussian mixture model approach to demonstrate that the network cohesion index indeed captured the entire network rather than just a small portion of voxels or specific edges. Colored outlines depict the a priori regions of interest that defined each network (With permission from Young et al. 2016)

2010). BA10 has dense input-output connections with higher-order association areas (primarily in PFC) and few connections with primary sensory, motor, or limbic areas. BA10 is divided in three sub-areas: 10p, 10m, and 10r, with area 10p covering the frontal pole, and the other two areas spanning the ventro-medial part of the PFC (Ongür et al. 2003). *Frontal pole cortical area*, 10m, is composed of thin layers 2 and 4 and a more prominent layer 5 (with a role in *top-down* executive connectivity). In contrast, area 10r has a prominent layer 2 (with a role in *integrative* connectivity) and a thicker layer 4 (with a role in *ascending* sensory input). Pyramidal cells are larger in layer 3 of BA10p and also in BA10r (Ongür et al. 2003). In functional terms, the frontal pole cortex is involved in monitoring or evaluating self-generated decisions (Tsujimoto et al. 2010), in rule processing (Mansouri et al. 2015), in working memory (Funahashi et al. 1989; D'Esposito 2007), and multiple-task coordination (Fuster and Alexander 1971; Bauer and Fuster 1976; Funahashi et al. 1989; Burgess et al. 2007. However, the PFC is functionally organized along a rostral-caudal gradient of abstraction with more abstract representations/processes associated with more rostral areas (Nee et al. 2014). The frontal pole cortex, as the apex of executive/sensorimotor hierarchy may be regarded as a key hub in the functional connectome.

Prefrontal-Premotor Connections

Premotor cortex (BA6) is strongly interconnected (by afferent-inputs and efferent-outputs) with the primary motor cortex (BA4), the supplementary motor area, the parietal (BA7) and the prefrontal (BA46) cortices. It also projects subcortically to the striatum (putamen), the motor thalamus, and the spinal cord. Neurons in the monkey dorsal premotor cortex respond to the sensory (vibratory or visual) cue and often remain active during the delay period or preparation/pre-movement time before the monkey performed the instructed movement (Lebedev et al. 2004). Dorsal premotor cortex (BA6) is more involved in planning or preparing for movement while the primary motor cortex (BA4) is more involved in movement execution. Inter-laminar interaction between premotor neurons in layer 2/3 and 5 has demonstrated the sensorimotor integration and the binding of *perception-to-action* (Opris et al. 2011, 2012a, b, 2013, 2014). Premotor cortex plays a role in motor planning and sensorimotor integration/perception-to-action cycle (Wise et al. 1996).

Prefrontal-Parietal Connections

Parietal-prefrontal connections are hypothesized to be crucial for the short-term maintenance of visuo-spatial information as part of the *reverberatory circuit* in which feedback projections from PFC serve to maintain excitation of parietal-to-prefrontal feed-forward pathways (Chafee and Goldman-Rakic 1998). Caudal and lateral prefrontal areas (BA8 and BA46) receive projections from intraparietal

and posterior parietal areas associated with oculomotor/reaching movements and attentional processes. Cortical input to areas BA46 and BA8 is complemented by projections from the thalamic multiform and parvocellular sectors of the mediodorsal nucleus associated with oculomotor functions and working memory.

Prefrontal-Temporal/Hippocampal Connections

Dorso-lateral prefrontal cortex (dlPFC) is connected with the hippocampal formation (HPC) and the associated cortical areas by two distinct pathways: one lateral and the other medial (Goldman-Rakic et al. 1984). Several communication channels link the dlPFC and the hippocampus via the parahippocampal gyrus, subiculum, presubiculum, and adjacent transitional cortices (Goldman-Rakic et al. 1984). These prefrontal projections may carry highly specific information for memory consolidation into the hippocampus, whereas the reciprocal projections may allow retrieval by PFC of memories stored in the hippocampus. The HPC and medial prefrontal cortex (mPFC) have well-established roles in *memory encoding and retrieval*, while a direct pathway from the HPC and subiculum to the mPFC is critically involved in cognitive and emotional regulation of mnemonic processes. Recent evidence points to an indirect pathway from the HPC to the mPFC, via midline thalamic *nucleus reuniens* (RE), that may play a role in spatial and emotional memory processing (Jin and Maren 2015).

Prefrontal-Limbic Connections

The limbic system is tightly connected to the PFC, especially with the orbital and medial parts, and also with the anterior cingulate cortex (ACC). The anterior cingulate gyrus is considered part of the limbic system and plays a major role in higher level cognitive functions (Allman et al. 2006). The orbital and medial parts of the frontal lobe receive highly processed sensory afferents, and participate in high-level cognitive and emotional processes (Ongür and Price 2000). The emotion loop involving the orbitofrontal cortex (OFC) is running through the head of the caudate nucleus (CN) and the nucleus accumbens (NAcc).

Cortico-Striatal and Thalamo-Cortical Connections

Direct evidence for a parallel organization of cortico-striatal-thalamo-cortical loops has been recently provided for the human brain (Jeon et al. 2014; Santos et al. 2014). Cortico-subcortical loops exhibit functional specificity (motor, oculomotor, cognitive, and limbic). Such functional specificity depends on varying levels of cognitive hierarchy, as well as on their pattern of connectivity. Higher levels of activations emerge in the ventro-anterior part of the PFC, the head of the caudate nucleus, and the *ventral anterior* nucleus (VA) in the thalamus, while lower levels

of activation were located in the posterior region of the PFC, the body of the caudate nucleus, and the *medial dorsal* nucleus (MD) of the thalamus. This gradient-like pattern of activations was furthermore shown by the parallel connectivity in the anterior regions of the PFC with the head of the caudate nucleus and the VA of the thalamus, whereas the posterior activations of the PFC were "linked to" the body of the caudate nucleus and the MD nucleus of the thalamus.

Callosal Connections

The *corpus callosum* is a bundle of neural fibers along the longitudinal fissure beneath the fronto-parietal cortex used for communication across hemispheres. Inter-hemispheric interaction (via layer 3) is posited to aid attentional processing (both when attention is conceptualized as a resource and as a selective mechanism for gating sensory information) because it allows for a division of labor across the hemispheres, and allows for parallel processing so that operations performed in one hemisphere can be insulated from those executed in the other. Given this additional role for inter-hemispheric processing, it is suggested that the corpus callosum should be considered a key component in the network of neural structures that underlie attentional control (Banich 1998). While inter-hemispheric interaction is often thought as a mechanism for transferring sensory information and coordinating processing between the hemispheres, the corpus callosum also "plays a crucial role" in attentional processing (Banich 1998).

Prefrontal-Brainstem Connection

The brainstem reticular formation is mainly connected to the PFC, particularly to the lateral PFC and ventro-medial PFC (Jang and Kwon 2015). The frontal lobe contains most of the dopamine-sensitive neurons in the cerebral cortex. The dopamine system is associated with reward, attention, short-term memory tasks, planning, and motivation. Dopamine tends to limit and select sensory information arriving from the thalamus to the forebrain. Reduced dopamine activity in the PFC is related to poorer performance and inefficient functioning of that brain region during working memory tasks, and to a slightly increased risk for schizophrenia. Moreover, the *locus coeruleus* and its noradrenergic projections to the frontal lobe provide important contribution to the modulation of cognition and emotion (Sara 2009). The mPFC provides a potent excitatory influence on locus coeruleus neurons (Jodoj et al. 1998). The fact that inactivation of the mPFC suppressed locus coeruleus firing, indicates that the mPFC also provides a resting tonic excitatory influence on locus coeruleus activity.

Prefrontal Cortex Is an Integrative Hub of the Higher Brain Functions

The richly interconnected prefrontal cortical circuits, we discussed above, are part of the brain's functional connectome that integrates cortical signals from *sensory* (Fuster et al. 2000) (visual, auditory, touch, taste, and smell perception), *cognitive* (attention, memory, decision making, intention, free will, language), emotional (fear, joy, anger, etc.) and *motor* (skeleto-motor, oculomotor, pupil dilation) neural systems to support the emergence of mind. Brain hubs are formed by central interconnection nodes across distributed microcircuits, loops, and networks (van den Heuvel et al. 2013). PFC is a crucial integrative hub over multiple domains of the connectome, while the mind is the byproduct of such complex integrative processes involving sensory, motor, memory, and reward signals. It is noteworthy how cortical modularity provides flexibility to the emergence of mind by complex logic permutations of neural inputs.

4.3 Emergence of Mind in the Prefrontal Cortical Hub

4.3.1 Mind Functions

Perception to Action Cycle

The "perception-to-action cycle" has been described by Joaquin Fuster as a "circular flow of information" between a subject (animal or human) and its environment (Fig. 4.4) during a sensory-guided sequence of "actions" towards a goal (Quintana and Fuster 1999; Tishby and Polani 2011). Thus, each behavioral action performed by an animal/human modifies the environment through a top-down executive network from PFC to motor effectors.

Actions modify the animal's own perception of the environment in a bottom-up processing sequence through the perceptual network hierarchy, until the goal is achieved (Cutsuridis 2011). Cerebral cortical modules mediate the interactions between the environment and the perceptual-executive systems of the brain (Fig. 4.4). In fact, the inter-laminar prefrontal cortical microcircuits are assumed to bind perceptual and executive control signals to guide goal-driven behavior (Lebedev and Wise 2002; Opris et al. 2013).

Opris and his colleagues compared neuron firing recorded simultaneously in PFC layers 2/3 and 5/6 and caudate-putamen of Rhesus monkeys, trained in a spatial *vs.* object, rule-based match-to-sample task (Opris et al. 2013). They found that, during perception and executive selection phases of the task, cell firing in the localized prefrontal layers and caudate-putamen region exhibited similar location preferences on spatial-trials, but not on object-trials. Then, by stimulating the prefrontal infra-granular-layers with patterns "previously recorded from" supra-granular-layers (Opris 2013; Opris and Ferrera 2014), it "produced stimulation-induced spatial preference in percentage correct performance on spatial trials", enhancing the neural

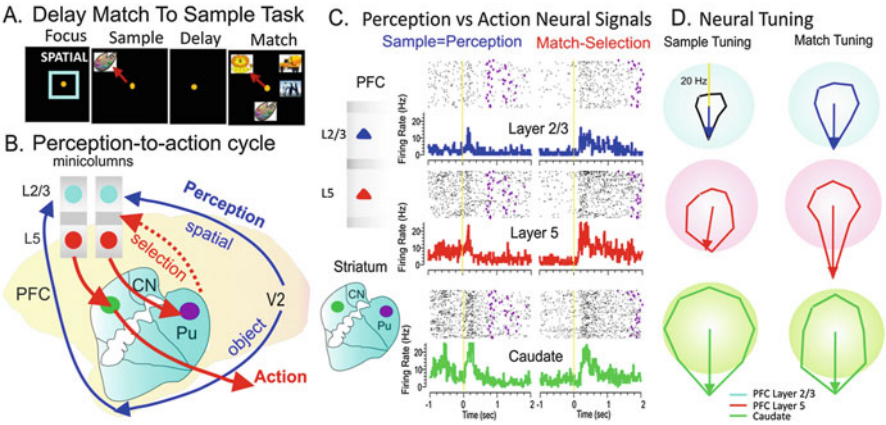

Fig. 4.4 Prefrontal cortical microcircuits and the perception to action cycle. (**a**) Behavioral paradigm showing the sequence of events in the spatial delay match to sample task (DMS) task. Each trial begins with 'trial start images' (*blue 'box'*) to initiate a 'spatial' trial. Then, the 'Sample Target' image is accompanied by a 'Sample Response' followed by a variable 'Delay' period of 1–40 s, with a blank screen. At the end of "Delay" period the 'Match' screen with Sample image is accompanied by 1–6 Non-match (distracter) images, requiring movement of the cursor into the correct Match target determined by 'trial start' screen (Spatial trial = same location on the screen) after presentation to receive a juice reward. (**b**) The illustration of the perception-to-action cycle. The diagram depicts the flow of spatial and object signals during perceptual and executive selection of target stimuli in a rhesus macaque brain. In visual area V2 visual information splits into dorsal (spatial signals) and ventral (object signals) pathways that send signals to the top of executive hierarchy in PFC, and then top-down through the cortico-striatal-thalamo-cortical loops. *Blue arrows* depict the perceptual flow of information while *red arrows* indicate the action (executive) signal flow from prefrontal cortical layer 5 to dorsal striatum, with the *red dotted arrow* indicating the thalamo-cortical projection in the cortico-striatal-thalamo-cortical loop. The two adjacent cortical minicolumns with *red* and *blue filled circles* indicate inter-laminar simultaneous recordings, while caudate-putamen recording is shown in *green* and *pink circles*. PFC-prefrontal cortex layers L2/3 and L5, and V2-secondary visual cortex region. **c** Neural signals during perception vs. selection phases of the DMS task. Example of simultaneous single unit activity (individual trial rasters and peri-event histograms) of single neurons recorded in prefrontal cortical layers L2/3 (*blue*) and L5 (*red*) with the conformal MEA and caudate nucleus (*green*) during Sample and Match target presentation on Spatial trials during a single session (n = 120 trials). **d** Neural tuning during spatial rule. Directional tuning plots (*left* panel for perception and for executive selection, *right* panels) depict firing preference, measured by the radial eccentricity (in spike/s or Hz) in the polygonal contour for the eight different target locations on the screen where images appear. The tuning plots compare firing preferences on spatial trials for the same cells. The same tuning vectors also show the magnitude of firing for preferred locations during the encoding (*left* panel) and selection (*right* panel) phases of the task on spatial trials. Spatial trials tuning vectors show the same preferred directionality (i.e. 270°) during the encoding and selection phases in both PFC layers and in caudate nucleus, suggesting parallel processing streams through cortical minicolumns and striatum and likely, through the entire thalamo-cortical loop. The radius of polar plots is represented in Hz and tuning amplitude is measured in Hz, as well. Asterisks: $^{**}p < 0.001$, ANOVA (With permission from Opris et al. 2013)

tuning (Opris et al. 2013). These inter-laminar prefrontal microcircuits may play crucial roles to the perception-to-action cycle by bridging perception circuits in supra-granular cortical layers with selection and executive function in infra-granular layers (Opris et al. 2013).

Memory

Functional insight into the cognitive role of PFC in working memory came from single unit recordings (Fuster and Alexander 1971; Funahashi et al. 1989), in prefrontal cortical cells displaying persistent, sustained levels of neuronal firing during the retention delay period, in tasks that required the monkey to retain information over a short period of time (Fig. 4.5). This sustained activity (representing a *signature* for working memory) is thought to provide a "bridge across time" between the stimulus cue (e.g. the location of a light stimulus) and its contingent response (e.g. a later delayed saccade to the remembered location of light stimulus). These results have been supported by functional neuroimaging studies in humans that have shown lateral PFC activity during performance on delay response tasks (for

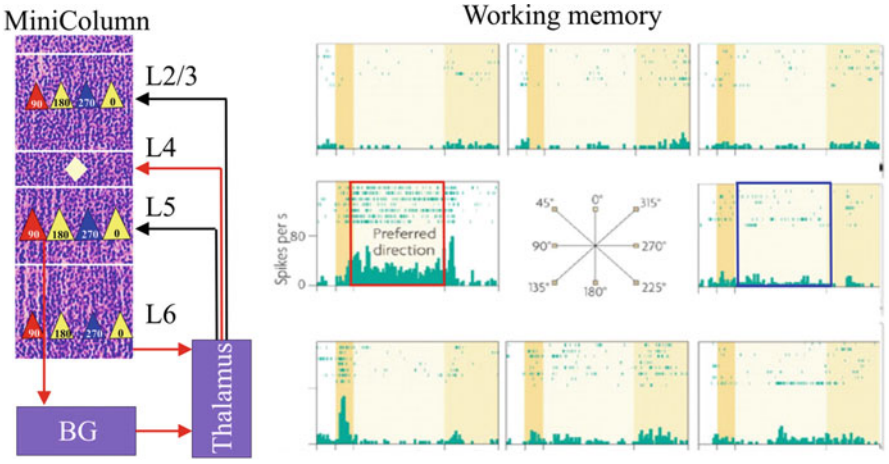

Fig. 4.5 Cortical microcircuit of working memory. *Left*: Neurons in the supra-granular layers L2/3 of the prefrontal minicolumn process spatial information about the location of the target, while cells in the infra-granular layers send the target information in a reverberatory loop. The minicolumns are interconnected with the basal ganglia (BG) and the Thalamus in a cortico-thalamic loop involved in executive control. Pyramidal cells are active when target location is at 90° (*red*), and inactive (*blue*) when targets are at opposite location. *Right*: an example of a dorso-lateral PFC delay neuron with spatially tuned, persistent firing during the delay period. This neuron shows increased firing for the cue, delay and response for the neuron's preferred direction (highlighted in *blue*), but not for nonpreferred directions (*white* backgrounds). The anti-preferred direction opposite to the neuron's preferred direction is shown in *red*. Note that subsequent figures show only the preferred and anti-preferred directions for the sake of brevity (With permission from Wang et al. 2011)

review, see Curtis and D'Esposito 2003). For example, in a functional magneto-resonance imaging (fMRI) study, using an oculomotor delay task similar to that used in monkey studies, it was observed not only the frontal cortex activity during the retention interval, but also that the magnitude of the activity correlated positively with the accuracy of the memory-guided saccade that followed later (Curtis et al. 2004).

Mnemonic (working memory) activity underlying persistent neural activity has been hypothesized to be sustained by synaptic reverberation in a recurrent circuit (Wang 2002). Neural circuitry may involve reverberatory thalamo-cortical (Wang 2002) and inter-laminar loops (Takeuchi et al. 2011; Opris et al. 2011, 2012a, b, 2013). Ben-Yakov and Dudai (2011) established that the hippocampus plays a role in the maintenance of working memory. The authors of this study identified, by fMRI, a bilateral hippocampus activity starting immediately after the presentation of stimuli. Maintenance of working memory by the hippocampus may be part of the long-term memory maintenance process that involves reverberation of neural activity through the cortico-hippocampal-thalamic loop.

Decision Making and Executive Control

As populations of neurons carry a large variety of signals correlated with external sensory events, internal mental states or impending behavioral responses, these signals are encoded, decoded, and remapped at several stages of the perception-to-action cycle, in order to provide the most appropriate course of action (Shadlen and Newsome 1998; Quintana and Fuster 1999; Fuster 2000, 2001; Opris et al. 2013). Decision making is a cognitive process (Koechlin and Hyafil 2007) (Fig. 4.6) with several features: (1) accumulation of sensory evidence (Shadlen and Newsome 2001, (2) integration of sensory signals, reward expectation and cognitive information (Curtis et al. 2004), (3) weighing of the options by comparisons between a subject's expected reward and prior experience (Schall 1999; Opris and Bruce 2005), and (4) the selection of behavioral response (Zhang et al. 2012). The flow of decision signals is depicted as a rise to threshold process described by the psychological diffusion model of decision (Ratcliff 1978, 2001, 2002; Reddi and Carpenter 2000; Ratcliff and Tuerlinckx 2002; Ratcliff et al. 2011). Ratcliff and colleagues hypothesized that buildup/prelude neurons in *superior colliculus* (SC) and in *frontal eye fields* (FEF) are part of a mechanism that implements the accumulation of sensory evidence in a decision process (Schall 2002). They compared neural firing rates to the paths of evidence accumulation for the diffusion process and found that collicular buildup/prelude activity closely follows the trajectory of the decision process described by a diffusion model (Ratcliff et al. 2011). Minicolumns in the PFC (Opris and Casanova 2014) are interconnected to each other through horizontal 'long range' projections in layer 2/3 (Kritzer and Goldman-Rakic 1995; Rao et al. 1997) and interlaminar mini-loops (Weiler et al. 2008; Takeuchi et al. 2011). The loop is then closed ('reverberatory loops') through

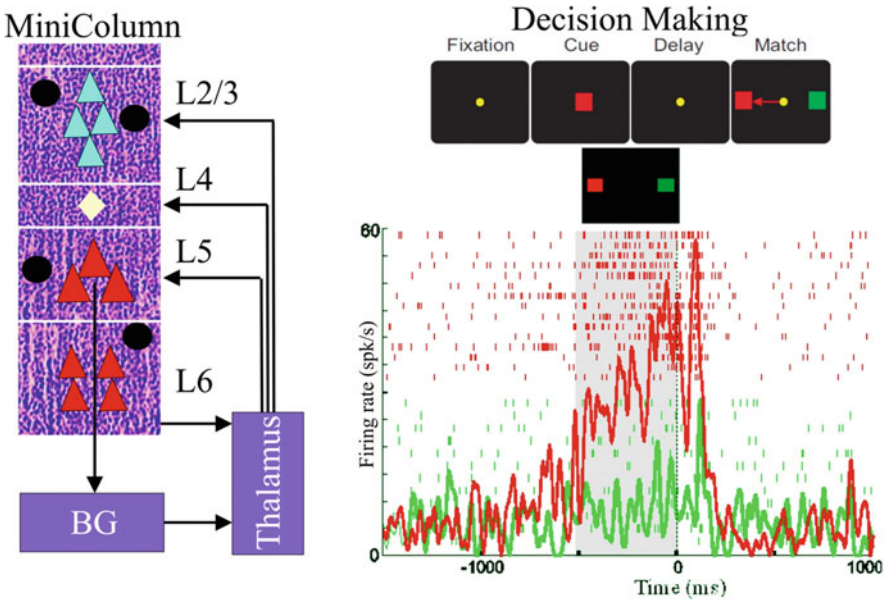

Fig. 4.6 Decision processing in prefrontal microcircuits. (**a**) Neurons in the supra-granular layers L2/3 of the prefrontal minicolumn process sensory evidence, while cells in the infra-granular layers process the selection of the target. The minicolumn is interconnected with the basal ganglia (BG) and the Thalamus in a cortico-thalamic loop involved in executive control. (**b**) Neural activity of a frontal eye field (FEF) cell in layer 5, recorded during target selection process. On *top* is shown the sequence of events in the color match-to-sample (MTS) saccade task. A centrally presented sample is on for 750 ms and must be remembered for a brief variable delay period (100–500 ms) before the match/non-match pair appears. Furthermore, after the peripheral stimuli appear the monkey is required to further delay his response for a brief wait period (200–1000 ms) until the fixation light is extinguished. The *raster lines* for trials where the match stimulus was in the cell's response field (RF) are *red* and the trials where the stimulus was opposite to the RF (xRF) are *green*. Consistent with the rise to threshold mechanism of decision process, buildup activity begins well prior to the saccades in the RF trials, but not in the xRF trials (Adapted with permission from Opris and Bruce 2005)

projections to the subcortical basal ganglia nuclei and thalamus (Alexander et al. 1986; Wise et al. 1996; Swadlow et al. 2002).

Such 'reverberatory loops' may be regarded as the 'basic functional unit' of cognitive/executive mechanism because they: (1) combine incoming signals of the different input layers (2) store mnemonic information through feedback connections in 'persistent' spiking activity (Wang 2012); and (3) compare input signals to a threshold criterion triggering an output response (selection), which constitutes the ability to make a decision (Ratcliff et al. 2003). Thus, a cortical minicolumn with integrative, selective, and threshold abilities can play the role of a *decision module* (Opris and Casanova 2014).

Rule Processing

PFC is functionally organized along a rostral-caudal gradient of cognitive processing with more abstract representations/processes associated with more rostral areas (Nee et al. 2014). PFC network models suggest the enabling of specific "rule-coding" units that control the flow of information between segregated input, memory, and output layers. Such basic mathematical rules and the numerical magnitudes appear to be encoded by primate PFC neurons (Eiselt and Nieder 2013; Bongard and Nieder 2014). PFC influences action/behavior largely through its connections with other association cortices. To address the role of PFC on behavior, Crowe et al. (2013) simultaneously recorded the activity of neurons in prefrontal and posterior parietal cortices of monkeys performing a rule-based spatial categorization task. Parietal cortex receives direct prefrontal input, and parietal neurons, like their prefrontal counterparts, exhibit signals that reflect rule-based cognitive processing in this task. Crowe et al. (2013) obtained evidence that signals reflecting rule-dependent categories were selectively transmitted in a top-down direction from prefrontal to parietal neurons, suggesting that prefrontal output is important for the executive control of distributed cognitive processing.

Response Inhibition

Basal forebrain neuronal inhibition enables rapid behavioral stopping. The inhibition of behavioral response is a key feature of the executive control mechanism. Response inhibition deals with the suppression of actions that are no longer useful or are inappropriate behaviors in the ever-changing environments (Schall 2001; Verbruggen and Logan 2008). The neuronal mechanism of response inhibition at the microcircuit level is based on interneurons that gate the inputs to a network and regulate its outputs relevant to behavior (Tierney et al. 2008; Packer and Yuste 2011) (Fig. 4.7).

This implies an involvement of the dense, unspecific connectivity of neocortical parvalbumin-positive GABA-ergic interneurons at the microcircuit level. The temporal focalization of interneuron response is based on *dopaminergic* (DA) influence on the timing of PFC interneuron firing. This DA influence on interneuron excitability is responsible for filtering out weak excitatory inputs. The mechanism by which DA influence can modulate the temporal dynamics of feed-forward inhibition in PFC microcircuits is based on the increase in temporal precision of interneuron firing. The cognitive mechanism for information processing is, therefore, relevant in the generation of an inhibitory response, in the monitoring of stopping performance, and in understanding how behavior is controlled (Schall 2001; Verbruggen and Logan 2008).

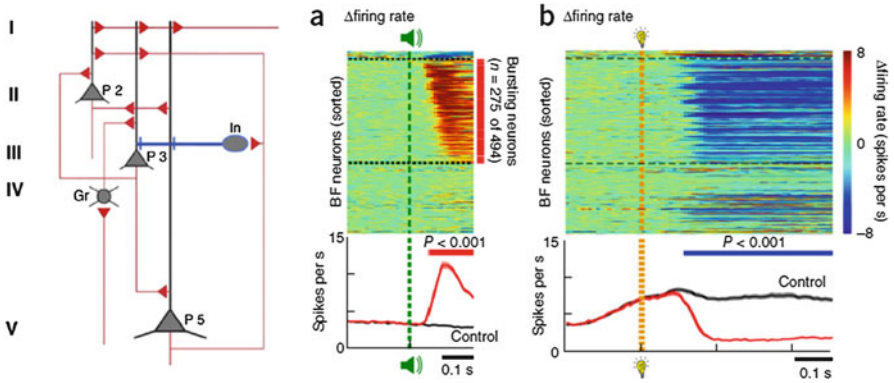

Fig. 4.7 *Left panel*: Response inhibition. Diagram of cortical columnar circuitry that may explain normal feedback processing. The connections between neurons depict the excitatory and inhibitory interaction between cortical layers. (Redrawn from Lison et al. 2014). *Right panel*: (**a, b**) Basal Forebrain neurons with bursting responses to the go signal (**a**) were inhibited nearly completely by the stop signal (**b**), irrespective of whether successful stopping was rewarded (With permission from Mayse et al. 2015)

4.3.2 Unity or Diversity of Prefrontal Functions

As shown in the previous paragraphs, the *executive functions* (EFs) are high-level cognitive processes associated with the frontal lobes that control lower level functions for the purpose of *goal-directed behavior*. Executive functions include: (a) abilities such as working memory, set shifting, updating of action planning, and response inhibition, and (b) show a general pattern of shared but distinct functions, a pattern that is described as "unity and diversity" (Friedman and Miyake 2016). To delineate the "unity and diversity" of tonic and phasic components of EFs, Marklund et al. (2007) measured the "load-dependent activation overlaps" as indices of common components characterizing the extent to which unitary EFs might be shared across separate "domains" of episodic and working memory. "Unitary" control modulations were temporally dissociated into (a) shared tonic components involving mPFC and lPFC, striatum, cerebellum, and superior parietal cortex, "assumed" to govern "enhanced" top-down context processing, monitoring and sustained attention throughout task epochs and (b) stimulus-synchronous phasic components involving posterior intra-parietal sulcus, "assumed" to support the dynamic shifting of attention among internal representations. Although an extensive part of the "regional" load effects "constituted differential control modulations" in both sustained and transient responses, "commonalities" were found to implicate a "subset" of executive "core" mechanisms consistent with the concept of unitary or domain general control. It follows that converging evidence point to the conclusion that EF (updating, shifting, and inhibition) is characterized by both unity and diversity of processes (Collette et al. 2005; Marklund et al. 2007).

4.3.3 Does the Emergence of Mind Follows a Power of Two Permutation Logic?

A recent article by the group of Joe Tsien (Xie et al. 2016) proposed an elegant solution to the problem of how neuronal assemblies perform computations. These authors proposed that brain computations are performed by computational building blocks, called *functional computational motifs* (FCMs). Processing of information by FCMs eventually generates all higher brain functions. The principles of FCM operation are based on the theory of connectivity previously proposed by the same group (Tsien 2015a, b; Li et al. 2016). The theory of connectivity defines mathematical rules that govern the organization of microcircuits and neuronal assemblies. This connectivity architecture incorporates specific-to-general computational connections that, according to Tsien and his colleagues, underlie the emergence of knowledge and adaptive behaviors. These researchers argue that FCMs obey the power-of-two-based permutation logic described by the equation $N = 2^i - 1$, where N is the number of projection-neuron cliques and i is the number of inputs. The set of cliques represents all possible permutations of specific-to-general input configurations. It follows from the permutation rule that each FCM contains principal projection neurons that receive very specific inputs and the neurons receive multiple convergent inputs. This neuronal composition covers all possible patterns defined by the power-of-two-based permutation logic (Fig. 4.8a, b left panel). The proposed connectivity and computation rules explain how information is represented by neural assemblies that utilize specific input coding, assemblies that perform combinatorial operations, and assemblies with generalized representation properties.

The proposed computational architecture agrees well with what we known about microcircuitry of cortical layers. Tsien and his colleagues describe the corresponding computational modules as cortical FCMs. In cortical FCMs, the power-of-two-based computational logic is implemented as a gradient of specific-to-general processing units across cortical laminae (Tsien 2015a; Li et al. 2016). The connectivity is random in superficial laminae, i.e. L2/3, and nonrandom in deep laminae, i.e. L5/6, where the superficial laminae project. The random connectivity and specific encoding in superficial cortical layers facilitates such neural computations as extraction of novel patterns and sparse encoding of patterns. The non-randomness and generalized encoding in the deep layers facilitate various types of feedback control, including control of emotions, motivation, behaviors, and consciousness. Tsien and his colleagues obtained convincing experimental evidence favoring their theoretical framework. They conducted experiments in mice, where they used tetrode arrays to record signals from cortical neurons located in L2/3 and L5/6 (Figs. 4.8 right panel).

The mice were exposed to four types of fearful events: (1) an air puff applied to the mouse's back, (2) an "earthquake" induced by shaking the chamber where the animal was placed, (3) "free-fall in the elevator" produced by placing the animal in a box, and then lifting and dropping the box, and (4) electric foot-shock. After

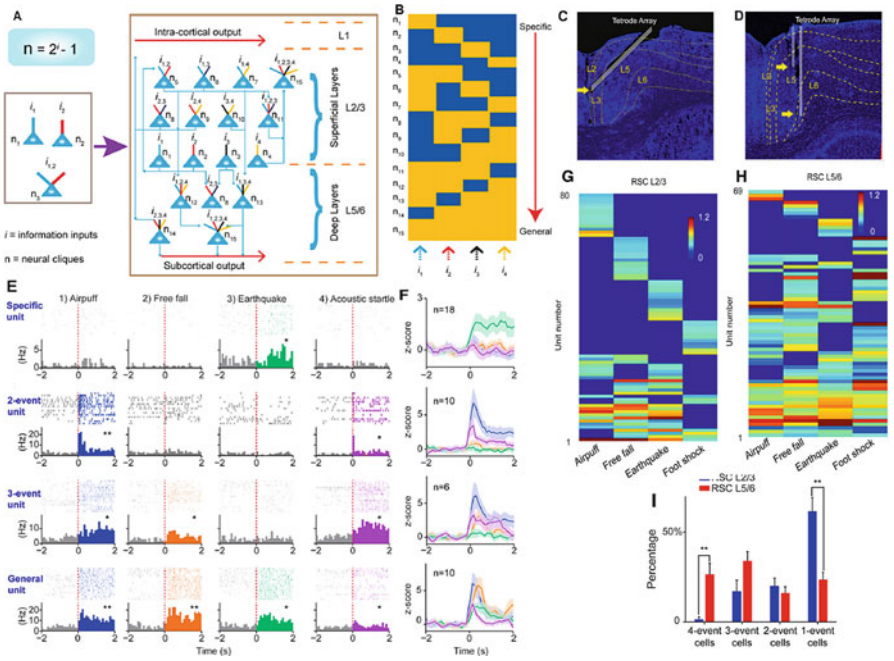

Fig. 4.8 Emergence of the mind follows a power of two permutation logic for governing the specific-to-general wiring and computational logic of cell assemblies. (**a**) The logic is applicable from the simplest circuits to the high level human brain function. Implementation of the power-of-two-based computational logic is shown in the cortex via various cliques across laminae. In the six-layered cortex, the layer 4 hosts most of the specific cliques while in the three-layered cortex (illustrated here), there is no layer 4. As such, the cortex is divided into the L1, the superficial layers (L2/3) which preferentially host low-level combinatorial cells, and deep layers (L5/6) which host more high-level combinatorial cells. The implementation of this power-of-two-based logic can be repeatedly utilized as cortical expansion occurred over evolution. (**b**) Schematic "bar-code" illustrates the specific-to-general cell-assembly activation patterns, which can be measured by electrodes or imaging techniques, from the 15 distinct neural cliques (N1–15), processing four distinct inputs (i1, i2, i3, i4). The orange color represents the stimulus-triggered activation above the baseline state (in *blue*). The *arrow* on the right side illustrates the number of distinct neural cliques exhibiting specific, sub-combinatorial, as well as generalized, responsiveness. Specific neural cliques encode specific features, whereas various permutation rule-based neural cliques encode various convergent patterns, representing relational memories and generalized concepts. This ensemble activation pattern allows pattern-separation, pattern-categorization, and pattern-generalization of various experiences at the cognitive level. (**c**, **d**) Histological confirmation of recording tetrode location in the layers L2/3 (in C) and L5/6 (in D) of the retrosplenial cortex (RSC). (**e**) Specific cells firing in response to air puff, free fall, earthquake and acoustic starle. (**f**) The population response of the cells to the same events as in (**e**). (**g**, **h**) Hierarchical clustering plot revealed that the general four-event clique and three-event cliques constituted a larger proportion. (**i**) There are significant differences in the distributions of specific cells vs. the general cells between L2/3 and L5/6 (With permission from Xie et al. 2016)

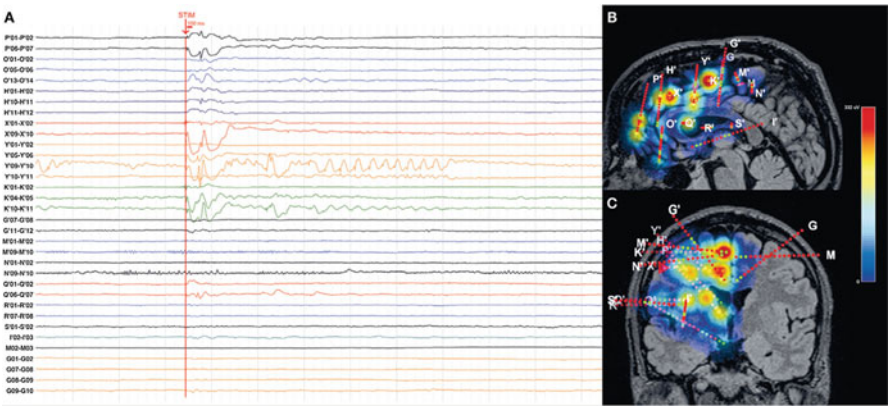

Fig. 4.9 Intrusive thoughts. (**a**) Intracranial EEG illustrating the response to a single stimulation pulse in P2. (**b**, **c**) Maximum-intensity projections of the magnitude of the early responses on patient's sagittal (**b**) and coronal (**c**) MRI views (With permission from Popa et al. 2016)

the authors examined different types of neuronal responses to these stimuli, they found that of the total of 197 neurons recorded in L2/3, about 65 % exhibited specific responses to only one stimulus type. A much smaller proportion, 1 %, responded to all four stimuli and therefore belongs to the general clique. Responses to three stimuli were observed in 14 % of the recorded neurons. Two-events neurons constituted 20 % of the recorded sample (Fig. 4.9c, e). The recordings from the neurons located in L5/6 showed a different pattern of responses (Fig. 4.9d). Here, a much smaller proportion of neurons (20%) were selective to one stimulus only, whereas 23% of the neurons responded to all four stimuli. About 55% of the L5/6 neuronal sample responded to either three or four events (compared to just 15% in L2/3). Thus, superficial laminae clearly contained mostly specific cliques, whereas the deep laminae contained mostly general cliques. The authors interpreted these findings as an evidence of a vertical implementation of FCM governed by the power-of-two-based permutation logic.

These and additional experiments of Tsien's group convincingly demonstrated that the power-of-two logic is found in many cortical and subcortical areas and in several animal species. Moreover, they showed that the logic applies to various modalities and physiological functions, including neural processing of emotional, appetitive, and social signals. The logic was even preserved if NMDA receptors, known to be important for memory and plasticity, which were deleted after postnatal development, indicating that the brain's computational architecture is preconfigured and does critically depend on learning. Finally, they found that modulatory DA neurons follow simpler logical rules. Overall, these findings support power-of-two-based permutation logic as a fundamental computational rule employed by the brain. The seemingly simple mathematical rule explains neural computations across a broad range of species, from the simplest nervous systems to very complex.

The computational logic proposed by Tsien and his colleagues is probably applicable to the human brain, as well, even though it contains 86 billion neurons (Herculano-Houzel 2009) each of which having many thousands of synapses (Andersen 1990). Given such an enormous complexity, it is very important that we search for unifying computational principles that govern such a network. In this context, the theoretical considerations and experimental findings of Tsien's group definitely represent a step in the right direction.

4.3.4 Intrusive Thoughts

A recent report by Popa et al. (2016) demonstrated *intrusive thoughts* (ITs) in the human brain while stimulating the dorso-lateral prefrontal cortex and the white matter in the prefrontal region (Opris et al. 2005). The ITs are psychological processes present in different neurological and psychiatric disorders. Intellectual auras like ITs, also known as *forced thinking* (FT), have been reported during frontal seizures. The term FT was first used by Penfield and Jasper, to describe a rare ictal manifestation of frontal seizures (Penfield and Jasper 1954).

To highlight the effective connectivity explaining this clinical response, the authors of the study analyzed the cortico-cortical potentials evoked by single pulse electrical stimulation (Popa et al. 2016). During frontal lobe stimulation, ITs were elicited by pushing away the patient' own thoughts, with no emotional involvement. The responses were clearly different from auditory hallucinations or the inner speech phenomena described as verbal thinking (Alderson-Day et al. 2016). The stimulation was performed in dorso-lateral PFC in patient P1 and in the white matter underlying the PFC mantle in patients P2 and P3. In P2 and P3, the ITs were elicited when stimulation was applied in the white matter. The stimulated axons were part of the cognitive thalamo-cortical loop (Alexander et al. 1986; McFarland and Haber 2002; Santos et al. 2014). Thus, the IT, generated by the application of electrical current, recruited different circuits than those where "natural" thought emerges in the absence of electrical stimulation. It seems likely an involvement of local activation of cortical modules that received mismatched feedback from the thalamic projections (Popa et al. 2016). These novel results demonstrate that FT can be initiated by stimulating very well-defined regions of the PFC that may be involved in these behavioral and psychological manifestations.

4.3.5 Enhancement of Cognitive Functions Through Reasoning Training

Cognitive training. Solid evidence suggests that "cognitive training" is enhancing the cognitive performance of the brain of normal and clinical subjects (Knowlton et al. 2012; Chapman et al. 2015). Higher-order cognitive functions, such as

reasoning, may promote generalized changes in cognitive abilities necessary for all aspects of daily life. The perspective of Chapman and colleagues highlights brain ability changes measured in randomized clinical trials that train populations "ranging from teenagers to healthy older adults" with brain injury to those at-risk for Alzheimer's disease. The "evidence" presented by Chapmen across studies supports the potential for "reasoning training" to strengthen cognitive performance in trained and untrained "domains" and to engage "more efficient communication" across widely distributed neural networks that support higher-order cognition. The meaningful "benefits of reasoning training" provide "compelling motivation" to examine "meditation", physical exercise, and/or improved sleep in future research.

4.4 Conclusion

To conclude, the neuroanatomical and functional substrate for the human mind is provided by the laminar-columnar arrangement of the neurons in the cerebral cortex that enable the emergence of various features of the mind, such as attention, memory, decision making, and motor planning. We foresee that future investigations of the brain's microcircuits (DeFelipe 2010; Opris and Casanova 2014; Opris et al. 2015a, b, c), including computational, structural, and physiological approaches, will lead to new insights and paradigm-shifting ideas regarding the emergence of the human mind. Although the complexity of human brain circuits is immense, getting to the essence of mind is a feasible task.

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Chapter 5
The Hierarchical Circuit for Executive Control of Movement

Brian R. Noga and Ioan Opris

Abstract A major challenge in neuroscience research is the understanding of the vast universe of human brain and its mind. In this context, the ability of the mind to control behavior relies upon the executive control of movement. Herein, we focus on the hierarchical circuitry of the brain that exercises the executive control of movement. This executive mechanism spans hierarchically over frontal/parietal/temporal cortices, subcortical structures in basal ganglia and thalamus, brainstem and spinal cord. To address the hierarchical executive mechanism of movement, we will examine its frontal/parietal cortical microcircuits interconnected in thalamo-cortical loops via cortico-striatal projections, and further to the mesencephalic locomotor region and central pattern generators in the spinal cord for locomotor control. Spinal locomotor circuits are enabled by parallel activation/modulation from descending reticulospinal and monoaminergic pathways. The use of various stimulation approaches developed recently is examined in terms of preclinical (animal experiments) and clinical applications to human brain disorders. Future clinical studies on the pathological aspects of movement will employ novel, deep brain stimulation that is capable to function in a closed-loop manner, adjusting therapy delivery to the patient's level of disease impairment.

Keywords Executive control • Microcircuit • Brainstem • Movement • Prefrontal cortex • Striatum • Spinal cord • Deep brain stimulation

5.1 Introduction

There is no question about the fact that the most challenging topic in neuroscience research is the understanding of the "vast universe" of human brain and its mind. As Penfield emphasized by expressly using the word "Surely" in the beginning of

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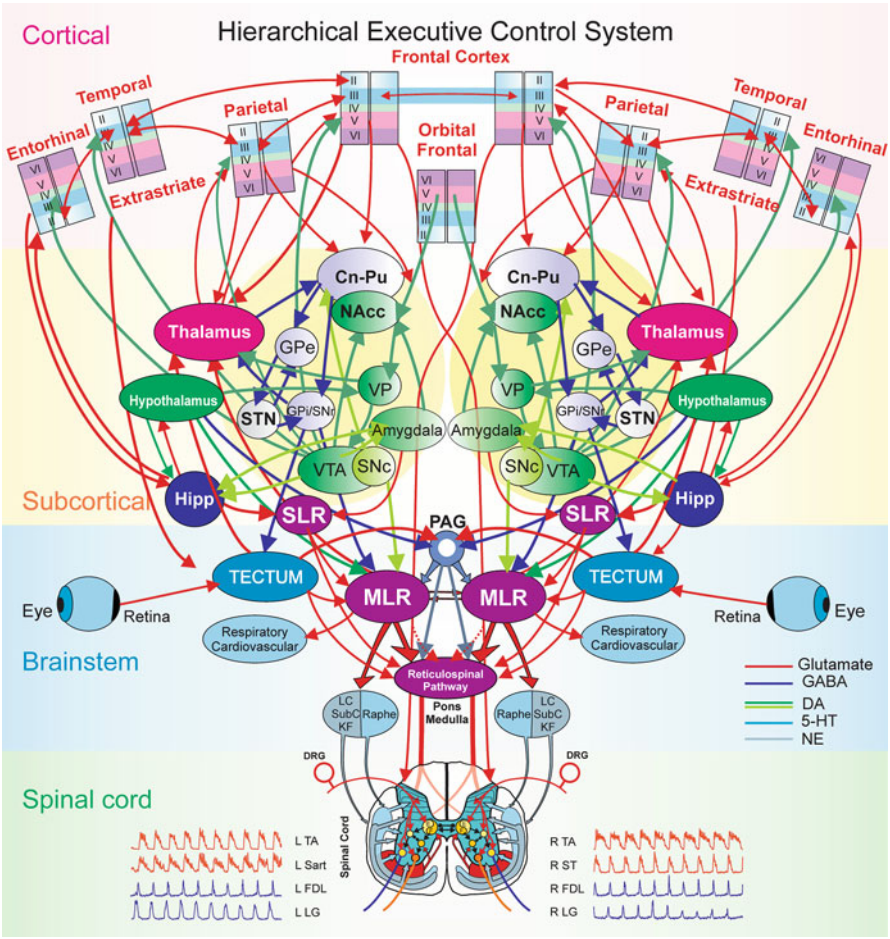

Fig. 5.1 The hierarchical executive control system for movement. The executive control system is anatomically organized via a hierarchical architecture of cortical modules (layers, minicolumns with microcircuits), subcortical nuclei (basal ganglia and thalamus with cortical-subcortical-thalamic loops; hippocampus and hippo-thalamus), brainstem (midbrain, pons, medulla with cortical-brainstem networks), and spinal cord (locomotor central pattern generators, CPG). At the higher level in the hierarchy are the columnar laminar modules of frontal (cognitive), parietal (motor), extrastriate (visual), temporal, orbital frontal cortices (emotion) and entorhinal (limbic), Beneath, are the subcortical structures: striatum (Caudate, Cn, Putamen, Pu and Accumbens, Acc), Globus Pallidus [GPe/GPi (external/internal segments), the dopaminergic Ventral Tegmental Area (VTA), the Ventral Pallidum (VP), Substantia Nigra (SNc/SNr: pars compacta/pars reticulate parts), Subthalamic Nucleus (STN) and the Thalamus. The motivation and emotion is processed by the Hypothalamus, and respectively, Amygdala. The coordination of the navigation systems involves the frontal cortex and the hippocampus (Hip). Subthalamic locomotor region (SLR) is a subcortical center for coordinating locomotion. Brain-stem and Spinal Cord level. Locomotion is initiated by the direct activation or disinhibition of the mesencephalic locomotor region (MLR) and/or the reticulospinal (RS) pathway. Stimulation of the MLR activates reticulospinal neurons which project through the ventrolateral funiculus to activate spinal locomotor central pattern generator neurons, in part, by the release of excitatory amino acids. The reticulospinal pathway is considered to comprise the primary 'command pathway' for the initiation of locomotion.

his statement: "there is no problem in any field more vast than the problem of the mechanisms of the brain and its relation to the mind" spanning "the vastness ... of the mind" remained to be solved by future generations of neuroscientists (Penfield 1958).

The executive control has been defined as brain's ability "to control thought and action" (movement), by coordinating "multiple systems and mechanisms across multiple brain areas" to pursue a goal (Miller and Phelps 2010). Examples of executive control functions are: attention, working memory, decision making, intention or motor plan and behavioral inhibition, while the corresponding executive dysfunctions are: attention deficit disorder (ADD), dementia, addiction, dyspraxia. Thus, the ability of the mind to control behavior relies upon the hierarchical circuitry of the brain that exercises the executive control of movement.

The hierarchy of brain functions was introduced by Fuster (2000, 2001); Fuster et al. (2000) based on Hughlings Jackson assumption that the cortex was the highest level of the nervous system that controlled (activated and/or inhibited) the functions of lower levels so that cortical disease led to two sets of symptoms, 'negative' from loss of the controlling cortex and 'positive' from the emergence of the lower center (Fuster 1990; York and Steinberg 2011). This implied an anatomical and physiological hierarchy of higher and lower centers, with the higher ones suppressing the function of the lower ones (Fuster 1990; York and Steinberg 2011).

Our focus in this chapter is on the hierarchy of neuronal circuitry of the executive control of movement (Fig. 5.1) that spans over frontal and parietal cortices, subcortical structures in basal ganglia and thalamus, brainstem and spinal cord. Furthermore, we focus the chapter with respect to the initiation of locomotion. There are three components of the hierarchical circuit integrating locomotion initiation Hirabayashi et al. (2013b): (i) exploratory, (ii) primary appetitive, and (iii) primary defensive systems (Sinnamon 1993). According to Sinnamon, "Locomotion serves different roles in the three systems. For the primary appetitive systems, locomotion functions bring the organism in contact with incentive/consummative stimuli. For the primary defensive system, locomotion functions increase the distance between the organism and threatening or painful stimuli. In the higher order exploratory system, locomotion is directed to distal stimuli that comprise the features of an environment and the behavioral goal." To address the hierarchical executive mechanism of movement, we will approach the executive hierarchy in a top-

Fig. 5.1 (continued) MLR stimulation also activates in parallel, multiple monoaminergic descending pathways during centrally-generated locomotion. The flexor (F) and extensor (E) components of the locomotor CPG are activated/modulated by descending bilateral reticulospinal and monoaminergic projections as well as by crossed excitatory (►) and inhibitory (●) segmental projections from the CPG opposite to it. Sensory afferents from skin and muscles innervate spinal neurons in the dorsal horn, intermediate zone and ventral horn to fine-tune the locomotor step cycle. Details of the flexor and extensor components of the CPG are omitted in order to emphasize general interconnections between them and their target neurons. *LC* locus ceruleus, *SubC* subceruleus, *KF* Kölliker-Fuse, *DRG* dorsal root ganglia, *L* left, *R* right, *TA* tibialis anterior, *Sart* Sartorius, *FDL* flexor digitorum longus, *LG* lateral gastrocnemius, *ST* semitendinosus

down manner, first, examining its frontal (premotor) and parietal (motor) cortical microcircuits (Wise et al. 1996), and then their interconnections in thalamo-cortical loops via cortico-striatal projections and further to the mesencephalic locomotor region and central pattern generators in the spinal cord (Wise et al. 1996; McFarland and Haber 2002; Opris 2013).

5.2 Cognitive Level: Cortical Microcircuits in the Premotor and Motor Cortices

(**a**) **Premotor cortical microcircuits** for perception to action (integration and selection). In 1957 Mountcastle proposed the cortical minicolumn, a new concept for cerebral cortex, based on a modular architecture that efficiently supports its functionality in perceptual (visual, auditory, touch), cognitive, and behavioral functions (Mountcastle 1957, 1997; Shepherd and Grillner 2010; Opris et al. 2011, 2012a, b, 2013, 2015a, b, c, d; Opris and Ferrera 2014; Buxhoeveden and Casanova 2002). These modules are composed of vertical arrangements of cortical neurons, called minicolumns (Casanova et al. 2008; Mountcastle 1997; Szentágothai and Arbib 1975; Hubel and Wiesel 1969). In each minicolumn, neocortical neurons are organized in six layers (or laminae): supra-granular layers (L2/3), granular layer (L4) and infra-granular layers (L5/L6) (Fig. 5.2). Granular layer receives input from thalamus (Constantinople and Bruno 2013), while the infragranular layers send

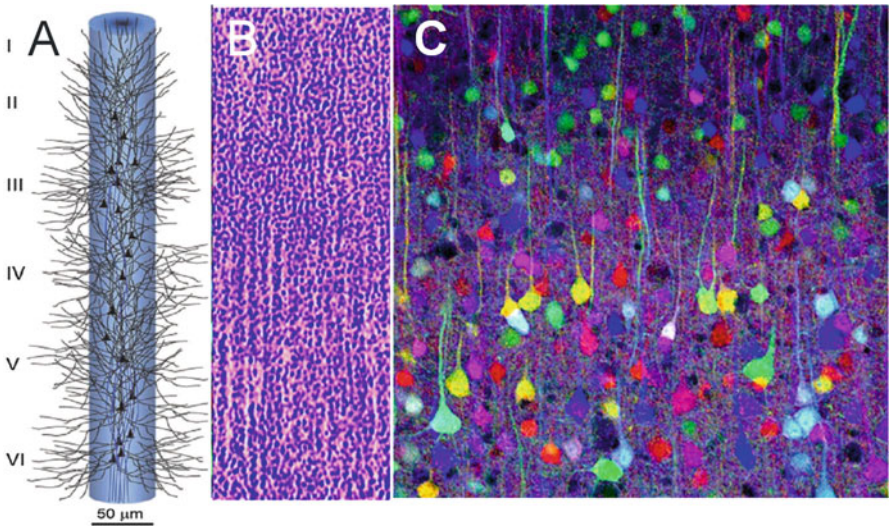

Fig. 5.2 The illustration of the cortical minicolumns. (**a**) Diagram of a cortical minicolumn with pyramidal cells. (**b**) Columns in the prefrontal cortex of the human brain in area 39. (**c**) Population of neurons illustrating the complexity of cortical microcircuits

outputs to the subcortical structures (striatum and thalamus; Alexander et al. 1986; Mountcastle et al. 1955, 1957; Opris et al. 2013).

Prefrontal cortical microcircuits, at the top of sensorimotor hierarchy, are in a unique position to coordinate the multitude of stimuli being interconnected with virtually the entire brain. Therefore, prefrontal microcircuits are there to integrate and categorize signals over a broad spectrum of sensory stimuli and various modalities (Wilson et al. 1993). While the integration of signals carrying sensory/perceptual information is likely to be performed in the supra-granular layers, the output of this computation is sent to the infra-granular layers and to other areas comprising the network. For example, the microcircuits in prefrontal cortex are involved with the elementary operations for the executive control of behavior (Opris et al. 2012b, 2015c), while the microcircuits of the temporal cortex use inter-laminar synchrony to maintain items in long term memory (Takeuchi et al. 2011; Hirabayashi et al. 2013a).

5.2.1 Integration

The integrative role of cortical module (Leise 1990) stems from the ability of horizontal and vertical projections within the same columnar space. The supragranular layers L2/3 are a major source of cortico-cortical projections receiving sensory information from neighboring areas, while the infragranular layer L5 is the column's output to subcortical structures involved in behavior/movement (Miller and Cohen 2001). Thus, "inter-laminar connections form microcircuits that connect sensory-related signals with behavior/movement related outputs" (Opris et al. 2011). This "sensorimotor integration" (Fig. 5.3) was shown by Opris et al. (2011, 2013) by means of "inter-laminar correlated firing" between supragranular layers that carry "perceptual" (visual spatial information) and the infragranular layers that carry "action" related information. Such "transformations of neural signals" may likely reduce the output degrees of freedom within the cortical minicolumn by selecting only the "relevant" signals for representing the movement. This "integrative process that occurs in "canonical microcircuits" binds parallel "streams of minicolumnar processing" within the executive control network (Fuster and Bressler 2012; Miller and Cohen 2001).

5.2.2 Selection and Executive Decision

Recent evidence suggests that prefrontal cortical minicolumn might be the first stage in the transformation of spatial sensory/perceptual information in a behavioral goal in the cortico-striatal-palidal-thalamo-cortical loop (Alexander et al. 1986; Opris et al. 2013). A key role in the selection (executive control) is played by the GABAergic interneurons of minicolumns (Raghanti et al. 2010) that shape the tuning for preferred direction/location by means of lateral inhibition. Minicolumnar

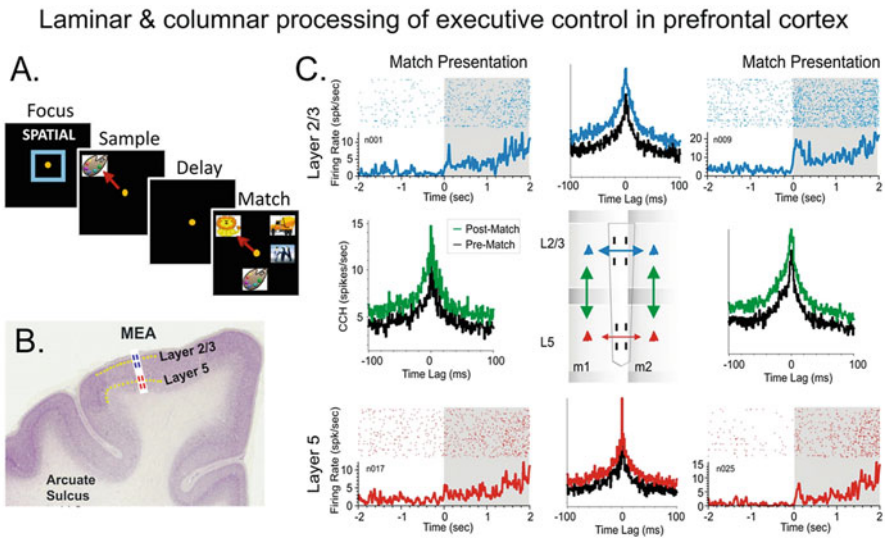

Fig. 5.3 The laminar and columnar processing of executive control in prefrontal cortex. (**a**) Decision task or delay match to sample behavioral paradigm. (**b**) Coronal section through the prefrontal cortex that shows the multielectrode arrays in place for recording in adjacent cortical minicolumn and layers. (**c**) Synchronized firing in prefrontal cortical minicolumns during executive decision making

role in plasticity is associated not only with the tuning (Fig. 5.3) of synaptic activity states, but also with optimal selection among alternate subnetworks of microcircuits developing within a given context. Such parallel subnetworks may process complementary submodalities within a defined receptive/memory field. Alternatively, they may provide overlapping response characteristics to a common input. Competition among networks allows for circuit optimization (selection), in particular by means of learning.

A decision circuit is defined as a closed neural network that measures the probable value of a signal element and makes an output signal based on the value of the input signal and a predetermined criterion or threshold (Ratcliff et al. 2003; Opris and Casanova 2014; Wang 2002). Minicolumns in PFC are interconnected to each other through horizontal "long range" projections in layer 2/3 (Kritzer and Goldman-Rakic 1995; Rao et al. 1997) and interlaminar mini-loops (Weiler et al. 2008; Takeuchi et al. 2011). The loop is then closed ("reverberatory loops") through projections to the subcortical basal ganglia nuclei and thalamus (Alexander et al. 1986; Swadlow et al. 2002). Such "reverberatory loops" may be regarded as the "basic functional unit" of cognitive/executive mechanism because they: (i) combine incoming signals of the different input layers (Casanova et al. 2007); (ii) store mnemonic information through feedback connections in "persistent" spiking activity (Wang 2012); (iii) compare input signals to a threshold criterion triggering an output response (selection), which constitutes the ability to make a decision

(Ratcliff et al. 2003). Thus, a cortical minicolumn with integrative, selective and threshold abilities can play the role of a decision module (Opris and Casanova 2014).

We assume that minicolumnar diversity provides the substrate for this competition and the basis for adapting learned behavior to context. During development, neurogenetic programs interact with epigenetic factors to regulate formation of cortical microcircuit templates (Rakic 1988; Jones 2000; Jones and Rakic 2010; Kaas 2012), which are then shaped and pruned by differential patterns of sensory activity. This means that increased minicolumnar diversity may give rise to greater potential for combinatorial activity of microcircuits within overlapping networks, resulting in enhanced learning and behavioral flexibility (Casanova 2008). Cortical minicolumns may, therefore, play a crucial role in behavioral selection that is in fact the substrate of executive function (e.g., attention, executive control/decision making).

(**b**) **Motor cortical columns** play an important role in blending the cognitive/executive features of the movement with the motor control involving the spatial tuning–sharpening the directional preference (Fig. 5.4). Directional tuning is a fundamental property of the neurons in motor cortex (Georgopoulos et al. 2007) together with the tuning of the speed (Perel et al. 2015). In Fig. 5.4a, it is illustrated

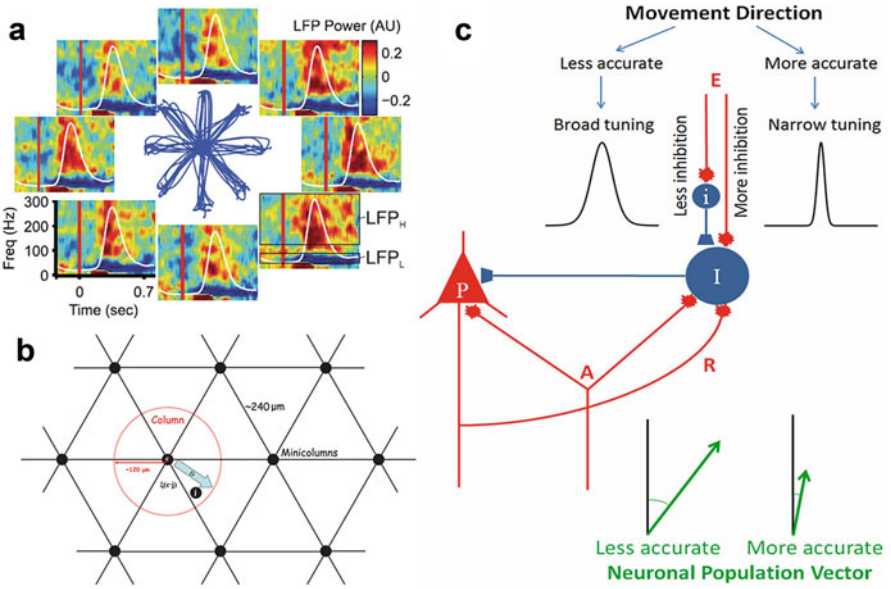

Fig. 5.4 The directional tuning in motor cortex. (**a**) Trial-averaged LFP shows both directional and speed modulation: time-frequency PS for the LFP from 1 example electrode, averaged over repeated reaches to the eight targets. This channel demonstrated simultaneous speed and directional tuning (Perel et al. 2015). (**b**) Schematic model of mapping of the preferred direction in motor cortex (Georgopoulos et al. 2007). (**c**) Schematic diagram to illustrate the hypothesis of directional accuracy via availably tuned circuit. *Red* and *blue* terminals indicate excitatory and inhibitory synapses, respectively *P* pyramidal cell, *I* and *i* inhibitory interneurons (Mahan and Georgopoulos 2013)

simultaneous speed and directional tuning during reaching movement to the 8 targets, by using the time-frequency power spectrum of the local field potentials (LFP) from one electrode (Perel et al. 2015).

To provide evidence for the "orderly mapping of the preferred direction" in motor cortical columns perpendicular to the surface, Georgopoulos and coworkers used multiple microelectrode penetrations in the arm area of the motor cortex while monkeys made free reaching 3D movement. As is shown in the diagram from Fig. 5.4b, they estimated that the directional minicolumns are ≈30 μm in width, while the minicolumns with similar preferred directions tend to repeat every ≈240 μm (estimated width of a column) with intermediate preferred directions "represented in a gradient" (Georgopoulos et al. 2007). A nice illustration of the directional accuracy is shown in Fig. 5.4c within a tuned circuit by excitatory and inhibitory synapses (Mahan and Georgopoulos 2013). The diagram depicts two distinct mechanisms "controlling the inhibitory drive" of interneuron I, one is purely excitatory and the other inhibitory (exerted through interneuron I), although a simple "continuous modulation of the excitatory input alone would be sufficient" (Mahan and Georgopoulos 2013).

5.3 Subcortical Level: Thalamo-Cortical Loops

5.3.1 Thalamo-Cortical Loops

The frontal cortex, basal ganglia and thalamus form a four loops cortico-basal ganglia-thalamo-cortical circuitry, with neural pathways in the brain consisting of modulatory dopaminergic projections from the substantia nigra pars compacta (SNc) and ventral tegmental area (VTA), as well as, excitatory glutamatergic projections from the frontal cortex to the striatum, where these projections make synapses with excitatory and inhibitory pathways that "relay back" to the frontal cortex (Alexander et al. 1986; DeLong and Wichmann 2017). The circuitry consists of dopaminergic modulatory signals originating in SNc and excitatory cortical inputs into the striatum, where the two pathways originate. One pathway is inhibitory, and is called the indirect pathway; in which it projects into and inhibits the external globus pallidus (GPe), resulting in the disinhibition of the internal globus pallidus (GPi), leading to inhibition of the thalamus. This pathway also, disinhibits the subthalamic nucleus (as a result of inhibiting the GPe), which results in excitation of the GPi, and thus, the inhibition of the thalamus.

The other is the "excitatory pathway", also called the "direct pathway", which inhibits the GPi, resulting in the "disinhibition of the thalamus". The "direct pathway" relies in principal of "monosynaptic connections" driven by dopamine receptor D1, Adenosine A1 receptor, and muscarinic acetyl-choline receptor M4, while the "indirect pathway" consists of connections driven by dopamine receptor D2, adenosine A2A receptor, and muscarinic acetylcholine receptor M1 (Parent and Hazrati 1995).

The two pathways are relevant for switching of cortico-basal ganglia loop functions by the thalamo-striatal system (Kimura et al. 2004). The loops may also be divided into limbic and motor loops, with the motor loops containing indirect and direct pathways, which is interconnected with the limbic loop that projects into the ventral striatum (Accumbens; DeLong and Wichmann 2017).

The cognitive ability of prefrontal cortical mechanism is hypothesized to emerge from the "laminar-columnar" architecture of the prefrontal cortical minicolumns, that are interconnected (Fig. 5.5) with basal ganglia and thalamus in recurrent loops (Bugbee and Goldman-Rakic 1983; Goldman-Rakic 1996; Opris et al. 2011, 2013).

5.3.2 Cortico-Striatal Circuits

Transformation of Spatial Perceptual Signals into Action

During the perception-to-action cycle, our cerebral cortex "mediates the interactions between the environment and the perceptual-executive systems of the brain" (Opris et al. 2013). At the top of the executive hierarchy, prefrontal cortical microcircuits are assumed to "bind" perceptual and executive control information to guide goal-driven behavior. These results show the integration of the prefrontal cortical inter-laminar microcircuits with the striatum (caudate nucleus) to enable the executive control of behavior (Fig. 5.6).

Cell firing (during perception and executive selection phases) (Lebedev and Wise 2002; Quintana and Fuster 1999) in the localized prefrontal layers and caudate-putamen region exhibited a similar "location preference" on spatial-trials, but less on object-trials (Opris et al. 2013). This spatial preference (spatial neural tuning) was augmented when the perceptual microcircuit became "facilitated" by electrical stimulation of prefrontal infra-granular-cell layers with signal patterns recorded from neurons in the supra-granular-layers. This facilitation produced "stimulation-induced" spatial preference in the correct performance mostly during spatial trials. These findings suggested that "inter-laminar" prefrontal microcircuits play "causal roles" to the executive control of movement/behavior during the transformation of spatial perception into action (Opris et al. 2013; Lebedev and Wise 2002; Quintana and Fuster 1999).

5.4 The Brainstem Level: The Mesencephalic Locomotor Region and the Medial Reticular Formation

Several brain areas may elicit locomotion when stimulated and include areas within the diencephalon and mesencephalon (Grillner et al. 1997; Jordan and Sławińska 2014; Kiehn 2016; Takakusaki et al. 2016). The mesencephalic locomotor region

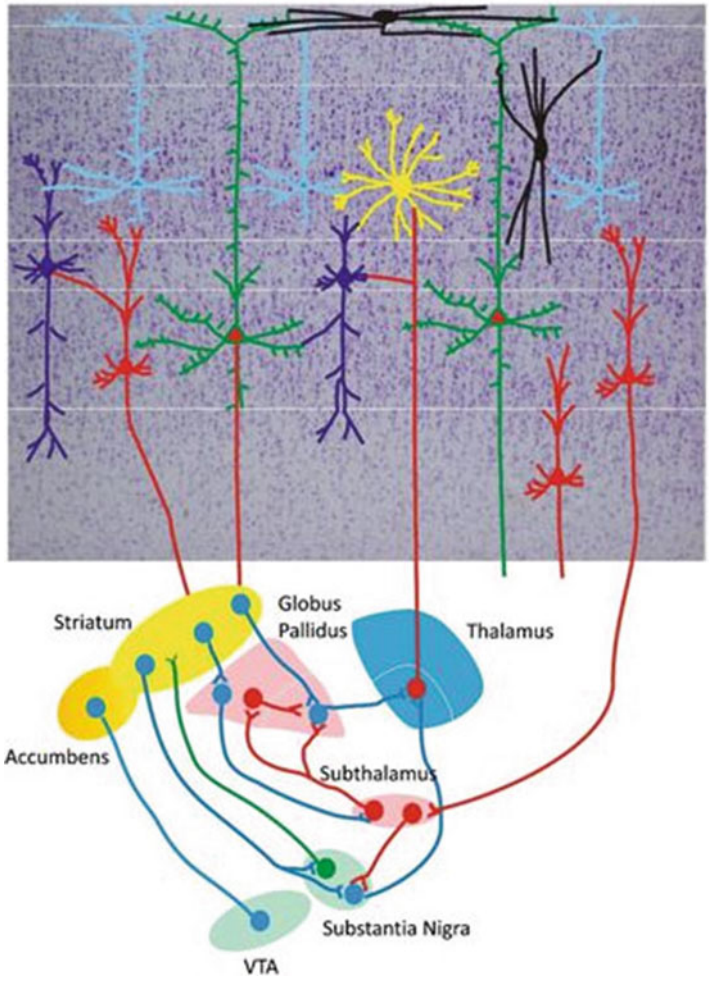

Fig. 5.5 Laminar and columnar display of the major cell types in prefrontal cortex together with its connections to basal ganglia and thalamus. The six-layered cortex is showing on a Nissl background the pyramidal cells and the cortical interneurons. The cells are connected to the thalamus and basal ganglia, as shown on the lower panel. *VTA* ventral tegmental area. Such columnar recurrent 'microcircuit' may be regarded as the 'basic functional unit' of the cognitive function. Its cognitive relevance emerges from the 'computational' ability of the inter-laminar microcircuit to: (**a**) integrate incoming signals of the input layers, (**b**) store information through feedback connections in reverberatory loops, and (**c**) to compare input signals to a threshold criterion, triggering an output response i.e. the ability to make a decision

(MLR) was described for the first time in 1966 by Shik and colleagues, who demonstrated that electrical stimulation of this region induced locomotion in decerebrate (intercollicular transection) cats (Shik et al. 1966). The MLR, highly conserved throughout multiple phylogenetic groups, is thought to be critical to **initiation** of

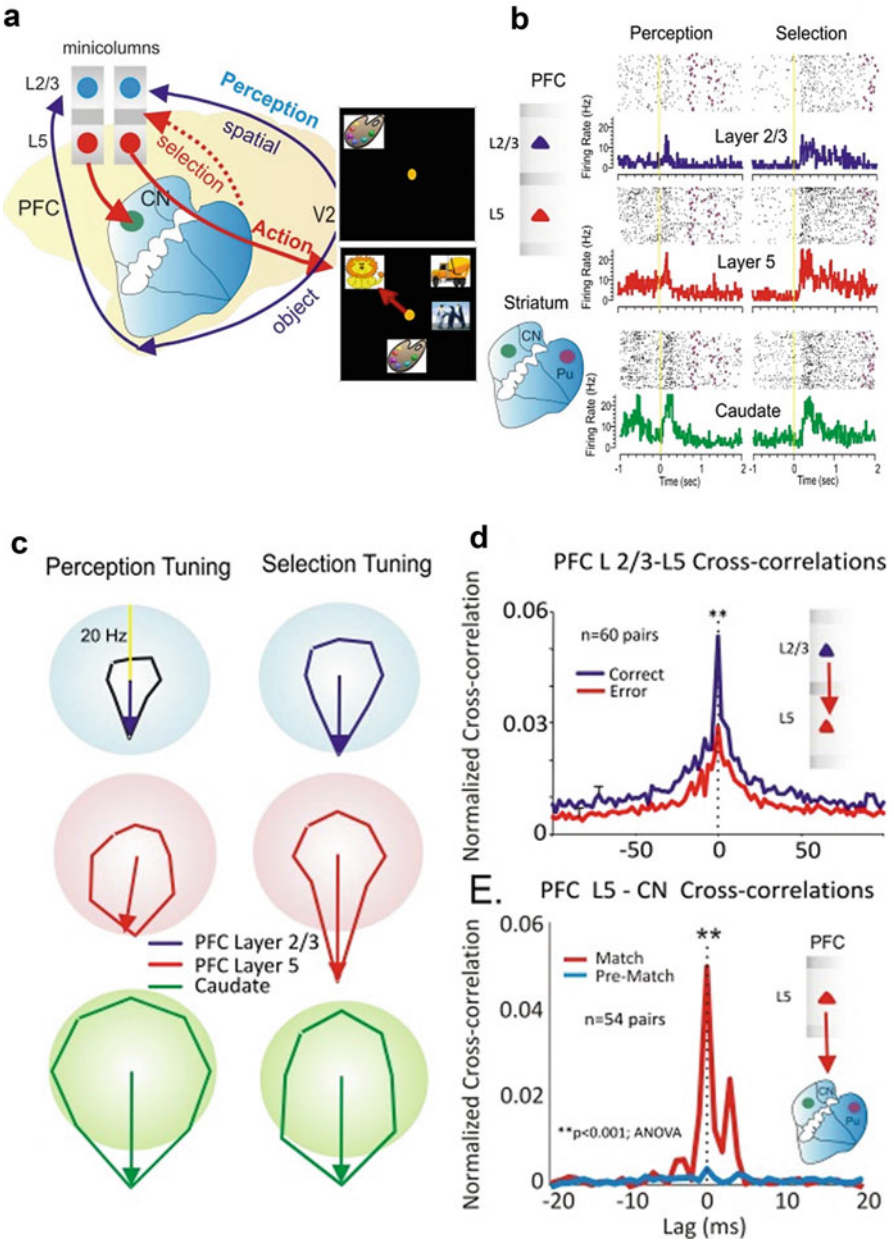

Fig. 5.6 The transformation of spatial information into action in prefrontal cortex. (**a**) Flow of the signals in the brain during the perception to action cycle. (**b**) Simultaneous recording of prefrontal cortical layers 2/3 and 5 and striatum (caudate) during the perception and selection phases of the delay match to sample task. (**c**) Neural tuning during perception and selection phases. (**d**, **e**) Cross correlation demonstrate the transformation of perceptual information in action during a reverberating process

the descending locomotor command (Jordan et al. 2008). It's importance as a major coordinating center is underscored by the observations that: (1) neurons within the MLR are strongly influenced by inputs from motor cortex and basal ganglia (Takakusaki et al. 2003, 2016); (2) there is an MLR in humans (Jahn et al. 2008; Piallat et al. 2009); (3) damage to areas including the MLR in humans results in gait disorders (Masdeu et al. 1994) and, (4) the MLR is a safe and clinically relevant target for improvement of locomotion in persons with Parkinsonism (Mazzone et al. 2005).

5.4.1 What Are the Anatomical Components of the MLR?

The anatomical components of the physiologically-defined MLR are not clearly understood. The original study by Shik and colleagues (1966) demonstrated that stimulation sites were co-extensive with the cuneiform nucleus (CnF) and subsequent studies confirmed these original observations (see: Mori et al. 1989, 1992; Grillner et al. 1997; Jordan 1998; Noga et al. 2003; Takakusaki et al. 2003; Ryczko and Dubuc 2013; Jordan and Sławińska 2014; Noga et al. 2017a). However, locomotor inducing sites within the midbrain have also been report to encompass other areas including the subcuneiform nucleus (subCnF), the lateral pontine tegmentum (LPT) the deep mesencephalic nucleus (DpME) as well as the pedunculopontine nucleus (PPN) (Melnikova 1975; Garcia-Rill et al. 1987; Milner and Mogenson 1988; Coles et al. 1989; Jordan 1998; Milner and Mogenson 1988; Noga et al. 2003; Shik et al. 1967; Steeves and Jordan 1984; Takakusaki et al. 2003; Thankachan et al. 2012; Cabaj et al. 2016; Noga et al. 2017a).

The PPN, a cell cluster consisting of cholinergic, glutamatergic and GABAergic neurons has been implicated in the pathology of gait disorders in Parkinson's disease (Hirsch et al. 1987; Zweig et al. 1989; Rolland et al. 2009; Karachi et al. 2010) and has been targeted clinically using DBS methods to improve locomotion (e.g., Stefani et al. 2007; Ferraye et al. 2010; Hamani et al. 2011). Previous studies with lesions or injections of neuroactive substances into these structures, however, have led to conflicting results (reviewed by Alam et al. 2011; Jordan 1998; Winn 2006; Karachi et al. 2010; Jordan et al. 2014). However, a recent study by Gut and Winn (2015) has shown that complete lesions of the PPN do not abolish locomotor capabilities nor produce gait deficits in the rat. Additionally, intravenous administration of cholinergic antagonists at doses sufficient to block central cholinergic neurotransmission fail to change MLR locomotor (electrical) thresholds, nor do they affect locomotor patterns in any consistent manner (Jordan et al. 2014). Most convincingly, a recent optogenetic study demonstrated that glutamatergic neurons within the MLR encode the locomotor state and speed and are necessary and sufficient for generating locomotion (Roseberry et al. 2016). GABAergic neurons within the MLR reduce or stop locomotion by their actions on the glutamatergic neurons. Although cholinergic neuron stimulation does not initiate locomotion from a standstill, it can modulate ongoing locomotion (Roseberry et al. 2016). Extensive

studies by Takakusaki and co-workers (2003, 2005, 2016; Takakusaki 2008, 2013) have compared the effects of CnF and PPN stimulation in the decerebrate cat. They demonstrated that CnF stimulation elicits locomotion, while PPN stimulation modulates muscle tone (producing atonia) and may actually suppress locomotion via connections with caudally located pontine reticular formation. Interestingly, a recent optogenetic study (Bouvier et al. 2015) has described a glutamatergic RS neuron population in the rostral medulla/caudal pons that halts locomotion when stimulated (the V2a "stop neuron"). These neurons which descend to the spinal cord to activate inhibitory interneurons, are found in the same area (the dorsal tegmental field) previously shown to arrest locomotion and decrease muscle tone due to inhibition of motoneurons (Mori et al. 1978, 1982, 1989, 1992; see review by Takakusaki et al. 2016). Whether these neurons receive excitatory inputs from the PPN remain to be seen.

Effective MLR sites are not co-extensive with cholinergic neurons defining the location of the PPN. However, successful overground locomotion requires the appropriate integration of muscle tone (posture) and locomotor rhythm generation (Takakusaki et al. 2016). In this sense then, cholinergic PPN neurons may be important in both initiation and termination of locomotion via its effects on muscle tone (Takakusaki et al. 2003; see also, Karachi et al. 2010). In support of this conclusion, Garcia-Rill and Skinner (1988) have shown that neurons within the PPN fire tonically with a predilection to fire at the onset and/or termination of locomotor activity, whereas neurons located in more dorsal locations within the CnF fire in a bursting pattern linked to the locomotor cycle. Consistent findings have been reported for the non-human primate and human. Mesencephalic reticular formation neurons, including regions of the CnF, subcuneiform and PPN, are activated during treadmill locomotion, with rhythmically active cells preferentially located in more dorsal locations than tonically activated ones (Goetz et al. 2016). These latter cells are located in a region with higher densities of choline acetyl transferase labelled (cholinergic) neurons. In humans with PD, voluntary mimicked stepping is associated with an increased tonic firing rate in neurons within the subcuneiform nucleus (Piallat et al. 2009) in contrast to those in the PPN (Weinberger et al. 2008). However, such studies are conducted in patients with PD who may have suffered cholinergic neuronal loss within the PPN (Hirsch et al. 1987) that may influence or possibly include locomotor-related neurons. Additionally, such areas may be under the influence of abnormally high (dysfunctional) basal ganglia inhibition in the Parkinsonian state (Takakusaki et al. 2003). In contrast, increased activation of CnF/subCnF/PPN areas has been reported during mental imagery of locomotion in normal persons, possibly related to modulation of locomotion (la Fougére et al. 2010; Jahn et al. 2008; Karachi et al. 2012).

Neurons activated during locomotion (identified using the activity-dependent marker Fos) are found in the CnF and other nearby areas including the DpMe and periaqueductal grey (PAG) (Jordan 1998; Vianna et al. 2003; Heise and Mitrofanis 2006; Noga et al. 2017a; Fig. 5.7), but less so in the PPN. Increased oxygen utilization (detected through the use of 2-deoxyglucose labeling) has also been reported for the CnF, but not PPN, following MLR-evoked locomotion in cats

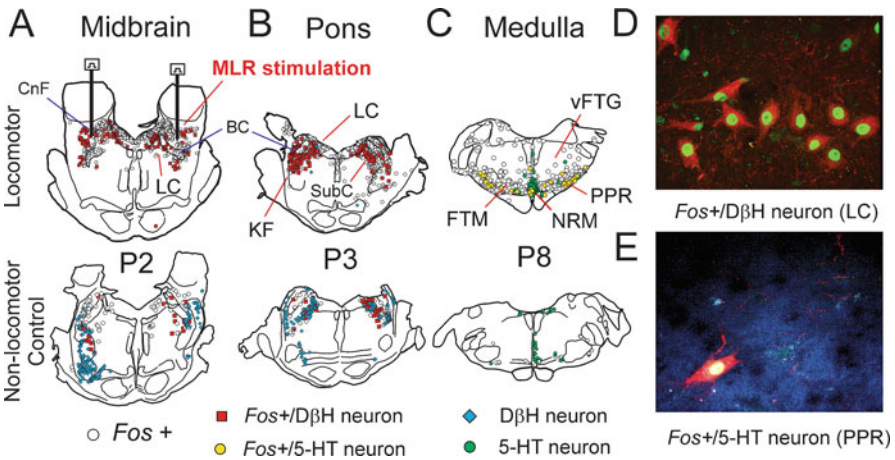

Fig. 5.7 Reticulospinal and monoaminergic cells in midbrain (**a**), pons (**b**) and medulla (**c**) show activity-dependent *Fos* labeling following MLR evoked locomotion in the decerebrate cat. *Fos* labeled noradrenergic neurons within locus ceruleus (LC), subceruleus (SubC) and Kölliker Fuse (KF) were identified using dopamine-β-hydroxylase (DβH) labeling. Serotonin (5-HT) neurons with co-localized *Fos* protein were observed in nucleus raphe magnus (NRM) and parapyramidal region (PPR) of the medulla. Stimulation sites (**a**) corresponding to the mesencephalic locomotor region (MLR). Large numbers of neurons within the cuneiform (CnF), subcuneiform nuclei, magnocellular tegmental field (FTM) and ventral gigantocellular (vFTG) and lateral tegmental fields (LTF) of the medulla also show labelling with *Fos*. Non-locomotor control animals show fewer *Fos*-labeled neurons. (**d**, **e**) Confocal images of *Fos*-immunoreactive noradrenergic and serotonergic cells in the LC/SubC and NRM/PPR, respectively. *BC* brachium conjunctivum

(Shimamura et al. 1987). Furthermore, the large areas that are effective in producing locomotion have led to the suggestion that the MLR may be a distributed system (Sinnamon 1993). In this view, the MLR includes several cell groups involved in producing locomotion in different behavioral contexts so that lesions in one part of the system does not necessarily result in abolition of locomotion unless they are sufficiently large (Masdeu et al. 1994; Demain et al. 2014; see also, Gut and Winn 2015). It has also been suggested that the PPN is important for integration of sensory and motor data that is related to action-outcome association (rather than locomotor induction per se) which is, nevertheless important for locomotor production (Winn 2006; Karachi et al. 2012). In this context Lee et al. (2014) have shown that optogenetic stimulation of the MLR (CnF and PPN) enhances visual cortical responses in parallel with locomotion, indicating that it modulates cortical processing according to behavioral state. It is unclear whether other like influences on extrastriate visual cortex, auditory cortex and hippocampus during locomotion (Andermann et al. 2011; Kemere et al. 2013; Zhou et al. 2014) are mediated by the same circuit.

5.4.2 How Does the Brainstem Enable Locomotor Movements?

To generate locomotion, a complex integrative neuromodulation process within the brainstem microcircuits must occur.

Activation of Reticulospinal (RS) Neurons

The MLR does not directly project to the spinal cord but rather activates spinal neurons controlling locomotion (Shefchyk and Jordan 1985; Noga et al. 1995, 2003; Dai et al. 2005) via a pathway originating in the medullary medial reticular formation (Orlovsky 1969a, 1970a, b; Garcia-Rill et al. 1983a; Garcia-Rill and Skinner 1987a, b; Noga et al. 1988, 1991, 2003; Steeves and Jordan 1984) and descending bilaterally through the ventral funiculus (Steeves and Jordan 1980; Noga et al. 1991, 2003). MLR projections to these RS neurons are glutamatergic rather than cholinergic (Roseberry et al. 2016). This conclusion is supported by the report that PPN neurons do not strongly project to the medulla (Sherman et al. 2015). The RS pathway, considered to be the 'command pathway' for initiation of locomotion (Jordan 1991; Orlovsky 1970a, b; Shik et al. 1967), activates spinal locomotor neurons by the release of glutamate (Douglas et al. 1993; Hägglund et al. 2010). In the cat, these RS neurons originate primarily within the nucleus reticularis magnocellularis and ventral nucleus reticularis gigantocellularis (Iwakiri et al. 1995) (Fig. 5.7) in areas known to induce muscle (extensor) tone augmentation and consequent postural changes, facilitation of MLR evoked locomotion, or locomotion per se, when electrically or chemically stimulated (Mori et al. 1978, 1982, 1989; Noga et al. 1988; Takakusaki et al. 2016).

The majority of MLR fibers terminate ipsilaterally within the medial reticular formation (Garcia-Rill et al. 1983b; Steeves and Jordan 1984). The RS pathway, in turn, descends ipsilaterally and/or contralaterally in the ventral funiculus (Garcia-Rill and Skinner 1987a, b; Orlovsky 1969a, 1970a, b; Perreault et al. 1993) with a preponderance to projections on the same side (Kuypers and Maisky 1977; Tohyama et al. 1979). Nevertheless, locomotion evoked by stimulation of the MLR on one side produces bilateral locomotion, likely due to crossed spinal or segmental pathways (Noga et al. 2003). In spontaneous or voluntary locomotion, it is likely that MLR activity is bilateral and a balanced descending RS input to the spinal locomotor neurons is present (see discussion in Noga and Opris 2017).

Reticulospinal neurons are rhythmically active during treadmill and fictive locomotion (Drew et al. 1986; Iwakiri et al. 1995; Perreault et al. 1993). Detailed analysis of this activity has revealed that the firing patterns of individual RS neurons are linked to the activity of specific muscles during locomotion (Drew and Rossignol 1984). Furthermore, site specific effects are observed with electrical (Ross and Sinnamon 1984; Garcia-Rill and Skinner 1987a) or chemical stimulation (Noga et al. 1988) of the medial reticular formation indicating that there may be a somatotopic organization for locomotor pattern and a differential control of trunk

and hindlimb muscles for postural and non-postural motor control (Szokol et al. 2008) within the reticular formation. Candidate RS neurons for mediating the effects of MLR stimulation in the mouse have been described (Bretzner and Brownstone 2013). These neurons express the transcription factors Lhx3 and Chx10, defining a glutamatergic phenotype and are activated during MLR evoked locomotion, as indicated by their expression of the activity dependent label, Fos. Furthermore, they are innervated by fibers projecting from the MLR (primarily CnF) and they project to the spinal cord. Lastly, their location coincides with the motor related areas of the medial and ventral reticular formation described for the cat (Iwakiri et al. 1995; Noga et al. 1988, 1995; Takakusaki et al. 2016; Fig. 5.7). Whether they are necessary and sufficient for locomotion remains to be demonstrated.

Activation of Monoaminergic Neurons

Monoamines play a key role in the activation of spinal locomotor networks. Intravenous administration of NE and 5-HT precursors, produces reflex discharges that resemble locomotion (Jankowska et al. 1967; Miller et al. 1975; Viala and Buser 1969) and it has been suggested that MLR activates a noradrenergic descending system which controls the spinal locomotor generating network (Grillner and Shik 1973). In addition to cerulear neurons (Rasmussen et al. 1986), serotonergic neurons are also rhythmically active during locomotion (Jacobs and Fornal 1995; Veasey et al. 1995) and can be included in this hypothesis. Direct pathways from the MLR to monoaminergic brainstem nuclei are known (Behbehani and Zemlan 1986; Edwards 1975; Steeves and Jordan 1984). Our recent anatomical studies demonstrate that monoaminergic neurons located in the nuclei of origin of descending monoaminergic pathways innervating the spinal cord (Clark and Proudfit 1991; Kwiat and Basbaum 1992) are activated during MLR-evoked locomotion (Fig. 5.7). Thus, in addition to reticulospinal command neurons (Noga et al. 1988, 1991, 2003), descending modulatory monoaminergic neurons comprise a major component of the central descending pathways controlling locomotion activated by the MLR. Altogether, the stimulation results show the emerging of a complex pattern of integrative innervation of brainstem neurons by the mesencephalic locomotor region.

Monoaminergic Pathways Innervate Spinal Locomotor Activated Neurons

Spinal locomotor-activated neurons are innervated by descending monoaminergic fibers (Fig. 5.8) and possess key serotonergic (5-HT) and noradrenergic (NE) receptors (Noga et al. 2009, 2011) implicated in the control of locomotion (Delivet-Mongrain et al. 2008; Liu and Jordan 2005; Majczynski et al. 2006; Marcoux and Rossignol 2000). In the rat, pharmacological and lesion studies have shown a rostral-to-caudal gradient of rhythmogenic potential extending from low thoracic to lumbar cord, acting on the locomotor network within the intermediate zone (Cazalets et al.

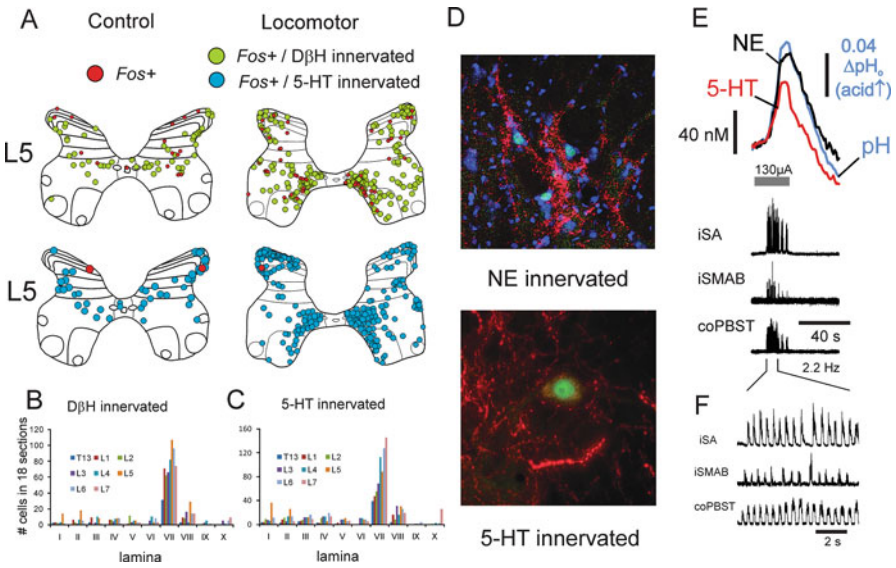

Fig. 5.8 Monoaminergic innervation of spinal locomotor activated neurons and spinal release of monoamines during fictive locomotion in the decerebrate cat. (**a**) Distribution of activity dependent labeled Fos immunoreactive neurons with or without DβH or 5-HT contacts in the L5 lumbar segment of Control and Locomotor cats. Each diagram includes all labeled cells from 18 (DβH) or 19 (5-HT) sections of that segment. Significantly more cells were seen in animals undergoing fictive locomotion than in the control. (**b**, **c**) Laminar distributions of innervated, locomotor-activated neurons in the lumbar segments of the locomotor animal. (**d**) Locomotor-activated neurons with Fos+ labelled nuclei (*green*), juxtaposed to fibers and varicosities (*red*) stained positive for DβH and 5-HT (After Noga et al. 2009, 2011). (**e**) Changes in monoamine and pH levels in medial lamina VI of the L6 lumbar segment during MLR-evoked fictive locomotion (130 μA, 20 Hz, 1 ms duration pulses) as detected using fast cyclic voltammetry (After Noga et al. 2017b). Electroneurogram activity from hindlimb peripheral nerves is indicated in bottom panel of E and in F (expanded). *SA* Sartorius, *SMAB* semimembranosus anterior biceps, *PBST* posterior biceps-semitendinosus, *i* ipsilateral, *co* contralateral (to recording)

1995; Cowley and Schmidt 1997; Kjaerulff and Kiehn 1996; Kremer and Lev-Tov 1997). Neurons in the rostral segments are particularly sensitive to 5-HT (Cowley and Schmidt 1997). Furthermore, intraspinal transplantation of monoaminergic neurons into the lower thoracic segments of chronic spinal rats (Gimenez y Ribotta et al. 2000; Yakovleff et al. 1989, 1995) improves locomotion.

Activation of Descending Monoaminergic Neurons by Stimulation of the MLR Results in the Spinal Release of Monoamines During Locomotion

Pharmacological approaches in intact or decerebrate animals have shown that lumbar microinjection or intrathecal application of monoaminergic antagonists blocks

spontaneous (Delivet-Mongrain et al. 2008; Giroux et al. 2001; Majczynski et al. 2006) or MLR evoked locomotion (Schmidt and Jordan 2000). Direct measurement of monoamine release in the spinal cord using microdialysis has revealed a complex pattern of release in the adult rat's lumbar spinal cord during treadmill locomotion (Gerin et al. 1994, 1995, 2008; Gerin and Privat 1998). To improve temporal/spatial resolution, we utilized in vivo voltametric methods (Brumley et al. 2007; Hentall et al. 2003, 2006; Noga et al. 2004) to study spinal monoamine release during MLR evoked fictive locomotion (Noga et al. 2017b). Our measurements reveal widespread monoamine release during MLR-evoked locomotion (Fig. 5.8): in the intermediate zone/ventral horn, in areas with centrally-activated locomotor neurons (Dai et al. 2005; Noga et al. 2009, 2011); and in the dorsal horn, where additional neurons are activated by sensory feedback during overground locomotion (Dai et al. 2005). Transmitter levels are sufficient to activate monoaminergic receptors on spinal locomotor-activated neurons (Noga et al. 2009, 2011). That the extracellular levels of monoamines are dynamically regulated in widespread regions of the spinal cord at concentrations that are pharmacologically relevant indicate that extrasynaptic neurotransmission (Ridet et al. 1993) is a significant mechanism for the control of motor function. Alterations in the level of activity in descending monoaminergic pathways and ultimately the extracellular levels of monoamines may thus be one of the principal mechanisms mediating physiological "state changes", so that neural excitability within the spinal cord is fine tuned (Noga et al. 2017b).

5.4.3 How Do Higher Brain Centers Activate the MLR/RS Pathway to Produce Goal Directed Locomotion?

Basal Ganglia (Dorsal Pathway) Inputs for Cognitive Control

The MLR receives input from a variety of structures. Probably, its primary direct input for controlling goal directed behavior is mediated by the basal ganglia, through a process of disinhibition. The major inhibitory GABAergic input arises from the substantia nigra zona reticulate (SNr) of the globus pallidus, targeting MLR glutamatergic neurons (Roseberry et al. 2016). It provides a strong tonic inhibition of the MLR affecting both postural muscle tone and locomotion (Takakusaki et al. 2003, 2011) which needs to be removed in order for the MLR to be activated (Garcia-Rill et al. 1985, 1990). In Parkinson's disease, these GABAergic outputs are enhanced (DeLong and Wichmann 2007) resulting in both rigidity and freezing of gait (Takakusaki et al. 2003; Sherman et al. 2015). This tonic inhibition may be removed by activation of inhibitory GABAergic projections from medium spiny projection neurons of the striatum to the SNr (Hikosaka et al. 2000). Removal of this inhibition increases locomotion (Kravitz et al. 2010). The striatal neurons are controlled by inputs from the visual, parietal and motor cortex and the thalamus (reviewed by Grillner et al. 2008). Central to this control is dopamine and without this innervation of the striatal neurons, a Parkinson-like condition will develop.

Limbic System/Diencephalic Inputs (the Ventral Pathway) for Emotional Control

The limbic system supports a variety of functions which include motivation, emotion and behavior. Limbic structures important in the context of motor control include the nucleus accumbens, amygdala, hippocampus, and hypothalamus. Direct inhibition of the inhibitory output neurons of the ventral pallidum (VP) and the SNr by GABAergic projections from the nucleus accumbens releases locomotor activity by disinhibition of the MLR (Swanson and Mogenson 1981; Lynd-Balta and Haber 1994). The nucleus accumbens also receives inputs from the ventral tegmental area (VTA), hippocampus and amygdala and may be involved in reward-oriented behavior (Takakusaki 2017). Chemical activation of the central nucleus of the amygdala elicits locomotion (Brandão et al. 1999) possibly by its projection to the subthalamic (lateral hypothalamus) locomotor region (SLR). Interestingly, the amygdala is also involved in freezing behavior through its projection to the PAG (discussed below). The hippocampus is well known its spatial coding of navigational information (e.g., "place cells") (O'Keefe and Dostrovsky 1971; Moser et al. 2008). Its role in navigation is thought to be related to its function in memory organization (mapping) into cognitive space of the navigational task (Eichenbaum 2017). The hippocampus may participate in the control of locomotor speed (Bland and Oddie 2001; López Ruiz et al. 2015). It connects to the nucleus accumbens and the SLR (Takakusaki 2017). The subthalamic locomotor region (SLR), a region in the lateral hypothalamus (Orlovsky 1969b) also elicits locomotor activity when stimulated. The SLR extends caudally in two strips (Parker and Sinnamon 1983; Sinnamon 1984; Kasicki et al. 1991) and projects either to the MLR (Garcia-Rill et al. 1981, 1983a, b) or to the pontomedullary reticular formation (Takakusaki 2017). Its actions do not require the MLR (Shik et al. 1966). Interestingly, the onset of locomotion is characterized by theta frequency oscillations of local field potentials in the hippocampus, subthalamic locomotor region/posterior hypothalamus (Sławińska and Kasicki 1995, 1998; Bender et al. 2015) and MLR (Noga et al. 2017a). It has been suggested that "the theta oscillatory filed potentials may thus coherently bind cooperating neuronal ensembles during locomotor activity in order to encode the animal's position during spatial navigation" (Noga et al. 2017a).

Dopamine Inputs

A projection from the substantia nigra to the MLR in the cat has been described which, when activated, produces spastic locomotion (Garcia-Rill et al. 1983b). Dopaminergic projections to both the CnF and the PPN (Rolland et al. 2009) originate in the SNc (Ryczko et al. 2016). It has been suggested that dopamine may potentiate the actions of MLR neurons and that the loss of dopaminergic neurons in Parkinson's disease may also diminish the MLR output and contribute to freezing of gait (Ryczko and Dubuc 2017). The SLR also encompasses the A11 and A13 dopaminergic nuclei, of which the A11 projects to the spinal cord (Skagerberg

and Lindvall 1985). Dopamine is well known to have modulatory properties on spinal locomotor networks (Humphreys and Whelan 2012), but it is unclear to what degree these pathways contribute to the generation of locomotion in normal or neuropathological states.

Tectal and Periaqueductal Grey (PAG) Inputs (Aversive/Defensive)

The optic tectum (superior colliculus or SC) is an important structure for controlling eye and spatial orientation movements and may be involved in pursuit or escape behavior (Furigo et al. 2010). It receives visual input from the retina and the extrastriate cortex and integrates a myriad of other sensory data which guides the orienting decisions. It projects to a number of structures including the MLR, the pontomedullary reticular formation, the thalamus, SNc and the PAG (Furigo et al. 2010). Direct stimulation of the SC may activate the MLR to induce contralaterally directed locomotion (Dean et al. 1986). Through its (reciprocal) connections to the SNr, the SC promotes motor learning for future appetitive responses (Redgrave and Gurney 2006). Through its connections to the thalamus, the SC influences the ventrolateral striatum, prefrontal, motor and somatosensory cortex, modulates stereotypic hunting motor patterns (dos Santos et al. 2007) and affects motor planning and arousal (Herkenham 1979; Carello and Krauzilis 2004). The SC forms part of a subcortical loop involving the ventrolateral striatum, SNr and parafascicular nucleus important for prioritizing simultaneous, potentially incompatible inputs (Groenewegen et al. 1993; McHaffie et al. 2005). Lastly, through its connections with the PAG, the tectum is involved in motor circuits involved in decision making in switching adaptive behavioral responses (Sukikara et al. 2006). Stimulation of the medial SC also produces defense-like responses, freezing and/or flight and associated effects on blood pressure and heart rate (Sahibzada et al. 1986; Dean et al. 1989), mediated by projections to the PAG, CnF and pontine reticular nuclei (Mitchell et al. 1988).

Defensive behavior including freezing or flight in response to threat is controlled by circuits within the PAG Watson et al. (2016). As described by Tovote et al. (2016), glutamatergic neurons of the ventrolateral PAG (vlPAG) induce freezing responses to learned and innate threats via projections to the pontomedullary (magnocellularis) reticular formation. These neurons are normally inhibited by local GABAergic circuits but are disinhibited by the central nucleus of the amygdala, resulting in freezing behavior (Koutsikou et al. 2015). In contrast, stimulation of dorsolateral (dlPAG) or lateral (lPAG) glutamatergic neurons results in marked flight responses, often interrupted with short periods of freezing (Tovote et al. 2016; Deng et al. 2016), suggesting that circuits within these areas of the PAG are involved in the integration of complex motor behaviors. A pathway from periaqueductal gray (PAG) activating reticulospinal cells either directly or indirectly through the MLR has been proposed (Grillner et al. 1997). Interestingly, the glutamatergic dl/lPAG neurons inhibit vlPAG glutamatergic neurons via the excitation of GABAergic neurons of the vlPAG thus inhibiting the freezing response. The PAG also receives inputs from

the prefrontal cortex (Halladay and Blair 2015), hippocampus, and hypothalamus (Wang et al. 2015) which promote a range of defensive behaviors.

Cortical Inputs

While direct stimulation of the motor cortex fails to elicit locomotion, the motor cortex is essential for the control of visually guided locomotion (Drew et al. 2008). Lesions of the motor cortex, pyramidal tract or corticospinal pathway result in deficits in locomotor capability and the inability to adapt locomotion to difficult terrain (Drew et al. 2002). Cortical pyramidal cells are rhythmically active during locomotion and modulate their discharge rates during voluntary gait during avoidance of obstacles (Drew 1993; Kably and Drew 1998). Cortical areas that are important for planning and execution of goal directed locomotion are many (Fukuyama et al. 1997). In the frontal lobe, the prefrontal and premotor cortices are important for adapting to locomotor speed and in the control of running (Suzuki et al. 2004; Wise et al. 1996). The posterior parietal cortex contributes to the planning of visually guided locomotion by its action in assessing the position of an animal relative to objects in its path (Andujar et al. 2010). The motor cortex in contrast, is important in gait modifications for specifying limb trajectory and limb placement by modulating the activity of different (synergistic) muscles at differing times during the gait cycle (Drew et al. 2008) and is less involved in moment-to-moment control of stereotypic locomotion (Serradj et al. 2014). How the motor cortex accomplishes its task is unclear. As discussed previously, corticostriatal inputs are important for controlling the level of striatal inhibition of the SNr and ultimately of the MLR through disinhibition. Long-latency, multisynaptic responses of MLR neurons to stimulation of the precruciate motor cortex in the cat have also been described (Garcia-Rill 1983), but the location and nature of the intercalated neurons in this pathway have not been established. Interestingly, cortical pathways arising from the premotor (area 6) and primary motor (area 4) cortex (Brodal 1981) may bypass the MLR altogether. Instead, they may descend through the internal capsule and cerebral peduncle to terminate onto pontomedullary RF neurons as a separate path or innervate RS neurons via the collaterals of corticospinal fibers (Kuypers 1981; Keizer and Kuypers 1984), thus forming the corticoreticular pathway. Corticoreticular input is mostly excitatory and direct (Peterson et al. 1974; He and Wu 1985; Matsuyama and Drew 1997; Matsuyama et al. 2004). The action of the corticoreticular pathway on RS neurons is also likely primarily one of facilitation. Only when the pyramids are transected, thereby interrupting the direct effects on spinal interneurons and motoneurons which may interfere with the smooth execution of stepping, does stimulation of the pyramids evoke locomotion (Shik et al. 1968).

5.5 Summary

The development of neuro-technological approaches allowed an unprecedented insight into the understanding of the human mind and its hierarchical mechanism for the executive control of movement. This executive mechanism spans hierarchically over frontal/parietal/temporal cortices, subcortical structures in basal ganglia and thalamus, brainstem and spinal cord. At the core of this mechanism are its frontal and parietal cortical microcircuits interconnected in thalamo-cortical loops via cortico-striatal projections. A high level locomotor command is further processed in the mesencephalic locomotor region and in the spinal cord. Spinal locomotor circuits are enabled from descending reticulospinal and monoaminergic pathways. Recently developed deep brain stimulation approaches will be employed in therapy delivery according to the patient's level of disease impairment.

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Chapter 6
Symmetry and Noether Theorem for Brain Microcircuits

Liviu Bilteanu, Manuel F. Casanova, and Ioan Opris

Abstract Symmetry as a feature of beauty and harmony is a concept that emerged in ancient times during the Greek and Roman antiquity. In contrast, the modern concept of symmetry refers to the properties of a geometrical object or a physical system that preserves the same form features when subjected to a specific group of transformations defined by mathematical operations, e.g., reflection, rotation, translation. While the applications of symmetry range from physics to computational neuroscience, this chapter will deal with how brain function in the normal and pathological state can be understood as a result of symmetry breaking (SB).

Keywords Noether theorem • Symmetry • Laws of conservation • Minicolumn • Brain • Symmetry breaking

6.1 Introduction

6.1.1 Brief History of Symmetry Concept

Symmetry as a feature of beauty and harmony is a concept that emerged in ancient times, during the Greek and Roman antiquity. Symmetry refers to the property of a

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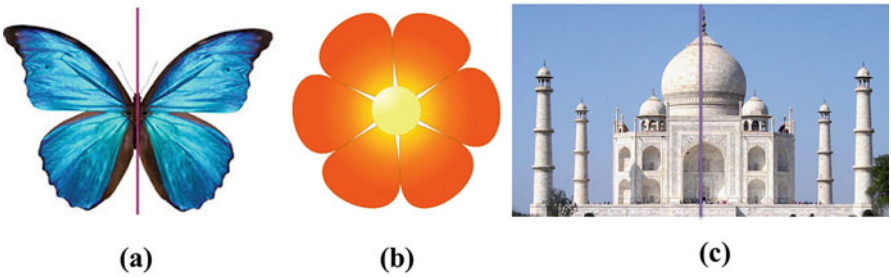

Fig. 6.1 Examples of "shallow" symmetries in nature (**a**, **b**). The butterfly in (**a**) exhibits bilateral symmetry which is also a feature of ancient architecture (**c**). The flower (**b**) exhibits hexagonal symmetry

geometrical object or of a physical system that allows it to preserves its form when reflected in a mirror, as well as when rotated or displaced.

Nature is very rich in examples of symmetrical entities, e.g., human body exhibits bilateral symmetry; some flowers exhibit pentagonal symmetry; honeycombs exhibit hexagonal symmetry. The vast number of fields exhibiting symmetry led the philosophers to formulate symmetry as a transcendent principle. The observable symmetries (such as radial or bilateral symmetries or relatively more complicated symmetries specific to crystalline or molecular structures) are sometimes called "shallow" symmetries (Fig. 6.1). They bear almost no analogy to the deep symmetries "hidden" by the physical world and are not yet well defined for biological systems (Amundson 1994). Deeper symmetries although not directly observable, become more informative after being broken (Collier 1996).

6.1.2 Symmetry as a General Concept of Physical Universe

The epitome of symmetry properties is encompassed by the crystalline solids where the symmetry principles are used to describe the structure and properties of solids. These systems have been described in a quasi-analogical way that has been the object of classical Physics. The same principles have been applied to complex material systems with symmetry features having mechanical, electric or magnetic properties (Striedter 2007). The collective oscillation modes are assimilated to quasi-particles such as phonons (oscillatory modes of spring linked material particles), polarons (oscillatory modes of the electric momenta) or magnetons (oscillatory modes of the magnetic momenta).

The development of symmetry principles have been further developed by "group theory" constructs that allow the transfer of symmetry concepts to complex systems or to abstract objects such as mathematical equations expressing the laws of Physics (Feynman et al. 1963). When applied to these latter objects, the symmetry principles

become invariant properties as first identified in Newtonian mechanics and then transferred to other branches of modern Physics. Recently, a further step has been taken by transferring concepts from the physical laws to complex biological systems (Davies 1982; Brooks and Wiley 1988; Antonovics and Van Tienderen 1991; Kauffman 1993; Carroll 2001; Koslow and Subramaniam 2005). In this chapter, we focus on describing neural systems by using Lagrangian mechanics and exploring the possibilities opened by such an approach.

Symmetry principles (SPs) have multiple roles in the sciences: classification, normation, unification, and explanation or prediction (Brading and Castellani 2003). The typical examples of the classification role are the crystalline *structures* as well as the more modern classification of *elementary particles* (Feynman and Weinberg 1987) which is the foundation of the so-called "structuralist" approach of modern Physics. From this perspective, symmetry is viewed as the result of redundancy in world models constructed from a rather limited number of elementary building blocks (Fig. 6.2).

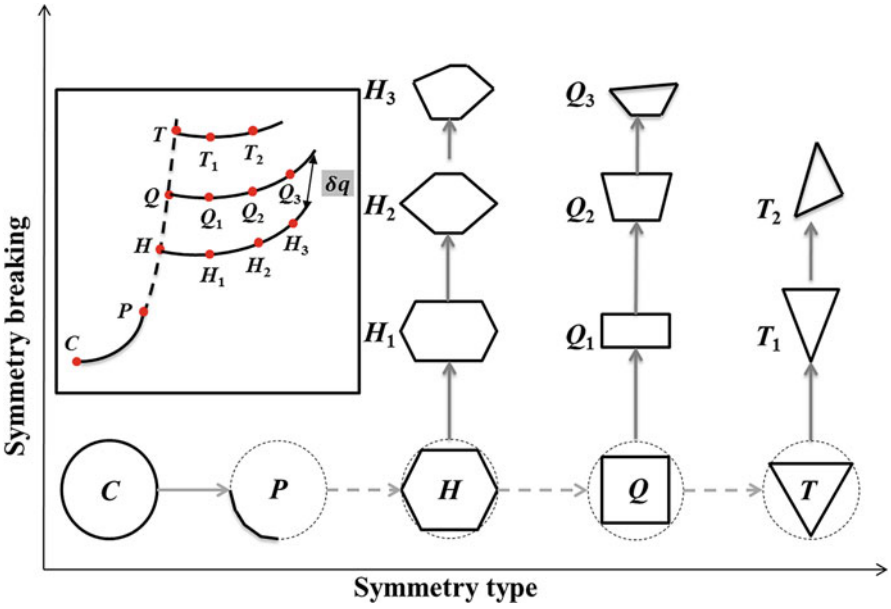

Fig. 6.2 Symmetry breaking illustration. On the horizontal direction the perfect symmetry circular (C) shape is transformed into a polygons with a finite number of equal length edges (P) through a set of quasi-continuous set of symmetry transformations (*continuous arrow*). Further through discrete symmetry transformations (*dotted arrows*) H, Q and T are obtained. Branching phenomena through symmetry breaking is illustrated by reducing symmetry elements of H, Q and T, respectively through continuous symmetry transformations (*continuous arrows*) on the vertical. In the inset are represented the SB trajectories in a phase space obtained by solving the Euler-Lagrange equations while the transition from one branch trajectory to another is made through an infinitesimal variation, δq

6.1.3 Symmetry Breaking

Finally, the focus of our chapter is illustrated by the first Noether theorem which connects conservation laws with symmetries (Finkelstein and Misner 1959), as a way of mathematically explaining the sub-sequent occurrence or non-occurrence of physical phenomena via spontaneous or non-spontaneous SB.

SB is a highly encompassing concept which takes various forms in the living world and is a useful instrument in explaining various phenomena at different levels of the organization. It can explain phylogenetic branching featured by evolutionary novelties such as directional asymmetry (e.g. heart orientation, Garfinkel et al. 1997) arising "from non-heritable origins almost as often as from mutation". Since ontogenesis is considered sometimes a mere small scale recapitulation of some episodes of the evolutionary process i.e. phylogenesis (Margulis 1970; Maturana and Varela 1973; Hofman 2001; Willmer 2003; Striedter 2007) one may feel entitled to apply SB to explain form and more importantly, function emergence during the development of biological systems (Gowers 1902; Antonovics and Van Tienderen 1991; Gressens and Evrard 1993; Kauffman 1993; Carroll 2001; Palmer 2004; Kirschner and Gerhart 2005). Evolution in the sense of physical systems motion of a trajectory in phase space is achieved by SB (Fig. 6.2, **inset**). Biophysical systems make no exception in this sense. The attempt to describe such systems by analogy with simpler ones via fundamental physical theories is then fully justified.

Neurons are submitted to the rules of symmetry the simplest observation in favor of this is their development pattern. In the initial phases, the cell body exhibits several outward immature processes called neurites while in few days one of this neurites develops into a longer branch with several ramifications. This phenomenon can be easily classified into "shallow" or "superficial" asymmetry specific to this type of cells and less observable to cells in other tissues. The behavior of neurons is highly homogenous: independently on the neurites count, neurons exhibit SB at the same rate (Howell and Shen 2011; Wissner-Gross 2012; Wissner-Gross et al. 2013) under the action of two proteins HRas and shootin1, in disagreement with theoretical models predicting faster SB for neurons with fewer neurites.

Beyond the spectacular aspect of neuron development, aberrant SB has been correlated to development of neuropsychiatric diseases such as schizophrenia (Bellon 2007) and autism (Casanova 2008; Bauman and Kemper 1985, 1994; Raymond et al. 1995; McClelland 2000; Casanova et al. 2002, 2003; Baron-Cohen 2004; Geschwind and Levitt 2007; Markram et al. 2007; van Kooten et al. 2008; Rinaldi et al. 2008; Sudhof 2008; Wegiel et al. 2010). The coordinated SB leads to synchronized polarization of neurons in developing organisms (Lohmann and Köppen 1995; Arimura and Kaibuchi 2007; Barnes and Polleux 2009; Tahirovic and Bradke 2009; Yu et al. 2009; Inagaki et al. 2011). These examples show that: (1) asymmetry emerges from symmetry, i.e. neurons exhibiting non-differentiated neurites mature into polar neurons exhibiting an axon; (2) this process develops under the mediation of two proteins which leads us to consider asymmetry in a

broader multiscale sense, and (3) in this context, the pathology may be defined as absent, insufficient or aberrant asymmetry, in contrast with the static view of symmetry as an expression of normal or healthy context.

6.2 Symmetry in Brain Structures and Functions

The physical (macroscopic) universe, thanks to its geometric nature, exhibits some intrinsic, directly observable general symmetry (Finkelstein and Misner 1959; Feynman et al. 1963) such as the isotropy of physical space or the uniformity of time. In classical Physics these principles are often viewed as interdependent, being thus called *global space-time invariance principles*. These invariance principles apply to "suitable spatio-temporal regions where there is a sufficient stability and regularity for the events and for the laws of Nature to be discovered" (Brading and Castellani 2003) and to the vast majority of material systems, including the biological systems such as the brain (Peters et al. 1991; Arbib and Érdi 2000; Ballesteros Yáñez et al. 2005). Beyond the global space-time invariance, both brain's gross anatomy and histology (Herculano-Houzel et al. 2006, 2007) exhibit bilateral symmetry, while the functional areas distribution (Ramachandran 2011) does not follow exactly such pattern since it's brain origin is at the microscopic level (Peinado et al. 1993; Humboldt 1999; Hugdahl 2005; Molnár et al. 2006; Weyhenmeyer and Gallman 2006; Miyazaki et al. 2016).

At the microscopic level, there are specific symmetry properties called "dynamical symmetries" (Wigner 1939) or *local symmetries,* which are not subjected to direct observation. The first nonspatio-temporal symmetry was the permutation symmetry. This was introduced by Heisenberg when stating the indistinguishability of the identical quantum particles (Berestetskiĭ 1965; Froggatt and Nielsen 1991). In the quantum context, the symmetry principles are most effective in describing complex biological systems, composed of a large number of entities. The axiomatic permutation symmetry seems applicable to neurons of the cerebral cortex (and neural systems, in general) since it is hardly difficult to distinguish between neurons when doing measurements with "non-single neuron" instruments (Koslow and Subramaniam 2005). However, the indistinguishable features of these entities are of different origins: the quantum particles are by definition indistinguishable, while the neurons are indistinguishable due to technological limitation, hence such a principle would be applicable in a *bottom-up* study (see below). The effectiveness of SPs applied to quantum particles is due to the "linear nature of the state space of a quantum physical system" which allows the construction of a global system state by superimposing individual quantum states. Moreover, these states evolve from one another by applying symmetry operations, a property that has to be obeyed by neural states.

When describing the neural systems (such as various areas of the cortex) in terms of symmetry, a first conceptual difficulty arises: the organization of neuron systems do not obey the invariance to an extended group of transformations like

the crystalline systems do (Barreiro et al. 2016; Esposito et al. 2014; Gerard and Slotine 2006). However, neuronal systems exhibit preeminent functional symmetry sharing, like: energy minimization paths or collective oscillation modes summing up to give specific EEG patterns (Ingber 2009).

In the context of SPs, the physiological phenomena emerge due to spontaneous SB, while the pathological phenomena occur due to non-spontaneous SB. After SB occurs, some neuron system still exhibits some structural symmetries denoted as "persistent". These are features of the neuron system stability, while reversely, the spontaneous SB are features of systems instability.

6.3 Lagrange Formalism of Neuronal Networks

Another example of SB is perception. This is an information producing process (Laughlin 2004) by the sensory system (peripheral and central) which is initially statistically symmetrical and reacts under outside stimuli which yields a perturbing force. It has been argued for decades that cognition is the product of SB as well, a fact that has been proven right as it will be discussed later in this chapter (Mountcastle 1978; Skarda and Freeman 1987; Studdert-Kennedy and Goldstein 2003; Linden 2007; Marcus 2008; Opris 2013; Opris et al. 2013). Our Lagrangian approach is then motivated by two assumptions: (1) biological systems are initially statistically symmetric and (2) their responses are initiated by non-equilibrium internal or external forces (see the formalism below). The initial statistically symmetric state is an idealization which is excluded by internal fluctuations. Internal or external forces are to be defined with respect to the system borders. For example, when analyzing homeostatic processes external forces are related to "inputs coming outside the body". However when analyzing perception a phenomenon resulting from multiple subsystems interactions, then "external" is a less specific label.

Modelling biological systems and neuron systems, in particular, by making the assumption of an initial equilibrium state (global or at least local) is an idea that comes from Physics and applied successfully in cosmology or in sub-atomic physics. Such systems are a governed by SB-based dynamics driven by external and internal forces which make the system seek a new equilibrium state characterized of course by other symmetry features (Layzer 1991).

6.3.1 Lagrange Equations of Discrete Systems

Before formulating the Noether theorem in order to derive SB rules in brain activity, let us remind the reader of the Lagrange equations for both discrete and continuous systems. Lagrange equations are derived from *D'Alembert* and Hamilton principles. D'Alembert principle refers to the minimization of force action during

the evolution of physical systems, while the Hamilton principle is a variational method providing the minimal energy path in the state's space. Both of them lead to the Lagrange equations albeit in different ways. The Lagrangian function expression emerges by rewriting the virtual work principle in the coordinate transformation introducing the generalized coordinates, while the Hamilton principle assumes the existence of Lagrangian functions to which the variational principle is applied. This generalization of mechanics can be performed based on the fact that the Lagrange and Hamilton's principle are providing a recipe for getting the mechanical equations of motion. This possibility extends to all the cases where variational principles are applicable to find "motion-like" evolution equations making the variational principle the basis for a structural analogy.

For the purpose of analogy building, let us summarize some basic concepts of the mechanical evolution of a system of N particles of masses $m_i, i = \overline{1,N}$, each particles, in a Cartesian framework (position vector $\overrightarrow{r}_i$), being subjected to a force $\overrightarrow{F}_i$ summing up both the external action ($\overrightarrow{F}_i^{(e)}$) and the internal constraints, $\overrightarrow{F}_i^{(c)}$, hence, $\overrightarrow{F}_i = \overrightarrow{F}_i^{(a)} + \overrightarrow{F}_i^{(c)}$, such that each particle is in equilibrium has a linear momentum, $\overrightarrow{p}_i$.If the whole system evolves infinitesimally such that each particle is subjected to a virtual displacement $\delta\overrightarrow{r}_i$such that, the virtual work of the internal constraints vanishes: $\sum_i \overrightarrow{F}_i^{(c)} \cdot \delta\overrightarrow{r}_i = 0$.

Within a biological system, such as a neuron network, this condition is interpreted as a statistical equilibrium of "internal" forces expressed as gradients of various quantities (concentrations, electrical charge, local electric fields, etc.).

However, in these terms, the system is defined morphologically, while we have previously argued that SB in neuron system is most likely functional. Therefore, we need to define the system through a new set of parameters by performing a *coordinate transformation*:

$$\overrightarrow{r_i} = \overrightarrow{r}_i(q_1, q_2, \ldots, q_n, t); i = \overline{1,N} \tag{6.1}$$

where q_i are new generalized coordinates chosen to functionally describe neurons. By writing (6.1) we state that each neuron's evolution depends functionally on others to which it might be connected (dependence on the general coordinates, q_i) and that each neuron evolves with time (time dependence is essential in order to imply any energy considerations).The *general form of Lagrange equations* (Goldstein et al. 2002) in terms of q_j is:

$$\left[\frac{d}{dt}\left(\frac{\partial T}{\partial \dot{q}_j}\right) - \frac{\partial T}{\partial q_j}\right] - Q_j = 0 \tag{6.2}$$

where $Q_j = \sum_i \overrightarrow{F}_i \cdot \frac{\partial \overrightarrow{r}_i}{\partial q_j}$ are the generalized forces leading to the system kinetic energy, T (Greiner 2003; Lifshitz and Landau 2007):

$$T = M_0 + \sum_j M_j \dot{q}_j + \frac{1}{2} \sum_{j,k} M_{jk} \dot{q}_j \cdot \dot{q}_k \tag{6.3}$$

with

$$M_0 = \sum_i \frac{1}{2} m_i \left(\frac{\partial \overrightarrow{r}_i}{\partial t} \right)^2 M_j = \sum_i m_i \frac{\partial \overrightarrow{r_i}}{\partial q_j} \cdot \frac{\partial \overrightarrow{r}_i}{\partial t} \; M_{jk} = \sum_i m_i \frac{\partial \overrightarrow{r_i}}{\partial q_j} \frac{\partial \overrightarrow{r_i}}{\partial q_k} \tag{6.4}$$

In the case of forces derived from a scalar potential, V, depending exclusively on positions (*conservative system*), one can write:

$$\overrightarrow{F_i} = -\nabla_i V = -\frac{\partial V}{\partial \overrightarrow{r_i}} \tag{6.5}$$

where $V = V\left(\overrightarrow{r}_1, \overrightarrow{r}_2, \ldots, t\right)$, the generalized forces become:

$$Q_j = -\frac{\partial V}{\partial q_j} \tag{6.6}$$

Equations 6.2 and 6.6 lead to the *Lagrange equations* for a system subjected to potential-derived forces (Lifshitz and Landau 2007):

$$\frac{d}{dt}\left[\frac{\partial L}{\partial \dot{q}_j}\right] - \frac{\partial L}{\partial q_j} = 0 \tag{6.7}$$

where L is called the *Lagrange function* defined as:

$$L = T - V \tag{6.8}$$

Since most potentials, $U\left(q_i, \dot{q}_i\right)$, are dependent on the generalized velocities $(\dot{q}_i)$, the generalized forces can be rewritten as:

$$Q_j = -\frac{\partial U}{\partial q_j} + \frac{d}{dt}\left(\frac{\partial U}{\partial \dot{q}_j}\right) \tag{6.9}$$

while the Eq. 6.7 holds. The classical example of such potential is a charge moving in electromagnetic fields which extends the analogy possibilities to neuron systems under the action of external fields, e.g. electric and magnetic stimulation.

6.3.2 Lagrange Equations Applied to Oscillating Systems

Networked neurons have been considered as oscillators (Ermentrout and Chow 2002). The basic neuron model emerges from the mechanical-electrical analogy which provides the resonant frequency:

$$\omega_0 = \frac{1}{\sqrt{LC}} \tag{6.10}$$

where L is the inductance of the electrical circuit and C its capacitance.

Neurons can be modeled as coupled oscillators, their coupling being described as weak with leaky integrated-and-fire-methods. This provides the first step towards modeling neurons as dynamical system which create the network collective modes (Gray 1994; Ermentrout and Chow 2002; Paydarfar et al. 2006; Kouh and Poggio 2008; Kundu et al. 2013).

We apply the Lagrange formalism to the systems of neurons modeled by analogy to ordered crystalline structures. This is supported by several results (Peters and Sethares 1991, 1996, 1997; Weliky et al. 2003; Ohki et al. 2005) on primary visual cortex (V1) pattern formation which have been discussed in analogy to crystalline-like structure whose fundamental unit is the hypercolumn. Hypercolumns interact laterally by long-range connections linking similar cells. Brain activity patterns are explained through the SB involving O(3) group and lattice symmetry (Bressloff and Cowan 2002; Bressloff 2002). The general form of the Lagrangian of interacting point particles in a 2D quadratic lattice (Fig. 6.3a) is given by the following expression which accounts all interactions with neighbors of different orders:

$$L = \frac{1}{2}\sum_{a}\left(m\dot{q}_a^2\right) - \frac{1}{2}\sum_{ab}\left(k_{ab}q_a q_b\right) - \frac{1}{2}\sum_{abc}\left(k_{abc}q_a q_b q_c\right) - \ldots \tag{6.11}$$

where $q_{a,b,c}$ are the displacements of the particles from the equilibrium positions and $k_{a,b,c}$ are couplings. The first term represents the kinetic energy, the second term stands for the first order interaction, and the third one represents the second order interaction, and so on.

Within a 2D hexagonal lattice of identical mass particles connected by elastic springs each particle is connected to 12 neighboring particles organized in two layers and referred through their plan projection indices (Fig. 6.3b).The spring elastic constants of the connections between the reference particle and those in the first and second coordination sphere are K_1 and K_2, respectively (Metrikine and Askes 2006), such that the Lagrange function of the (m, n) indexed particle is

$$L = \frac{1}{2}M\sum_{i=1}^{2}\left(\dot{q}_i^{(m,n)}\right)^2 - \frac{1}{2}K_1\sum_{j=1}^{6}\left(\Delta l_j^{(m,n)}\right)^2 - \frac{1}{2}K_2\sum_{j=1}^{6}\left(\Delta L_j^{(m,n)}\right)^2 \tag{6.12}$$

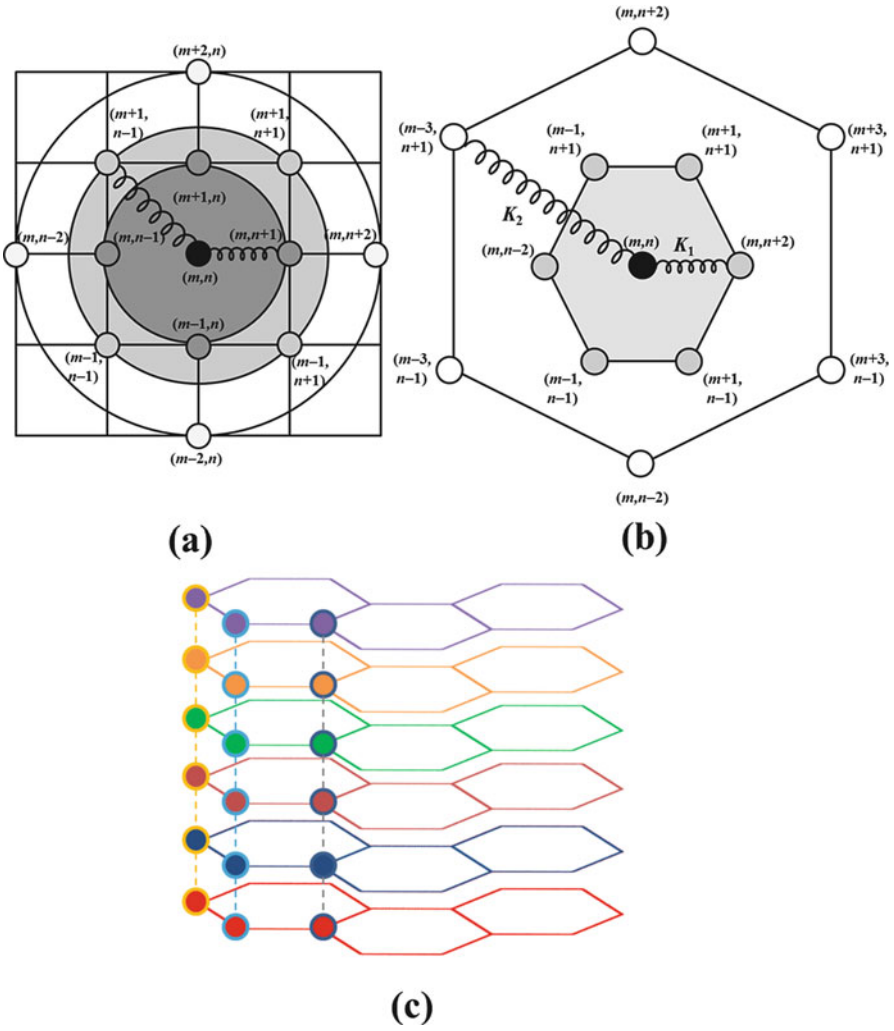

Fig. 6.3 Applications of Lagrangian formulation to electrical coupled oscillators. Two-dimensional quadratic (**a**) and hexagonal (**b**) lattices. (**c**) Multi-layer hexagonal symmetry lattice

where $q_i^{(m,n)}$ are the displacements of the particle (m,n) from its equilibrium position, $\Delta l_j^{(m,n)}$ and $\Delta L_j^{(m,n)}$ are elongations of the springs of the inner and outer layers depending on $q_i^{(m,n)}$.

More complicated models can be imagined closer to the structural reality of the cortex (von Economo and Koskinas 1925; Ringo et al. 1994; Douglas and Martin 1998, 2004; Vercelli et al. 2004; Doty 2007) such that a hexagonal symmetric arrangements of minicolumns of neurons (Fig. 6.4a, b) interacting both locally (within each hypercolumn) and laterally (between hypercolumns). In these

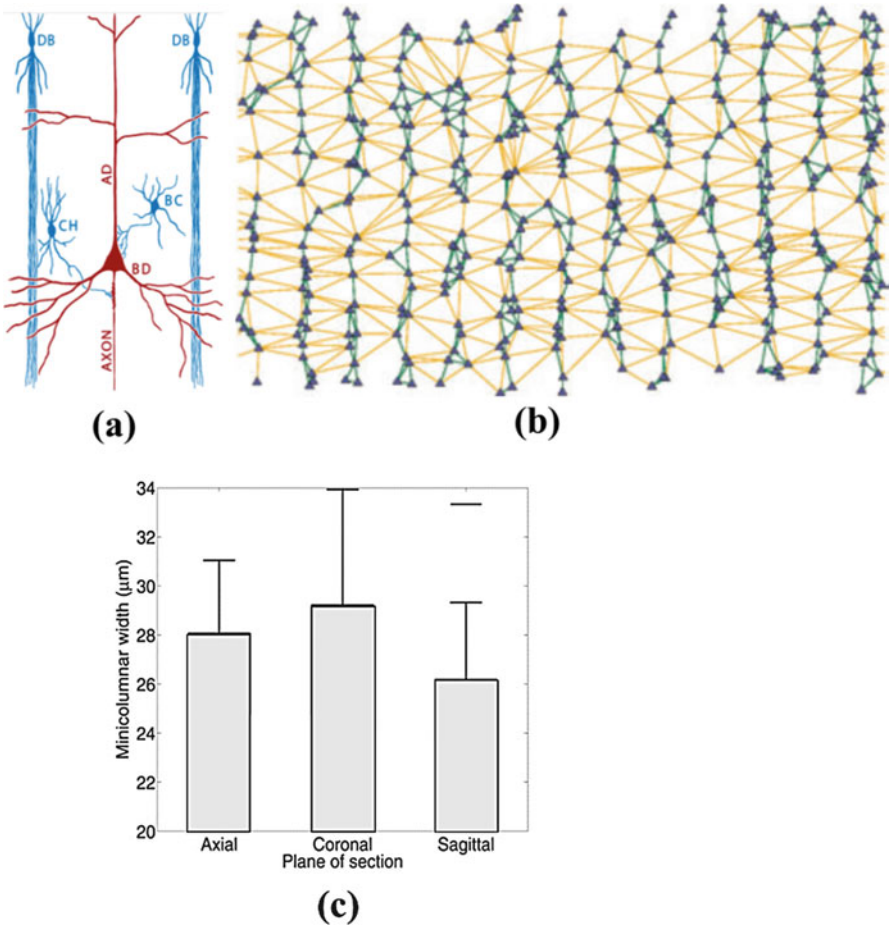

Fig. 6.4 Quasi-crystalline arrangement of cortical modular structure. (**a**) Defining the minicolumn terms of symmetry. (**b**)The Delaunay triangulationis a graph with vertices belonging to a given point set. Three points are mutually joined by edges of the graph when the *circle* through those points contains no other point in its interior. This figure illustrates the construction for a randomly generated set of points, clustered into vertical columns. Some edges of the triangulation have been omitted because of boundary effects. The edges for intercolumnar distances are depicted in yellow while those for intracolumnar distances are depicted in *green*. (**c**) Box plots of minicolumar width measurements in Brodmann area 17 (human). Width was estimated using a single section of Nissl-stained tissue cut along one of the three principal axes. Materials for this study included eight brains cut in the transverse plane (four male, four female, age 40–72 years), 15 brains cut in the coronal plane (ten male, five female, age 1–94 years), and 11 brains cut in the sagittal plane (five male, six female, age 4–87 years). Minicolumnar width was estimated using computerized image analysis of micrographs of these regions of interest (Casanova and Switala 2005). There was one possible outlier at 33.3 μm in the sagittal plane. There is no significant dependence of width estimates on the plane of section ($F_{2,8} = 1.05$; $p = 0.410$) (Taken with permission from Casanova et al.2011; Vinters and Kleinschmidt De Masters 2008; Wegiel et al. 2010)

models, brain function and dysfunction are explained by the interplay of constants in expressions like (6.11) and (6.12), i.e. pathological disruption of synapses (McClelland 2000; Ferrer et al. 2008; Vinters and Kleinschmidt De Masters 2008; Wegiel et al. 2010) is modeled by the suppression of one of the interacting terms or by the modification of one of the constants such that symmetry is modified.

6.4 Noether's Theorem and Neuron System Symmetries

6.4.1 Physical Quantities Conservation

Lagrange formalism provides a set of n second order differential equations describing the evolution of a system with n degrees of freedom. Solving such system requires leads to $2n$ constants of integration determined by the initial conditions, i.e., the initial values of the nq_j and the $n\dot{q}_j$s. In few selected cases, all the equations are integrable, while in most of the case they are not. When complete solutions cannot be obtained, it is often possible to extract a large amount of information about the physical nature of the system motion such as conservation of some physical quantities. If a coordinate, q_j in a set of linearly independent coordinates $\left(q_i, i = \overline{1,N}\right)$ is not included in the expression of Lagrange function, this coordinate is said to be *cyclic* or *ignorable*:

$$\frac{\partial L}{\partial q_j} = 0 \tag{6.13}$$

which combined with the Lagrange (6.7) will get

$$\frac{d}{dt}\left[\frac{\partial L}{\partial \dot{q}_j}\right] = 0 \rightarrow \frac{\partial L}{\partial \dot{q}_j} = \text{constant} \tag{6.14}$$

Therefore, the quantity, $p_j = \frac{\partial L}{\partial \dot{q}_j}$, called the *generalized momentum of the cyclic coordinate*, q_j is conserved. However, when the constraints exist (Ray 1966) when the constraints exist i.e., the coordinates, $q_i, i = \overline{1,N}$ are not linearly independent any more. This means that conservation of the generalized momentum of a variable (not included in the Lagrange function) do not hold anymore. It is expected that real neuron networks evolve under some constraints, hence finding conserved quantities (Finkelstein and Misner 1959) will not be straightforward.

A one dimensional system of nearest neighbor interacting particles can be described in terms of waves, η depicting the collective displacement of particles from their equilibrium positions. Such a system is described by Lagrangian density, $\mathcal{L}$, of the form (Goldstein et al. 2002; Greiner 2003; Lifshitz and Landau 2007):

$$\mathcal{L} = \mathcal{L}\left(\eta, \frac{d\eta}{dx}, \frac{d\eta}{dt}, x, t\right) \tag{6.15}$$

It is now easy to observe that for systems of n discrete degrees of freedom d'Alembert principle provides n Lagrange equations of motion while the evolution of a continuous system i.e., having an infinite number of degrees of freedom, is described by only one Lagrange equation. This illustrates the usefulness of describing the neuron network as a continuous system which is a totally appropriate method to be correlated to the instrumental method probing several neurons. In this respect, the discrete Lagrange function describes a neuron system in the view of correlation with high resolution instrumental method probing one or two neurons.

6.4.2 Noether's Theorem Formulation in Continuous vs. Discrete Systems

Invariance properties of the physical motion equations are found in the textbooks of analytical mechanics (Goldstein et al. 2002). In the case of complex systems exhibiting complicated interaction potentials, the Jacobi method is used as a way of splitting the total Hamiltonian into simple operations by applying variable transformations that will leave invariant the Hamiltonian equations. This classical example opens the path to the more general purpose of studying physical theories in relation to their transformation properties and further, in our case, finding conservation-like laws obeying invariance to transformations in the case of neural systems. There are two approaches to this question: either one states the equations and then one search for their symmetry properties, or one postulates the symmetries and attempt to find the dynamical equations. The first approach is possible in the *bottom-up* models of neural systems i.e., firing neurons are connected via oscillating models and spike generation as a dynamical collective behavior (Steriade et al. 1993; Pfister and Gerstner 2006; Singh et al. 2016) while the second approach is conceivable when observing the system behavior and implying from it some symmetry laws, for example in the case of V1 visual cortex observation (*top-down* model).

Our aim is to find conserved quantities and identify the situations known as SB in which conservation laws are not obeyed anymore. The formalism we shortly reminded before and adapted for the neuron networks, allow to look for the existence of conserved quantities when Lagrange function exhibits symmetry properties. A straightforward method to find such physical quantities is to identify generalized coordinates (q_j) on which the Lagrange function do not depend and, thus the corresponding quantity defined by the canonical momentum is conserved. In the Lagrange function, the independence on the given generalized coordinate, q_j, means that L will not be affected by a coordinate transformation; in other words L:it is invariant or symmetric. If L is invariant to time displacement, then the energy

is conserved. The relation between invariance or symmetry and conservation is formally grounded within Noether's theorem valid for both continuous and discrete systems.

Let us formulate for Noether's theorem in the continuous system for which the Lagrange function is a density function $\mathcal{L}\left(x^{\mu}, \eta_{\rho}(x^{\mu})\right)$ dependent on system variables x^{μ} and on some functions η^{ρ} which are at their turn dependent on x^{μ}.

Noether's theorem implies the following two conditions: the *form invariance* and the *action integral invariance*. The form invariance states that the Lagrange density function will have the same functional dependence on both original and transformed quantities: hence the motion equations will have the same expressions in terms of both original and transformed coordinates. The second condition states that action integral has the same value independently in which coordinates express the Lagrangian density, $\mathcal{L}$ (Goldstein et al. 2002):

$$\int_{\Omega} (dx^{\mu}) \frac{d}{dx^{\nu}} \left\{ \frac{\partial \mathcal{L}}{\partial \eta_{\rho,\nu}} \bar{\delta} \eta_{\rho} + \mathcal{L} \delta x^{\nu} \right\} = 0 \tag{6.16}$$

whereas δx^{μ} and $\delta \bar{\eta}_{\rho}(x^{\mu,\delta})$ are infinitesimal variations linearly dependent on r functions $X_r^{\nu}(x^{\mu})$ and $\Psi_{r\rho}(x^{\mu})$

Further developing (6.16) we get:

$$\frac{d}{dx^{\nu}} \left\{ \left(\frac{\partial \mathcal{L}}{\partial \eta_{\rho,\sigma}} \eta_{\rho,\sigma} - \mathcal{L} \delta_{\sigma}^{\nu} \right) X_r^{\sigma} - \frac{\partial \mathcal{L}}{\partial \eta_{\rho,\nu}} \Psi_{r\rho} \right\} = 0 \tag{6.17}$$

This family of equations is the main statement of *Noether's theorem* which says that, if the system i.e., the Lagrange density function has the symmetry properties, such that form invariance and action integral invariance are obeyed during infinitesimal linear variations depending on r functions, X_r^{ν} and $\Psi_{r\rho}$, then there exist r conserved quantities. The Noether's theorem does not specify, however, which quantities are conserved.

To obtain the Noether's theorem for the discrete system is sufficient to perform in (6.18) the following formal replacements:

$$\begin{aligned} &\mathcal{L} \rightarrow L \\ &x^{\mu} \text{ or } x^{\nu} \rightarrow t \\ &\eta_{\rho} \rightarrow q_k \\ &\eta_{\rho,\nu} \rightarrow \dot{q}_k \end{aligned} \tag{6.18}$$

Getting in this way the analogous expression for Noether's theorem (Goldstein et al. 2002; Doty 2007):

$$\frac{d}{dt}\left[\left(\frac{\partial L}{\partial \dot{q}_k}\dot{q}_k - L\right)X_r - \frac{\partial L}{\partial \dot{q}_k}\Psi_{r,k}\right] = 0 \tag{6.19}$$

Noether's theorem is an abstract formulation of criteria leading to conservation laws. Further work should be performed in order to define well the variables and constants in Lagrangian such as in Eqs. 6.11, 6.12, and 6.2, then, submit them to variable transformation in order to discover conservation laws. This might be achieved by exploiting the experimental results on mapping brain activity related to motion (Opris et al. 2011; Opris et al. 2012a,b, 2013; Moser et al. 2013; Krupic et al. 2013; Chen et al. 2016; Grossberg 2015; Bellmund et al. 2016; Sasaki et al. 2015), vision (Markan et al. 2013; Bressloff and Cowan 2003; Bressloff et al. 2001) or cognition (Buldyrev et al. 2000; Casanova 2004; Casanova et al. 2008, Opris and Bruce 2005; Pu et al. 2013; Opris and Ferrera 2014; Opris and Casanova 2014; Heneka et al. 2015; Casanova et al. 2015; Rosenberg et al. 2015; Opris and Ferrera 2014).

6.5 Application of the Symmetry Approach to Cortical Minicolumns

One of the main implications of the symmetry-related perspectives is in the field of Neuroscience (Casanova et al. 2011). While the application of symmetry ranges from neuroanatomy to the brain disorders, the understanding of brain function and dysfunction, and the concept of SB gains more attention due to its explanatory power.

It has been proposed that the cytoarchitectonic relations among certain minicolumnar elements (i.e., pyramidal cells) are conserved under spatial and temporal variation. Specifically, minicolumns are observed to exhibit translational (across the central axis of the minicolumn) and rotational (displacement in different planes of section) symmetries (see Fig. 6.5), transitive symmetry with respect to geometric scaling of morphometric relations in different cortical areas, and temporal symmetry (see Fig. 6.6) of morphometric relations during cortical development and maturation (DeFelipe et al. 1990; Mountcastle 1997; Buxhoeveden and Casanova 2002; Skoglund et al. 2004; DeFelipe 2005; Trippe and Casanova 2005; Casanova et al. 2007; Casanova 2008; Casanova et al. 2008; Casanova et al. 2009a; Casanova 2010). As discussed in this chapter, maintenance of continuous symmetry with these operations is a defining characteristic of physical systems in which conservation laws can be derived from the stochastic or random activity of its elements (Noether 1971).

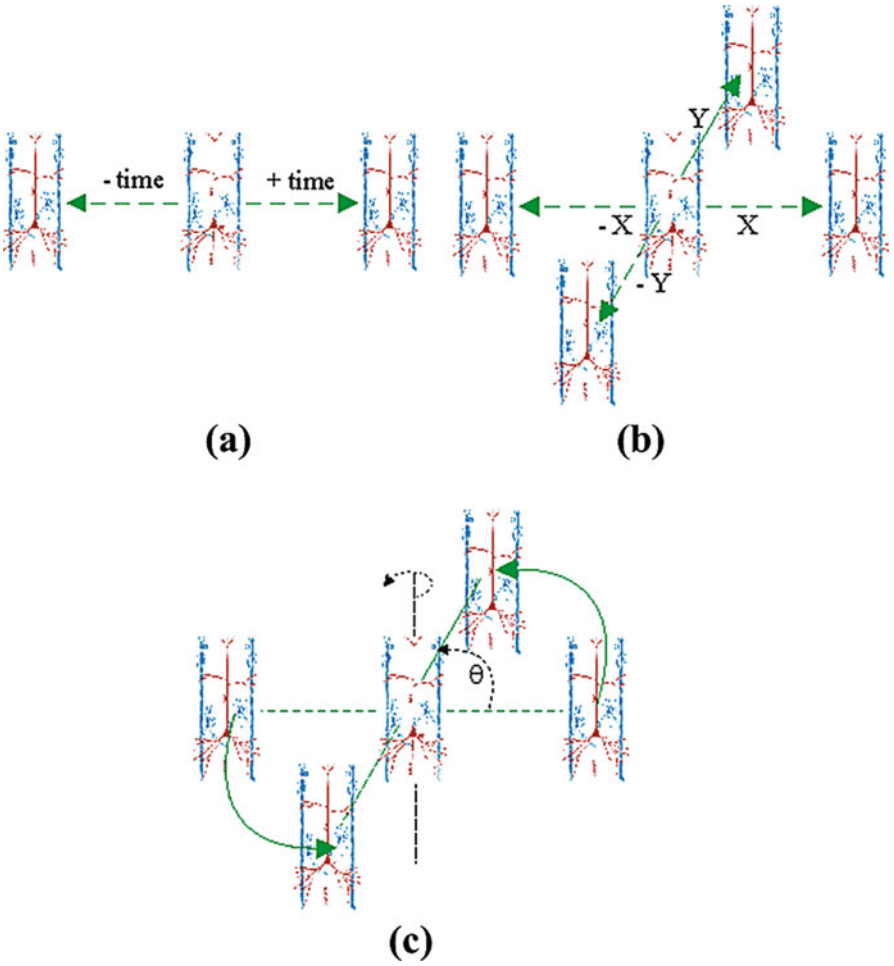

Fig. 6.5 Theminicolumn and the symmetry operations. (**a**) Symmetry of minicolumnar arrangement with respect to time. (**b**) Symmetry to translation, and (**c**) Symmetry to rotation

Similar arguments apply to the translation of pyramidal cells along the central axis of the cell minicolumn (Del Río and De Felipe 1997; Casanova et al. 2008). The central axis is an imaginary line through the core of the minicolumn that serves as a reference point when making symmetry measurements. Although, early in cortical development, pyramidal cells arrange themselves in a rectilinear pattern, the aging process disturbs their placement making it more difficult with the passage of time to recognize their integration into an anatomical unit. Nevertheless, the vectorial

sum of pyramidal cell translations, along the central axis of the minicolumn, is zero regardless of the brain region of origin (Fig. 6.3). The resultant arrangement links symmetry in space (i.e., translation of cells in different brain regions) with time (i.e., aging).

The final transformation discussed in this chapter is the preservation of the relative size of pyramidal cells (Buxhoeveden et al. 2000) as related to minicolumnar width (Fig. 6.6). Geometrical resizing (also called dilation or even expansion) is a conversion where objects or systems become bigger or smaller while leaving unaltered the content and relationship of their component elements (Doty 2007). In the case of the minicolumn the validity of these geometric transformations lends credence to Creutzfeldt's early proposal of a canonical circuit readily observable throughout the cerebral cortex (Creutzfeldt 1977).

The mammalian cortex has grown by adding supernumerary minicolumns while preserving the relative number of cells per minicolumn (Schlaug et al. 1995). In primates, a recent study showed a linear relationship between structure, size, and number of neurons (Herculano-Houzel et al. 2007). It is noteworthy that, among the six primate species analyzed in this study, the neuronal size and density did not vary significantly with brain size.

Some other comparative anatomy studies (Buxhoeveden and Casanova 2005; Doty 2007; Casanova et al. 2009a; Raghanti et al. 2010), in primates, found that despite major changes in minicolumnar width across species, the core spaces remain the same (Casanova et al. 2009b; Buxhoeveden and Casanova 2005; Casanova et al. 2009a; Raghanti et al. 2010). The central or core compartment of the minicolumn is comprised of pyramidal cells and their projections. These basic constitutive elements of the minicolumn's core compartment appear to be irreducible (Casanova and Tillquist 2008). Variability, when present, is inherent in the peripheral neuropil space which is comprised of non-pyramidal cellular elements derived from assorted sources and a different developmental pathway (e.g., tangential migration) (Casanova et al. 2009b).

A conservation law is the statement that there exists a measurable quantity that does not change when subject to a specified physical process. Such a physical measure is called a conserved quantity. The fact that minicolumns exhibit scalar properties relating pyramidal cell size and minicolumnar core size, rotational symmetry, and conservation of translational movements helps to conceptually organize the cytoarchitecture of the cerebral cortex. In an isolated system (i.e., one where the brain does not directly exchange energy or matter with its surroundings), SB is a pre-requisite of directionality wherein changes always display greater entropy. In essence, increased entropy requires that the result of different operations have less symmetry than their predecessors. With the passage of time, the processes that require greater entropy seemingly diminish the hegemony of the minicolumn in cortical organization. One could say that the "significance" of the minicolumn in

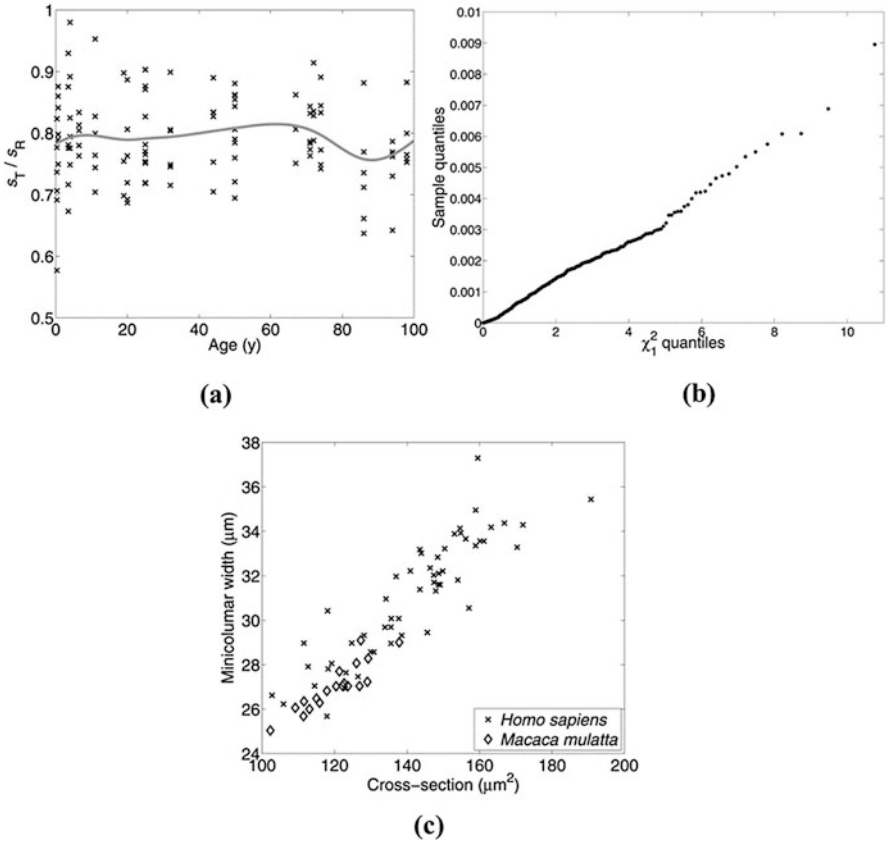

Fig. 6.6 Experimental support for minicolumnar symmetry. (**a**) Temporal symmetry of minicolumns. Small change is seen in minicolumnar structure among 19 persons with a range of ages at death from 4 months to 98 years. The neuropil distribution is derived from the empirical "linear contact distribution," the distribution of distances from points within the neuropil to the nearest Nissl-stained object, measured along a line with fixed orientation (Casanova et al. 2007). Taking the orientation parallel to the minicolumar axis, the median of the distribution is termed the radial neuropil space, sR, while the same measurement in the orthogonal direction (parallel to the laminar boundaries) provides the tangential neuropil space, sT. Mean sT/sR (*solid curve*) was estimated with a smoothing spline over measurements (points) from up to six cortical areas in each of 19 individual brains. The ratio of tangential neuropil space sT to radial neuropil space remains nearly constant at approximately 0.8 throughout the human lifespan. (**b**) Translation and rotation symmetry proof for columnar distribution of cortical cells. The minicolumns were identified in each of 192 micrographs using a line tracing method that groups cells into minicolumns by finding the shortest cell-to-cell paths from one end of the layer to the next. Using the clusters so identified, cell dispersions about the minicolumnar axes were compared to a chi-square distribution with one degree of freedom, which is what one would expect if the neurons were located at random

modern studies diminishes as the module seemingly loses its rectilinear orientation; however, its influence on cortical organization remains tangible as proven by the existence of laws of conservation.

6.6 Conclusions

Noether's theorem is based on the invariance of certain laws of Physics. The theorem states that for each continuous symmetry there is a conserved quantity (Lederman and Hill 2004). These invariants, or conserved properties, are the same regardless of the viewpoint from which they are examined. In this chapter we have studied how cytoarchitectonic relations among select minicolumnar elements (i.e., pyramidal cells) are conserved under spatial and temporal variation. Specifically, the minicolumns are observed to exhibit translational (across the central axis of the minicolumn) and rotational (displacement in different planes of section) symmetry, transitive symmetry with respect to geometric scaling of morphometric relations in different cortical areas, and temporal symmetry of morphometric relations during cortical development and maturation (Casanova et al. 2007). Maintenance of continuous symmetry while applying these mathematical operations is a defining characteristic of physical systems in which conservation laws can be derived from the stochastic or random activity of its elements (Noether 1971). The authors spouse symmetry as a tool or technique to better describe changes in the organization of the cerebral cortex. The work presented here shows that despite changes accrued to time, there is a preservation (i.e., conservation) of parameters related to the symmetry of the minicolumn. In this regard measurements of symmetry for the cell minicolumn serve as a pattern classification scheme, the existence of mathematical ways of describing modular interactions, and simplify understanding the integrative function of multiple anatomical elements of the cerebral cortex. The existence of such conserved quantities generalizes the known physical principles to the brain.

Fig. 6.6 (continued) at random positions in space under a symmetric distribution. The mean displacement of neurons from the minicolumnar axis was nearly zero, consistent with symmetry. (**c**) Relationship between average size of minicolums and pyramidal cells. Material included 55 micrographs of Nissl-stained human tissue comprising Brodmann areas 4, 9, 17, 21, 22, and 40; and 19 micrographs of area 17 in the macaque. The average cross-section of pyramidal cell somata is positively correlated with the minicolumnar width estimated from the same set of micrographs. Minicolumnar width was estimated using the established methodology (Casanova and Switala 2005), while the average neuronal cross-sectional area was estimated using the Boolean model (Casanova et al. 2006). The high degree of linear correlation ($r = 0.913$; $p < 0.0001$) is evident (Taken with permission from Casanova et al. 2011)

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Chapter 7
From Symmetry to Symmetry-Breaking in Locomotion

Brian R. Noga and Ioan Opris

Abstract The locomotor system is a hierarchical mechanism consisting of several functional components, including the decision mechanism, navigation map, locomotion command, central pattern generators and the EMG muscle activity patterns. In this chapter we discuss the role of symmetry/asymmetry and symmetry breaking of neural states during the emergence of locomotion and movement. We review recent results that show that inhibition plays a critical role in decision making, in the formation of grid cells and place cells for navigation, the locomotor command and central pattern generators. We employ the analogy with symmetry breaking in physical systems where at a bifurcation point on the phase diagram, infinitesimal perturbations result in a transition to a new global attractor state. This observation may have major implications for both understanding normal locomotion and therapeutics of spinal cord injury, as triggered by neuromodulatory/inhibitory causes.

Keywords Locomotion • Symmetry • Symmetry breaking • Navigation • Decision making • Neural tuning • Lateral inhibition • Central pattern generators • Spinal cord injury

7.1 Introduction

The symmetry breaking concept applies to both physical and neural processes (Cocchi et al. 2017; Munro and Bowerman 2009; Van der Gucht and Sykes 2009). In Fig. 7.1a is shown a waterwheel toy model to provide an intuitive notion of a mechanical symmetry-breaking. Symmetry breaking occurs when a small fluctuation is crossing a critical point to induce changes that shape the behavior of the whole system, by selecting one branch of a bifurcation curve (Fig. 7.1b) or the

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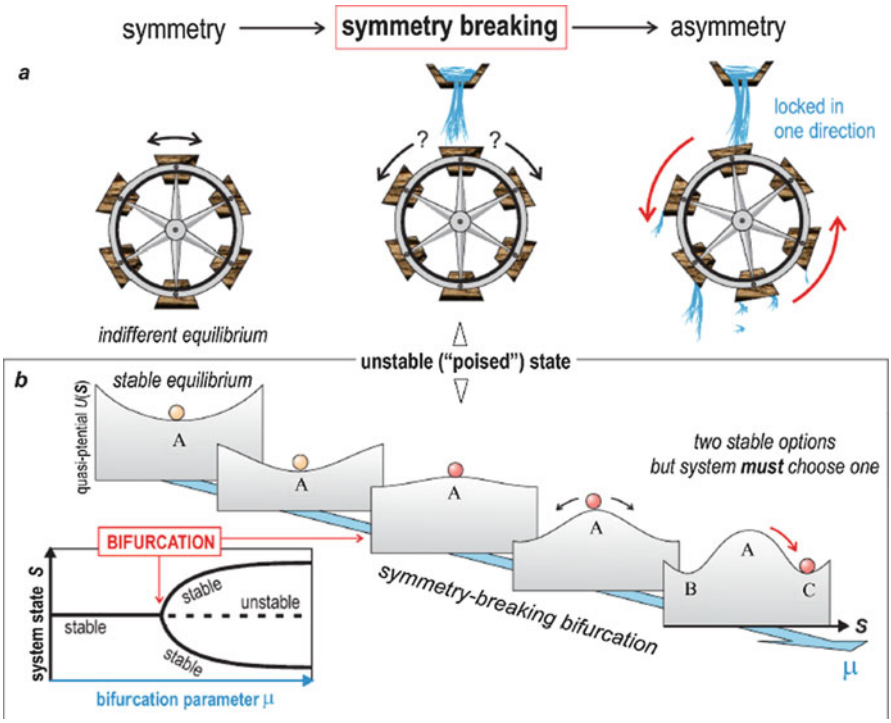

Fig. 7.1 Symmetry breaking. Schematic example that illustrates the concept of symmetry-breaking. (**a**) The waterwheel toy model that provides an intuitive notion of a mechanical symmetry-breaking. (**b**) The non-linear dynamics concept of a "pitch fork" bifurcation that breaks the symmetry of stable state A and its representation as quasi-potential landscape (With permission from Sui Huang 2016)

other (Cocchi et al. 2015; Huang 2016). This means that when the system crosses the critical point, instead of a unique stable state the system has more than one (usually two) broken-symmetry (ordered) states (Anderson 1997).

A magnetic system, for example, can exist in a "disordered" paramagnetic phase, above the Curie temperature, and also in a ferromagnetic phase (below the Curie temperature), characterized by a "net value" of magnetization (Kittel 1971; Mnyukh 2012). The variable that bifurcates is called order parameter (e.g. magnetization of a ferromagnet) and the variable which affects system's behavior is called a control parameter (e.g. temperature). This process is called symmetry "breaking", because such transitions usually bring the system from a symmetric but disordered state (e.g. a paramagnetic phase) into one or more ordered states (e.g. ferromagnetic phase), which are equivalent from physics perspective. The symmetry breaking process takes place when the rotation symmetry of magnetization vector gets broken by a small fluctuation of a local magnetic field (that usually results in formation of specific magnetic domains with well-defined orientations; Kittel 1971).

Symmetry breaking phenomena are closely related to physical phase transitions, because many processes (but not all) involve broken symmetries (Huang 2016).

Phase transitions in most physical systems have been qualitatively and quantitatively elucidated due to the advances made by the Renormalization Group Theory, in the 1970s (Wilson and Kogut 1974). These aspects come from the "role" of the control parameters (e.g. temperature) that drive the systems to "instability" when approaching their "critical values" and the "resultant" changes in the corresponding "order parameters" (for example, the value of net magnetization in a ferromagnet) that describe the "major physical changes" in the critical system studied (Anderson 1997).

The fundamental principle that is used to determine the state of equilibrium of a macroscopic system is the Second Law of Thermodynamics (also known as the law of increasing entropy). In the case of thermally and materially isolated systems, this translates into the condition that the entropy S, a measure of the disorder degree in the systems, should achieve a maximum value ($\Delta S > 0$). However, phase transitions usually occur in systems that are not isolated from their surroundings but are in continuous contact with a heat reservoir at a fixed temperature, T, which requires minimizing the Gibbs free energy function, G (i.e. $\Delta G < 0$).

The major difference between living and inanimate systems is that living matter exists in states that are "far from thermodynamic equilibrium". Living organisms survive only because they are "open systems" that allow for a "transfer of matter and energy" between them and their surroundings, and an "export of entropy" into their surroundings to compensate for the "creation and maintenance of structural order" (entropy reduction) and functional organization. Nevertheless, phase transitions also exist in physical systems far-from-equilibrium, like for example, the case of Bénard instability (Hohenberg and Halperin 1977; Hohenberg and Krekhov 2015), when a fluid heated from below makes a "transition" from a uniform to a convective phase at a "critical temperature" gradient threshold.

However, the amplification systems (neural circuits) can break the symmetry by turning local and transient signals (or noise) into stable and system-level asymmetries that are of particular importance (Jilkine and Edelstein-Keshet 2011). At the core of amplification mechanisms in both physical and neural systems are positive feedback loops, resulting from excitatory and/or inhibitory microcircuit interactions between cells and the neuromodulatory components (Opris 2013; Opris and Casanova 2014; Opris et al. 2011, 2012a, b). In fact, the symmetry breaking" is a result of the "interplay between the system dynamics and the internal or external cues that initiate and/or direct the outcome" (Kubicki et al. 2010; Li and Bowerman 2010).

As it was shown in a previous chapter, the locomotor system consists of: (a) high level prefrontal-premotor and motor cortices, (b) neostriatal-thalamo-cortical loops, (c) brainstem command generation, (d) central pattern generators in the spinal cord). The locomotor system involves symmetries and asymmetries in both stepping and gait.

Here we will look into the symmetry breaking in locomotion: from decision making, navigation, brainstem command-cooling, central pattern generators, EMG patterns and stepping.

7.2 Symmetry Breaking in Decision Making

Decision making is a selection process (choice) of optimal alternative from a set of two or more alternatives, with several defining features. First, decision making does not consist of simple reflexive responses. Second, decision making is an integrative process of accumulating information. Third, the choice alternatives involve a deliberation process for which the expected outcomes can be assessed. To illustrate the decision making process, Xiao-Jing Wang very accurately simulated the experiments of Newsome and Shadlen involving perceptual discrimination of random dots coherence (Wang 2002, 2012; Shadlen and Newsome 1998; Opris et al. 2013). In Fig. 7.2a, is shown the simulation of a model network, at zero coherence that makes decisions randomly. In both instances, the stimulation begins with a slightly larger input to one group (A in red). Interestingly, the network dynamics does not converge immediately to attractor A.

Instead, the firing rates (r_A and r_B) of the two neurons remain comparable during the initial stage of stimulation (lasting several hundreds of milliseconds). Then, the activities of the two neuron populations participating in the decision process undergo a dramatic divergence. In the first trial (left) the attractor A wins the competition, whereas in the second trial (right), the attractor B wins (Fig. 7.2a). An interesting way to illustrate the decision-making dynamics may be depicted by plotting the two firing rates rA and rB against each other in a state space or "decision space" (Fig. 7.2b). The decision processing in the network is depicted by a "random walk", shown by the diagonal line ($r_A \cong r_B$) in the state space, corresponding to the "initial phase of stimulation" when the decision is not yet made (Fig. 7.2b). Then, during deliberation, the trajectory "wanders" in the state space toward one

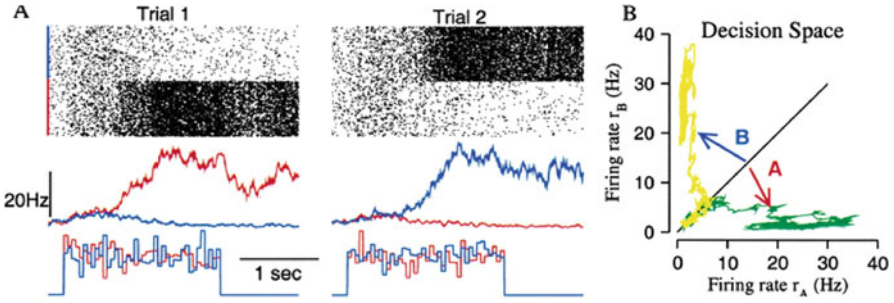

Fig. 7.2 Illustration of symmetry breaking mechanism for the decision making function. (**a**) Two groups of neurons firing selective for two distinct choices-graded ramping followed by winner-take-all competition, in a simulation of motion direction discrimination task where the task difficulty is quantified by motion coherence. Raster, population firing rates r_A and r_B, stochastic inputs, and time integrals of inputs. In these two examples, decision choice (*A* or *B*) is correlated with the larger time integral of the input. (**b**) Network dynamics is displayed in the state/decision space of firing rates r_A and r_B in (*A*). Note the initial random walk along the diagonal line (when the population activity is similar for the two groups); afterwards the network converges to one of the two attractors (at [$r_A = 20$ Hz, $r_B = 3$ Hz] and [$r_A = 3$ Hz, $r_B = 20$ Hz]

of the two steady states (attractors, corresponding to the decision options). If the trajectory "converges" to attractor A (near the x axis: $r_A \cong 20$ Hz, $r_B \cong 3$ Hz), the network has reached the choice A, whereas if the network "converges" to attractor B (near the y axis: $r_A \cong 3$ Hz, $r_B \cong 20$ Hz), the network's preference is for choice B.

7.3 Symmetry Breaking in Navigation

The first suggestion for a navigational system upstream from the hippocampus was made by John O'Keeffe (1976). O'Keeffe noticed that "each place cell receives two different inputs: one that conveys information about a large number of environmental stimuli or events, and the other from a navigational system which calculates where an animal is in an environment independently of the stimuli impinging on it at that moment. The input from the navigational system "gates" the environmental input, allowing only those stimuli occurring when the animal is in a particular place to excite a particular cell". Next, he infers that "one possible basis for the navigational system relies on the fact that information about changes in position and direction in space could be calculated from the animal's movements. When the animal had located itself in an environment (using environmental stimuli) the hippocampus could calculate subsequent positions in that environment on the basis of how far, and in what direction the animal had moved in the interim". Furthermore, he concludes that "in addition to information about distance traversed, a navigational system would need to know about changes in direction of movement either relative to some environmental landmark or within the animal's own egocentric space" (O'Keeffe 1976).

McNaughton and colleagues (2006) elaborated further on the idea of 'path integration' of self-motion during navigation and spatial representation in the 'cognitive map' of hippocampal formation Hafting et al. (2005). Their starting point was the insightful proposal of Alan Turing in 1952 claiming that a "simple reaction-diffusion chemical mechanism could produce spatially organized structures spontaneously, through competition between activators and inhibitors" (Turing 1953). Thus, "if inhibitors diffuse faster than activators, spatial patches can emerge in which the activator concentration is high, surrounded by areas of high inhibitor concentration" (McNaughton et al. 2006). Therefore, if such "spontaneous symmetry breaking" mechanism that has been observed to operate in chemical reactions can create structures with periodic spatial properties, such as stripes or grids that resemble the grid fields in Medial Entorhinal Cortex (MEC), this would imply that neuronal implementation should resemble the simple reaction-diffusion mechanism (Swindale 1980). Thus, if a network of excitatory and inhibitory neurons has the inhibitory cells extending over a wider range than the connections of excitatory cells (Murray 1989), forming a Mexican hat connectivity profile, the symmetry can be broken, allowing for patterns to emerge spontaneously (Fig. 7.3).

This connectivity profile is related to that of the continuous attractor networks in which a global, uniform inhibition leads to a stable state with a single activity

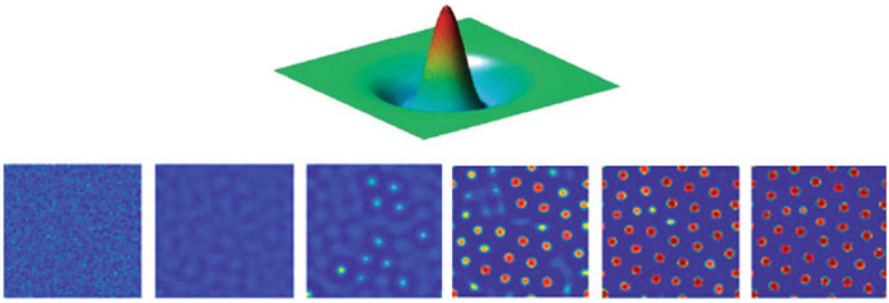

Fig. 7.3 The Turing symmetry-breaking mechanism has a simple analogy in the behaviour of neural nets with feedback excitation and surround inhibition. A network simulation demonstrating the emergence of an ordered activity pattern from random initial conditions. The cells are arranged in a 75-by-75 array representing a cortical sheet. Initially the activity of the cells has no spatial structure, but with time the initial symmetry is broken and patches of increased firing emerge arranged in a triangular rhomboidal) structure. Eventually this pattern stabilizes. *Colors* represent firing rates of the neurons in the array: *warm colors* represent high activity, progressively *cooler colors* represent progressively lower activity (McNaughton et al. 2006)

bump (Wimmer et al. 2014). In the case of the Mexican hat connectivity, the finite range of the inhibition allows for continuous attractors with multiple activity bumps. In a two-dimensional domain, several types of structure can emerge, such as: (i) a striped firing pattern that resembles the ocular dominance columns in the visual cortex; or (ii) a grid-like arrangement of activity bumps. The striking and unexpected regularity of both the Turing symmetry breaking and the grid cell phenomenon is so compelling (Jensen et al. 1996; Fuhs and Touretzky 2006; Mullins 2009).

7.4 Symmetry and/or Symmetry Breaking in Locomotor Systems

7.4.1 Spinal Central Pattern Generators

Locomotor activity is produced by a central pattern generator (CPG) localized to the spinal cord of vertebrates which produces coordinated patterns of alternating contractions of flexor and extensor (antagonist) muscles of each limb. According to the "half-center model" for the spinal CPG proposed by Graham Brown (1914) and expounded by Lundberg and colleagues (Jankowska et al. 1967a, b; Lundberg 1981), each limb is thought to have a separate CPG with two excitatory half-centers, one for flexors and one for extensors. In order to ensure separate activation of one or the other half centers, the half centers are connected by mutually inhibitory circuits. An intrinsic "fatigue" process gradually enables phase switching between opposing half centers as the mutual inhibition diminishes. In this way inhibition of antagonists are tightly coupled to the excitation of agonists. The complex patterns of discharge of some muscle nerves observed in deafferented decerebrate animals, however, led Grillner and Zangger (1975) to suggest that the CPG was

organized in a more complex fashion and to the proposal of separate "unit burst generators" for controlling subsets of motoneurons. The complex interactions of sudden sensory stimulation affecting phase duration without affecting cycle period (Guertin et al. 1995) and the appearance of "non-resetting deletions", where the absence of rhythmic activity in multiple synergist motoneuron pools is reflected by the appearance of tonic activity in antagonists at the same time without resetting the locomotor cycle (e.g., Lafreniere-Roula and McCrea 2005), cannot be explained by single-level CPGs. As discussed in length by McCrea and Rybak (2008), these and other objections do not necessarily preclude the basic half-center organization. They have proposed instead a two tiered distributed CPG comprised of a half-center rhythm generator (RG) which controls a pattern formation (PF) network responsible for motoneuron activation. Reciprocal inhibition between the flexor and extensor RG half centers are controlled by inhibitory interneuron populations. Rhythmic excitation of motorneurons is controlled by excitatory input from the different components of the PF circuitry and rhythmic inhibition, by additional sets of inhibitory interneurons driven by the PF network. The model accounts for many of the observed experimental phenomena including deletions, effects of afferent stimulation and the differential effects of drugs on frequency or pattern (e.g., Kriellaars et al. 1994; Perreault et al. 1995; Guertin et al. 1995; Stecina et al. 2005). The model is symmetrical for generating flexor and extensor activity and accounts for the appearance of both flexor and extensor deletions in different experimental situations (Lafreniere-Roula and McCrea 2005). Additionally, in this model, locomotor phase durations and cycle periods can be independently regulated by altering the descending drive from the mesencephalic locomotor region (MLR) to the RG half-centers (Rybak et al. 2006; McCrea and Rybak 2007) (see below). For quadrupedal locomotion, the circuitry would be replicated in all four limbs with additional networks for altering gait and maintaining coordination.

A number of studies have indicated that the spinal CPG for locomotion is symmetrically organized (Lafreniere-Roula and McCrea 2005; Yakovenko et al. 2005; Rybak et al. 2006; McCrea and Rybak 2007) and any asymmetry in locomotor flexor/extensor phase durations requires the presence of feedback asymmetries to occur. Juvin et al. (2007) have elegantly shown, for example, that flexor/extensor phase durations vary symmetrically as locomotor speed increases in an isolated spinal cord (with or without brainstem attached, and induced by either drug bath application or electrical stimulation of the medio-ventral surface of the brainstem) and in the absence of sensory feedback (see additionally Whelan et al. 2000). This contrasts to intact animals walking overground which typically show that extensor bursts vary more with cycle period than flexor bursts (Grillner 1981). In the hindlimb-attached spinal cord preparation, drug-induced locomotor-like movements showed the characteristic extensor-dominated burst patterns. These data indicate that sensory inputs are responsible for imposing extensor biasing on otherwise symmetrically alternating extensor/flexor oscillators. Interestingly, the flexor/extensor burst relationships also vary as a function of load on the limb (Iles and Coles 1991).

In a closed loop neuromechanical model of locomotor rhythm generation, Spardy et al. (2011a, b) have also demonstrated that "changes the strength of a tonic supra-spinal drive to the CPG may yield asymmetric alterations in the durations of different locomotor phases, despite symmetry within the CPG itself." The model accounts for a dominance of either the flexor or extensor phase of the step cycle, or both, as locomotor speed increases, as is observed in different decerebrate animals subject to fictive locomotion experiments (Yakovenko et al. 2005; see also Iles and Nicolopoulos-Stournaras 1996 for decerebrate rats). These data show that the locomotor CPG is not inherently extensor- or flexor-biased (Yakovenko et al. 2005). Rather, the pattern of "dominance" is likely determined by changes in background excitation of neural timing elements in the locomotor CPG.

With these considerations in mind, we next examine the organization of descending locomotor pathways activating the spinal CPG and the potential means by which the descending drive may be altered to enable symmetry breaking and alterations in rectilinear gaits to enable turning and/or circling behaviors.

7.4.2 Symmetry Breaking by Descending Locomotor Pathway

Organization of the Descending Locomotor Pathway

We have previously described in detail (this volume) the hierarchical organization of locomotor pathways (Noga and Opris 2017). Briefly, locomotion is produced by the direct activation or disinhibition of the MLR and/or the reticulospinal (RS) pathway originating within the medial reticular formation (MedRF). The MLR, an integrative center within the midbrain, directly activate RS neurons and does not project to the spinal cord directly. The RS pathway descends within the ventrolateral funiculus (VLF) of the spinal cord to activate CPGs located within the spinal enlargements. MLR stimulation also activates descending monoaminergic pathways (locus ceruleus/subceruleus/Kolliker Fuse and raphe nuclei including the parapyramidal region) which affect spinal locomotor activated interneurons possessing monoamine receptors implicated in the control of locomotion (Noga et al. 2009, 2011), through the release of norepinephrine (NE) or serotonin (5-HT). While the RS pathway is considered to be the "command pathway" for locomotor initiation, the monoaminergic pathways may be viewed as neuromodulatory pathways enabling additional control of locomotor pattern as well as frequency. Thus, from the MLR perspective, the descending locomotor pathway is multiple and parallel.

Organizational Principles of Descending Locomotor Pathways Revealed with Reversible Cooling of the RF and VLF

An interesting approach to test causal relationships to locomotion in animal brain circuits is by cooling certain parts of the brain (Noga et al. 2003). Cooling of the brainstem to temperatures that block synaptic transmission within the medial reticular formation (MedRF) (bilaterally) was performed to examine the effects of brain stem cooling on unilateral MLR-evoked post-synaptic potentials (PSPs) and locomotor drive potentials (LDPs) recorded intracellularly from motoneurons as well as electroneurogram (ENG) activity recorded from hindlimb peripheral nerves during fictive locomotion (Fig. 7.4a–c). Cooling of the MedRF abolished or significantly reduced MLR-evoked PSPs, LDPs, and motoneuron spiking activity as observed from intracellular or bilateral ENG recordings. Cooling of the MedRF also reduced the amplitude of the MLR-evoked positive waves (Noga et al. 1995) recorded from the surface of the spinal cord (cord dorsum potential or CDP). Step cycle lengths increased during cooling, prior to blocking of the locomotor rhythm. These effects were reversed on rewarming.

Extradural cooling to block fiber transmission through the VF (Fig. 7.4d) decreased the amplitude of ENG locomotor activity. Locomotor activity was mostly abolished on the side of cooling (ipsilateral), regardless of the side of stimulation. The amplitude of flexor and extensor ENG locomotor activity was always reduced on the side contralateral to cooling. The burst frequency of the remaining ENG activity was also affected (often increased). Occasionally, contralateral ENG activity was abolished. In these cases, extensors were the most vulnerable, and usually when the MLR stimulation and the VF cooling sites were on the same side. Cooling of the dorsal aspect of the spinal cord to temperatures blocking synaptic transmission in the adjacent gray matter rarely depressed MLR-evoked fictive locomotion.

These results, summarized in Fig. 7.5, demonstrate that MLR stimulation activates a reticulospinal pathway in the MedRF which projects bilaterally through the VF of the spinal cord to activate spinal networks for locomotion (Steeves and Jordan 1980). Bilateral projections from the MLR to the MedRF in the cat are known (Garcia Rill et al. 1983a, b; Steeves and Jordan 1984) and, as confirmed by these results, unilateral stimulation of the MLR may activate reticulospinal neurons which descend on both sides of the spinal cord in the VF (Garcia Rill and Skinner 1987a, b; Orlovsky 1969, 1970a, b; Perreault et al. 1993). However, the cooling results also demonstrate that there is a slight asymmetry to the RS output, with a greater relative strength of the signal on the side of MLR stimulation. Garcia-Rill and Skinner (1987a, b) have also found that the majority of activated RS neurons project through the VF on the same side as the stimulated MLR and anatomically, the efferent projection of the MLR is mostly uncrossed to the MedRF (Steeves and Jordan 1984). RS neurons located in similar areas project primarily through the ipsilateral VF to terminate on ipsilaterally located lumbar spinal neurons (Tohyama et al. 1979; Holstege and Kuypers 1982). Although unilateral stimulation of the MLR may produce a slight asymmetry in RS output, it is assumed that spontaneous locomotion would provide a balanced descending input to the spinal locomotor

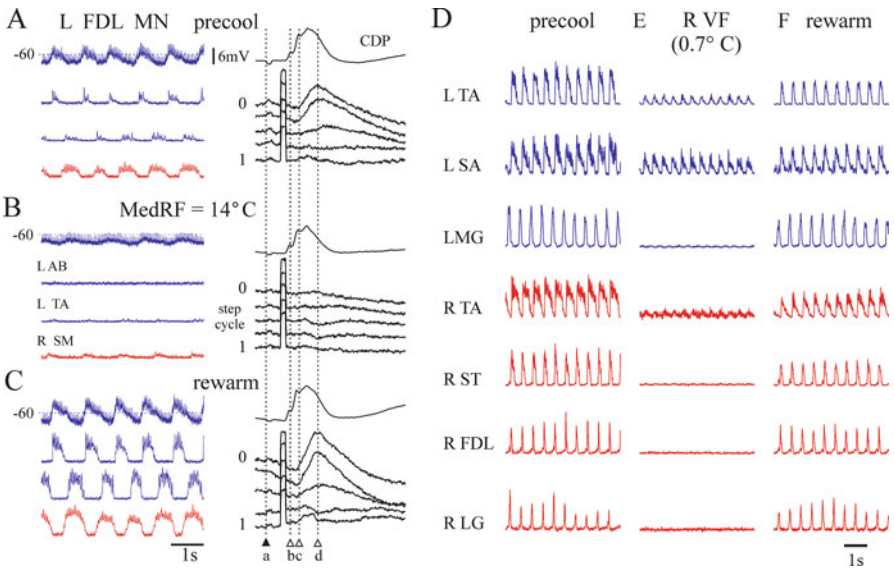

Fig. 7.4 Effects of temporary interruption of signal propagation through the descending locomotor pathway during fictive locomotion produced by unilateral stimulation of the MLR. (**a–c**) Cooling of the medial reticular formation (*MedRF*) blocks locomotor drive potentials and short-latency MLR evoked excitatory post-synaptic potentials (*PSPs*) recorded from a flexor digitorum longus (*FDL*) motoneuron and bilateral locomotor activity as seen in electroneurograms (*ENG*) recordings from hindlimb flexor and extensor nerves. Locomotion produced by stimulation of the right MLR. *Left side*: *top* – intracellular recording of left FDL motoneuron activity; *bottom* (three traces) – anterior biceps (*AB*), tibialis anterior (*TA*) and semimembranosus (*SM*) ENG on right (*R*) or left (*L*) sides. *Right side*: averaged cord dorsum potentials (CDP) (*top trace*) and motoneuron PSPs (*bottom traces*) obtained from MLR stimulus triggered traces sorted according to their occurrence during the normalized step cycle for precool, cool, and rewarm trials, respectively. Lines *a*, *b*, *c* and *d* indicate the timing of the MLR stimulus artifact, the peak of the first positive wave recorded from the cord dorsum and the onset and peak amplitude of the MLR-evoked EPSP, respectively. (**d**) Effect of unilateral cooling of the right ventral funiculus (*VF*) of the thoracic (*T12*) spinal cord on MLR evoked fictive locomotion. Locomotion was produced by stimulation of the right MLR. Locomotion was blocked on the same side of cooling and decreased on the opposite side of cooling. All ENG waveforms are at constant gain. Sartorius (*SA*), medial gastrocnemius (*MG*), semitendinosus (*ST*), lateral gastrocnemius (*LG*) (After Noga et al. 2003)

centers. It should be noted that for the lamprey, a primitive limbless vertebrate, MLR inputs from each side activate RS neurons in a balanced and symmetrical manner (Brocard et al. 2010). The significance of this difference is unclear but may related to the evolution of limbs and the requirement for more sophisticated/precise control mechanisms to control walking overground.

A crossed spinal or segmental pathway also contributes to the generation of locomotor activity from unilateral stimulation of the MLR (Fig. 7.5) and a similar result has been observed by Yamaguchi (1987) who showed that unilateral stimulation of the spinal cord could evoke locomotor activity on the contralateral side.

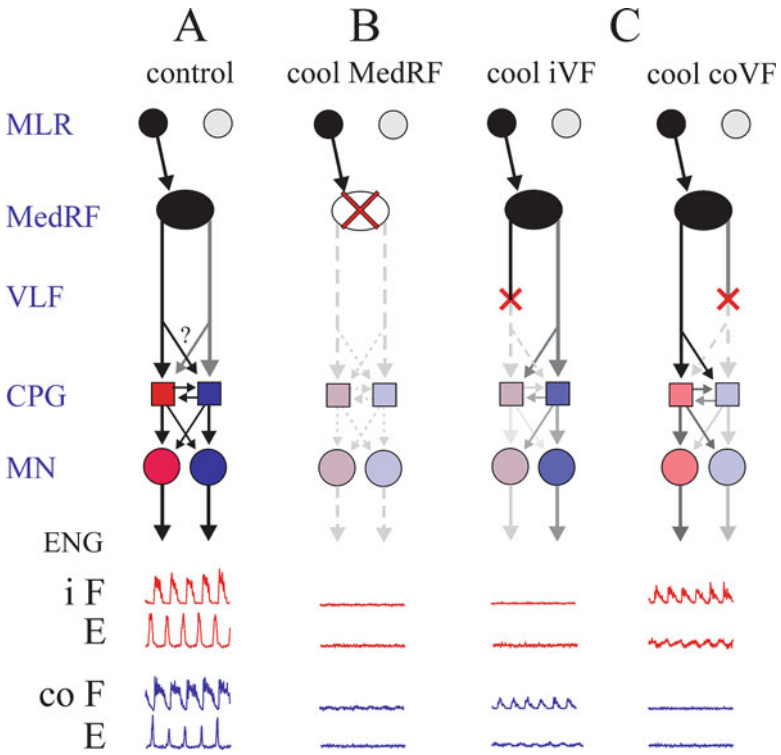

Fig. 7.5 Theoretical model of the locomotor induction pathway in the decerebrate cat activated during unilateral stimulation of the MLR and the effect of cooling to interrupt signal propagation through the brainstem relay (*MedRF*) or its descending (reticulospinal) projection in ventral lateral funiculus (*VLF*). *i* ipsilateral, *co* contralateral to the side of stimulation. The locomotor central pattern generators (*CPG*) on either side of the spinal cord are activated by bilateral reticulospinal projections from the MedRF and by crossed segmental projections from the CPG opposite to it. Signal strength through the descending reticulospinal pathway is greater on the side of stimulation indicating a slight asymmetry with unilateral stimulation. This is indicated by the relative darkness of the pathway (*VLF*) and the intensity of the color of the CPG/MN symbols at the spinal cord level. The amplitude of electroneurogram (*ENG*) activity recorded from different hindlimb flexor (*F*) and extensor (*E*) nerves during cooling indicates the degree of activation of the motoneuron (*MN*) pools relative to the control values. According to this scheme, cooling of the MedRF will block the descending signal bilaterally and the LPG will not be activated. Cooling of the VF will block the descending signal on the same side and block its direct or indirect (via segmental neurons) activation of the opposite CPG/MN. This will result in the loss of activity on the side of cooling and a reduction or loss in the activity on the opposite side of cooling, regardless of the side of MLR stimulation. The unaffected side of the VLF will then provide the only remaining route of activation of the CPG

There are two possibilities to explain this that may occur alone or in combination. Reticulospinal axons may cross to innervate contralateral spinal neurons directly (Holstege and Kuypers 1982; Kausz 1991) or may activate commissural neurons (Jankowska and Noga 1990) that are either components of the LPG or relay

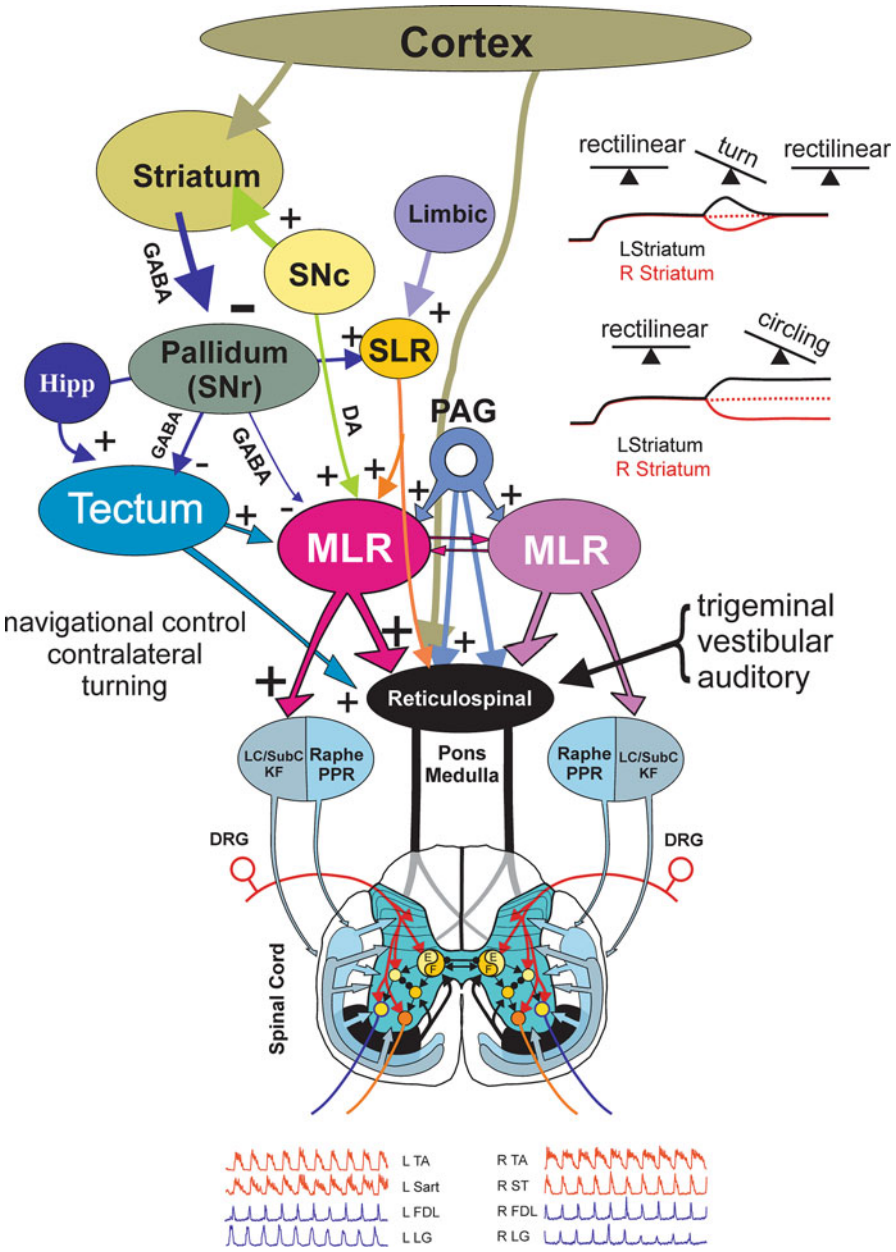

Fig. 7.6 Theoretical model for symmetry breaking of rectilinear locomotion by asymmetrically adjusting the level of activity of the descending locomotor pathway. An example of alterations in the output of the left or right striatum and how it may affect the output of the mesencephalic locomotor region (*MLR*) input to reticulospinal neurons to produce turning or circling behavior is indicated on the right. An increase in striatal inhibition (via cortical excitation) of the pallidum

interneurons. Crossed segmental pathways arising from the contralateral CPG are known (Kjaerulff and Kiehn 1997; Kremer and Lev-Tov 1997) which may form the substrate for interlimb coordination during locomotion.

Modulating Locomotor Symmetry Through RS Pathways

The RS neurons play a key role in the control of posture, locomotion (Takakusaki 2017), equilibrium and steering (Deliagina et al. 1993, 2008; Fagerstedt et al. 2001). As mentioned previously, in freely moving animals, forward or rectilinear locomotion likely occurs through bilaterally symmetric commands transmitted by the MLR and RS pathways. In contrast, during turning movements, an asymmetric command is likely generated and transmitted along RS pathways to modulate CPGs on the same side. Such a command would need to be strong enough or be directed to specific populations of ipsilaterally projecting RS neurons so as to overwhelm compensatory mechanisms from contralaterally projecting RS neurons as well as indirect projections through segmental commissural neurons (Noga et al. 2003). The duration of the asymmetric drive likely dictates the duration of the turning event, so it may be surmised that circling behavior will continue as long as the asymmetric drive is maintained. A theoretical model for symmetry breaking of rectilinear locomotion by adjusting the level of activity of components of the descending locomotor pathway is presented in Fig. 7.6. Here we summarize the possible ways higher brain centers and afferent inputs may modulate the bilateral descending signals to enable asymmetric drive to locomotor CPGs within the spinal cord.

An asymmetric drive has been shown for the lamprey during turning movements (Wannier et al. 1998; Deliagina et al. 2000). In the lamprey, contralateral turning responses (Fagerstedt and Ullén 2001) may be initiated by a brief stimulus applied to the skin on the side of the head (away from the side of the stimulus). This effect is mediated by trigeminal afferents to produce an asymmetric turn command. In cats, stimulation of trigeminal afferents or the trigeminal nucleus in the lateral tegmentum

Fig. 7.6 (continued) (*SNr*) disinhibits the MLR. Initially this disinhibition is symmetrical and rectilinear locomotion is generated. To engage a turn, a temporary increase in the striatal output on one side will produce an asymmetrical activation of the ipsilateral RS pathway. Striatal activity on the contralateral side may remain unchanged or may decrease. To enable circling activity, the striatal activity may be maintained on the one side. The asymmetric activation of the MLR is indicated. By asymmetrically adjusting the output of the MLR and/or the reticulospinal locomotor pathway directly, the hippocampus, tectum, SNc, limbic system, SLR, PAG, and the trigeminal, vestibular and auditory systems may also achieve symmetry breaking of rectilinear locomotion. *SNc* substantia nigra pars compacta, *SNr* substantia nigra pars reticularis, *SLR* subthalamic locomotor region, *PAG* periaqueductal grey, *LC* locus ceruleus, *SubC* subceruleus, *KF* Kölliker Fuse, *PPR* parapyramidal region, *Hipp* Hippocampus, *DRG* dorsal root ganglia, *DA* dopamine, *GABA* gamma-aminobutyric acid. Left (L), right (R), tibialis anterior (TA), Sartorius (Sart), flexor digitorum longus (FDL), lateral gastrocnemius (LG), semitendinosus (ST)

(an area previously known as the pontomedullary locomotor strip) may also induce, facilitate or modulate ongoing locomotion (Noga et al. 1988) via actions on neurons within the medial RF (Noga et al. 1991).

The vestibular system, while acting on spinal neurons directly via the vestibulospinal pathway to affect posture, may also act on the RS as well, thus affecting descending locomotor commands to effect turning and or/steering of the animal (Deliagina et al. 1992a, b; Deliagina and Fagerstedt 2000; Deliagina and Pavlova 2002; Pavlova et al. 2004). This input is excitatory and in the lamprey originates from the contralateral vestibular afferents. In the mammal, pontomedullary RF neurons receive convergent vestibular and limb inputs and likely are important for balance control (Peterson and Abzug 1975; Miller et al. 2017). Multiple areas of the brain including the thalamus, cortex and cerebellum also receive input from vestibular afferents relaying information about three dimensional head rotations and translations (Takakusaki 2017). Such information is integrated with other sense modalities including visual information to ensure proper compensation for maintenance of balance. Thus information relaying vestibular signals may additionally access descending locomotor pathways by indirect pathways.

Precise posture and gait control requires knowledge not only of body orientation (position) and motion but also requires information on the motion and spatial localization of objects in extra-personal space (Mergner and Becker 2003). This is achieved by the acquisition of vestibular (discussed above) as well as visual information. Visual information is relayed to a number of brain areas including the cortex, thalamus, and tectum (superior colliculus). The tectum controls eye and orientation movements and is important for pursuit or escape behaviors. Thus it has a major role in modulating rectilinear locomotion. The tectum is interconnected with the extrastriate cortex and receives input from the hippocampus. It projects to a number of structures including the MLR, the pontomedullary reticular formation, the thalamus, SNc and the PAG (Furigo et al. 2010) and is involved in motor learning, modulating stereotypic hunting patterns, motor planning and arousal and defense-like responses (see Noga and Opris 2017). Direct stimulation of the SC induces contralaterally directed locomotion by activation of the MLR (Dean et al. 1986). The tectum is strongly controlled by the basal ganglia, limbic and cortical structures (Chevalier et al. 1984). To initiate an orienting movement, the contralateral SC must be disinhibited by blocking SNr inhibition which allows the cortex to excite the collicular neurons (Hikosaka and Wurtz 1983).

RS neurons are also controlled by higher brain motor centers including the MLR, subthalamic locomotor region (SLR), cortex (via corticoreticular pathways) (Noga and Opris 2017) and cerebellum (see Takakusaki 2017 for review of cerebellar influences). The inputs are bilateral and it is suggested that changing the gain of any of these inputs unilaterally will result in asymmetric activation of spinal locomotor networks and enable steering. Activation of the RS pathway by the MLR is controlled by the basal ganglia. The major input is inhibitory (from the substantia nigra zona reticulate (SNr) of the globus pallidus (Roseberry et al. 2016). Disinhibition of the MLR occurs with the activation of inhibitory

GABAergic projections from medium spiny projection neurons of the striatum to the SNr (Hikosaka et al. 2000) and the removal of this inhibition increases locomotion (Kravitz et al. 2010). Any alteration in the level of inhibitory drive to the MLR on one side could theoretically modulate the RS input during ongoing rectilinear locomotion. The striatal neurons are controlled by inputs from visual, parietal and motor cortices and the thalamus (reviewed by Grillner et al. 2008). Central to this control is dopamine and without this innervation of the striatal neurons, a Parkinson-like condition will develop. The SLR may also control locomotion by its actions directly on the MLR (Garcia-Rill et al. 1981, 1983a, b) or the RS pathway (Takakusaki 2017). It is controlled by limbic inputs from the nucleus accumbens, amygdala, hippocampus and hypothalamus. As discussed in Sect. 7.3 (Symmetry Breaking in Navigation), the hippocampus encodes spatial navigational information and may participate in the control of locomotor speed. Its main influence is via the SLR and the tectum. By temporarily changing the output of these structures it may alter the symmetrical drive to the RS pathways (Fig. 7.6).

Lastly, the ability to engage locomotor activity in normal conditions requires first that the level of excitability of spinal networks generating locomotor activity be appropriately set (Harris-Warrick 1988). This is likely accomplished, in large part by the descending monoaminergic pathways (e.g., Barbeau and Rossignol 1990). For example, they modulate the responsiveness of sensory neurons to inhibit reflex pathways which would otherwise interfere with the smooth execution of movement (Jankowska et al. 1967a, b; Yoshimura and Furue 2006). Furthermore, they modulate the responsiveness of premotor spinal neurons to segmental (Barbeau and Rossignol 1990; Bras et al. 1990) propriospinal and descending inputs (Buchanan and Grillner 1991; Jankowska and Noga 1990) to activate specific subpopulations of neurons that produce locomotion and suppress those irrelevant or deleterious to the movement. Monoamines also modulate the intrinsic circuitry of the central pattern generator network and its output neurons (e.g., Hounsgaard et al. 1988; Merrywest et al. 2003). Lastly, monoamines modulate locomotor burst frequencies and amplitudes differentially (e.g., Kiehn and Kjærulff 1996). As these pathways are engaged during MLR-evoked locomotion (Noga and Opris 2017) it is possible that they could contribute to an asymmetric drive that could affect rectilinear locomotor activity providing that their release can be differentially controlled.

7.5 Concluding Remarks

The hierarchical mechanism of locomotion consisting of several functional components, including the decision mechanism, navigation map, locomotion command, central pattern generators and the EMG muscle activity patterns was examined Hafting et al. (2005). The analogy to symmetry breaking in physical systems where at a bifurcation point on the phase diagram, infinitesimal perturbations result in a transition to a new global attractor state provided subtle insights into the decision mechanism. The central role of symmetry/asymmetry and symmetry breaking of

neural states during the emergence of locomotion and movement was emphasized for brainstem and spinal central pattern generators.

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Chapter 8
Symmetry Breaking in Cognitive Disorders

Ioan Opris, Brian R. Noga, Liviu Bilteanu, and Manuel F. Casanova

Abstract In this chapter we discuss the effect of symmetry breaking and the emergence of brain/psychiatric disorders such as Alzheimer disease (AD), autism spectrum disorder (ASD), schizophrenia (SCZ), aging, and drug addiction. A common denominator in these brain disorders seems to be a faulty inhibition mechanism that plays a key role in the optimal functioning of neuronal microcircuits, loops and networks. When inhibition becomes suboptimal a transition from healthy mental states to pathological states starts to occur. A perspective that views mental disorders from the standpoint of symmetrical probability distributions may offer a paradigmatic shift for both diagnosis and therapeutical interventions.

Keywords Psychiatric disorders • Alzheimer disease • Autism spectrum disorder • Schizophrenia • Depression • Inhibition • Microcircuit • Symmetry breaking

8.1 Introduction

The emergence of brain functions ultimately occurs via the modulation of neuronal firing. The amplification of neuronal circuits' activity can break their symmetry (like in the case of "grid" cells) by "turning" local and transient signals or

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noise into stable and system-level asymmetries (Jilkine and Edelstein-Keshet 2011; McNaughton et al. 2006). At the core of various amplification mechanisms are positive feedback loops, resulting from excitatory and/or inhibitory microcircuit interactions between cells and their neuromodulatory components (Opris et al. 2009, 2011, 2012a, b). In fact, "symmetry breaking" is a result of the "interplay between the system dynamics" and the internal or external "cues" that initiate and/or direct the "outcome" (Li and Bowerman 2010).

It is clear that perturbation of normal symmetry breaking has an increasingly important role in the emergence of brain disorders, such as Alzheimer disease (AD), autism spectrum disorder (ASD), schizophrenia (SCZ), aging, and drug addiction. The common denominator among these disorders is the faulty inhibition within the cortical microcircuits in the brain (DeFelipe et al. 2012; Mountcastle 1957, 1978, 1997, 1998; Opris et al. 2009, 2011, 2012a, b). In fact, it has been suggested that disruption of neural activity subserving mental states results in brain pathology/disorders (McNaughton et al. 2006; Cocchi et al. 2017). The brain's function (software) changes according to the brain's state of activation, while the microcircuitry (hardware) is almost the same for all animals and guarantees brain's stability (Cocchi et al. 2015, 2017).

In this chapter we discuss the disruption of symmetry breaking in the context psychiatric disorders AD, ASD), SCZ, aging, and drug addiction. A common denominator in these brain disorders seems to be a faulty (out of balance) inhibition mechanism that plays a key role in the optimal functioning of neuronal microcircuits, loops and networks. When inhibition becomes suboptimal a transition from a healthy mental state to a pathological one starts to occur. This symmetry breaking approach may have major implications for both the diagnostics and therapeutics of mental disorders.

8.2 Symmetry Breaking in Alzheimer Disease

The earliest stages of Alzheimer's disease (AD) are characterized by the formation of mature tangles in the entorhinal cortex (EC) with behavioral manifestations of disorientation and confusion when navigating familiar places (Fu et al. 2017). Neurodegenerative changes (namely the senile plaques in Fig. 8.1a, and neurofibrillary tangles in Fig. 8.1b provide the "main diagnostic features of AD". Depending on the disease severity, small clusters of "neurofibrillary tangles" populate the cortex, "across the supra- and infra-granular layers" (Pearson et al. 1985). The overall disposition of "neurofibrillary tangles" defines a minicolumnopathy (or pathological minicolumn) where the "intralaminar circuitry and corticopetal fibers" are both "impaired" in a selective manner (Chance et al. 2006; Esiri and Chance 2006).

Changes in such modular structure performed with "minicolumnar morphometry analysis with computerized image processing tools" in monkeys, has been shown to "bear a direct correlation" to the declining cognitive abilities (Cruz et al. 2004; Opris and Casanova 2014). Not surprisingly, "minicolumnar thinning"

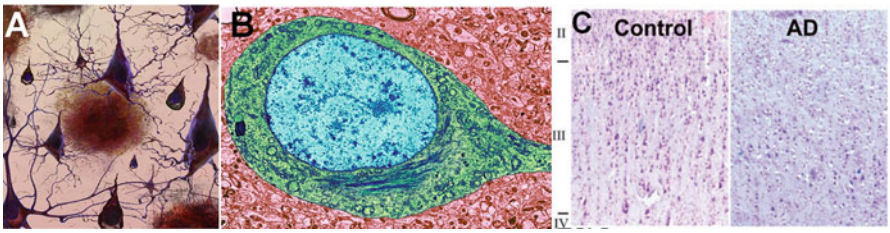

Fig. 8.1 Key features of the Alzheimer disease. (**a**) Neuron and plaque in Alzheimer disease. Illustration of neurons and amyloid plaques, courtesy of the National Institute on Aging. Proteomics – analyzing in an "unbiased" way how all the proteins in the brain accumulate or disappear – could provide clues to alternative mechanisms and even treatment strategies, scientists think. (**b**) Tau tangles damage brain GPS in Alzheimer's disease. A colored transmission electron micrograph of a tau tangle in a nerve cell from the brain of a patient with Alzheimer's disease. The tangle (*dark blue*) lies in the cytoplasm (*green*) of the cell body. Such tangles in the brain's GPS cells may explain why wandering is an early symptom of the disease. (https://cosmosmagazine.com/biology/excess-tau-damages-brain-gps-in-alzheimer-s-disease). (**c**) Example of prefrontal cortical minicolumn in a patient with Alzheimer's disease (*AD*) as compared to a neurotypical subject (*left*). Comparison of the minicolumnar width in Alzheimer's disease versus normal control subjects for planum temporale (*PT*) and primary auditory region of Heschl's gyrus (*HG*), of prefrontal Brodmann areas 22 (Chance et al. 2011)

(Fig. 8.1c) is a "concomitant" of "normal human ageing" and is an early change noted in "mild cognitive impairment". A more severe, "minicolumnar thinning" is seen in most cases of AD (Chance et al. 2011). A study on "minicolumnar morphometry" by van Veluw et al. (2012) has shown a "direct relationship" between the width of this modular structure and IQ decline. This correlation "holds" for the dorsolateral prefrontal cortex, but "not" for the parahippocampal gyrus (van Veluw et al. 2012). These observations translated to a two-stage model for AD, whereby "minicolumnar thinning" in normal ageing "precedes" the minicolumnar "degeneration" that accompanies the "onset" of dementia (Chance 2006). The "loss" of a significant number of minicolumns may "disrupt information processing" within "distributed networks"; thus, favoring the cognitive decline. The loss of neurons in AD does not allow for compensatory changes within the cell minicolumn. Thus, the standard ratios of cell volumes to minicolumnar space, neurodegenerative changes in pyramidal cells, and accretion of amyloid products, leads to distortions in the modular organization of the cerebral cortex which exemplify symmetry breaking. In this regard, we must consider that a rupture of the blood brain barrier in AD makes the brain an open system and one which would not obey laws of conservation.

The medial entorhinal cortex (MEC) contains specialized neurons called "grid cells" that map a person's location like a personal GPS, and form part of the spatial navigation system (Fu et al. 2017). When abnormal "protein aggregates" called *tau tangles* are formed, the brain's GPS is damaged, and disorientation/wandering symptoms of AD may be a direct result of excess protein in a patient's grid cells (Finkel 2017). This aspect was examined in a "transgenic mouse model" expressing

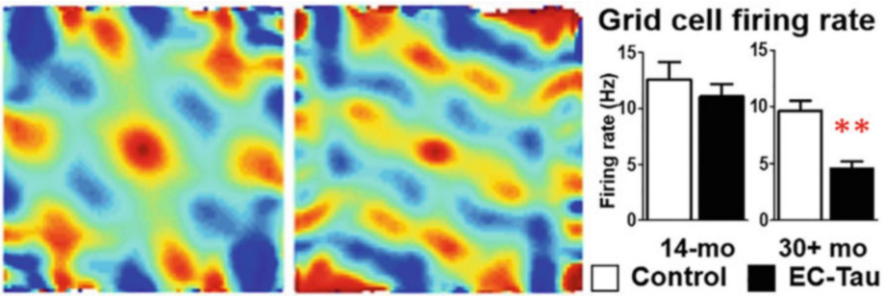

Fig. 8.2 Symmetry breaking in Alzheimer disease. The grid cell firing pattern in a mouse with tau pathology in the entorhinal cortex is weaker than in an age-matched control. Activity maps were severely affected in 30+−month EC-Tau mice (**a**) when compared to age-matched controls (**b**). (**c**) Peak firing rates of grid cells were reduced in 30+−month EC-Tau mice when compared to age-matched controls (peak firing: 30+− month EC-Tau mice, 4.5 Hz, n = 26 grid cells; 30+−month control mice, 9.6 Hz, n = 30 grid cells, $p < 0.0001$, Mann-Whitney U, 127.5). All data are expressed as mean ± SEM. (With permission from Fu et al. 2017)

"mutant" human tau proteins in the EC, showing that the "formation of mature tangles in old mice was associated with excitatory cell loss and deficits in grid cell function", including "destabilized" grid fields (Fig. 8.2) and "reduced" firing rates, as well as "altered" network activity (Fu et al. 2017). Overt "tau pathology" in the aged mice was accompanied by spatial memory deficits (Fig. 8.2). Therefore, "tau pathology" initiated in the EC could lead to "deficits in grid cell firing" and underlie the "deterioration of spatial cognition" seen in humans with AD (Fu et al. 2017).

8.2.1 Disruption of Local Cortical Microcircuit Activity in Alzheimer's Disease

To characterize the reduced activity of cortical neurons in AD and to evaluate their "consequences" for cortical processing, Lison et al. (2014) recorded the local field potentials (LFP) of laminar cortical activity in 9-month old anesthetized mice. LFP distribution was measured with a multielectrode array in all six cortical layers of the primary auditory cortex (Fig. 8.3a). Consistent with other studies, laminar LFP recordings were confirmed using current source density (CSD) analysis, providing an enhanced spatial representation of the orientation, location, and intensity of transmembrane currents underlying the evoked potential (Lison et al. 2014). Cortical responses were evoked with single pulses bipolar microstimulation in the granular layer and in deep layer VI at 500 μm distance from the recording electrode (Lison et al. 2014).

In Fig. 8.3a are shown color-coded current source density (CSD) plots highlighting current sinks (in granular, infragranular IG1, supragranular SG, and infragranular IG2) in blue and sources of current in red (Lison et al. 2014). The

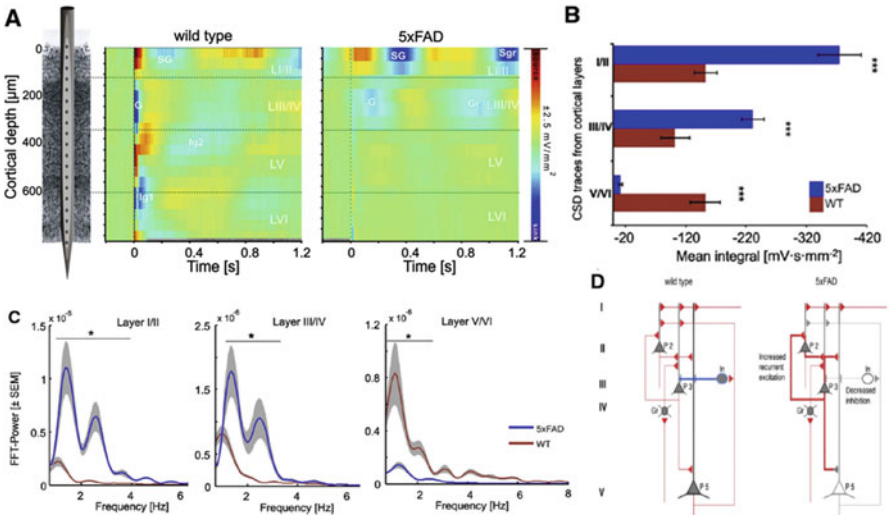

Fig. 8.3 Disrupted cross-laminar cortical processing in β amyloid pathology precedes cell death. Disruption of laminar processing in 5xFAD mice. (**a**) Current source density analysis of wild type vs. 5xFAD mice is shown. In wild type mice, the canonical pattern with a granular sink G accompanied by a deep infra-granular IG1 followed by a supra-granular SG and an infra-granular IG2 is seen. In 5xFAD mice, G and SG are still present, but IG1 and IG2 are not observed. Instead, additional SG sinks appear **(Gr, SGr)**. (**b**) Quantification of the amount of current flow over time in the adjacent CSD traces of 3 mice in each group. (**c**) Analysis of the local field potentials with Fast Fourier Transformation (FFT). FFT-power spectra show the contained frequency components in synaptic activity of layers I/II (*left*), layers III/IV (*middle*) and layers V/VI (*right*). Unpaired t-test, wt mice: n = 3; 5xFAD: n = 3, *p < 0.05; and ***p < 0.001. (**d**) Schemes of cortical columnar circuitry tentatively explaining normal feedback processing in (**a**) and its selective deficits in the 5xFAD cortex in (**b**)

current sinks reflect depolarizations due to excitatory synaptic input, while current sources reflect passive return currents. Single pulses applied in layers III/IV and layer VI through bipolar electrodes caused a layer-specific alternation sequence of current sinks and sources that lasted at least 1.2 s. In control (wild type) mice the laminar CSD profile showed a spatiotemporal feed-forward processing of excitatory synaptic activity with cross-laminar interactions (Fig. 8.3a, left). In transgenic mice, the CSD analysis (Fig. 8.3a) revealed a complete lack of the strong and early current sink in infragranular layers IG1 and IG2 sink indicating a significantly reduced synaptic excitation within infragranular layer V (Fig. 8.3a, right). The initial current sink in the granular layers was not phasic (as in the control type), but lasted almost 400 ms. Furthermore, the authors showed, that supragranular layers exhibited a repetitive pattern of sources and sinks (seen in the control case), but with two extremely strong sinks that indicate an increasing excitatory input. The sequence of sinks and sources (blue and red) was at opposite phase in granular layers III/IV and superficially adjacent layers I/II (Lison et al. 2014).

Significant differences between sink components in control and transgenic mice in all cortical layers are shown in Fig. 8.3b. As expected from the CSD plots, transgenic mice showed significantly higher depolarizing current flow in layers I/II but also in III/IV and a significantly lower current flow in layers V/VI. Since the CSD reflects synaptic inputs, the reduced staining of infragranular pyramids suggests that these neurons loose excitatory inputs.

Layer-specific functional alterations observed in transgenic mice, were further characterized with Fast Fourier Transformation (FFT) of the CSD profiles (Fig. 8.3c) for the frequency components of the LFPs in the different cortical layers. In the control type a single frequency peak just below 1 Hz was found that showed small power in layers I/II, intermediate power in layers III/IV and very large power in layers V/VI. This layer V/VI peak was massively reduced in the transgenic mice. Conversely, the layer-specific FFT-analysis revealed highly increased spectral power of activation in granular and supra-granular layers in the low frequency range. In addition, the low frequency peak of the FFT-power spectrum of transgenic AD mice was shifted to slightly higher frequencies compared to control/wild type. These FFT results of Lison et al. (2014) provide evidence for a modified excitatory frequency pattern in granular and supra-granular layers, induced by the infra-granular hypoactivity.

8.2.2 Decreased Inhibition Between Infra- and Supra-granular Layers

An increased current flow within the supragranular layers together with the suppression of activity in the infragranular layers suggests decreased feedback inhibition from infra- to supra-granular layers. This inhibition decrease is shown in Fig. 8.3d (Alexander et al. 1986; Lison et al. 2014). While the existence of normal cortical loops is supported by recent findings (Douglas and Martin 2004; Opris et al. 2013) the abnormal CSD in the transgenic mice cortex is not only useful for the diagnostic of the processing deficit in AD, but also reveals more subtle properties of the normal circuitry, namely the inhibitory feedback (Fig. 8.3d).

Overall, there are several differences between the control and AD shown by mice cortices. First, the early current sink in layer V is completely missing. Second, the initial current sink in granular layers III/IV is not phasic but has a long duration indicating some reduced post-excitatory inhibition. Third, the late current sink SG in supragranular layers I/II is extremely powerful and is followed by an even later (1 s) strong current sink SGr (Figs. 8.3a, b). The last two phenomena point to a strong role of inhibitory interneurons in granular and supragranular layers that are normally activated by feedback from layer V pyramids (Dantzker and Callaway 2000) and are no longer active in the transgenic cortex. Thus, the superficial layer processing in the transgenic cortex seems to be essentially reduced to the small excitatory feedback loop between layers III and II pyramids. The lack of both, excitatory and inhibition feedback from layer V pyramids for spatiotemporal integration with feedback from

the small loop may also explain the abnormal Fourier frequency of the superficial CSD in the 5xFAD cortex (Fig. 8.3c).

8.3 Symmetry Breaking in Autism

Autism spectrum disorder (ASD) is a neurodevelopmental brain disorder that impairs child's social ability to communicate and interact with others (Casanova 2005, 2008). The phenotype of this pervasive developmental disorder is reflected in various described abnormalities of brains microanatomy. Indeed, computerized image analyses of pyramidal cell arrays have shown "minicolumnar abnormalities" in the cerebral cortex of autistic patients (Casanova et al. 2002a, 2006a, b; McKavanagh et al. 2015). These studies have shown "reduced" (see Casanova et al. 2002a, 2006a, b) or "wider" (see McKavanagh et al. 2015) horizontal spacing with ageing in-between minicolumns, which is most "salient" within their peripheral neuropil space (Casanova et al. 2002a, 2003a). The initial findings of a minicolumnopathy have been reproduced when using the grey level index (GLI) as a parcellation technique (Casanova et al. 2002b). This technique allows for the pseudo 3-dimensional reconstructions of the minicolumns as they zig zag in and out of the plane of section of an otherwise 2-dimensional microscopic image or photograph. Findings of a minicolumnopathy are not unique to autism but have been described in other conditions such as schizophrenia where irregularities in cell spacing suggest a laminar abnormality and the possibility of a monoaminergic deficit. In autism, however, the findings of abnormalities of cell mean spacing and minicolumnar narrowing accrue over all of the laminae examined (2–6) and seem specific to the condition when compared to other mental disorders, e.g., schizophrenia, rubella babies (Buxhoeveden et al. 2002; Casanova et al. 2002c, 2003b). Some control comparisons (i.e., Down syndrome) have taken into account the possibility that intellectual deficiencies could account for the described morphological findings (Buxhoeveden et al. 2002).

In autism, the minicolumnar findings bear an age dependent pattern, being broader initially but narrowing with aging (Casanova et al. 2002a, 2006a, b; McKavanagh et al. 2015). The narrowing occurs within the peripheral neuropil space of the cell minicolumns. This compartment includes many inhibitory elements whose deficiency could contribute towards the resetting of the excitatory-inhibitory bias of the cerebral cortex and thus help explain some of the symptoms observed in autism, namely the sensory abnormalities and convulsions.

The minicolumnopathy of autism has been further investigated with a Delaunay triangulation technique (Casanova et al. 2006a). Researchers have used this method of parcellation by thresholding lower size neurons (interneurons) and reducing larger neurons (pyramidal cells) to points. The Delaunay triangulation technique provides for a bimodal distribution of edges wherein larger ones denote interminicolumnar distances and smaller ones denote intraminicolumnar distances. In autism,

research suggests that the distance between minicolumns is reduced while the mean cell spacing of neurons within a given column remains normal.

Neuronomorphometric studies quantitating neuronal and nucleolar size in autism indicate a reduction in the latter (Casanova et al. 2006a). The nucleoli direct the metabolism of the cell. A smaller nucleolus is reflective of a cell with shorter connections. This biases connectivity in favor of mu projections as opposed to commissural connections. Neuroimaging studies collaborate this finding as they have described a smaller corpus callosum size (relative to whole brain volume) and a smaller gyral window. Changes in the connectome explain differences in processing of information that emphasize local (detail focused) over global information (Brosnan et al. 2004; Happe´ and Frith 2006). Altogether, the thinning and widening of minicolumn in ASD patients is, in fact, a symmetry breaking, as shown in Fig. 8.4a.

Contrary to expectation, but consistent with the symmetry breaking hypothesis, McKavanagh et al. (2015) found "wider minicolumns" (Fig. 8.4c) in autistic children, particularly at younger ages. It was suggested that such wider spacing of the minicolumns may contribute to the enhanced discrimination seen in some individuals with autism spectrum disorders. Thus, the broader distribution of the minicolumnar width in autistic children, may contain two distinct types of

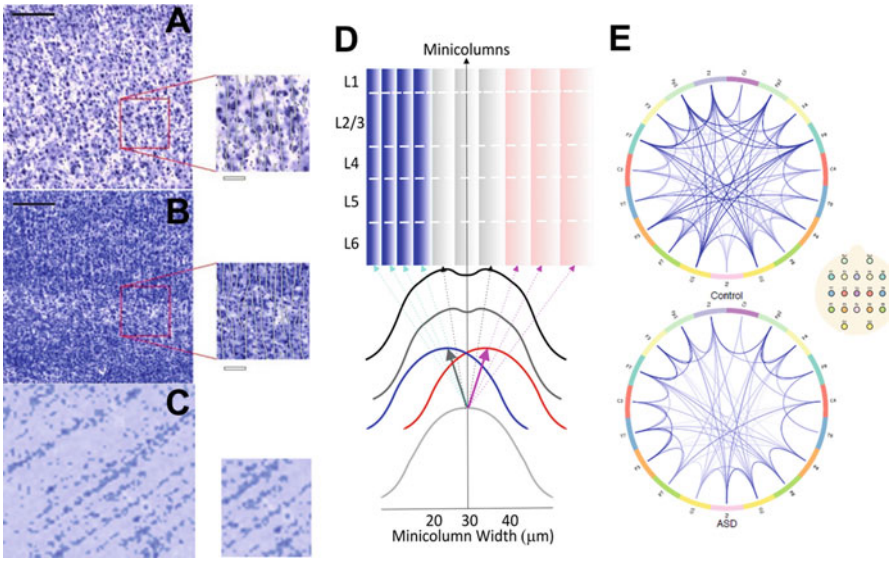

Fig. 8.4 Symmetry breaking in autism. (**a–c**) Example of prefrontal cortical minicolumns in autistic patients (*normal columns* in **a**, *thinner columns* in **b**, *wider columns* in **c**). Minicolumns in autistic brain may be thinner (**b**), or wider (**c**), compared with a normal control subject (**a**). (**d**) Illustration of symmetry breaking in autism. (**e**) Connectivity change in control vs. autism. Illustrations of the functional networks of a control subject, a non-syndromic autistic patient (With permission from McKavanagh et al. 2015 for **c**, and Peters et al. 2013 for **e**)

minicolumns depending on the age of the patients: thinner, as in the older patients in Casanova's studies (Casanova et al. 2002a, 2006a, b) and wider, as in the younger individuals in Chance's studies (McKavanagh et al. 2015). Figure 8.4d depicts the minicolumnar abnormalities from the perspective of symmetry breaking in autism.

The change in functional connectivity in control vs. ASD, is also responsible for symmetry breaking, as shown in Fig. 8.4 (McKavanagh et al. 2015; Peters et al. 2013). The analysis of network properties revealed differences specific to ASD, such as decreased long- over short-range coherence and markedly increased network resilience (Peters et al. 2013). The increased resilience in ASD may reflect an excessively degenerate network with local overconnection and decreased functional specialization.

In Fig. 8.5a, b is compared the key lateral inhibition process in control *vs*. autism. Lateral inhibition was visualized by plotting the net activation of a minicolumn as a function of distance from the center of that minicolumn, tangential to the cortical surface. When a "healthy minicolumn" is active (panel A), its short range output is a combination of the excitatory (red) and inhibitory (blue) signals, which summed

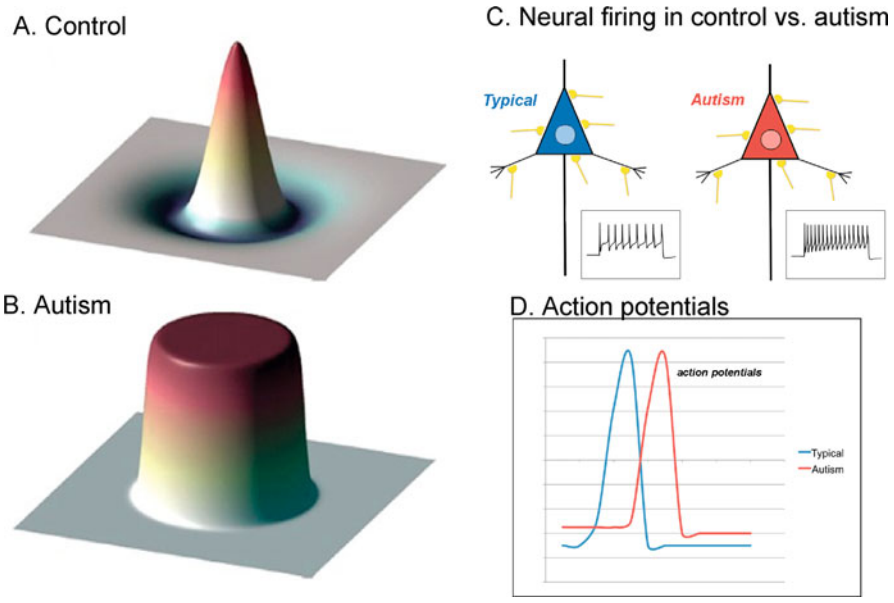

Fig. 8.5 (**a**, **b**) Lateral inhibition in control vs. autism. Lateral inhibitions may be visualized by plotting the net activation of a minicolumn as a function of distance from the center of that minicolumn, tangential to the cortical surface. When a "healthy minicolumn" is active (panel A), its short range output is a combination of the excitatory (red) and inhibitory (blue) signals, which summed create a "Mexican-hat profile of excitation-inhibition". Pathological minicolumns with an inhibition deficit mutually excite one another so that activation of any one tends to activate an entire module resulting in a "stovepipe hat" profile (panel B). (**c**, **d**) Electrophysiology in control vs. autism. Neural firing **c** is faster in autistic brain compared to normal controls. Action potentials (**d**) have a lower threshold in autism compared to normal brain

create a "Mexican-hat profile of excitation-inhibition". Pathological minicolumns with an inhibition deficit mutually excite one another so that activation of any one tends to activate an entire module resulting in a "stovepipe hat" profile (panel B). Then, neural firing (Fig. 8.5c) is faster in autistic brain compared to normal controls. The action potentials (Fig. 8.5d) have a lower threshold in autism compared to normal brain.

8.4 Symmetry Breaking in Schizophrenia

Schizophrenia is a brain disorder of thoughts, feelings and perceptions with outcomes in the disturbance of behavior (Butler and Zeman 2005). The disturbance of the brain function and structure is due to both genetic and environmental factors. Schizophrenia is associated with deficits in cortical plasticity that affect sensory regions of the brain and lead to impaired cognitive performance (Kantrowitz et al. 2016). Schizoaffective patients show highly significant deficits in auditory plasticity that contribute to cognitive, occupational and social dysfunction. Recent read studies involving N-methyl-D-aspartate receptor (NMDAR) suggest that; (i) NMDAR dysfunction may contribute to underlying cortical plasticity deficits, and, (ii) repeated NMDAR agonist administration may enhance cortical plasticity in schizophrenia (Kantrowitz et al. 2016).

It has been postulated that the prefrontal cortex of schizophrenic patients has significant alterations in their neuropil space (Casanova et al. 2008; Opris and Casanova 2014). In schizophrenia, minicolumnar analysis using a threshold technique in order to exclude smaller neurons have reported a normal width and verticality. However, researchers have shown (Fig. 8.6a) variability by lamina and cortical area examined with respect to cell density and intercellular distances (Casanova 2007; Casanova et al. 2008). The lack of abnormalities within the neuromorphometric features of cells within the core compartment of the minicolumns alongside abnormalities of cell mean spacing indicate a neuropil defect in lamination (Akil et al. 1999; Casanova et al. 2007b). Since the core features of the minicolumns remain intact, these laminar abnormalities postdate the development of the minicolumns, possibly involving the second trimester of gestation. Researchers have suggested that this may correspond to the cortical innervation by monaminergic projections which coincides with the putative genesis of other risk factors in schizophrenia (Akil et al. 1999).

In more recent studies, Chance et al. (2008) and Di Rosa et al. (2009) have added that in schizophrenia the spacing of minicolumns is altered in a sex-dependent manner as a result of the absence of age-related minicolumnar thinning. This was interpreted as a "failure of adult neuroplasticity" to maintain the neuropil space. Cognitive abilities are based on the "capacity to bind together the multiple features of perception". The ability to "bind together different features of perception" is a "distributed feature" of the cortex coded by gamma frequencies. EEG studies in schizophrenia have shown "reduced power and coherence" at gamma frequencies (Yeragani et al. 2006). These abnormalities, usually demonstrated on working memory tasks and recordings from the dorsolateral prefrontal cortex, "correlate

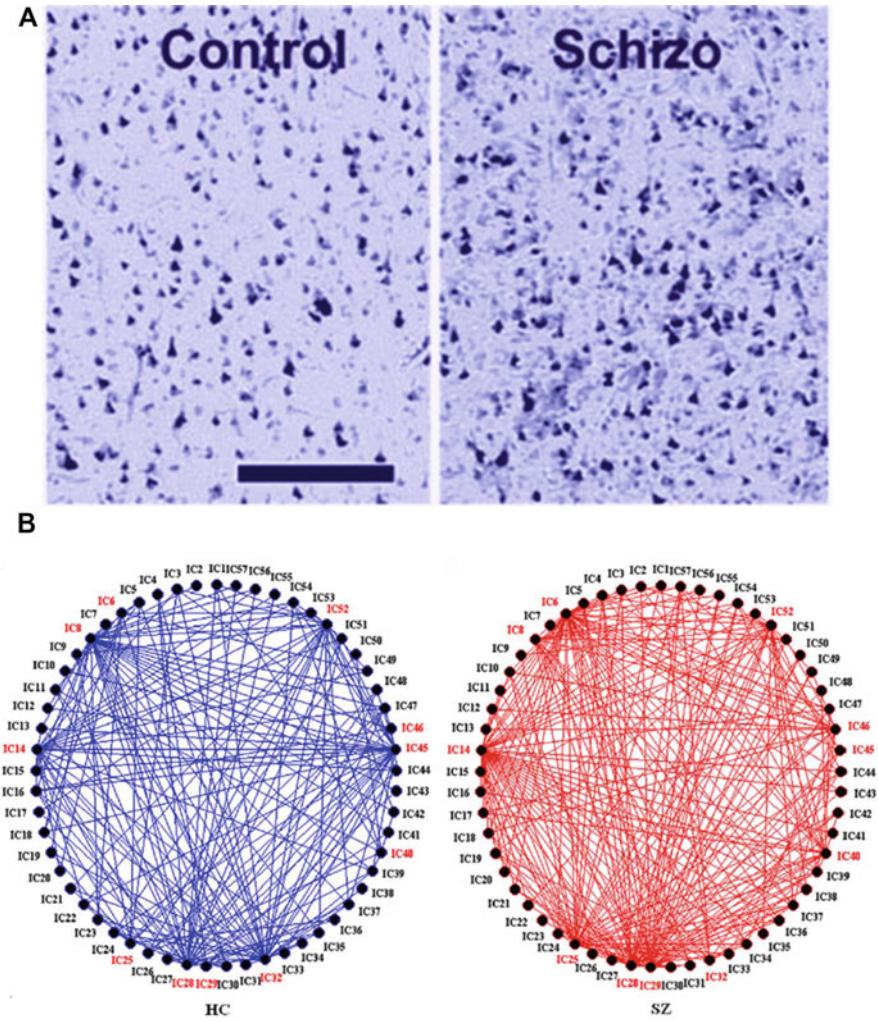

Fig. 8.6 (**a**) Example of prefrontal cortical minicolumn in schizophrenic patient compared to normal control (*left*). Comparison of the minicolumnar width in schizophrenic versus normal control subjects for layers III and V, across prefrontal Brodmann area 9 (Casanova et al. 2008). Bar length was 25,050 um. Adapted from Opris and Casanova 2014. (**b**) Examples of network connection patterns for healthy controls (*left*) and schizophrenia patients (*right*). The networks were built from mean absolute z-score (partial correlation) matrices at a typical cost (Kcost = 0.382, corresponding z-score threshold values: in controls: 0.318; in SCZ patients: 0.336). *Red* named nodes indicates graph indices were altered in schizophrenia for those components (Adapted from Yu et al. 2011)

to the observed cognitive deficits" in schizophrenic patients (Light et al. 2006). Monoamines serve to modulate signal processing within minicolumnar circuits. This is in agreement with the idea that in schizophrenia the basic modulation of minicolumns by monoaminergic systems is abnormal but the circuitry intrinsic to this module remains unaltered (Casanova 2007).

Abnormal cortico-cortical connections are a likely cause for the impaired long-range synchronization observed in SCZ patients (Fig. 8.6b). Studies involving lesions and developmental manipulations indicate that gamma-band activity and its synchronization are mediated by cortico-cortical connections. These long-range, predominantly excitatory pathways, not only link reciprocally cells situated in the same cortical area but also cells distributed across different areas and even across the two hemispheres (Engel et al. 1991). Accordingly, abnormalities in the number and organization of anatomical connections should impair long range synchronization. Early evidence from in vivo and post-mortem studies suggests that white matter volume and integrity are altered in patients with schizophrenia (Kubicki et al. 2007). This evidence is further supported by the more recent findings that revealed alterations in the organization of the connectome in SCZ.

Figure 8.7 shows a diagram of auditory cortex circuitry relevant to "impaired frequency discrimination" in schizophrenia (Lewis and Sweet 2009). Cortical processing of auditory stimuli is "initiated via projections from the thalamus", especially, the medial geniculate nucleus. These projections are arranged "tono-topically" (i.e., along a frequency gradient). The activation of a reciprocally connected "isofrequency network" of layer3 pyramidal cells (light blue) amplifies "selectively" a narrower range preferred frequency, "refining" the thalamic tuning curve. Densities of dendritic spines and axonal boutons are "reduced" in deep layer 3 of schizophrenia patients, "potentially limiting activation and current flow in the pyramidal cell network". Pyramidal neurons are "co-tuned" (i.e., they receive "concurrent stimulation" from thalamic or cortical projection neurons) with local inhibitory neurons (green), leading to a "stereotyped excitatory-inhibitory sequence" of postsynaptic potentials, which "increases the temporal precision of depolarization" and "enhances phasic activity" of the pyramidal neuron network. When alterations in GABA neurons firing occur (as in subjects with schizophrenia), they may further contribute to "impaired activation of isofrequency pyramidal neuron networks". The "tuning mechanism" being altered caused the "disruption" in the function of the auditory circuitry.

8.5 Conclusion

In conclusion, the disruption of symmetry breaking has profound implications in the emergence of Alzheimer disease, autism, schizophrenia, aging, or drug addiction. These disorders have in common a faulty inhibition mechanism that perturbs the optimal functioning of neuronal microcircuits, loops and networks (Bastos et al.

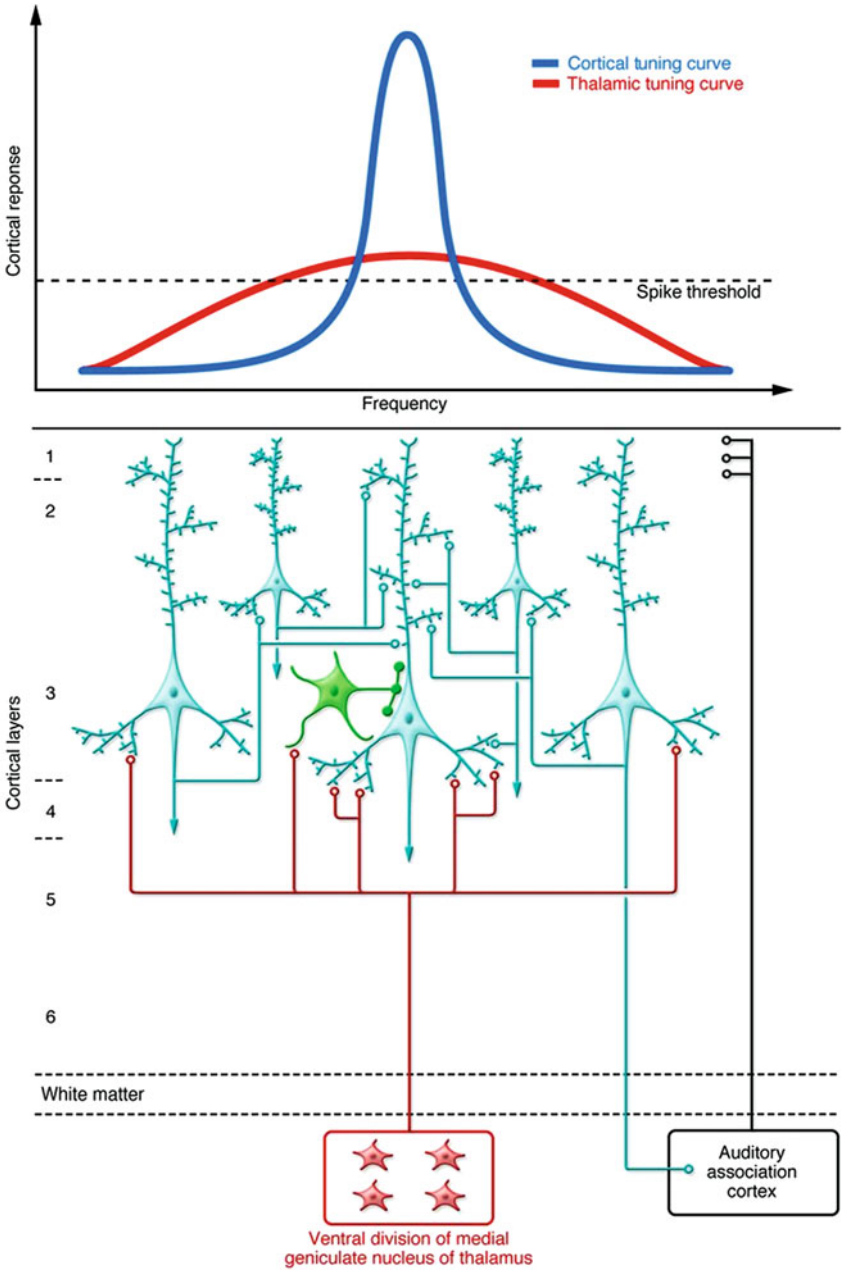

Fig. 8.7 Schematic of auditory cortex circuitry relevant to impaired frequency discrimination in schizophrenia. Auditory cortical processing is initiated by the medial geniculate nucleus of the thalamus. These geniculate projections are arranged tonotopically (i.e., along a frequency gradient that is broadly tuned). The subsequent activation of a reciprocally connected isofrequency network of pyramidal cells (*light blue*) within layer 3 selectively amplifies a narrower preferred frequency, refining the thalamic tuning curve (With permission from Lewis and Sweet 2009)

2012; Buxhoeveden and Casanova 2002; Mountcastle et al. 1955; Opris 2013; Opris et al. 2009, 2011, 2012a, b). This perturbed inhibition causes a transition from healthy mental states to pathological states and provides a suitable explanation to clinicopathological correlations.

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Chapter 9
Gauge Fields in the Central Nervous System

Arturo Tozzi, Biswa Sengupta, James F. Peters, and Karl J. Friston

Abstract Recent advances in neuroscience highlight the complexity of the central nervous system (CNS) and call for general, multidisciplinary theoretical approaches. The aim of this chapter is to assess highly organized biological systems, in particular the CNS, via the physical and mathematical procedures of gauge theory – and to provide quantitative methods for experimental assessment. We first describe the nature of a gauge theory in physics, in a language addressed to an interdisciplinary audience. Then we examine the possibility that brain activity is driven by one or more continuous forces, called *gauge fields*, originating inside or outside the CNS. In particular, we go through the idea of *symmetries*, which is the cornerstone of gauge theories, and illustrate examples of possible gauge fields in the CNS. A deeper knowledge of gauge theories may lead to novel approaches to (self) organized biological systems, improve our understanding of brain activity and disease, and pave the way to innovative therapeutic interventions.

Keywords Brain • Symmetry • Transformation • Mapping • Lie group • Topology • Gauge field • Coordinate system • Geometry • Consciousness

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9.1 Introduction

Current technical advances in systems neuroscience (Dayan et al. 2013; Mattei 2014; Huth et al. 2016; Taylor et al. 2015) try to establish causal relations between specific aspects of neuronal activity and system-level consequences. Multidisciplinary theoretical approaches, which offer a bridge connecting the scientific languages of biology, mathematics and physics, are clearly required. One might wonder if the unpredictable complexity of biology – neuroscience included – could hope for that kind of theories. An affirmative answer results from a treatment of living systems – and in particular the central nervous system (CNS) – via the physical and mathematical procedures of a gauge theory approach.

A possible role for gauge fields (Sengupta et al. 2016a) and symmetries (Tozzi and Peters 2016a) has been recently proposed in order to elucidate physiological and pathological features of brain activity. In the search for a dynamic interplay, a cross-over of the physics of elementary particles and cortical brain dynamics, gauge theory takes into account the possibility that brain activity is driven by one or more continuous forces represented by gauge fields, originating inside or outside the CNS. Three main ingredients are required to sketch gauge theory of the CNS:

- A system equipped with a symmetry and a correlated, measurable Lagrangian
- A continuous Lie group of local forces (transformations) which break the symmetry locally.
- One or more gauge fields, (possibly) external to the system, able to restore the broken symmetry and to keep the Lagrangian invariant, despite the local transformations.

The importance of such an approach rests upon the implicit ability to measure unknown quantities: if we knew two of the ingredients (for example, the values of the Lagrangian and the total forces applied to the system), we can extrapolate and calculate the value of the third (for example, the gauge field), via procedures from differential geometry. Indeed, vector projections can be used in order to assess CNS diseases in the powerful probabilistic framework of gradient descent trajectories along manifolds equipped with negative curvatures (Sengupta et al. 2016a).

The three above mentioned ingredients are interchangeable. System, local forces and gauge field may indeed play different roles in the CNS, depending on our initial assignment. Sengupta et al. (2016b) framed the required ingredients in the context of the free-energy principle and focused on the methodological implications of gauge theory for parameterisation and new inference schemes in data analysis. There are, however, other neurobiological possibilities, that speak to a neuronal gauge theory. It is conceivable that brain dynamics constitute more than one symmetry breaking and more than the expression of a single gauge field. A complex interaction among many actors might take place in the CNS, each with its specific role in preserving more than one Lagrangian – and our cognitive functions and associated pathologies could be the result of a mixture of many functional elements.

This chapter comprises six sections, and extends neuronal gauge theories for brain function to consider several scenarios. The first section informally describes a gauge theory in physics. We address this introduction to a broad interdisciplinary audience and try to make it accessible to experts from different fields. The second section focuses on the features required for a gauge theory for the CNS; e.g., vector spaces and symmetries, while the third is an effort to describe what gauge theories bring on the table – in the evaluation of brain function. Section 9.4 provides the mathematical formalism for technical readers. In Sect. 9.5, we provide gauge theories within the framework of the free-energy principle. Finally, Sect. 9.6 considers about other possible biological or functional candidates for brain symmetries/gauge fields.

9.2 What Is a Gauge Theory?

A gauge theory is a field theory, in which the Lagrangian (a function that summarizes the dynamics of the system) is invariant under a continuous group of local transformations (Zeidler 2011). The most important physical theories of the last centuries; i.e., electromagnetism, general relativity and quantum field theory, can be framed in gauge theories. The underlying concept is quite simple: *gauge* means *choice*. A *gauge* is nothing more than a *coordinate system* that varies depending on one's *location* with respect to some *base space*.

The cornerstones of gauge theories are the concept of *symmetries* and the Noether theorem, which states that for every continuous symmetry there is a conserved physical quantity. The global symmetry of the system is preserved, in spite of local changes, by a continuous force, called the *gauge field*. A gauge theory can be studied via normalized mathematical procedures (t'Hooft 1971), so that the local forces acting on each point of the system can be quantified and investigated through differential geometry. We will try to explain what a gauge theory is, conveying the geometric intuition rather than the rigorous formalism.

To illustrate the formalism, we might start with a ball, representing a system. Local forces, depicted as vectors, act just on a few zones of the ball surface (Fig. 9.1a). Indeed, vector spaces have noteworthy properties that make them attractive for representation models and for encoding complex structures as single multidimensional vectors (Snaider and Franklin 2014). The ball is unfolded and flattened into a two-dimensional reconstruction, allowing the entire surface to be transferred to a bidimensional *circle* (Fig. 9.1b). The local forces are arbitrarily described as vectors of different lengths and orientations, originating from the circle surface (Fig. 9.1b). The local forces on the circle surface can be described in terms of a broken line (the dotted line in Fig. 9.1c). In this case, the symmetry is considered as locally *broken* or, better, *hidden*. In order to keep the global symmetry invariant, we need to introduce a balancing force (Fig. 9.1d). This force is the *gauge field*. When the gauge field comes into play, we obtain a system equipped with continuous and unbroken line (the dotted line parallel to the circle surface in Fig. 9.1e). This

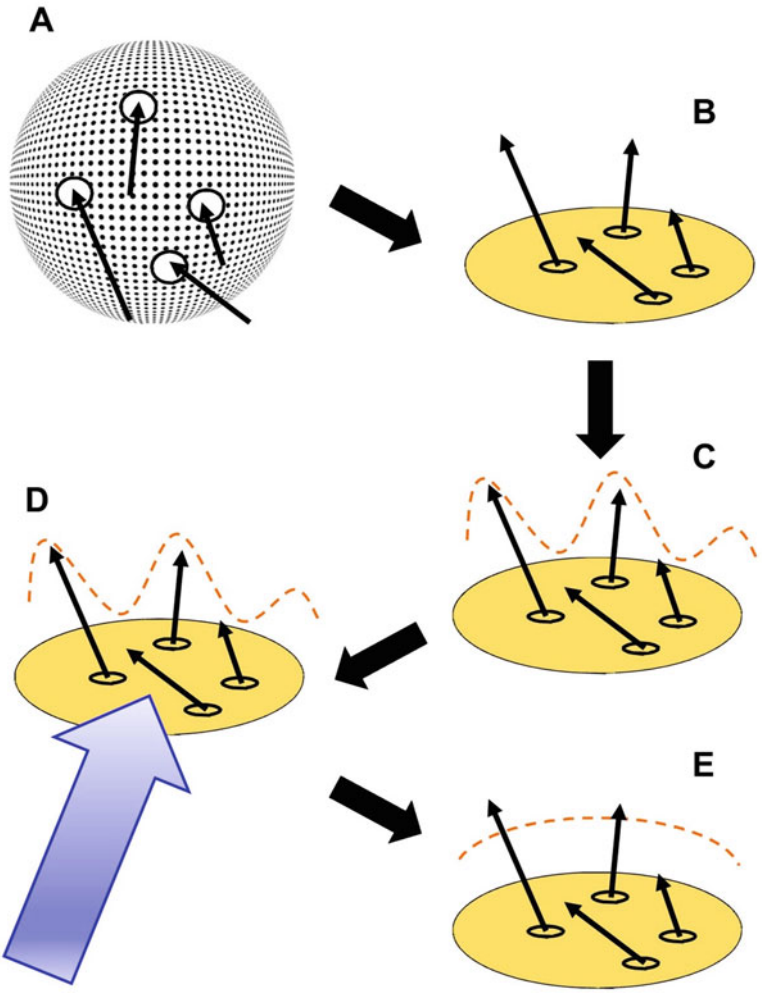

Fig. 9.1 A geometrical illustration of a gauge theory. The gauge field, a sort of mathematical *deus ex machina,* balances local transformations (See text for further details)

line stands for the Lagrangian, roughly corresponding to the global symmetry. In summary, if we want to keep the Lagrangian invariant, despite local changes, we have to transform the broken line of Fig. 9.1c into the continuous line of Fig. 9.1e, with the aid of a counteracting force. When a system preserves its own symmetry despite the action of local forces, it is said to be equipped with a gauge symmetry and we have a gauge theory.

When one sketches a gauge theory, one can arbitrarily choose a symmetry *a priori*: by fixing *a gauge*, the model then becomes easier to analyze mathematically. However, this does not automatically mean that every hypothesized gauge theory

should be accepted as valid. Deciding exactly how to fix a gauge is a key issue: the tractability of the resulting problem is heavily dependent on the choice. Although gauge theories approach their task speculatively, they build entirely upon the results of the physical sciences. They must be not only logically, but also physically tenable. In sum, a gauge theory is an abstract conjecture that needs to be tested by empirical investigations. As an example, the Higgs boson was first hypothesized via a gauge symmetry (Higgs 1964), then confirmed with the Large Hadron Collider.

9.3 In Search for Symmetries in the CNS

In this section, we focus on the key problem in sketching a gauge theory for the CNS. To do this, we need a continuous symmetry to break and restore. The search for nervous symmetries is not easy. Due to our incomplete knowledge of brain function, we do not know exactly which, and how many, symmetries are hidden in the CNS. Furthermore, symmetries need to be constrained and it is unrealistic to seek – in biology – the mathematical simplicity of physics. Even if we knew the requisite symmetries, it is doubtful if our current technology would be able to calculate all the necessary variables at each point in the CNS. For example, recent studies suggest that cognitive functions do not depend solely on electrical pulses, but on multifactorial intra- and extra-neuronal causes, involving supramolecular interactions among biologically active macromolecules (Tozzi 2015). It is also important to remember that any hypothetical descriptions cannot unambiguously characterize the etiology of fluctuation properties, as similar symmetric properties may stem from qualitatively different generators, which may be difficult to distinguish with finite data (Papo 2014).

Despite these limitations, gauge theories could pave the way to a novel approach to organized living systems. The prevalence of complex fluctuations would allow not only treating the brain as a physical system, but also help classify cognitive processes as operators acting on symmetries. Moreover, the computational neuroscience community is currently undertaking an effort to provide a systematic way to characterize symmetry and asymmetry in the network structures of the connectome – by inspecting the eigenvalues of different types of connectivity matrices (Esposito et al. 2014). Gauge theories for the brain are reminiscent of a mechanism of homeostasis, in which: (a) the conserved variable is a symmetry, often hidden from our observation, and (b) the *balancing* force must be continuous. In what follows, we present a brief list of known symmetries in CNS that could be tested in the frame of a gauge theory. The following treatment recalls recent results by Tozzi and Peters (2016a, b).

The brain generates scale-free fluctuation, even in the absence of exogenous perturbations (Papo 2014). It has been suggested that scaling properties allow cognitive processes to be framed in terms of complex but generic properties of brain activity at rest and, ultimately, during functional operations, limiting distributions, symmetries, and possibly their universality classes (Papo 2014). The stability

of spectrum exponents (of many neuronal processes) suggests that a universal scaling characterizes a large class of brain systems and physiological activities. Complex scaling and intermittency are generic spatiotemporal properties of the brain and, more importantly, could contain information on how observable large-scale behaviours arise from the interactions of many small-scale processes (Papo 2014).

The $1/f^n$ structure – of time evolving neuronal activity – offers a parameterisation that summarizes the values of the frequency and amplitude of cerebral activity over a given time. This means that a high number of possible source configurations of brain currents, in different cortical areas (i.e., *local transformations*, such as gamma oscillations in somatomotor cortex during states of enhanced vigilance, or alpha waves in posterior zones with the eyes open) give rise to a set of measured potentials characterized by a general scaling property. In a gauge theory, the global invariant power law might stand for the complete Lagrangian density of the total brain currents – and can therefore regarded as a global symmetry; while the local changes in frequency and amplitude are the local gauge symmetries. In summary, if we knew the frequencies and amplitudes of activity at each point of the brain, we could be able to estimate frequency and amplitude of the required, hypothetical gauge field.

Another neuronal symmetry has been recently discovered. A constant excitatory/inhibitory (E/I) ratio between the total amount of excitatory and inhibitory stimulation has been described, both in vitro and in vivo (Haider et al. 2006). The balance between the two opposing forces affects many cortical functions, such as feature selectivity and gain (Xue) and memory of past activity (Lombardi). The E/I ratio could also be interpreted as evidence of a homeostatic mechanism between strengthening and weakening processes in the adaptation of synaptic neuronal connections. Homeostatic systems induce a distinction between inhibitory and excitatory connections that could contribute to symmetry breaking, leading to directed coupling and information transfer (Tognoli and Kelso 2014). From our point of view, E/I ratio might be regarded as the Lagrangian of the intact and spontaneously active cerebral cortex. The experimental evaluation of local symmetry breakings in cerebral cortex could provide a map of the continuous forces acting on brain, in order that the gauge field could be calculated via differential geometry.

Thus far, gauge theories of CNS have been already proposed in the framework of quantum mind theories (Freeman and Vitiello 2008; Matsui 2001). Some of these models are equipped with a local gauge symmetry and resemble lattice gauge theory of high-energy physics. They are grounded on the notion of spontaneous symmetry breaking (Freeman and Vitiello 2008). The symmetry that is broken is the rotational symmetry of the electric dipole of the vibrational field of water molecules. Environmental stimuli may therefore act as a trigger for the breakdown of such symmetry.

It has been suggested that the cerebral cortex exhibits a fairly uniform microarchitecture, e.g., the minicolumns, characterized by a modular connectivity with invariant properties (Casanova et al. 2011). Specifically, minicolumns exhibit a

translational symmetry across their central axis and rotational symmetry; i.e., displacement in different planes of section. Furthermore, they are equipped with transitive symmetry, with respect to geometric scaling of morphometric relations in different cortical areas, and with temporal symmetry of morphometric relations during cortical maturation. Evaluation of how architectonic relations among mini-columnar elements (e.g., pyramidal cells) are conserved under spatial and temporal variation might lead to a better understanding of diseases characterized by columnar anomalies, such as autism, schizophrenia, Alzheimer's and drug addiction (Opris and Casanova 2014).

Last, but not the least, the free energy principle (FEP) for adaptive biotic systems (Friston 2010) might be regarded as another symmetry hidden in the CNS (Sengupta et al. 2016a). This is the most important candidate, because it encompasses all the above symmetries into a very general framework. Given its broad explanatory scope, we will return to the FEP later, in a dedicated section.

9.4 Gauge Theories: What Are They Good For?

Gauge theories originate from physics. However, they could, in principle, be applied to countless fields of biology, such as cell structure, bodily physiology, and so on. In this chapter, we focus on the CNS. The first and most important question is the following: is it possible to transfer powerful gauge symmetries from their natural environment of physical particles to the *soft* (and much more complex) living structures of biology? In other words, are we allowed to sketch a gauge theory of brain function?

The importance of a gauge theory calls on the possibility of applying differential geometry to CNS activity, in order to quantify unknown, hidden or latent variables. The possibility of using vector spaces and geometrical structures instead of neurons and wires for a representation model of the CNS has been already explored. To give an example, a modular small-world topology in functional and anatomical cortical networks has been shown considered as an information processing architecture (Jarman). Furthermore, researchers have demonstrated that visual experience is two-scaled, with a smaller dimension at shorter length scales and another at longer scales (Sreekumar). Moreover, it has been proposed that entorhinal grid cells reflect a stable two-dimensional manifold that contains the activity of individual neuronal representations, driven by continuous attractors (Yoon et al. 2013).

A central hypothesis, in this context, is that the information encoded in place-cell replay should reflect the topological structure of the experienced surroundings, thus capturing the spatial complexity of our environment (Wu and Foster 2014). In order to use vectorial models in the assessment of the brain, the spatial characteristics of neuronal connectivity need to be considered. For this purpose, some scientists endow networks with a metric by embedding them into a physical space. This provides an adaptive rewiring model with a spatial distance function and a corresponding spatially adaptive (local) rewiring bias, which predicts observed

connectivity architectures (Jarman). Further, by linking notions from Lagrangian and Hamiltonian mechanics of rigid bodies, some investigators have defined human shape as a Riemannian metric space, generalizing D'Arcy Thompson's classical formulation of mathematical morphology of shape and form, with the metric structure defined by the geodesic flow of coordinates connecting one shape to another (Djamanakova).

Software schemes offer tools for integrating structural and functional information across anatomical scales, thus connecting information across multiple physiological scales (Djamanakova et al. 2014). Also various neuro-epistemological approaches are based on vectors. This idea was first put forward by Alfred North Whitehead (Whitehead 1919) and Kurt Lewin (Lewin 1935) and then pursued, among others, by eliminative materialism (Churchland) and integration information theory (Tononi 2008).

In common with the above, gauge theories also allow the projection from a *real*, external space onto an *abstract*, more manageable space equipped with sufficient statistics. However, a gauge framework is much more powerful and accurate (Fig. 9.2). Gauge fields have a practical advantage: their forces may be exactly calculated through a difficult, but feasible experimental energy-based variational approach. Gauge theories can be evaluated through topological tools such as the Borsuk-Ulam theorem (BUT). BUT states that (Borsuk 1933; Dodson and Parker 1997):

> Every continuous map $f : S^n \rightarrow R^n$ must identify a pair of antipodal points (on S^n).

This means that the sphere S^n maps to an n-dimensional, Euclidean space R^n (Tozzi and Peters 2016b). Points on S^n are *antipodal*, provided they are diametrically opposite. For the use of BUT and its variants, see Peters and Tozzi (2016). It has been recently proposed that symmetries lie on the S^n sphere in guise of antipodal points, while the broken symmetries lie on the corresponding R^n manifold (Tozzi and Peters 2016a). Here, the gauge field stands for the continuous function required to go from a level to another (Fig. 9.3). This approach allows us to assess vector and tensor projections also by using the powerful tools of algebraic topology (Peters 2016).

9.5 Mathematical Formalism of a CNS Gauge Theory

There are many possible ways to handle a gauge theory of the CNS in a differential geometric sense. Analytically, this is simple but the numerics can be tortuous. Sengupta et al. (2016a) used Levi-Civita connections to project from an abstract space to another, more manageable space. Here we will focus instead on another type of transport, e.g., the Ehresmann connection.

As an example, we will consider the hypothetical case of a system of cerebral electric potentials equipped with a global invariant $1/f^n$ scaling symmetry. A procedure to quantitatively assess the required gauge fields is as follows.

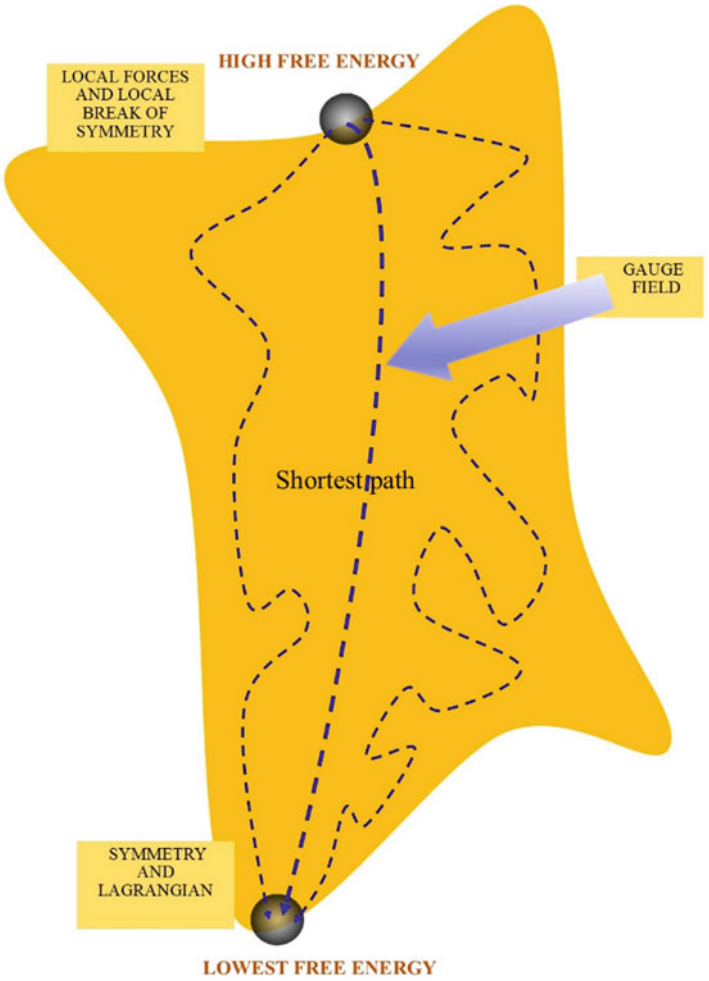

Fig. 9.2 Neuronal phase spaces equipped with sufficient statistics allow a rigorous way of measuring distances on concave manifolds. This means that dynamics transporting one distribution of neuronal activity to another is given by the shortest path from point to higher energetic levels to lower ones. In mathematical terms, the gauge field is a Levi-Civita connection, which allows exponential mapping and parallel transport, following the steps of a Langevin equation (For further details, see Sengupta et al. (2016a))

Neurophysiologic measures of brain activity in humans usually use a simple, non-invasive electroencephalogram (EEG). These measures exhibit significant 1/f-like power spectrum scaling (Pritchard 1992). Subjects would undergo 10–20 EEG measurements during active concentration and rest, eyes open and closed. In Fig. 9.4a, as an example, we choose four random cerebral areas with hypothetical frequency and amplitude measures of EEG activity. The **n** value of recorded EEG

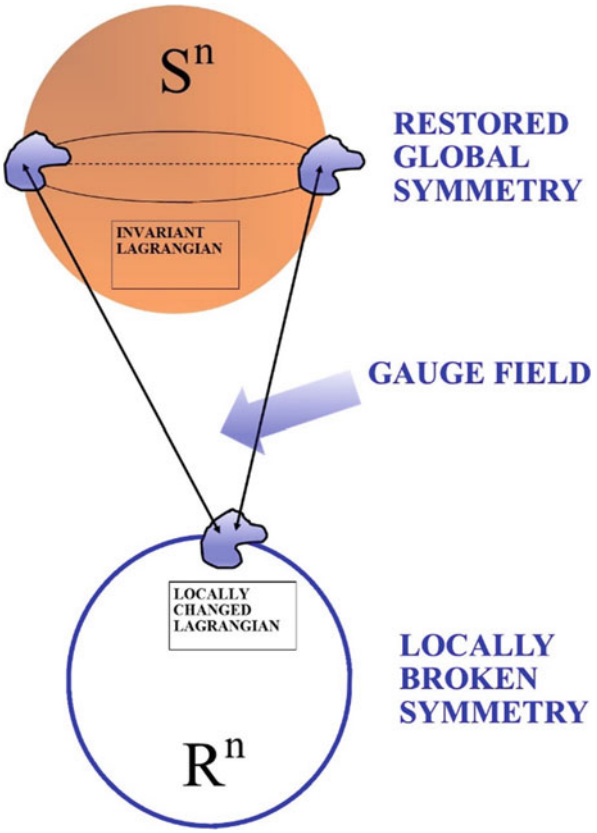

Fig. 9.3 Borsuk-Ulam theorem and gauge fields. BUT and its variants require a function which needs to be continuous. In the same way, a gauge theory requires a gauge field which needs to be continuous

segments could be estimated by fractal analysis techniques (Ihlen 2012). The most interesting cognitive phenomena occur in time windows shorter than seconds (Buzsáki and Watson 2012). Consequently, EEG frequencies and amplitudes might be evaluated in sub-seconds frames.

Once acquired, data from each point of the cortex can be investigated using the formalism of differential geometry. Technically speaking, a continuous group of transformations is applied on the tangent bundle, then a local section of the principal bundle is chosen and the covariant derivative is calculated via an Ehresmann connection. Practically, this would involve the following. The cerebral hemispheres (Fig. 9.4a) are unfolded and flattened into a two-dimensional reconstruction (Van Essen 2005), allowing the entire cortical surface to be transferred to an atlas $\mathbf{M}$ of $\mathbf{C^K}$ (differentiable), $\mathbf{C^\infty}$ (smooth), finite dimensional manifolds, each one mapping a brain area (Fig. 9.4b). The set of power spectra describing each cortical area's frequencies and amplitudes now stand for a continuous group of local transformations acting on sections of $\mathbf{M}$. $\mathbf{M}$ is arbitrarily equipped with a constant matrix $\mathbf{G}$ belonging to the SO(3) Lie group, isomorphic to the rotation group of the sphere (Fig. 9.4b).

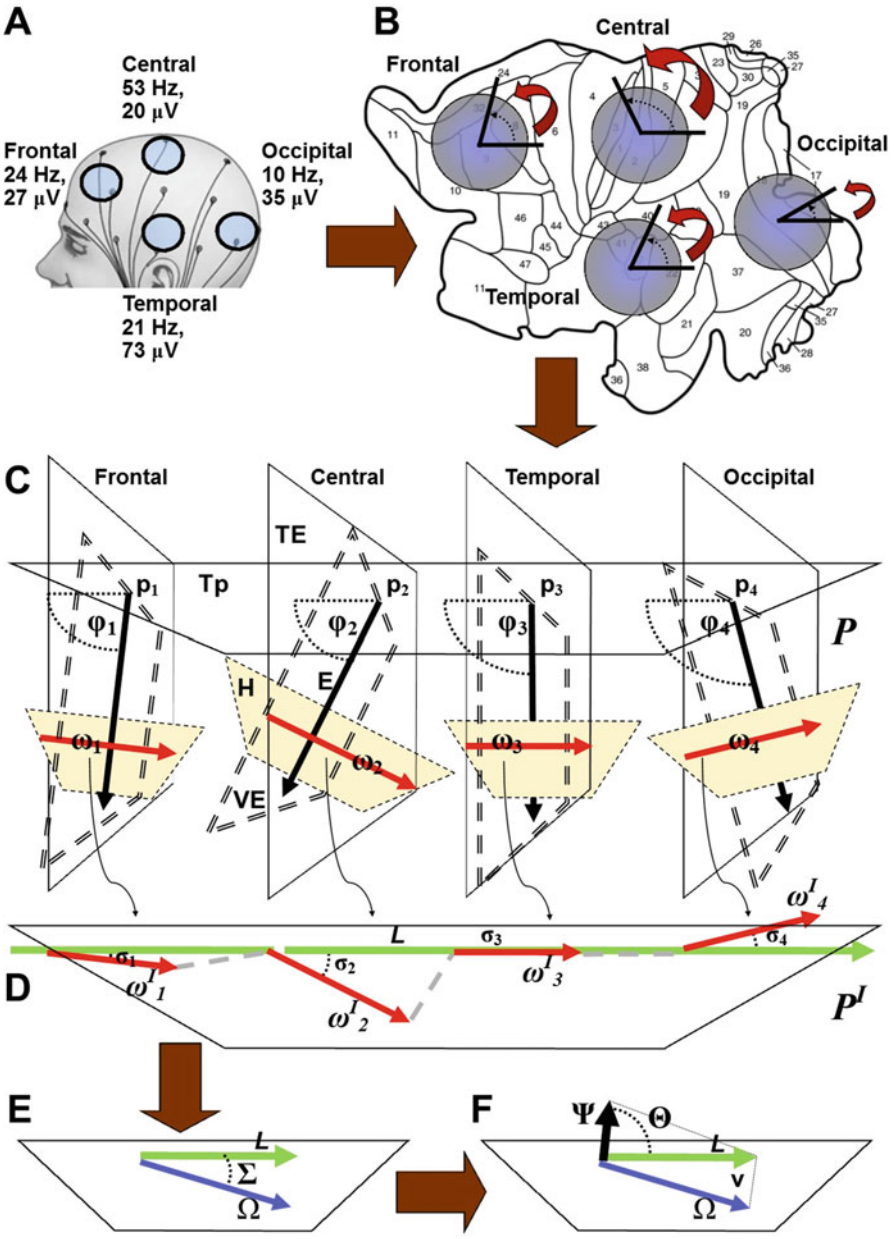

Fig. 9.4 Dynamics of cortical electric fields, described in terms of sections of fiber bundles, jet manifolds, Lie groups and Ehresmann connections (See the main text for further details)

M is a principal G-bundle ***P*** characterized by a trivial, smooth and differentiable fiber bundle, by vector bundles **E** and by a tangent bundle **TE** (Fig. 9.4c). The electrical forces are described by numbers, arranged in vectors and angles, representing the action **G** on a chosen local section **E** of ***P***. Four forces **G** are depicted in Fig. 9.4c in the guise of four vector bundles **E** arising from four points **p** in the tangent space $\mathbf{T_p}$. They are equipped with four n-dimensional rotation angles $\varphi(\varphi_1, \varphi_2, \ldots, \varphi_n)^T$ standing for the local $1/f^n$ scaling of each of the four brain areas. Rotations through tiny angles link nearby transformations of angles φ arising from points **p**. As a result, the linear approximation of the function **G** at **p** (and its angle φ) in each dimension can be described by introducing a partial derivative. In brief, changes in degrees of φ in selected brain areas match with different power spectra and hence with different electric configurations.

In a gauge theory, the geometric *link* between ***L*** and φ can be defined in terms of a connection form, the Ehresmann connection (Ehresmann 1950). If we identify the horizontal space **H**, perpendicular to the vertical space **VE**, we can extrapolate the Ehresmann connection $\boldsymbol{\omega}$, which is a vector on **TE** (Fig. 9.4c). The Lagrangian density ***L*** is indeed a function of **TE** and **H**. It would be correct to formulate all rates of change of $\boldsymbol{\omega}$ and φ in terms of covariant derivative, a linear differential operator in each associated **TE**, which allows different points (and their angles) to be compared. Mapping every vector $\boldsymbol{\omega}$ of ***P*** into the bijective, diffeomorphic $\boldsymbol{P^I}$ space, enables one to derive a curvature form (Fig. 9.4d). When the vectors $\boldsymbol{\omega^I}$ intersect the unique horizontal lift – corresponding to the invariant ***L*** – the angles $\boldsymbol{\sigma}$ are obtained.

The behavior of the vectors $\boldsymbol{\omega^I}$ and angles $\boldsymbol{\sigma}$ can be compactly written by pointwise vector addition of the partial derivatives of the function **G** at each point. As a result, we get a single vector: $\overrightarrow{\Omega} = \overrightarrow{\omega_1} + \overrightarrow{\omega_2} + \cdots + \overrightarrow{\omega_n}$ The angle $\boldsymbol{\Sigma}$ is introduced (Fig. 9.4e), standing for the interaction Lagrangian $\boldsymbol{L_{int}}$ and expressing the $1/f^n$ scaling values of vector addition obtained from our experimental procedure. If the lines ***L*** and $\boldsymbol{\Omega}$ are parallel, $\boldsymbol{\Sigma}$ equals the zero, $\boldsymbol{L_{int}}$ equals ***L*** and the symmetry of the system is preserved. Otherwise, if ***L*** and $\boldsymbol{\Omega}$ are not parallel (as is usual in physiological systems), $\boldsymbol{\Sigma}$ departs from zero, $\boldsymbol{L_{int}}$ is different from ***L*** and the system displays a broken or absent symmetry. In this case, in order to ensure the invariance of ***L*** and to restore the symmetry, we need to define a covariant derivative such that the derivative of $\boldsymbol{\Sigma}$ will again transform identically with $\boldsymbol{\Sigma}$. According to the covariant version of gauge theories, the correction terms are reinterpreted as couplings to an additional divergent counter-term, the gauge field, by allowing the symmetry parameter to vary from place to place in the local coordinate system.

Figure 9.4f shows the above procedure in a very abridged form. If we ignore ***L*** and examine the vector $\boldsymbol{\Omega}$ and its angle $\boldsymbol{\Sigma}$, we observe nothing else than a single force. If we instead regard ***L*** as a vector, whose basis results from the scalar components of its vector space **v**, then $\boldsymbol{\Omega}$ (and its angle $\boldsymbol{\Sigma}$) turns out to be just one of the covariant components of ***L***. In order to keep ***L*** invariant, we need to add another component into **v**: we introduce the vector Ψ, equipped with the angle Θ (Fig. 9.4f). The angle $\boldsymbol{\Theta}$ stands for the gauge field Lagrangian $\boldsymbol{L_{gf}}$ and expresses the global value of $1/f^n$ scaling of the required gauge field. We are thus allowed

to make accurate predictions of forces: we can extrapolate from $\boldsymbol{\Theta}$ the values of time, frequency and amplitude of the gauge field required to keep invariant the $1/f^n$ scaling during cortical activity. This provides a practical example of how one can apply gauge theories operationally to electromagnetic recordings of the sort that are currently available in systems neuroscience.

A mathematical formulation for technical readers and a tutorial are provided in Sengupta et al. (2016a), Supporting Information.

9.6 Gauge Theories and the Free-Energy Principle

The free energy framework is the most natural candidate for a gauge theory of the CNS (Sengupta et al. 2016a). The free energy principle says that self-organizing system that is at nonequilibrium steady-state with its environment must minimize its free energy, thus resisting a natural tendency to increase its disorder or entropy (Friston 2010). The principle of minimising variational free energy (an information theoretic construct for systems that attain non-equilibrium steady-state), is about trying to understand how homeostasis is maintained (Sengupta et al. 2013). The free energy principle separates the agent (the internal states) from the environment (the external states), which encompasses the external and internal milieu. Because entropy is also the long-term average of *surprise*, the brain will appear to minimise surprise (aka *surprisal* or self information), in order to ensure that the probability of interoceptive and exteroceptive sensory states; i.e., the entropy of sensory exchanges with the environment remains low.

Agents can suppress surprise by changing the two things that surprise depends on: either they modify sensory input by acting on the world, thus minimizing prediction errors, or they adjust their perceptions, by changing their internal states, thus optimizing accuracy of predictions (Friston 2010). The feasibility of calculations based on entropy has been proved useful for a basic understanding of neuronal complexity. Research looking at fluctuations in brain signals provided evidence that the complexity of those signals, as measured by entropy, conveys important information about network dynamics, e.g., local and distributed processing (McDonough). Efficient algorithms to calculate transfer entropy values between two systems have been introduced, allowing the estimation of functional connectivity between different brain regions (Ma). Furthermore, resting-state fMRI data from the Human Connectome Project (Van Essen et al. 2013) were used to measure, through multiscale entropy, the extent of neural complexity in the BOLD signal (McDonough). These studies affirm a prediction of the principle of minimum (variational) free energy that necessarily entails a high degree of mutual information (relative entropy) among distributed representations in neural networks – and a necessary critical slowing of the sort seen in scale free dynamics (Friston et al. 2012).

The time average of variational free energy is essentially a proxy for entropy, therefore minimising entropy production corresponds to minimising variational free energy at each point in time. Accordingly, we can treat variational free energy as a Lagrangian and, implicitly, a way of minimising entropy. One might imagine that the dynamics associated with this sort of Lagrangian are a necessary consequence of the resulting coupled dynamical system (with a random dynamical contracting set), and a resulting eigen-spectrum with a countably large number of eigenvalues and associated multi-Lorentzian spectral density. As above, tensor values of the required gauge field could be calculated via differential geometry. For example, if the tensors are measured in energy units, we can estimate how much energy (originating from an external or internal gauge field) is required by mental states, in order to minimize entropy and variational free energy at each point in time. Table 9.1 recapitulates an account of a gauge theory based on the free-energy principle.

Table 9.1 The ingredients of a gauge theory within the framework of the free-energy principle

	Physical and biological context	Variational free-energy formalism	Possible corresponding nervous structures
System	CNS	Brain as an inferential machine in non-equilibrium steady-state; an agent with its neuronal or internal states	CNS
Lagrangian	Energetic homeostasis	Variational free-energy (sensory entropy)	CNS homeostasis
Local forces	Continuous external stimuli coming from the environment, or internal stimuli coming from the body	External states producing local sensory perturbations in the agent and increase of prediction errors, which gives rise to a Kullback-Leibler divergence between sensation and prediction	Sensory pathways, from the periphery to the CNS, and their corresponding, coupled cortical layers 1–3, which convey bottom-up messages
Gauge field(s)	External continuous force	Precision weighting of prediction errors (implicit in the encoding of uncertainty), leading to minimization of prediction errors through action and/or perception; Levi-Civita connection, joining together physical spaces and phase spaces	Cortical layers 5–6; they convey top-down messages
			Visual attention
			Other unknown structures

See Sengupta et al (2016a) for details

9.7 Other Candidates for Brain Gauge Theories

In summary, to sketch a CNS gauge theory, we require the neuronal homologues of the three ingredients: i.e., a system equipped with a symmetry, local forces and one or more gauge fields. Depending on our initial gauge choice, the three ingredients can be assessed in different combinations. Many possibilities arise, whose feasibility can be experimentally verified. In closing, we provide some discussion of further candidates for gauge fields.

9.7.1 Consciousness

In the search of the neural correlates of consciousness (Koch et al. 2016), gauge theories may provide a novel method to investigate this challenging phenomenon. In particular, when embedded in a gauge framework, consciousness no longer stands for unspecified brain activity, but for a quantifiable parameter that can be expressed in terms of vectors or tensors. Indeed, consciousness might correspond to a Levi-Civita connection; e.g., the gauge field. In absence of consciousness, the external states do not produce sensory perturbations; from the perspective of the free energy principle, this means, the symmetry of the variational free energy, e.g., the sensory entropy, cannot be restored. As an example, during sleep, in which consciousness is altered, a response to local sensory perturbations does not occur. In such a vein, if we assume that the system stands for the cortex, ascending arousal systems are potential candidates for gauge fields. The midbrain contains tonic neurons that ensure a continuous cortical neuromodulation. Tonic neurons are located in the locus coeruleus, in the dorsal raphe and central superior nuclei; e.g., along the pathway of the ventral branch of ascending arousal system, and in the reticular thalamic nucleus, which is the final step of the dorsal branch of the ascending arousal system (Nieuwenhuys et al. 2008). Recent data suggest that the neural correlates of consciousness might be associated with posterior cortical hot zones (Koch et al. 2016). If this was the case, we could be allowed to assimilate qualitative notions of conscious level into the quantitative gauge theoretic framework of cortical function.

9.7.2 Blood Flow

If we hypothesize that the system is the entire CNS and the gauge field is located in other bodily systems, it is possible that local forces stand for the cortical oscillations evoked by the stimuli from the external environment, while the continuous gauge field stands for haemodynamic fluctuations. The idea that blood

circulation influences brain activity dates back to the pioneering work of Angelo Mosso (1896) and is still evident in brain mapping studies that predominate in modern neuroscience (Nieuwenhuys et al. 2008; Friston et al. 2014). A recent paper is particularly intriguing in this regard (Park et al. 2014). In humans, cardiovascular fluctuations underlie behaviourally relevant activation in multifunctional cortical areas. Neuronal events locked to heartbeats before stimulus onset predict the detection of a faint visual grating in the posterior right inferior parietal lobule and the ventral anterior cingulate cortex. Heartbeats therefore shape visual conscious experience, by contributing to neuronal representations. Similar coupling in the interoceptive domain would mean that the introception of autonomic signals might underlie subjectivity and sense of self (Park et al. 2014). Furthermore, emotions can be influenced by cardio-circulatory mechanisms. It has been demonstrated that short-term interoceptive fluctuations enhance perceptual and evaluative processes related to the processing of fear and threat. The processing of brief fear stimuli is selectively gated by their timing in relation to individual heartbeats and these interoceptive signals influence the detection of emotional stimuli at the threshold of conscious awareness, altering emotional judgments of fearful and neutral faces (Garfinkel et al. 2014). Resembling a novel version of Fechner law, gauge theories might quantitatively correlate stimuli and perceptual processing.

9.7.3 Environmental Stimuli

In an *autopoietic* account of the gauge framework, the system might stand for the brain, equipped with self-sustained continuous forces producing local, self-generated perturbations. In this case, the best candidate for a gauge field is the continuous afference from the external world. In such a framework, the spontaneous activity of the brain cannot be simply reduced to background noise, uncorrelated to the system's response (Lombardi et al. 2012). We are presented with an auto-referential system, in which the role of spontaneous fluctuations is to preserve brain's internal symmetry. Homeostatic plasticity ensures that neuronal networks assume a sub-critical state, independently of the initial configuration. Surprisingly, increasing the external stimuli modifies the network set-point towards criticality (Priesemann 2015).

9.7.4 Time

It has been recently suggested that some brain functions could be dictated by the principle of minimum frustration, a concept borrowed from energetic landscapes of protein folding (Tozzi et al. 2016). The brain is equipped with many timescales,

ranging from nanoseconds to several days. According to this novel formulation, structural changes in the brain lead to energy decrease at very long CNS timescales. With the passage of time, the trajectories of neuronal processes, such as memory and perceptual recognition, tend towards the low-energy basins of narrow funnel-like attractors. As with the free energy principle, the minimum frustration principle states that the gradient descent (energy decrease) dictated by Langevin equations takes place over long brain timescales (see Fig. 9.2). In such a vein, time becomes a gauge field. Indeed, at least at the non-relativistic scales typical of biological systems, time is a continuous function. This function can restore the global symmetry; e.g., the lowest possible variational free energy, which has been broken by local forces, e.g., environmental inputs. Time stands in this case for a known parameter, which affords the possibility to evaluate unknown parameters.

9.8 Conclusions

When emphasizing the circular causality between the nervous system and the world in which it is embodied, a proper consideration of this holistic aspect of information processing in the brain is required. Starting from this conceptual background, our aim was to introduce the general, abstract model of a physical gauge theory in biology and evaluate its possible implications for the CNS. Brain functions and neuropsychiatric diseases can be approached from the physicist's point of view – appealing to the basic observation that the CNS is an open system; continuously interacting with its environment. The ensuing dissipative character of the brain turns out – from a gauge theoretic perspective – to be the root of its dynamics, behaviour and persistence.

Such an approach holds promise because it directs us into new ways of thinking, offers new perspectives, and shows how it is possible to reformulate old problems. Gauge symmetries could lead to novel approaches to organized biological systems, improve our understanding of brain function and pave the way to innovative therapeutic strategies. To take some examples, visual attention, consciousness, spontaneous neuronal activity and functional regimes at the edge of criticality are impaired in many pathological conditions, such as autism, schizophrenia, drug addiction, Alzheimer Disease, depression *etc*. A potential medical application for gauge fields is epilepsy, in which, according to a gauge theory, the Lagrangian might be disrupted by pathological spikes. Seizures could be counteracted, or even removed, by carefully constructed 'artificial gauge fields' (e.g., via selective application of electric waves of specific frequency on target micro-areas, or via drugs) able to *recover* the Lagrangian and restore the electric symmetry. We hope that this brief survey of the potential of a gauge theoretic approach hints at the possibility of such developments in the future.

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Chapter 10
Brain and Nonlinear Dynamics: Slow-Wave Sleep Regulates to the Edge of Chaos

D. Alistair Steyn-Ross and Moira L. Steyn-Ross

Abstract We present a theoretical modeling study that predicts that the EEG waveforms observed during the passage from wake through the stages of deepening natural sleep arise from the evolving interactions between symmetry-breaking transitions in the brain. These non-equilibrium transitions are brought on by modulations from naturally occurring neurotransmitters, primarily acetylcholine and GABA, whose concentrations vary dynamically during sleep. In particular, we find that the slow-wave oscillations of deepest nonREM sleep are fundamentally chaotic in nature, arising spontaneously from a competitive interaction between Turing (spatial) and Hopf (temporal) instabilities. We show that by introducing an activity-based regulation of inhibitory gap-junction diffusion, the sleeping cortex can move towards the edge of chaos defined by the boundary between the disordered slow-wave state and a pathologically ordered seizure-like state. We suggest that such self-organization could allow the brain to dwell in a state that is optimized for pruning and consolidation of memories.

Keywords Slow-wave sleep • EEG • Spatiotemporal instability • Birfurcation • Non-equilibrium states • Hopf oscillations • Turing patterns • Self-organization • Edge of chaos

10.1 Introduction

One of the most intriguing ideas in complexity theory is the notion that some systems can organize dynamically to a point critically poised between order and disorder, hovering at the so-called "edge of chaos." For example, as grains of sand are added to a sand-pile it organizes to a critical slope such that the addition of a single grain can lead to avalanches of all sizes (Bak and Paczuski 1995). It has been proposed by many researchers that the computational performance (i.e., information and memory processing) of neural networks—both artificial and

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biological—is optimized when close to the order–disorder phase transition (Langton 1990; Bienenstock and Lehmann 1998; Bornholdt and Röhl 2003; Bertschinger and Natschläger 2004; Beggs 2008; Toyoizumi and Abbott 2011; Boedecker et al. 2012). In this chapter we explore the novel hypothesis that the human brain may be operating at the edge of chaos during the deepest phase of NREM (non-rapid-eye-movement) sleep.

The transition from wake into deep NREM sleep is identified as a progressive frequency-decline in EEG activity from wakeful alpha (8–13 Hz), through stage-1 NREM theta (3–7 Hz), eventually slowing to the large-amplitude delta-band (0.5–2 Hz) oscillations that characterize NREM stages-3 and -4. Figure 10.8 (right-hand panel) shows representative EEG (electroencephalogram) traces recorded from human subjects as illustrated in the Rechtschaffen and Kale (1968) classic sleep-scoring reference manual. This progressive slowing is interrupted by transient K-complexes and thalamic spindles (11–16 Hz) in NREM stage-2. The eventual emergence of delta-band slow oscillations is a manifestation of irregular traveling waves of cortical potentials (Massimini et al. 2004); these oscillations between "Up" and "Down" states are closely similar to the large slow waves seen in patient EEG following loss of consciousness under general anesthesia (Murphy et al. 2011).

The passage from NREM stage-1 to stage-4 takes about 60 min, at which point a transition to REM (rapid eye movement) sleep occurs. Commonly referred to as paradoxical sleep, REM is characterized by EEG patterns that closely resemble those seen during normal wakefulness. Each cycling between NREM and REM phases lasts around 90 min, leading to four or five completed sleep cycles per overnight rest.

Theoretical studies (Phillips and Robinson 2007; Diniz Behn and Booth 2010) based on a conceptual sleep-wake flip-flop switch (Saper et al. 2001) are able to reproduce the strongly contrasting EEG patterns that distinguish sleep and wake, and also the transition between NREM and REM sleep states (McCarley and Hobson 1975; Diniz Behn and Booth 2010). However, the mechanisms responsible for the more graduated EEG changes observed during the slow descent into slow-wave sleep through stages-1 to -4 of NREM remain largely unexplored. In very recent work Costa et al. (2016) have combined a sleep regulation network with a neural-mass cortical model to generate EEG activity controlled by phased release of GABA, acetylcholine (ACh) and noradrenalin neurotransmitters acting to modulate neural gain and firing rate adaptation. This composite model is able to produce time-series that resemble the different stages of REM and NREM sleep, with emergence of large-amplitude slow-wave activity arising from proximity to a Hopf bifurcation. But being a point-mass model, there is no possibility of spatial instabilities which might interact with the Hopf mode to produce spatiotemporal patterns.

In this chapter we present a neural-field model in two spatial dimensions describing descent into deep slow-wave sleep. The model has access to a rich range of dynamics arising from interactions between two incipient instabilities: a Hopf mode supported by slowed inhibitory postsynaptic responses, and a Turing mode that can form when gap-junction connectivity between inhibitory neurons

is sufficiently strong. We show that the large-amplitude delta waves of SWS can emerge spontaneously in response to a gradual divergence in the relative concentration ratios of GABA and acetylcholine neuromodulators: the GABA increase boosts inhibition and gap-junction closure, while the ACh decrease suppresses membrane resting voltage and boosts excitatory synaptic gain. We find that the resulting slow delta waves are inherently chaotic in nature, but can become pathologically ordered and seizure-like if inhibitory gap-junction diffusion becomes too weak. We posit the existence of a protective regulatory mechanism that ensures that the slow oscillations dwell at the edge of chaos, rather than progressing to full epileptic seizure.

10.2 A Mean-Field Model of the Cortex

Rather than attempting to describe the individual actions of billions of interacting neurons in the cortex, our approach is to model the aggregate behaviors of neural populations. This philosophy, known as *mass-action* or *mean-field*, treats the cortex as a 2D continuum of excitable tissue containing populations of excitatory and inhibitory neurons that communicate via both chemical and electrical synapses (gap junctions). The mean soma voltages, (V_e, V_i), of the excitatory and inhibitory neural populations, are the primary state variables which vary with time t and 2D position $\mathbf{r}$. The mapping from population voltage $V_{e,i}$ to population firing rate $Q_{e,i}$ is described by a standard sigmoidal mapping,

$$Q_{e,i}(\mathbf{r},t) \;=\; \frac{Q_{e,i}^{\max}}{1+\exp\left[-C\left(V_{e,i}(\mathbf{r},t)-\theta_{e,i}\right)/\sigma_{e,i}\right]} \tag{10.1}$$

with $C = \pi/\sqrt{3}$. Here, θ is the threshold for firing, σ is its standard deviation, and $Q^{\max}$ is the maximum firing rate. The sigmoidal functions are plotted in Fig. 10.1; model constants are listed in Table 10.1.

The soma voltages are perturbed by excitatory and inhibitory synaptic inputs at chemical synapses, plus diffusive currents entering via gap-junction-mediated electrical synapses,

$$\tau_b \frac{\partial V_b(t)}{\partial t} \;=\; V_b^{\text{rest}} \;-\; V_b(t) \;+\; \underbrace{\rho_e\,\psi_{eb}(V_b)\Phi_{eb}(t) \;+\; \rho_i\,\psi_{ib}(V_b)\Phi_{ib}(t)}_{\text{chemical synapse}}$$

$$+\; \underbrace{D_{bb}\nabla^2 V_b(t)}_{\text{gap junction}} \tag{10.2}$$

with subscript $b \in \{e,i\}$. Here, τ is the relaxation time for the momentarily perturbed soma voltage $V(t)$ to decay to its resting value V^{rest}; ρ, with units [mV s], is the signed synaptic gain for chemical synapses ($\rho_e > 0$ at an excitatory synapse;

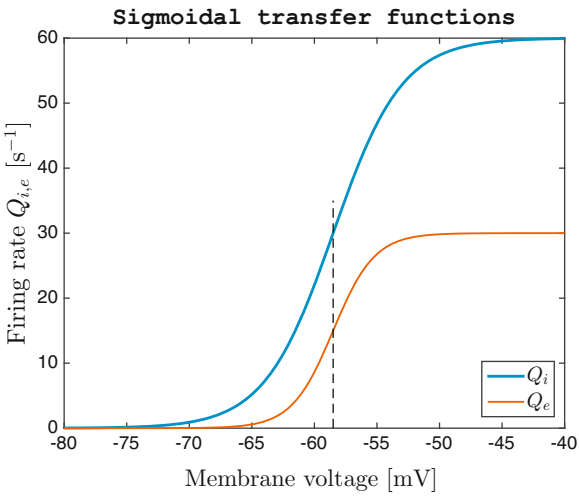

Fig. 10.1 Voltage-to-firing-rate sigmoidal transfer functions of Eq. (10.1) for inhibitory and excitatory neural populations. *Dashed vertical line* marks threshold voltage $\theta_{e,i}$

Table 10.1 Standard values for the neural model. Subscript label b means destination cell can be either of type e (excitatory) or i (inhibitory)

Symbol	Description	Value	Unit
$Q_{e,i}^{\max}$	Maximum firing rate	30, 60	s^{-1}
$\theta_{e,i}$	Threshold voltage for firing	-58.5, -58.5	mV
$\sigma_{e,i}$	Standard deviation for threshold	3.0, 5.0	mV
$\tau_{e,i}$	Soma time constant	0.040, 0.040	s
$V_{e,i}^{\text{rev}}$	Reversal potential for AMPA, GABA receptors	0, -70	mV
$V_{e,i}^{\text{rest}}$	Resting potential	-64, -64	mV
$\rho_{e,i}$	Synaptic gain at resting potential	$(1.00, -1.05) \times 10^{-3}$	mV·s
γ_e	AMPA rate-constant (for EPSP)	170	s^{-1}
γ_i	GABA rate-constant (for IPSP)	50	s^{-1}
N_{eb}^{α}	Long-range $e \to b$ axonal connectivity	2000	–
$N_{eb}^{\beta}, N_{ib}^{\beta}$	Local $e \to b$, $i \to b$ axonal connectivity	800, 600	–
$N_{eb}^{\text{sc}}, N_{ib}^{\text{sc}}$	Subcortical $e \to b$, $i \to b$ axonal connectivity	50, 0	–
$\langle \phi_e^{\text{sc}} \rangle$	Subcortical input flux	300	s^{-1}
v	Axonal conduction speed	140	cm s^{-1}
Λ_{eb}	Inverse length-scale for axonal connections	4.0	cm^{-1}

$\rho_i < 0$ at an inhibitory synapse); $\psi(V)$ is a dimensionless weighting function that scales synaptic input by the deviation of soma voltage $V(t)$ from the relevant ionic reversal potential V^{rev},

$$\psi_{ab}(V_b) = \frac{V_a^{\text{rev}} - V_b(t)}{V_a^{\text{rev}} - V_b^{\text{rest}}}, \quad \text{with} \quad a, b \in \{e, i\} \tag{10.3}$$

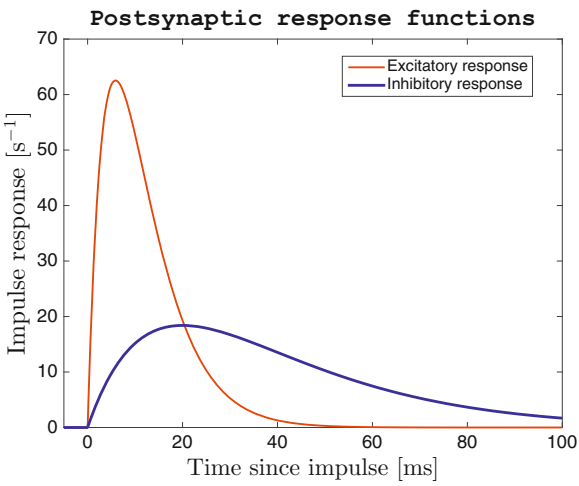

Fig. 10.2 Excitatory and inhibitory unitary response curves for dendrite equations (10.4). These graphs are alpha functions given by $\gamma^2 t \exp(-\gamma t)\,\Theta(t)$ where $\Theta(t)$ is the Heaviside step. Scaling by synaptic gain ρ transforms these to EPSP and IPSP curves. Maximal response occurs at $t = 1/\gamma$ with peak height γ/e

and $\Phi(t)$ is the incoming flux rate [spikes/s] at the receiving dendrite. The dendrite flux equations obey the second-order DEs,

$$\left(\frac{d}{dt} + \gamma_e\right)^2 \Phi_{eb}(t) \;=\; {\gamma_e}^2 \left[N^{\alpha}_{eb}\, \phi_{eb}(t) + N^{\beta}_{eb}\, Q_e(t) + \phi^{\mathrm{sc}}_{eb}(t)\right] \tag{10.4a}$$

$$\left(\frac{d}{dt} + \gamma_i\right)^2 \Phi_{ib}(t) \;=\; {\gamma_i}^2\, N^{\beta}_{ib}\, Q_i(t) \tag{10.4b}$$

with dendritic rate constant γ. The source terms on the right correspond to input from distant sources ϕ, local sources Q, and stimulation entering via the subcortex ϕ^{sc}. The N^{α} and N^{β} are the long-range and local connection strengths (Table 10.1). The dendrite equations (10.4) have characteristic "alpha-function" impulse responses defining the shape and time-course of the excitatory and inhibitory post-synaptic potentials (EPSP, IPSP); see Fig. 10.2.

The flux emanating from distant sources is assumed to propagate via a 2D damped wave equation (Robinson et al. 1997),

$$\left[\left(\frac{\partial}{\partial t} + v\Lambda_{eb}\right)^2 - v^2\nabla^2\right] \phi_{eb}(\mathbf{r}, t) \;=\; (v\,\Lambda_{eb})^2\, Q_e(\mathbf{r}, t) \tag{10.5}$$

where Λ is the inverse-length scale for axonal connections, and v is the axonal conduction speed. Here, $\nabla^2 \equiv \partial^2/\partial x^2 + \partial^2/\partial y^2$ is the Laplacian spatial derivative expressed in Cartesian coordinates.

The ϕ^{sc} subcortical input in Eq. (10.4a) is a constant excitatory background tone plus scaled white noise,

$$\phi^{\mathrm{sc}}_{eb}(\mathbf{r}, t) \;=\; \langle\phi^{\mathrm{sc}}_{eb}\rangle \;+\; a\sqrt{\langle\phi^{\mathrm{sc}}_{eb}\rangle}\,\xi(\mathbf{r}, t) \tag{10.6}$$

where a is a constant noise scale-factor, and ξ is Gaussian-distributed, zero-mean, spatio-temporal white-noise that is delta-correlated in time and space,

$$\langle \xi_m(\mathbf{r},t)\rangle \;=\; 0\,, \tag{10.7}$$

$$\langle \xi_m(\mathbf{r},t)\,\xi_n(\mathbf{r}',t')\rangle \;=\; \delta_{mn}\,\delta(t-t')\,\delta(\mathbf{r}-\mathbf{r}')\,. \tag{10.8}$$

The final $D_{bb}\nabla^2 V_b$ term on the right of Eq. (10.2) describes the diffusive current entering the soma via direct *i–i* and *e–e* gap-junction connections between resistively-coupled neurons. Gap junction connections between inhibitory neurons are abundant throughout the central nervous system (Galarreta and Hestrin 2001; Bennett and Zukin 2004), but relatively sparse for excitatory neurons (Wang et al. 2010), so we set the excitatory diffusive coupling strength D_{ee} to be a small fraction of the inhibitory strength, $D_{ee} = D_{ii}/100$, with D_{ii} estimated from measurements in cat visual cortex reported in Fukuda et al. (2006) and analyzed in Steyn-Ross et al. (2007). For convenience, we abbreviate the excitatory and inhibitory diffusion coefficients as $(D_{ee}, D_{ii}) \equiv (D_1, D_2)$.

10.3 Cortical Dynamics

With suitable settings for the model constants (e.g., Table 10.1), the mean-field cortical model described in Sect. 10.2 can exhibit a range of interesting and physiologically relevant dynamical behaviors. Broadly, these behaviors can be classified as,

(i) change of state near a saddle–node bifurcation
(ii) emergence of spatial activity patterns near a Turing bifurcation
(iii) emergence of nonlinear temporal oscillations near a Hopf bifurcation
(iv) generation of standing and traveling waves resulting from Turing–Hopf competition.

A change of state—e.g., a jump transition from high- to low-firing, as might happen during induction of general anesthesia (Steyn-Ross et al. 1999)—requires the existence of multiple steady states for a given set of control parameters. The homogeneous steady states (also referred to as equilibrium states) are located numerically from Eqs. (10.2), (10.3), (10.4), and (10.5) by setting the time- and space-derivatives to zero, suppressing the noise terms, and solving the resulting coupled nonlinear equations for the equilibrium firing rates (Q_e^o, Q_i^o) of the excitatory and inhibitory neural populations. Figure 10.3 shows that the distribution of Q_e^o steady states forms an S-shaped reentrant manifold when plotted over the two-variable domain $(\lambda_e, \Delta V_e^{\text{rest}})$ representing the dual effects of altering levels of acetylcholine neuromodulator: λ_e is a scale factor that multiplies the excitatory synaptic gain ρ_e, and ΔV_e^{rest} is the change in the excitatory resting voltage V_e^{rest}.

Local stability of these equilibrium states can be predicted from a linear stability analysis that considers small spatiotemporal perturbations about a given spatially

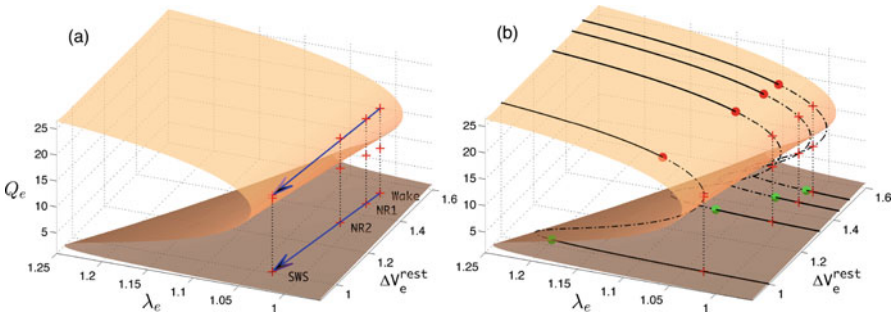

Fig. 10.3 Descent from Wake to slow-wave sleep (SWS) modeled as a neuromodulator-driven exploration of the unstable multi-root region of the manifold of cortical steady states. Early stages of sleep, non-REM stages 1 and 2 (NR1, NR2) are pictured as intermediate between Wake and SWS vigilance extremes. (**a**) Acetylcholine reduction causes resting voltage (V_e^{rest}) to diminish and excitatory synaptic gain (λ_e) to increase, while a boost in GABA abundance increases inhibitory gain and reduces inhibitory diffusion; net impact of deepening sleep is to move upper-branch resting state closer to the manifold turning point. (**b**) Extent and nature of cortical instability near the reentrant fold is determined by relative proximities of the Hopf (*red ball* on top-branch) and Turing (*green ball* on bottom-branch) bifurcations. *Dash-dot black line* = unstable; *bold-black* = stable steady states

homogeneous steady state (see Sect. II D of Steyn-Ross et al. 2013 for details). As shown in Fig. 10.3b, all points on the reentrant mid-branch separatrix (indicated with dashed lines) are unstable, as are points on the top and bottom branches close to the turning points. However, the nature of the instability on the two branches is quite distinct: *temporal* stability is lost via a low-frequency Hopf bifurcation on the top branch (red dots), but on the bottom branch *spatial* stability is lost via a Turing bifurcation (green dots) that precipitates formation of sustained spatial patterns of high and low neural activity.

Neuromodulator-induced changes to the inhibitory rate constant and gap-junction coupling have profound effects on cortical stability: reductions in the γ_i rate-constant can lead to the Hopf bifurcation whose extreme temporal oscillations have been interpreted as seizure (Kramer et al. 2005; Liley and Bojak 2005; Wilson et al. 2006); while increases in inhibitory diffusion D_2 can precipitate a Turing spatial pattern of activated and inactivated regions of cortex (Steyn-Ross et al. 2007). The Hopf and Turing instabilities can interact, giving rise to oscillating Turing patterns and traveling waves. We have previously suggested that the EEG patterns of resting wake might correspond to a point of delicate balance between oscillation and pattern formation (Steyn-Ross et al. 2009), and that a rebalancing in favor of the Hopf instability—brought on by GABAergic anesthetic drug—provides a possible explanation for the emergence of the slow-delta oscillations of general anesthesia (Steyn-Ross et al. 2013).

Numerical simulations reveal that Turing–Hopf competition underpins a surprisingly diverse range of spatiotemporal patterns, both regular and chaotic. Which instability is likely to dominate can be predicted, to some extent, from the relative proximity of a given steady state to the Turing and Hopf bifurcation points. For

example, the state labeled "wake" in Fig. 10.3 is temporally unstable on the top branch and marginally stable in space on the bottom branch, but because of the proximity to the Turing (spatial) instability here, we can expect emergence of activity patterns that oscillate in place. In contrast, the state "SWS" is much further from the bottom-branch Turing point, so the Hopf-driven oscillations are expected to strongly dominate. The strength of the Turing instability is controlled by D_2, the inhibitory diffusion coefficient. Figure 10.4 shows well-defined Turing patterns

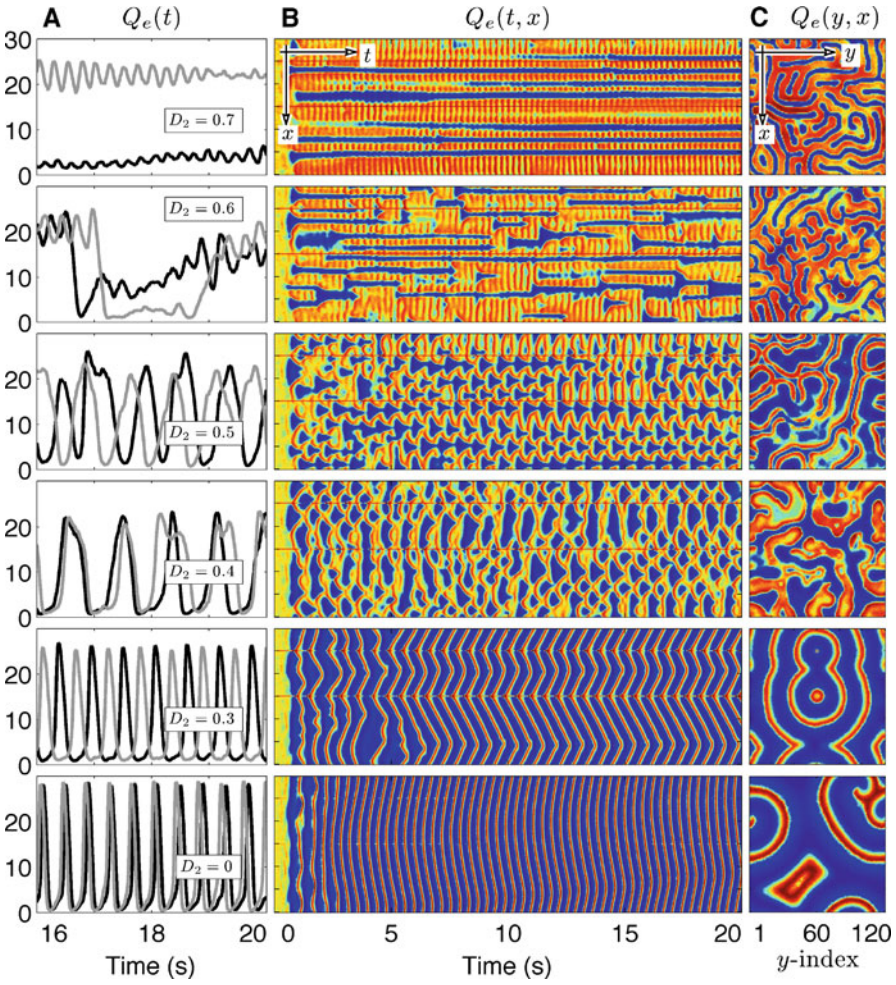

Fig. 10.4 Effect of inhibitory diffusion on "wake" state. Numerical simulations show dynamical effect of stepped reductions in diffusion strength from $D_2/\text{cm}^2 = 0.7$ (*top row*) to 0 (*bottom*). (**a**) Time-series extracts showing excitatory firing rates $Q_e(t)$ for final 4 s of a 20-s run at two pixels on the midline ($y = 60$) of the 120×120 cortical grid. (**b**) $Q_e(t, x)$ space–time strip-charts showing x-axis activity along $y = 60$ midline strip. (**c**) $Q_e(y, x)$ bird's-eye view of cortical activity at $t = 20$ s. Simulation settings: toroidal boundaries; time-step $\Delta t = 0.4$ ms; stimulus: spatiotemporal white noise with scale-factor $a = 4$ (Modified from Fig. 5 of Steyn-Ross et al. 2013)

when D_2 is large (top two rows). As D_2 is reduced, these sustained activity patterns disappear, being replaced by temporal oscillations as the Hopf instability gains influence.

We now discuss how this model can be tuned to follow the progression from normal wakefulness to deep slow-wave sleep.

10.4 Modeling the Emergence of Slow-Wave Sleep

It is well established that the arousal neuromodulator acetylcholine (ACh) is abundant during wakefulness and REM sleep, but strongly suppressed during NREM sleep (Steriade 2004). Recent measurements in awake and sleeping cats by Vanini et al. (2012) have revealed that GABA concentration is also strongly dependent on state of vigilance, with GABA levels being significantly higher during NREM sleep. Figure 10.5 illustrates the pronounced divergence in GABA(↑) and ACh(↓) concentration trends for Wake versus NREM states.

ACh activates the cortex by reducing K^+ leak currents, thus depolarizing the membrane resting potential, making the cell more excitable. Paradoxically, ACh also reduces the amplitude of the excitatory postsynaptic potential (EPSP) (Hasselmo 1995). Taking Wake as our reference state, we capture the *reduction* in ACh concentration during transition into NREM sleep as (i) a gradual lowering of the resting voltage $V_e^{\text{rest}} \rightarrow V_e^{\text{rest}} + \Delta V_e^{\text{rest}}(t)$, simultaneous with (ii) a boosting of the excitatory synaptic gain ρ_e by a time-dependant scale-factor λ_e: $\rho_e \rightarrow \lambda_e(t)\,\rho_e$.

GABA has an inhibitory effect on the cortex. We model this as an anesthetic-like prolongation of the inhibitory postsynaptic potential (IPSP) via (iii) a reduction in the inhibitory synaptic rate-constant $\gamma_i \rightarrow \gamma_i/\lambda_i(t)$ with compensating increase in inhibitory gain $\rho_i \rightarrow \lambda_i(t)\,\rho_i$ to enforce a constant-height IPSP in Fig. 10.2

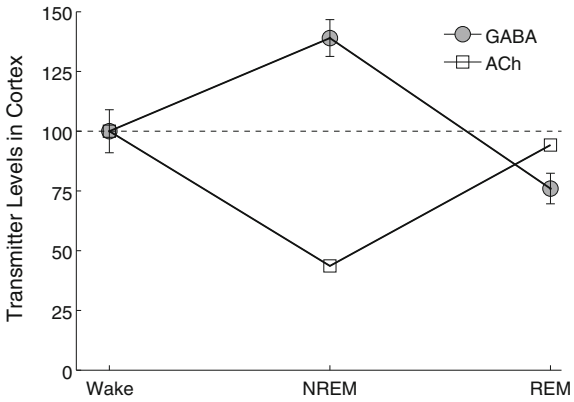

Fig. 10.5 Extracellular levels of GABA and acetylcholine (ACh) neuromodulators in cat cortex show strong differential changes during both non-REM sleep (NREM) and rapid-eye-movement sleep (REM) relative to wakefulness (Wake). Concentrations are expressed as a percentage of values measured in wakefulness (Figure adapted from Figs. 3 and 6 of Vanini et al. 2012)

Table 10.2 Parameter values for specific states of vigilance as a function of time t in hours since commencement of the sleep cycle. Values are computed from Eqs. (10.9). Synaptic gain factors $\lambda_{e,i}$ are dimensionless

Vigilance state	Time, t (h)	Time (min)	$\Delta V_e^{\text{rest}}(t)$ (mV)	$\lambda_e(t)$ –	$\lambda_i(t)$ –	$D_2(t)$ (cm^2)
Wake	0	0	1.5	1.0	1.0	0.7
NR1	0.13	8	1.435	1.0040	1.0019	0.658
NR2	0.37	22	1.315	1.0113	1.0056	0.581
SWS	1.0	60	1.0	1.0305	1.0150	0.380

(Steyn-Ross et al. 2013). Since anesthetics are known to inhibit gap-junction communication (Wentlandt et al. 2006), we also impose (iv) a slow reduction of the coupling strength between inhibitory neurons, $D_2 \to D_2(t)$. Assuming that the time to descend from Wake to deep slow-wave sleep takes 1 h, we apply the following linear time-dependant parameter modulations to represent the effects (i)–(iv),

$$\left.\begin{aligned} \Delta V_e^{\text{rest}}/\text{mV} &= 1.0 - 0.5t \\ \lambda_e &= 1.0 + 0.0305t \\ \lambda_i &= 1.0 + 0.015t \\ D_2/\text{cm}^2 &= 0.70 - 0.32t \end{aligned}\right\} \quad \text{for} \quad 0 \le t \le 1.0\,\text{h} \tag{10.9}$$

where setting $t = 0$ gives the parameter values for the initial state of wakefulness. The specific values used for the Wake, NR1, NR2, and SWS states are listed in Table 10.2.

10.5 Numerical Simulations and Results

Cortical equations (10.2), (10.3), (10.4), (10.5), and (10.6) were simulated numerically in MATLAB on a 25- × 25-cm square grid with periodic boundaries and a grid-density of 120 × 120 sample points, giving a symmetric grid resolution of $\Delta x = \Delta y = 2.08$ mm. Iterations were advanced using a forward-time, centered-space Euler scheme with fixed time-step $\Delta t = 0.4$ ms. Smaller time-steps were trialled, but behavior was not significantly altered, so we determined that our initial selection of time-step gave reliable results. All points on the grid were continuously stimulated with spatiotemporally independent white noises of low intensity; this stochastic background tone entered via the ϕ^{sc} subcortical flux terms of Eq. (10.4a). The MATLAB `randn` normally-distributed pseudorandom number generator provided the noise source,

$$\xi(\mathbf{r},t) \to \xi_n^{j,k} = \frac{\mathcal{R}_n^{j,k}}{\sqrt{\Delta t}} \quad \text{with } \mathbf{r} = (j\Delta x, k\Delta y),\ t = n\Delta t$$

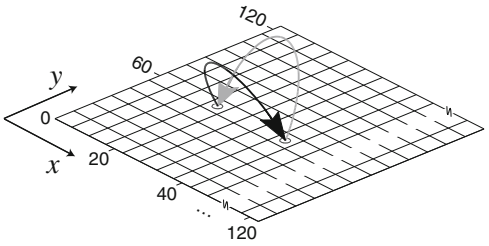

Fig. 10.6 Long-range two-point connections on the 25- × 25-cm cortical grid. Communication between connected points occurs after a time delay $\delta t = \delta r/v$ where v is the axonal conduction speed and δr is their physical separation (From Steyn-Ross et al. 2013)

where $\mathcal{R} =$ `randn`; *(j,k)* are the position indices (1:120, 1:120) on the grid; n is the time index. The $\sqrt{\Delta t}$ scaling ensures the correct white-noise limit for $\Delta t \to 0$ so that its integral is a Wiener process.

In addition to the continuous background noise, we imposed a pair of delayed point-to-point connections linking two well-separated grid points as diagrammed in Fig. 10.6. The purpose of these direct connections was to (i) introduce some minor heterogeneity in the grid geometry, (ii) simulate the effect of including some long-range myelinated axonal connections, and (iii) provide a source of internal stimulation to reduce the tendency of the model cortex to collapse into a coma-like quiescent state at the deepest stage of slow-wave sleep when inhibitory pressures (maximum GABA abundance with minimum ACh arousal) are extremal.

As illustrated in Fig. 10.3 and quantified in Table 10.2, each of the four vigilance states (Wake, NR1, NR2, SWS) is identified with its own set of $(\Delta V_e^{\text{rest}}, \lambda_e, \lambda_i, D_2)$ parameter values representing the neuromodulatory effects of slow changes in acetylcholine (↓) and GABA (↑) concentrations with deepening sleep.

We iterated the cortical equations continuously in time, starting from the (unstable) top-branch steady state for Wake, dwelling for 20 s, then making an abrupt switch to each $(\Delta V_e^{\text{rest}}, \lambda_e, \lambda_i, D_2)$ sleep coordinate in turn to map out the stepped trajectory from Wake → NR1 → NR2 → SWS for progression through the stages of NREM sleep. Results are shown in Fig. 10.7: the upper trace shows the excitatory voltage $V_e(t)$ at one pixel on the grid, while the lower trace displays the 0.53-Hz high-pass filtered version to better represent what might be captured on an EEG monitor that blocks the dc component.

We observe that the noise-driven voltage fluctuations become progressively larger and slower as sleep deepens. In Wake and NR1 the voltage oscillates about the upper-branch equilibrium (the "Up" state), with brief excursions towards the lower branch (the "Down" state) during NR2. In deepest SWS we see irregular (actually chaotic) delta-wave oscillation between the Up and Down states. At time ∼47 s into the simulation during NR2, a characteristic "K-complex" (named for its shape) emerges in the filtered (black) trace; relating this to the raw (red) voltage trace it is clear that the K-complex is generated by an abrupt there-and-back shift in dc-level over a time period comparable to the response-time (0.3 s) of the high-pass

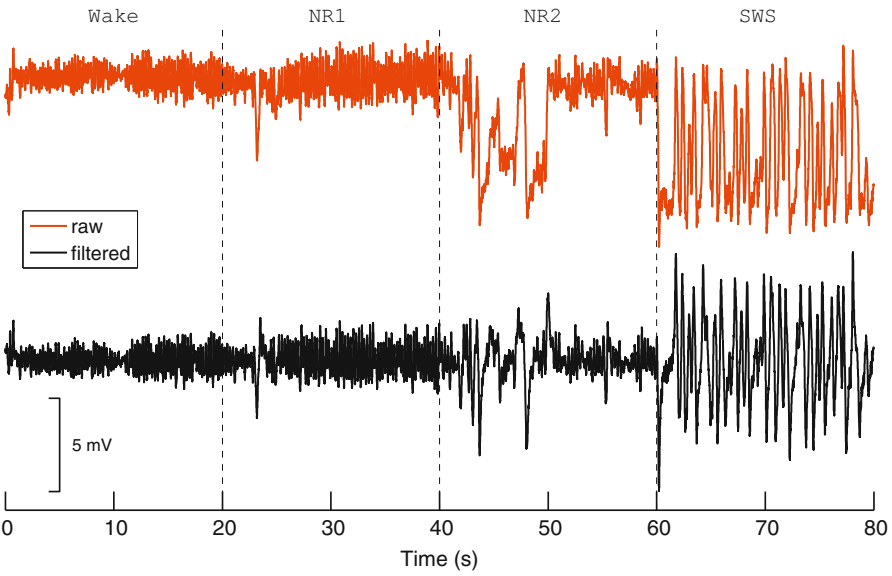

Fig. 10.7 Voltage traces for a grid-point on the noise-driven cortex for a simulated step-wise descent from Wake through sleep stages NR1, NR2 to slow-wave sleep (SWS). The model is held at a particular neuromodulator configuration for 20 s, then abruptly stepped to the next sleep stage, representing cortical activity that would be seen at times 0, 8, 22, 60 min after commencement of the first sleep cycle (see Table 10.2). Emergence of large-amplitude slow waves is a consequence of the progressive weakening of the Turing instability relative to the Hopf oscillation. *Red trace* is raw excitatory soma voltage V_e at a single pixel on the 120 × 120 cortical grid; *black trace* is the high-pass filtered signal representing the dc-blocked signal detected by a typical ac-coupled EEG amplifier. Filter settings: first-order Butterworth with high-pass corner frequency $f_c = 1/2\pi T = 0.53$ Hz to match the pen-recorder time-constant $T = 0.3$ s used in the Fig. 10.8b EEG traces from the Rechtschaffen and Kale (1968) sleep manual

filter. Thus the visualisation of this particular shape has no fundamental biological significance; rather it arises from the time-derivative response of the filter itself. This leads to the provocative notion that the distinctive K-complex shape used to identify NR2 light sleep may in fact be a simple filter artifact generated by a transient voltage change in the EEG.

In Fig. 10.8 we compare 10-s extracts of the high-pass filtered model voltages (black traces from Fig. 10.7) with exemplar 10-s EEG recordings extracted from the classic Rechtschaffen and Kale (1968) sleep-staging manual. Apart from the obvious difference in voltage scales (model ECoG in mV; scalp EEG in μV), both sets of time-series show a monotonic "growing and slowing" trend with the descent into deepest sleep signaled by the emergence of strong, irregular delta waves. We note that the time-series produced by our cortical model lacks spindles and alpha rhythms, but this is not unexpected given its lack of a thalamus: theoretical work by Robinson et al. (2001) and Freyer et al. (2011) predicts that the alpha resonance emerges from a thalamocortical loop delay of magnitude ∼80-ms.

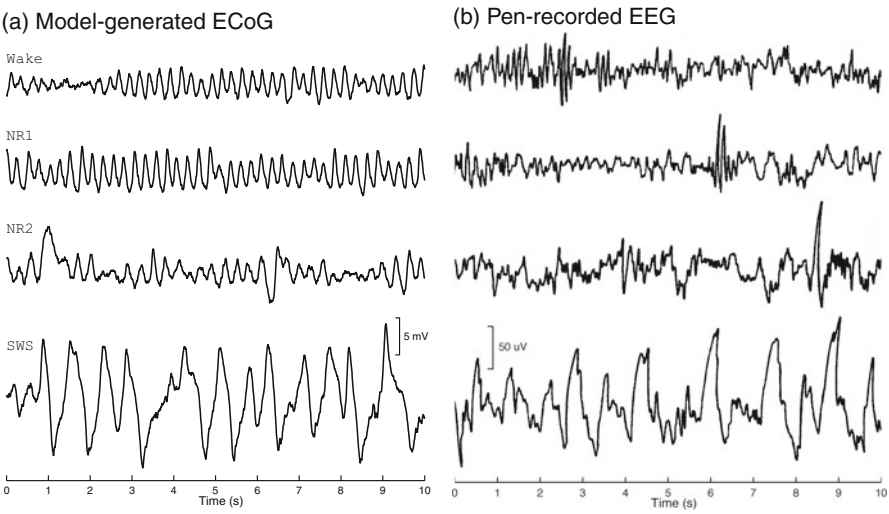

Fig. 10.8 Model-generated sleep electrocorticogram (*left traces*) compared with scalp-recorded human EEG (*right traces*) for four representative states of vigilance (Wake, NR1, NR2, SWS) during descent from wakefulness into deep slow-wave sleep. (**a**) Model predictions are 10-s extracts from the high-pass filtered time-series presented in Fig. 10.7; the 5-mV amplitude scale applies to all four traces. (**b**) Ten-second extracts from the Rechtschaffen and Kale (1968) EEG sleep-staging manual, scanned from figures 24, 26, 27, 30 respectively. Note the 50-μV scale bar. The chart-recorder time-constant (i.e., $1/e$ step-response) was set at $T = 0.3$ s. (The panel-(**b**) traces are pen-on-paper chart recordings, hence the distinctive arc-like curvature distortion evident on large-amplitude excursions)

10.6 Prediction of Chaotic Dynamics in NREM

As evident from Fig. 10.4, the form and oscillatory character of the spatial activity patterns are very sensitive to D_2, the strength of the inhibitory gap-junction diffusion. For strong diffusion, Turing patterns dominate, while for weak diffusion, the Hopf instability drives large-amplitude regular oscillations. For intermediate diffusion values, Turing and Hopf instabilities interact, resulting in turbulent spatiotemporal patterns that appear to be chaotic. To confirm deterministic chaos, we suppressed all noise, and ran pairs of numerical simulations looking for extreme sensitivity to initial conditions as evidenced by exponential divergence of trajectory pairs. For a given value of D_2, the rate of divergence is quantified by extracting the dominant Lyapunov exponent Λ from a semilog graph of divergence as a function of time (see Fig. 10.9): $\Lambda > 0$ (positive slope) signals exponentially growing separation between trajectories (chaos), while $\Lambda < 0$ (negative slope) indicates decay towards a common trajectory. Figure 10.10 confirms that for the midrange diffusion values $0.32 \lesssim D_2/\text{cm}^2 \lesssim 0.8$, cortical dynamics are indeed chaotic in time and space.

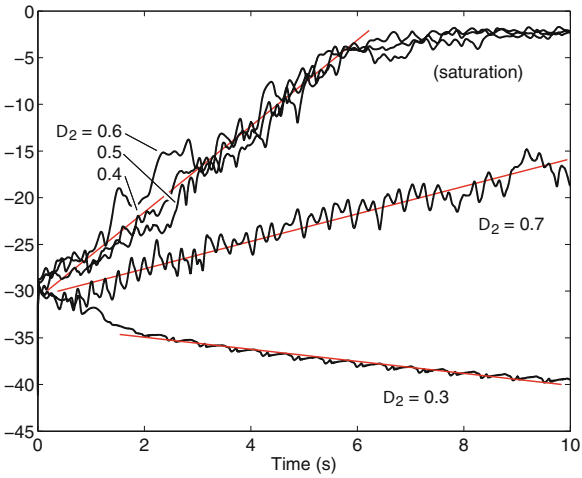

Fig. 10.9 Lyapunov exponent trend lines for noise-free Wake simulations. Graphs plot $\ln \epsilon(t)$ vs time for different values of inhibitory diffusion D_2 where $\epsilon(t) = \sum_{i=1}^{120} \left(Q_e^{(1)}(t,x_i) - Q_e^{(2)}(t,x_i)\right)^2 / \epsilon^{\max}$ is the normalized squared difference between paired runs $Q_e^{(1)}(t,x)$ and $Q_e^{(2)}(t,x)$ visualized in the space–time graphs similar to Fig. 10.4 (Modified from Suppl. Material accompanying Steyn-Ross et al. 2013)

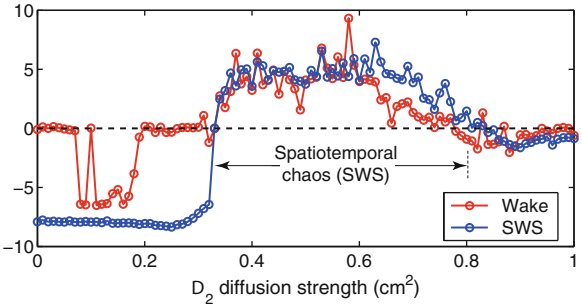

Fig. 10.10 Dominant Lyapunov exponent trend lines for noise-free Wake and SWS simulations. Positive values imply deterministic chaos: exponential divergence between paired runs beginning from minimally perturbed initial conditions (Modified from Suppl. Material accompanying Steyn-Ross et al. 2013)

Deeper NREM sleep corresponds to stronger GABA effects, diminished gap-junction connectivity and a strengthened Hopf temporal ordering in the spatiotemporal oscillations. But if the Hopf ordering becomes too strong, the chaotic slow-delta oscillations of deep sleep can transform into the pathologically-ordered non-chaotic travelling wavefronts that we identify with seizure. From Fig. 10.10, we see that the lower boundary for chaotic dynamics in deep sleep occurs near $D_2/\text{cm}^2 \approx 0.32$.

To investigate further the diffusion-induced transition between chaotic Turing–Hopf competitive dynamics and non-chaotic Hopf-dominated waves, we ran a stochastic 200-s grid simulation in which the D_2 inhibitory diffusion strength was steadily reduced from 1.0 to $0.0\,\text{cm}^2$; the three other sleep parameters $(\Delta V_e^{\text{rest}}, \lambda_e, \lambda_i)$ were kept fixed at their Table 10.2 SWS values. The space–time

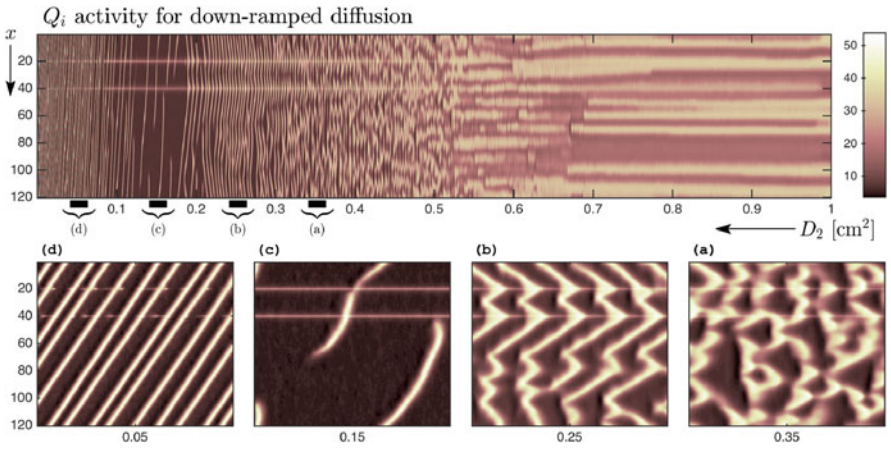

Fig. 10.11 Effect of gradual reduction of inhibitory diffusion D_2 on inhibitory firing-rate activity Q_i. Cortical model was initialized at SWS parameter settings (see Table 10.2), apart from inhibitory diffusion D_2 which was slowly reduced from 1.0 (*right*) down to 0.0 cm^2 (*left*) over a total simulation time of 200 s. The region of sparse activity $0.1 \lesssim D_2/\text{cm}^2 \lesssim 0.2$ marks the disorder/order transition between chaotic Turing–Hopf interactions (to the right) and pathologically ordered Hopf fronts (to the left). Subpanels (**a**)–(**d**) show zoomed detail from upper $Q_i(t, x)$ space–time chart. The pair of horizontal activity trails arises from the long-range excitatory connections joining pixels $(x, y) = (20, 60)$ and $(40, 60)$ as shown in Fig. 10.6. *Colorbar* indicates spike-rate (spikes/s)

strip-charts in Fig. 10.11 show clearly a qualitative change in spatiotemporal dynamics as the inhibitory gap-junction connectivity is reduced: the irregular localized patterns in space and time give way to global wavefronts of activity that sweep across the entire cortex at more or less regular intervals; if noise is suppressed, these Hopf waves become completely regular and clocklike (not shown).

Panel (c) of Fig. 10.11 highlights the critically-slowed boundary that marks the transition zone separating chaotic disordered dynamics ($D_2 \gtrsim 0.25\,\text{cm}^2$) from well-ordered "seizure" fronts ($D_2 \lesssim 0.10\,\text{cm}^2$). This zone is characterized by a pronounced minimum in cortical activity, and the depth of this minimum can be quantified by tracking the grid-averaged cortical rms (root-mean-square) activity as D_2 is reduced as shown in Fig. 10.12. Although $Q_i^{\text{rms}} > Q_e^{\text{rms}}$ throughout the range of D_2 values (note that we are plotting $Q_i^{\text{rms}}/2$), the diffusion-dependent *trends* in inhibitory and excitatory activity are strongly correlated.

Since most sleepers do not proceed to seizure, we propose the existence of a protective mechanism that regulates the naturally sleeping brain so that it remains close to—but does not cross—the disorder/order boundary during deepest sleep. There is clinical evidence that high cortical activity (e.g., in wake and also during seizure) is associated with increased concentration of intracellular free magnesium ions, $[Mg^{2+}]_i$, leading to *closure* of Cx36 (connexin-36) gap junctions (Palacios-

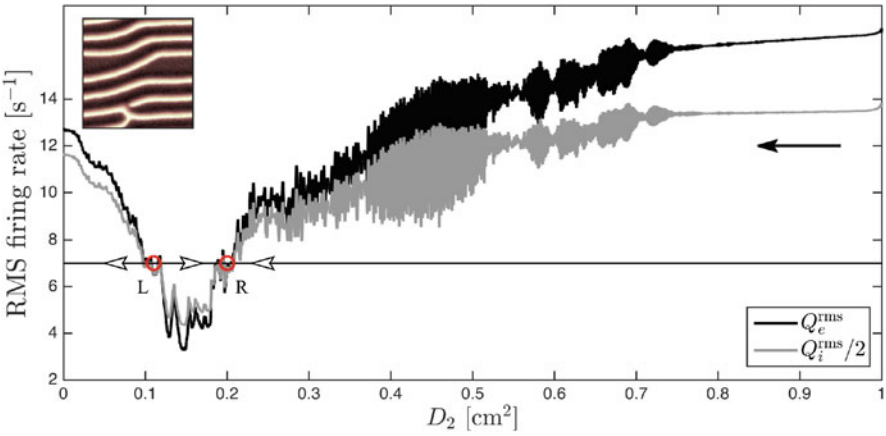

Fig. 10.12 Variation in grid-averaged excitatory and inhibitory firing rates $Q_{e,i}^{\rm rms}$ as a function of inhibitory diffusion D_2. These time-series were captured during the 200-s stochastic simulation reported in Fig. 10.11; time proceeds right-to-left (*solid arrow*). *Red circles* show the {L, R} steady states for the regulation rule of Eq. (10.10) investigated in Fig. 10.13: L is unstable ($\leftarrow \circ \rightarrow$); R is stable ($\rightarrow \circ \leftarrow$). Inset image shows "seizure" grid activity $Q_i(x, y)$ at the conclusion of the simulation when $D_2 = 0$. Grid resolution is 120×120; time-step $\Delta t = 0.4\times10^{-3}$ s (See Fig. 10.11 for *color-bar* calibration)

Prado et al. 2013). This observation motivates a simple regulation rule in which we suppose that there exists a target level of inhibitory activity, $Q_i^{\rm targ}$, and that if present activity lies above (below) target, then gap-junction inhibitory diffusion is decreased (increased):

$$\frac{dD_2}{dt} = \epsilon \left(Q_i^{\rm targ} - Q_i^{\rm rms}(t)\right) \tag{10.10}$$

where $Q_i^{\rm rms}(t)$ is the instantaneous spatial rms-average inhibitory firing rate across the model grid, and $Q_i^{\rm targ} = 14\,{\rm s}^{-1}$ is our selected target firing rate illustrated in Fig. 10.12 and chosen to allow a clear demarcation between chaotic SWS (to the right) and pathologically-regular seizure (to the left). Here, $\epsilon = 0.001\,{\rm cm}^2$ is a weak coupling coefficient linking firing activity to rate-change of inhibitory diffusion. As shown in Fig. 10.12, setting $Q_i^{\rm rms} = Q_i^{\rm targ}$ gives two set-points labelled R (stable) and L (unstable) near $D_2 = 0.11$ and $0.20\,{\rm cm}^2$ respectively. If $D_2 \gtrsim 0.11\,{\rm cm}^2$, we expect the cortex to regulate towards set-point R lying safely in the chaotic region, but if $D_2 \lesssim 0.11\,{\rm cm}^2$, strong Hopf-generated non-chaotic activity will cause regulation to fail, driving the cortex further into the Hopf seizure regime.

The three simulation recordings shown in Fig. 10.13 confirm these expectations: provided the initial value of D_2 lies to the right of the lower set-point, rule (10.10) enables the cortex to regulate its slow-wave dynamics, but regulation failure leads to seizure onset.

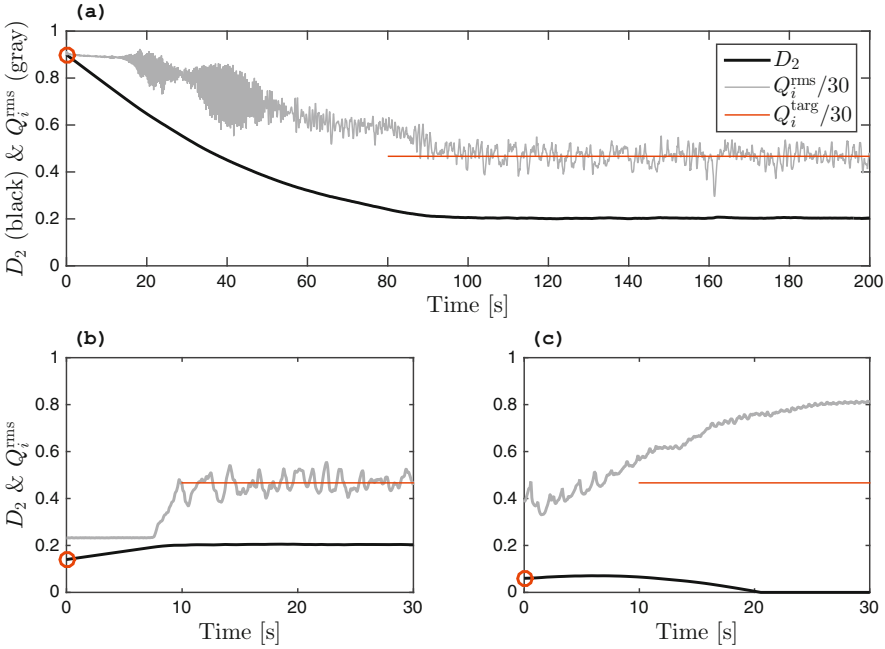

Fig. 10.13 Simulation tests of activity-driven regulation of inhibitory diffusion at three initial settings of $D_2/\mathrm{cm}^2(t=0)$: (**a**) 0.90; (**b**) 0.14; (**c**) 0.06 (*red circles*). As expected from Fig. 10.12, runs (**a**) and (**b**) regulate D_2 to $\sim 0.20\,\mathrm{cm}^2$ (from above and below respectively) corresponding to rms target activity $Q_i^{\rm targ} = 14\,\mathrm{s}^{-1}$ (*red line*), while in (**c**) regulation fails with activity evolving to Hopf-driven "seizure" as diffusion collapses to zero. *Black curve* = $D_2(t)$; *gray curve* = (scaled) rms activity, $Q_i^{\rm rms}(t)/30$

10.7 Discussion

The notion that the awake brain operates close to the boundary of criticality has enjoyed broad support since early work by Langton (1990) showing that computational performance in an artificial neural net is optimised when poised close to a phase transition. This led to suggestions that the brain might self-regulate to ensure continued proximity to regions of instability (Bienenstock and Lehmann 1998). Given that the brain spends one-third of its time sleeping, it is plausible to suppose that the purpose of sleep is more than merely restorative; if sleep has a role in information processing and learning (Walker and Stickgold 2004; Tononi and Cirelli 2006), then brain activation patterns exhibited during the various stages of REM and nonREM sleep might also correspond to near criticality, and, if so, this should be manifest in the temporal and spatial properties of surface (EEG and ECoG) and depth (LFP) cortical signals.

Pearlmutter and Houghton (2009) argue that the function of sleep is to enforce a retreat from criticality—and consequent pathological oscillations (e.g., epilepsy)—

that might occur with the unrestrained strengthening of recurrent synaptic circuits associated with wakeful learning and improved responsiveness. However, by examining the cascading activity in EEG neural avalanches, Meisel et al. (2013) demonstrated *fading* of critical signatures during extended periods of wakefulness, but a complete restoration of near-criticality of avalanche branching statistics after recovery sleep, contrary to the Pearlmutter and Houghton sleep-retreat hypothesis. Priesemann et al. (2013) were able to quantify the within-sleep changes in avalanche statistics by examining the intracranial LFP recordings of depth electrodes from epilepsy patients. They established that all stages of vigilence are minimally subcritical with SWS closest and REM sleep farthest from criticality, the latter being characterized by a more spatially fragmented cortical dynamics than either SWS or wakefulness.

In our cortical model, we find that the most interesting—and perhaps most physiologically meaningful—dynamics occurs when the model is situated close to the "overhang" bistability region (see Fig. 10.3) containing multiple steady states, providing optimum flexibility in cortical response with the cortex having access to both high-firing (activated) and low-firing (quiescent) states. Within this multi-root region, the upper and lower branches can be destabilized via either a Turing spatial instability that emerges when inhibitory diffusion is sufficiently strong, or via a Hopf instability that is evoked when the inhibitory postsynaptic potential (IPSP) is sufficiently prolonged by GABA abundance. When the Turing and Hopf instabilities are permitted to interact, then a wide range of spatiotemporal patternings are possible, ranging from weakly oscillating spatial modes that we have identified with wakefulness, to more strongly oscillating modes heralding the descent through the early stages of sleep, eventually terminating in the deepest stage of sleep whose large travelling waves identify the slow oscillations of SWS.

All of these putative "physiological" interacting Turing–Hopf modes are actually *chaotic* in an abstract mathematical sense, meaning that if the model is run *without noise perturbations*, then the deterministic trajectories for pairs of closely similar initial conditions are found to diverge exponentially (divergence continues until the inevitable saturation limits are reached: individual cortical elements are constrained by maximum and minimum firing rates), thus these "physiological" modes have positive Lyapunov exponent.

However, if the Turing instability is allowed to become too weak (i.e., insufficient inhibitory gap-junction diffusion), then the Hopf instability can become strongly dominant: all chaotic dynamics is lost, and the spatiotemporal oscillations become highly coherent, generating periodic large-amplitude wavefronts that sweep across the cortex. We propose that such extreme Hopf–Turing imbalance is pathological, and label it as "seizure" (Steyn-Ross et al. 2012).

In our model, the primary dynamic distinction between the large slow-wave oscillations of healthy SWS and the large slow oscillations of epileptic seizure is the loss of chaoticity arising from a too-weak Turing instability coupled with a too-regular Hopf oscillation. There are many clinical reports of seizure genesis occurring preferentially during slow-wave sleep (e.g., Steriade and Amzica 1998; Loddenkemper et al. 2011). But most individuals do not suffer seizures, so we infer

that there must exist a regulatory mechanism in healthy individuals that prevents the slow oscillation from losing its chaotic character, enabling the healthy deep-sleeping brain to operate at—but not beyond—its "edge of chaos".

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Chapter 11
Slow Oscillation in Prefrontal Cortex Underlying Local Computations and Large-Scale Interactions

Shigeyoshi Fujisawa

Abstract Slow oscillation (4–8 Hz) in the prefrontal cortex is widely observed across species during various cognitive processes such as working memory. In humans and primates, the slow oscillation observed in the frontal area is termed 'midline-frontal theta' (FM-theta) oscillation. In rodents, the slow oscillation in the prefrontal cortex is termed '4-Hz' oscillation. Although the generation mechanisms of FM-theta and 4-Hz oscillations have not been revealed yet, it is hypothesized that FM-theta in humans and 4-Hz in rodents have similar physiological properties and functions. Here, the roles of FM–theta and 4-Hz oscillations on cognitive functions and neuronal computations within local circuits and across large-scale brain networks are described.

Keywords Prefrontal cortex • Hippocampus • Ventral tegmental area • Synchronization • Frontal-midline theta oscillation • 4-Hz oscillation • Gamma oscillation • Cross-frequency coupling • Working memory • Goal-directed behavior

11.1 Introduction

Cognitive functions are achieved through flexible formation and segregation of cell assembles which are distributed across functionally specialized brain areas. It has been suggested that oscillatory activity underlies adaptive synchronization of neuronal activities for circuit computations. In the neocortex, oscillations with various frequency bands, such as delta (1-4 Hz), alpha (8–12 Hz), beta (15–30 Hz), and gamma (30–80 Hz), are observed depending on cognitive states (Buzsaki and Draguhn 2004). Oscillations with different frequency bands are generated with different physiological mechanisms and have distinct roles for neuronal computations

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(Buzsaki 2006). In general, oscillations with lower frequency bands are involved in modulations of neuronal activity across large-scale networks, whereas oscillations with higher frequency bands reflect neuronal activity within local networks (Buzsaki and Draguhn 2004; Canolty and Knight 2010).

In this chapter, I will focus on slow oscillation (4–8 Hz) observed in the prefrontal cortex (PFC) during employing higher cognitive functions such as working memory. Slow oscillation in PFC during cognitive activity have been widely observed in humans and primates, which is termed 'midline-frontal theta' (FM-theta) oscillation (Mitchell et al. 2008; Cavanagh and Frank 2014). Recently, slow oscillation in PFC has been focused in rodents, which is termed '4-Hz oscillation' (Fujisawa and Buzsaku 2011; Karalis et al. 2016; Dejean et al. 2016). Although the physiological mechanisms of generation of FM-theta and 4-Hz oscillations are still to be unraveled, it is hypothesized that FM-theta in human and 4-Hz in rodents are similar physiological properties and functions (Narayanan et al. 2013). Here, the roles of FM–theta and 4-Hz oscillations on cognitive functions and neuronal computations in PFC network will be discussed.

11.2 Slow Oscillation in PFC of Humans and Primates: Frontal-Midline Theta

11.2.1 Frontal-Midline Theta and Cognitive Functions

In humans and primates, slow oscillation (4–8 Hz) that is maximal in the frontal-midline regions is robustly observed in electroencephalographic (EEG) recordings during various cognitive processes. This slow oscillation of EEG is termed frontal-midline theta (FM-theta). Since the oscillation dipoles of FM-theta are often positioned in the frontal cortex, it is hypothesized that FM-theta oscillation reflects frontal cortical activities (Mitchell et al. 2008; Cavanagh and Frank 2014). Although the frequency band of FM-theta is close to hippocampal theta oscillation (Buzsaki 2002), these two rhythms are usually recognized as distinct oscillations due to the differences of the originate sites of them (Mitchell et al. 2008).

FM-theta oscillation is commonly observed in the processes of working memory (Mitchell et al. 2008; Roux and Uhlhaas 2014). Working memory is the ability to provide temporary storage and manipulation of the information, which is suggested to be divided into the central executive, the visuospatial sketchpad, and the phonological loop components (Baddeley 2003). Prefrontal cortex has been thought to support the central executive functions of working memory (Goldman-Rakic 1995). The power increase of FM-theta has been commonly reported in various type of working memory tasks such as the Sternberg task (Onton et al. 2005; Jensen and Tesche 2002), N-back task (Gevins et al. 1997), or visuo-spatial memory task (Gevins et al. 1997; Sauseng et al. 2005; Liebe et al. 2012). One of the important evidences that the FM-theta oscillation actually reflects prefrontal activity during working memory is that the power of FM-theta increases as the working memory load increases (Onton et al. 2005; Jensen and Tesche 2002). Moreover, the power

of FM-theta often predicts the performance of working memory. Increase of FM-theta power often correlate of reaction speeds and response accuracy (Gevins et al. 1997; Liebe et al. 2012). The dynamics of FM-theta oscillation is also dependent on the components of tasks. The power increase of FM-theta is often conspicuous in encoding and retention processes of working memory (Raghavachari et al. 2001; Onton et al. 2005).

FM-theta oscillation is also observed in action monitoring and controlling processes in goal-directed behaviors (Cavanagh and Frank 2014). Prominent increase of FM-theta activity has been reported in multitasking behaviors (Anguera et al. 2013), action control processes (Sauseng et al. 2007; Cavanagh et al. 2012), and attention selection (Lakatos et al. 2008). Conflict or interference between stimuli and responses also induce elevation of FM-theta power (Hanslmay et al. 2008; Nigbur et al. 2011; Cohen 2014). FM-theta oscillation is also evoked when the subjects detect their error responses in task trials (Cavanagh et al. 2009; Cohen and van Gaal 2013; Luu et al. 2004). Furthermore, FM-theta power increase is robustly observed in the process of feed-back learning (van de Vijver et al. 2011; Cavanagh et al. 2010, 2013; Narayanan et al. 2013). These observations indicate that the involvement of FM-theta activity in the prefrontal-basal ganglia circuit computations for reinforcement learning (Schultz and Dickinson 2000; Holroyd and Coles 2002; McNab and Klingberg 2008). This hypothesis is supported by the experiments which showed that FM-theta activity during decision making is affected by perturbations of cortico-basal ganglia loop (Cavanagh et al. 2011). Thus, FM-theta activity may reflect the communications of prefrontal cortex and basal ganglia regulating decision processes and reinforcement learning (Cavanagh and Frank 2014).

The observations of the power increase of FM-theta oscillation in working memory and goal-directed behaviors indicate that FM-theta activities emerge in cognitive processes which requires prefrontal cortical functions (Miller and Cohen 2001; Shackman et al. 2011), suggesting involvement of FM-theta in neuronal computations supporting these functional roles.

11.2.2 Frontal-Midline Theta Support Inter-regional Synchronizations

What is the physiological functions of FM-theta activities in these cognitive processes? The most prominent physiological feature of FM-theta is long-range synchronization, which may support inter-regional integrations of neuronal activities. Large-scale synchronization of FM-theta activities emerge often in a task-dependent manner. Highly coherent activities of FM-theta among PFC and other cortical areas during working memory (Sarnthein et al. 1998; Sauseng et al. 2005; Payne and Kounios 2009; Liebe et al. 2012) and goal-directed behaviors (Anguera et al. 2013; Sauseng et al. 2007; Cavanagh et al. 2009) are robustly observed. Difficulty of working memory also affects the strength of the FM-theta synchronization (Sauseng et al. 2005; Missonnier et al. 2006; Scheeringa et al. 2009). Degrees of FM-theta synchronization correlate the performances of the task, which can be improved after learning processes (Anguera et al. 2013). Importantly, the patterns of FM-theta

coherence across cortical areas dynamically change depending on the types or components of tasks (Sarnthein et al. 1998; Liebe et al. 2012; Cavanagh and Frank 2014). These observations indicate that FM-band synchronization are flexibly organized among different cortical areas depending on task demands.

11.2.3 Cross-Frequency Coupling of Frontal-Midline Theta and Gamma Oscillation

Then, how do FM-theta activities contribute to neuronal computations in inter-regional cortical circuits? In general, oscillations of different frequency bands are involved in neuronal activities in different network sizes (Canolty and Knight 2010; Hutchison et al. 2013). Low-frequency oscillations, such as FM-theta, modulate neuronal activity among long-range networks in long temporal window (Varela et al. 2001; Siegel et al. 2012). On the other hand, high-frequency oscillations, such as gamma, modulate neuronal activity within local networks at a fine timescale (Buzsaki and Wang 2012; Womelsdorf et al. 2007). Importantly, low-frequency and high-frequency oscillations often emerge concurrently and organize oscillation hierarchy; amplitudes of low-frequency oscillations generated in local networks are often phase-modulated by low-frequency oscillation in long-range network. This phenomenon is termed phase-amplitude cross-frequency coupling. Theories predict that the cross-frequency coupling underlies large-scale integration of neuronal activities among functionally specialized brain regions (Jensen and Colgin 2007; Schroeder and Lakatos 2009; Fries 2009; Canolty and Knight 2010).

Cross-frequency coupling of FM-theta and gamma-band oacillations are robustly observed in working memory (Canolty et al. 2006; Axmacher et al. 2010) and goal-directed behaviors (Luo and Poeppel 2007; Lakatos et al. 2008; Saleh et al. 2010), accompanied with task-dependent long-range synchronization of FM-theta oscillation. Thus, cross-frequency coupling of FM-theta and gamma oscillations may underlie the mechanisms of flexible formation and segregation of local and long-range cell assemblies depending on demands of cognitive processes (Canolty et al. 2010; Fell and Axmacher 2011).

11.3 Slow Oscillation in PFC of Rodents: 4-Hz Oscillation

11.3.1 PFC 4-Hz Oscillation in Working Memory

Slow oscillation in PFC during cognitive activity have been commonly observed across different animal species including rodents (Narayanan et al. 2013). In rodents, frontal slow oscillation is termed ‘4-Hz oscillation’, which is hypothesized to be the same oscillation of FM-theta in humans and primates. Here, I introduce recent our study about 4-Hz oscillation in PFC of rats (Fujisawa and Buzsaki 2011), and discuss about the similarity between 4-Hz and FM-theta oscillations.

In this study, we performed large-scale recordings of neuronal activities and local field potentials (LFPs) in the medial prefrontal cortex (mPFC) of rats performing a working memory task, using high-density silicon probes. We also simultaneously recorded hippocampal CA1 activities to compare PFC 4-Hz with hippocampal theta oscillations (Buzsaki 2002). The working memory task used in this study was odor-place matching, which required rats to associate an odor cue (chocolate or cheese smell) presented in the start box with spatial position of a reward (left or right arm of the T maze).

Figure 11.1 shows the LFP traces of PFC and hippocampus in the task periods. Time-frequency analysis of LFP during the task periods revealed that prominent increase of power of the 4-Hz oscillation in PFC. The frequency band of PFC

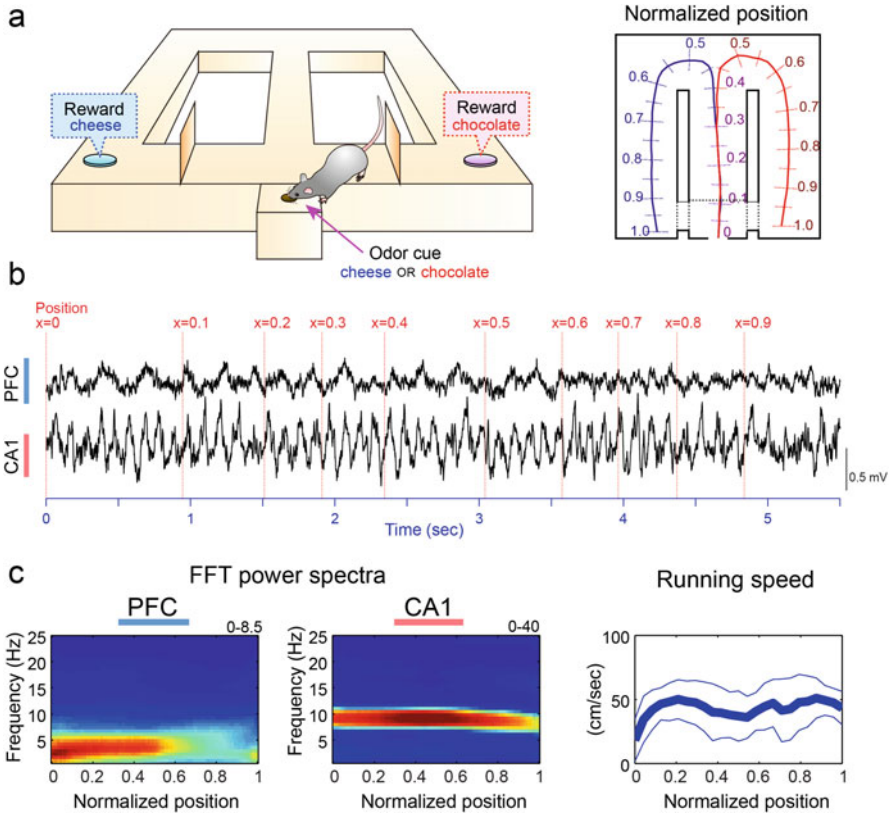

Fig. 11.1 4-Hz oscillation in PFC during working memory. (**a**) Schematics of working memory task. An odor cue (chocolate or cheese) is presented in a start box, which signs the availability of cheese or chocolate reward in the left or right goal area, respectively. Trajectories of the rat are linearized in one-dimensional lines. The central arm of the T-maze is the part which requires working memory. (**b**) Representative traces of local field potential simultaneously recorded from PFC and CA1 during a single trial of the working memory task. (**c**) Power spectrograms of LFPs of PFC and CA1. Prominent 4-Hz frequency band oscillations appeared in the central arm, which was not correlated with running speed of the rat (Panels are reproduced from Fujisawa and Buzsaki 2011)

4-Hz oscillation was clearly different from theta oscillation in the hippocampus. Interestingly, 4-Hz power was higher in the central arm of the T-maze, that is, working memory part of the task. Although the power of hippocampal theta oscillation was also high in the central arm, they remained elevated until the rat reached the goal location. Importantly, 4-Hz power elevation in the central arm was not observed in a control task which does not need working memory. Thus, 4-Hz oscillation was generated in a task dependent manner, especially in working memory periods. These results demonstrated that PFC 4-Hz and hippocampal theta rhythms are distinct oscillations.

Cross-Frequency Coupling of 4-Hz and Gamma Oscillations

In humans and primates, FM-theta oscillation often displays cross-frequency coupling with locally-generated gamma waves, as discussed in the previous section. Here we investigated whether PFC 4-Hz oscillation in rodents also organize cross-frequency coupling with gamma rhythm. During the working memory trials, gamma oscillation with a 50 Hz peak dominated in the PFC in the central arm, which were similar to the temporal dynamics of the 4-Hz power. The amplitude of gamma wave in PFC was phase modulated by the PFC 4-Hz oscillation (Fig. 11.2a), with the strongest modulation present in the central arm. To estimate the phases at which the 4-Hz oscillation modulated gamma power, we picked up troughs of the filtered gamma waves and calculated LFP averages in the periods of working memory. This analysis showed that the largest amplitude of gamma waves occurs on the ascending phase of the 4 Hz oscillation (Fig. 11.2b). Thus, PFC 4-Hz oscillation of rats also demonstrate robust cross-frequency coupling with gamma oscillation in a task dependent manner.

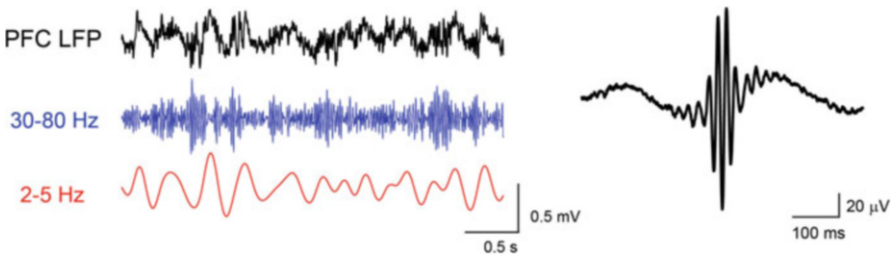

Fig. 11.2 Cross-frequency coupling of 4-Hz and gamma oscillations in PFC during working memory task. Filtered LFP traces with gamma-frequency band (30–80 Hz) displayed modulation of amplitude of high-frequency components by the phases of slow oscillation. Gamma-trough-triggered average revealed that gamma power increase appeared on the ascending phases of 4-Hz oscillation (Reproduced from Fujisawa and Buzsaki 2011)

Phase-Modulation of PFC Neuronal Activities by 4-Hz

Extracellular recordings using high-density silicon probes enable to obtain the information of firing activities of a large number of single neurons during task behaviors. We examined how 4-Hz oscillation modulate the timing of firing activities of PFC neurons. We found that large fraction of pyramidal neurons (∼20%) and interneurons (∼50%) in the PFC was significantly phase-modulated by the 4-Hz rhythm. The firing timing of these neurons mostly showed preference on ascending phases of 4-Hz oscillation. Phase modulation of neurons by 4-Hz oscillation was also compared between the working memory task and non-memory control tasks. Though the firing rates of the neurons in the PFC were similar in both of the tasks, almost twice as many PFC pyramidal cells were significantly phase modulated by 4 Hz rhythm in the working memory task than in the non-memory control task (Fujisawa and Buzsaki 2011).

Previous studies showed that PFC neurons stores working memory information with the forms of sustained firing activity (Goldman-Rakic 1995) and/or goal-predicting sequential activities (Fujisawa et al. 2008; Jung et al. 1998). Here, we estimated the 4-Hz phase-modulations on memory-coding neurons as well as non-memory neurons. The fraction of 4 Hz-modulated neurons was significantly higher in the memory-coding PFC pyramidal cell group, as compared to non-memory cells. Furthermore, the degree of phase locking of the memory-coding PFC neurons to 4-Hz oscillations was also significantly higher than that of the no-memory neurons (Fig. 11.3). Thus, 4-Hz oscillations selectively enhance phase-modulations on memory-coding neurons in the PFC during working memory task.

In addition to spike modulation, spike transmission efficacy between monosynaptically connected PFC neurons (Fujisawa et al. 2008) was also phase modulated by PFC 4 Hz oscillations (Fujisawa and Buzsaki 2011). This results indicate that 4-Hz oscillation may have phase–modulation on synaptic transmissions in PFC neuronal network.

Phase-Phase Interaction of PFC 4-Hz and Hippocampal Theta

So far, we have discussed about the physiological roles of 4-Hz oscillation of the local circuit activities in PFC. Then, whether and how 4-Hz oscillations organize long-range interactions across different cortical areas? First, we investigated the relationship between 4-Hz and theta oscillations, to understand the interactions between PFC and hippocampus. We found phase-phase cross-frequency coupling between 4-Hz and theta oscillations. Trough phases of PFC 4-Hz were significantly locked to the trough phases of CA1 theta waves (Fujisawa and Buzsaki 2011). The phase-phase relationship between these oscillations was also indicated by single neuronal data. Large amount of neurons in the PFC were significantly jointly

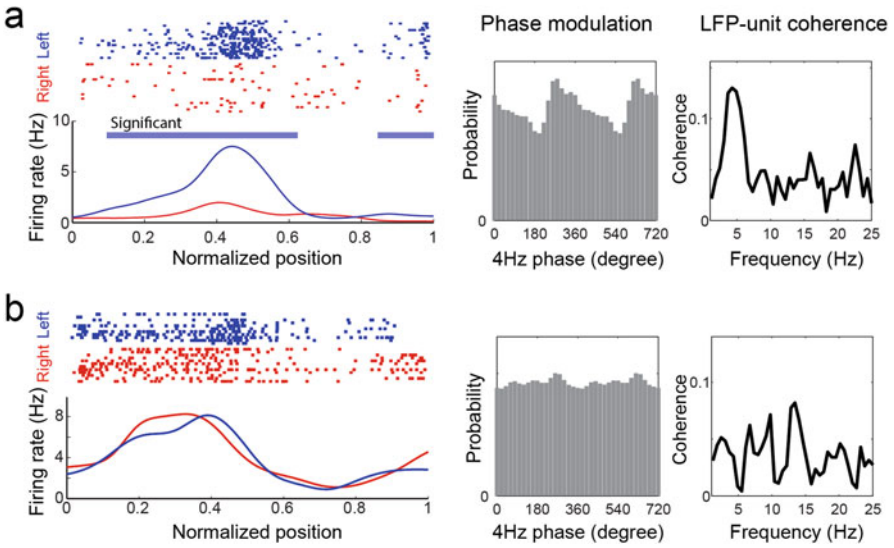

Fig. 11.3 4-Hz oscillation selectively modulate memory-coding neurons in PFC. (**a**) A representative neuron coding working memory. The neuron fired selectively in left trials, and was significantly modulated by 4-Hz oscillation. (**b**) A representative neuron not coding working memory. The neuron fired similarly in left and right trials, and was not modulated by 4-Hz (Adapted from Fujisawa and Buzsaki 2011)

modulated by PFC 4-Hz and hippocampal theta oscillations. Thus, 4-Hz and theta oscillations may contribute to inter-regional interactions between the PFC and hippocampus through phase-phase cross-frequency coupling.

4-Hz Oscillation Coordinates Communication of PFC and Basal Ganglia

As discussed in the previous section, studies of humans and primates indicate that FM-theta activity may reflect the communication of prefrontal cortex and basal ganglia. To assess the role of 4-Hz oscillation on the interactions of PFC and basal ganglia during working memory, we performed triple-sites simultaneous recording from PFC, hippocampus and midbrain ventral tegmental area (VTA). We found that 4-Hz oscillation was synchronized in the PFC and VTA when working memory is in use (Fujisawa and Buzsaki 2011). Importantly, in spite of the large anatomical distance between the PFC and VTA, gamma wave was also coherence among these brain areas, indicating that neuronal activity in the PFC and VTA also synchronizes at fine timescales. These observations suggest that 4-Hz oscillation is a basis of neuronal coalition in the prefrontal-basal ganglia network in working memory periods.

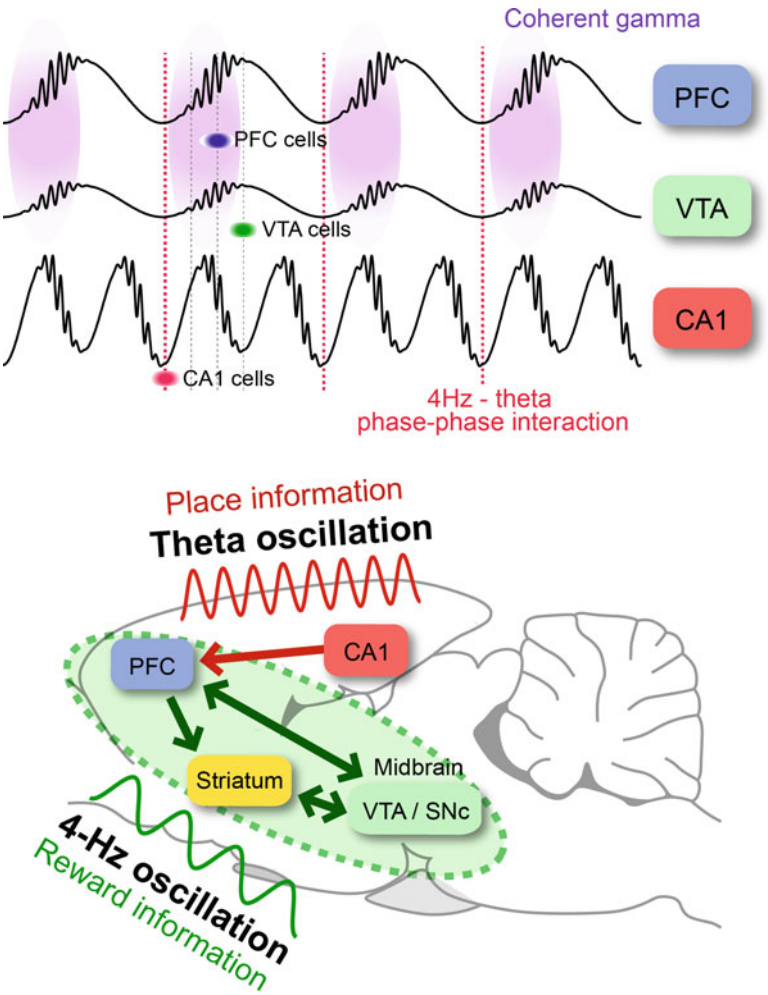

Fig. 11.4 4-Hz Oscillation dynamically synchronizes neuronal activities across the limbic and basal ganglia systems. In the prefrontal-basal ganglia network, 4-Hz oscillation is the dominant pattern, enhancing both coherent gamma oscillations and neuronal firing on the ascending phase. Through phase-phase interaction, 4-Hz and theta oscillations adaptively coordinate gamma activities and neuronal assembly dynamics depending on task demands

4-Hz Summary: PFC-VTA-Hippocampal System

These results demonstrate a triple time control of neurons in the PFC-VTA-hippocampus network (Fig. 11.4). The 4 Hz rhythm is the dominant pattern in PFC-VTA circuits, effectively modulating both local gamma waves and neuronal firing, whereas neuronal activities in the hippocampus is mostly under the control

of theta oscillations. Through phase-phase interaction, 4-Hz and theta oscillations jointly coordinate gamma oscillations and neuronal assembly patterns in a task-relevant manner. Previous studies also demonstrate that 4-Hz frequency band oscillation accompanied with cross-frequency coupling with gamma waves in the cortico-striatal circuits during goal-directed behaviors (Tort et al. 2008; von Nicolai et al. 2014). We hypothesize that these physiological mechanisms temporally coordinate neuronal populations within and across the prefrontal, limbic, and basal ganglia systems.

11.3.2 PFC 4-Hz Oscillation Modulates Fear Memory

4-Hz oscillation is widely observed during various prefrontal-mediated cognitive behaviors in rodents. Recently, Herry and colleagues reported that 4-Hz oscillation is involved in modulations of fear memory through controlling neuronal activities in PFC and amygdala (Karalis et al. 2016; Dejean et al. 2016). The prefrontal-amygdala circuit is crucial to various emotion-related memory, especially in extinction learning of fear memory (Herry and Johansen 2014). Synchronous 4-Hz oscillation is observed in the PFC and amygdala during freezing behavior when the animal is recalling fear memory (Karalis et al. 2016). Importantly, neurons coding fear memory in PFC are selectively phase-modulated on ascending phases of 4-Hz oscillation (Dejean et al. 2016), as similar to working memory (Fujisawa and Buzsaki 2011). Dejean et al., further investigated the importance of phase-modulation on the computations of fear memory in this network. Using real-time optogenetics manipulation techniques, they found that inhibiting neuronal activities in PFC only during the ascending phases of every cycles of 4-Hz oscillation block recalling fear memory (Dejean et al. 2016). Surprisingly, even artificial generation of 4-Hz oscillation in the PFC can evoke fear responses (Karalis et al. 2016). Thus, 4-Hz oscillation underlies the large-scale interactions and information integrations in the prefrontal-amygdala circuit to support emotion-related cognitive functions.

It is also suggested that 4-Hz oscillations control the activity of entorhinal cortex for selective modulation of cell assemblies. Due to the phase-phase interaction of PFC 4-Hz and hippocampal theta, PFC 4-Hz modulates alternating theta cycles, which would support segregation of specific cell assemblies in the entorhinal cortex (Brandon et al. 2013).

11.4 Summary

Slow oscillation in PFC, i.e., FM-theta oscillation in humans and primates and 4-Hz oscillation in rodents, underlies various cognitive functions such as working memory, goal-directed behavior, and emotion-related learning and memory. Cross-frequency coupling of slow oscillation and gamma rhythms organize ‘oscillation

hierarchy', which support both local circuit computations and large-scale neuronal interactions (Canolty and Knight 2010; Buzsaki 2006). Thus, I hypothesize that slow oscillation in PFC provides substrates for flexible formation and segregation of local and long-range cell assemblies on demands of prefrontal dependent cognitive processes. Although slow oscillation are widely observed in the various brain areas, the physiological mechanisms of generation is still to be revealed. Since slow oscillation often emerge in reward-related goal-directed behaviors, the involvement of dopamine is suggested (Fujisawa and Buzsaki 2011; Parker et al. 2014). Clarifying the generation mechanisms of slow oscillation would provide further understanding about detailed computation processes in the PFC and related areas underlying cognition.

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Chapter 12
Memory as Integration and Selection Processes Over Space and Time in Temporal Cortical Microcircuits

Masaki Takeda

Abstract Studies of memory processing in the brain-wide network have led to the development of several psychological models of different aspects of memory, such as the stages of memory information processing, memory span, and memory content. Of these aspects, the memory of space and time in a specific context has been extensively investigated as an episodic-like memory in animal models. Some seminal behavioral studies of episodic-like memory have accelerated the discovery of neuronal correlates of the memory of space and time. The medial temporal lobe memory system is known to be an important brain regions for this memory, which is supported and confirmed by anatomical and theoretical research. Recent methodological developments in functional imaging and multi-site neuronal recording in animals allows us to uncover the detailed circuit machinery of memory systems at the level of neuron-to-neuron interaction, inter-laminar information processing and inter-areal information processing. Although some fundamental issues remain to be elucidated, significant progress has been made toward understanding how the brain memorizes and retrieves items/events.

Keywords Long-term memory • Episodic-like memory • Medial temporal lobe • Neuronal circuit

12.1 Types of Memory

Our ability to memorize items/events and to retrieve them is essential to our daily life. Many psychological studies have struggled to explain how memory is processed in the brain, and have proposed experimental models of memory (Eichenbaum

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et al. 2007; Squire et al. 2007). From an information processing perspective, there are three main stages in memory processing. The first stage is encoding. In this stage, information from the outside world is sensed and encoded as physical or chemical stimuli. In the second stage, the storage of information for these stimuli is maintained over certain periods of time. Finally, the stored information is recalled, usually in response to a cue.

In terms of span, memory is divided into several types, i.e., sensory, short-term and long-term memory. Sensory memory is an automatic process that holds sensory information for less than one second (Sperling 1963). For example, iconic memory is characterized as visual sensory memory and is related to specific visual abilities such as change blindness and continuity of experience during saccades (Dick 1974). In contrast, short-term memory allows for the recall of items on an order of seconds without rehearsal. Using short-term memory, we can usually recall less than ten items (Cowan 2001), but the capacity of this memory can be improved by a process called chunking (Miller 1956). For example, when we recall a telephone number, the digits can be chunked into several groups, allowing us to more easily recall the telephone number than remembering a string of digits separately. In contrast to short-term memory that has a limited capacity and duration of memory, long-term memory can handle information indefinitely. Long-term memory can store a much greater number of item information for an unlimited duration. For example, we can remember a random seven-digit number for a few seconds using short-term memory, whereas we can remember a particular telephone number for many years by retrieving the appropriate information from the long-term memory that was stored by repetitive rehearsal.

Memory can also be divided into declarative and procedural memory types (Eichenbaum et al. 2007; Squire 1992; Squire and Zola 1996) (Fig. 12.1). Declarative memory is a conscious process of recall and thus it is often called explicit memory. Declarative memory is sub-divided into several types of memory including semantic memory and episodic memory. Semantic memory refers to a general knowledge of the world such as facts and items (Jones 2013; Squire 1992). We can encode abstract knowledge by semantic memory; for example, Tokyo is the capital of Japan. On the other hand, episodic memory refers to information that is specific to a particular context with information of a time and place. Using episodic memory, we can recall one's own life events. In contrast to declarative memory, procedural memory is not a conscious process of recall and thus it is often called implicit memory. Procedural memory refers to the implicit learning of something such as motor skills like swimming and piano.

Recent findings by psychophysiology, neuroimaging and electrophysiology studies have revealed the responsible brain regions and neuronal correlates of these aforementioned types of memory. For example, the hippocampus, part of the medial temporal lobe memory system, is involved in declarative memory (Squire 2002). It is hypothesized that general declarative memory is processed through interactions between the medial temporal lobe memory system, sensory association cortices and frontal cortex (Simons and Spiers 2003) (Fig. 12.2).

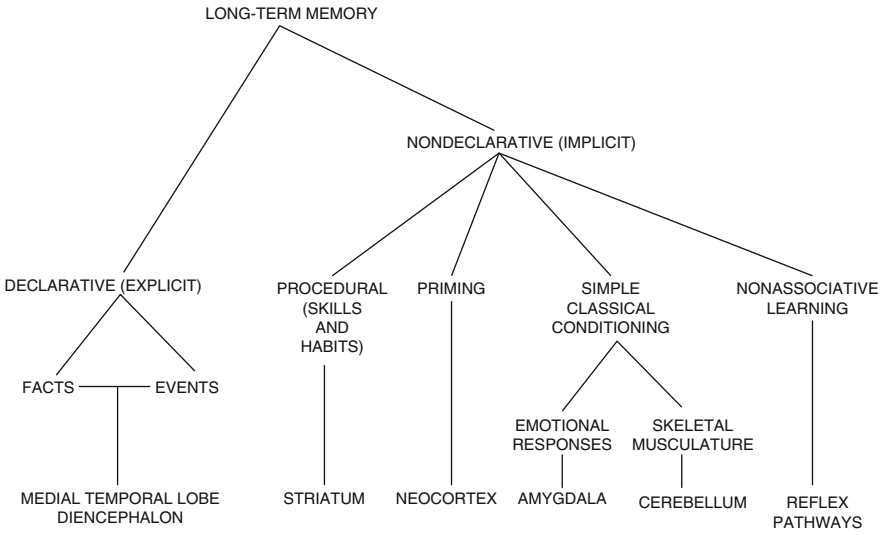

Fig. 12.1 Long-term memory systems together with the specific brain structures involved in each system (Adapted from Squire and Zora 1996)

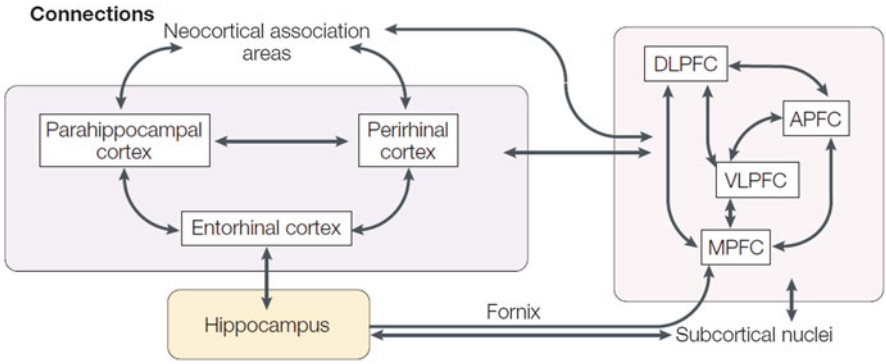

Fig. 12.2 Anatomical connections of brain areas for long-term memory. There are large cortico-cortical direct reciprocal connections between the prefrontal cortex and the medial temporal lobe, which pass through the uncinate fascicle, anterior temporal stem and anterior corpus callosum. The orbitofrontal and dorsolateral cortices have strong reciprocal connections with the perirhinal and entorhinal cortices. There are more connections from the prefrontal cortex to the perirhinal cortex than the opposite direction of connections. Unidirectional projections exist from the CA1 field to the caudal region of the medial prefrontal cortex. The subicular complex and neocortical medial temporal regions have reciprocal connections with the caudal medial prefrontal cortex. In addition, the medial temporal lobe receives information from a range of unimodal and polymodal sensory association areas. This information predominantly enters through the perirhinal and parahippocampal cortices, which project back to these regions. The prefrontal cortex has reciprocal connections with sensory association cortices including the temporal and parietal regions and many subcortical structures (Adapted from Simons and Spiers 2003)

12.2 Memory of Space and Time in a Specific Context

As mentioned in the previous section, our capability to memorize our specific life episodes is termed episodic memory and involves contextual "what", "when", "where", "who" and "why" knowledge. Although many researchers have investigated brain mechanisms of episodic memory, the neuronal correlates of episodic memory and neuron-to-neuron interactions that underlie episodic memory are poorly understood. One of the serious obstacles to understanding these mechanisms is the lack of animal models for episodic memory. Indeed it is currently unknown whether animals other than humans have episodic memory.

Several studies have struggled to identify the behavioral basis of episodic memory in non-human animals. Clayton and Dickinson demonstrated that western scrub jays (*Aphelocoma californica*) can remember where they cached different types of food as well as recover them depending on the perishability of the food and the total duration of the time that has passed since caching (Clayton and Dickinson 1998). In this study, the authors investigated whether scrub jays remembered when food items were stored by allowing them to recover perishable waxworms and non-perishable peanuts that they had previously cached in different locations. The authors found that the scrub jays searched preferentially for fresh worms (favored food) in a situation where they were allowed to recover worms shortly after caching. However, the jays learned to avoid searching for worms after a longer interval during which the worms had decayed. These results suggest that scrub jays have the ability to encode and retrieve information regarding what occurred during the episode of the cache, where the episode of the cache took place, and when the episode of the cache happened. The authors termed this memory "episodic-like memory" (Clayton et al. 2003, 2007).

Recently many other researchers have investigated episodic-like memory further in humming birds (Henderson et al. 2006), pigeons (Zentall et al. 2001), primates (Martin-Ordas et al. 2010), rats (Babb and Crystal 2006) and honeybees (Pahl et al. 2007). However, it has to be noted that this episodic-like memory is not strictly equivalent to episodic memory in humans because it is still unknown whether these animals have a conscious recollection, which is a major concept of human episodic memory (Crystal 2009; Morris 2001). Nevertheless, investigating episodic-like memory in animals is the best currently available method to dissect the neuronal mechanisms involved in episodic memory in humans.

12.3 Brain Mechanisms of Long-Term Memory with Regards to Temporal Order

In addition to the aforementioned behavioral studies of episodic-like memory in animals, several recent studies have investigated the neuronal correlates of episodic-like memory at the resolution of a single neuron using electrophysiological techniques. For example, Naya and Suzuki studied the neuronal correlates of episodic-like

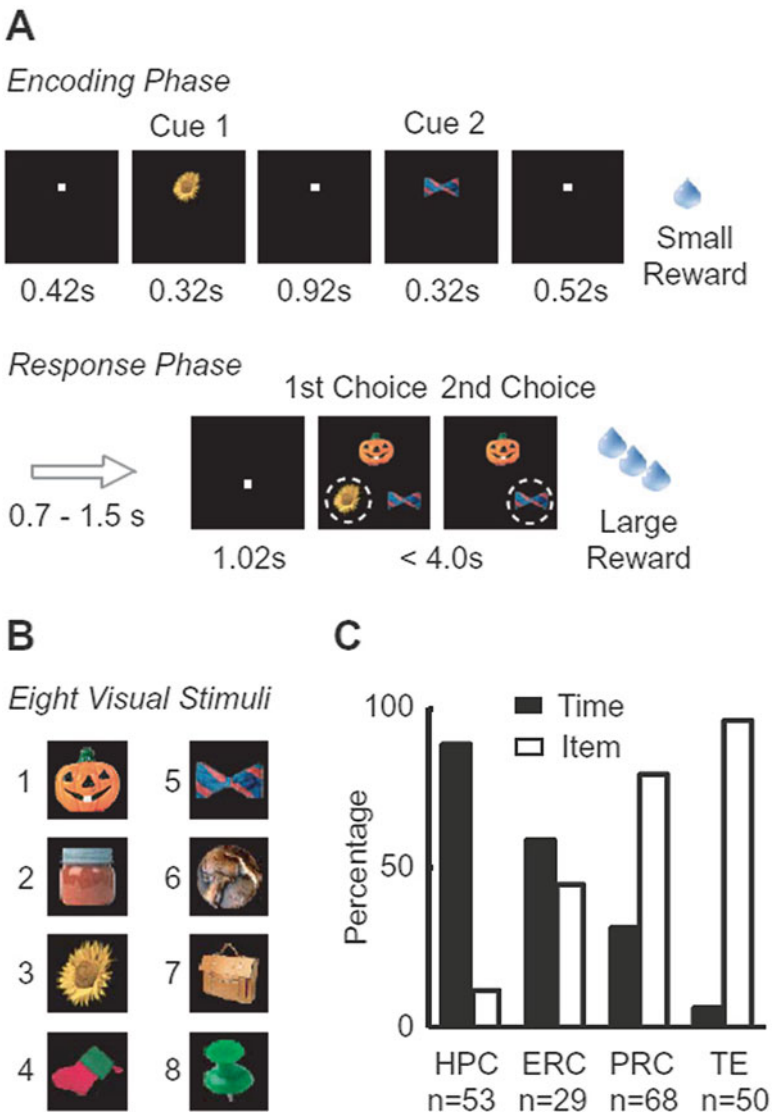

Fig. 12.3 (**a**) Schematic diagram of the temporal-order task. A sequence of two cue stimuli was presented in the encoding phase. The two cue stimuli and one distracter were presented at three different positions randomly in the response phase. Dashed circles indicate correct targets. (**b**) The eight visual stimuli used in the task. (**c**) Relative proportions of time cells and item cells in each area (Adapted from Naya and Suzuki 2011)

memory in the monkey medial temporal lobe (Naya and Suzuki 2011) (Fig. 12.3). In that study, the authors recorded the single unit activity and local field potential from the medial temporal lobe, while monkeys performed a temporal-order memory task

that required encoding of both visual items and their temporal order. In each neuron, they evaluated the effects of "time" and "item" on the cue responses separately. They defined neurons that differentiated cue 1 and cue 2 in their responses as "time cell". The time cells conveyed the signal for the temporal order of cue presentations. In addition, they defined neurons that showed stimulus selectivity in either cue 1 or cue 2 as "item cells". Then, they compared the proportions of these time and item cells across the subareas of the medial temporal lobe. They found that the highest proportions of item cells were observed in area TE, part of the visual association cortex, with a decreasing proportion observed in the perirhinal cortex, entorhinal cortex, and hippocampus. On the other hand, the highest proportions of time cells were observed in the hippocampus, with a decreasing proportion observed in the entorhinal cortex, perirhinal cortex, and area TE. Thus, the proportions of time and item cells were reversed through the possible information flow across the subareas of the medial temporal lobe. Next, the temporal dynamics of time cells were characterized using a population vector analysis. In the hippocampus, the distance of the vector for the cue 1 state increased at a constant rate during the period between cue 1 and cue 2 (delay period), suggesting that the time cells in the hippocampus provided an incremental timing signal for an estimate of the relative time from the last cue presentation. Such an incremental timing signal was not observed or was weaker in the perirhinal cortex and entorhinal cortex. Notably, neurons in the perirhinal cortex modulated their stimulus-selective responses across the cue periods, suggesting that these neurons integrate information of both the item and its temporal order. Taken together, this study demonstrated the functional role of subareas in the medial temporal lobe for the integration of item and timing information, i.e. the neuronal correlates of what and when information in episodic-like memory. How these subareas interact to output the integrated information of items and temporal order, as well as how the information of space is involved in this neuronal circuit remain to be elucidated in the near future.

Recently, numerous studies investigated brain-wide neuronal activity and its interactions for memory where information about the temporal context was included. For example, Jenkins and Ranganath reported prefrontal and medial temporal lobe activity during the encoding phase for temporal context memory (Jenkins and Ranganath 2010). In this study, the relationship between activity at encoding and subsequent memory for temporal context was investigated using event-related functional magnetic resonance imaging (fMRI). Brain-wide functional imaging was conducted, while subjects performed a serial order working memory task with pictures of common objects. These subjects were later tested for temporal memory at two different timescales. In the test phase of the coarse temporal memory, subjects viewed one object from each trial and were required to indicate approximately when it had appeared during the course of the experiment. In the test phase of the fine temporal memory, subjects viewed the remaining objects from each trial and were required to recall the originally presented order. Using this task, the authors reported that activity in the parahippocampal cortex predicted subsequent fine temporal accuracy, whereas coarse temporal accuracy was predicted by activity in several regions of the prefrontal cortex as well as in the hippocampus.

These results suggested that the medial temporal lobe and the prefrontal cortex contributed to the temporal context of memory at the time of encoding of items.

Other fMRI studies also demonstrated that the medial temporal lobe plays a critical role for the temporal context of memory. Tubridy and Davachi examined activation in the medial temporal lobe during the encoding of sequentially presented noun sequence (Tubridy and Davachi 2011). Using performance in the retrieval test, they found that encoding activations predicted the subsequent recognition of noun sequences. In addition, they identified activations that differentiated noun sequences that were subsequently recognized with and without memory for the original sequence of presentation. Within the medial temporal lobe, activations in the hippocampal and parahippocampal regions predicted subsequent order memory, with greater activations observed during the encoding of noun sequence subsequently correctly ordered than those subsequently misordered. Considering that activation in these regions did not correlate with old/new identification of noun sequence, these results suggest that the medial temporal lobe contributed to the encoding of episodic details supporting the subsequent recovery of sequence information.

Brain-wide functional imaging of neuronal activity not only enables investigation of the functional properties in each individual area but also the functional connectivity between brain areas. Konishi and his colleagues used fMRI to identify the neural correlates for memory representation in the temporal cortex (Yamashita et al. 2009). In that study, subjects initially learned the pairing of visual stimuli by performing the pair-association task. Then, approximately 8 weeks after the study, the subjects learned new pairs of visual objects, keeping the correct performance during the tests balanced across the two sets of stimuli. After the study of the two sets of pairs, authors compared brain activity during the retrieval of the stimuli learned long before the test (learned approximately 8 weeks earlier; remote memory) with that during the retrieval of newly learned stimuli (learned immediately before the scanning; recent memory) using fMRI. They found a significant signal increase in the hippocampus during the retrieval of newly studied pairs relative to the initially studied pairs. In contrast, signals in the anterior temporal cortex were significantly increased during the retrieval of initially studied pairs relative to the newly studied pairs. The greater activity during the retrieval of remote memory developed in the temporal cortex provides direct evidence of the formation of temporal cortical representation for stable long-term memory. Using the same experimental paradigm, they investigated functional connectivity in the brain-wide neuronal network for memory representation (Watanabe et al. 2012). In that study, two categories of stimuli, faces and scenes, were used for paired stimuli that subjects were required to retrieve. Brain activity during the retrieval of newly learned stimuli was compared with that during the retrieval of paired stimuli learned long before the test. They found that different posterior temporal cortical regions were activated during the retrieval of different categories of remote memory in a category-specific manner (Fig. 12.4). In addition, in a category-general manner, the anterior temporal cortical

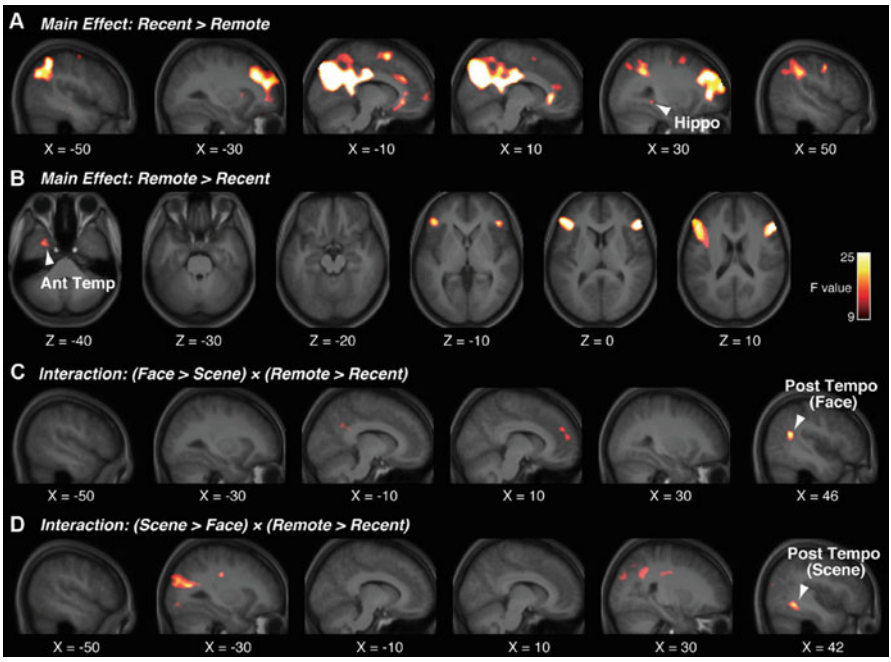

Fig. 12.4 Brain regions related to the retrieval of recent/remote memory. (**a**) In the temporal lobe, the hippocampal region was activated during category-general recent memory (main effect of recent vs remote). (**b**) The anterior temporal region was activated during retrieval of category-general remote memory (main effect of remote and recent). (**c**, **d**) The two different posterior temporal regions involved in the retrieval of category-specific remote memory (interaction of remote/recent × face/scene). Statistical significance is indicated using the color scale. Hippo, hippocampal region; Ant temp, anterior temporal region; Post tempo, posterior temporal region (Adapted from Watanabe et al. 2012)

region was activated during the retrieval of remote memory while the hippocampus was activated during the retrieval of recent memory. Furthermore, a multivariate pattern analysis of psychophysiological interactions during the retrieval of remote memory relative to recent memory demonstrated that the category-specific posterior temporal cortical regions interacted with the category-general anterior temporal region. These results suggest that the posterior temporal cortical regions are involved in the representation and retrieval of category-specific remote memory, whereas the anterior cortical temporal region is involved in category-general retrieval process of remote memory.

Recently, brain-wide neuronal imaging has been applied to non-human primates to bridge the gap between knowledge obtained from human functional imaging and knowledge obtained from studies using invasive techniques in non-human primates. One of the most usable imaging methods in non-human primates is fMRI, and many studies have used this technique (Arcaro et al. 2011; Arsenault et al. 2013; Baker et al. 2006; Bell et al. 2011; Brewer et al. 2002; Conway et al. 2007; Denys et al.

2004; Durand et al. 2007; Ekstrom et al. 2008; Gerits et al. 2012; Hadj-Bouziane et al. 2012; Kolster et al. 2009; Logothetis et al. 2012; Miyamoto et al. 2013; Moeller et al. 2008; Nakahara et al. 2002; Nelissen et al. 2005; Pinsk et al. 2009; Polosecki et al. 2013; Popivanov et al. 2014; Schmid et al. 2010; Vincent et al. 2007; Wilke et al. 2012). Using fMRI, the brain network involved in the memory of temporal order was also investigated in monkeys (Osada et al. 2015). In this study, monkeys were scanned while they performed a temporal contextual memory task. The authors found that the activated areas formed a hierarchical hub-centric network based on task-evoked directed connectivity, with the hub at 9/46d. Using a novel simulated-lesion method based on a support vector machine, they also reported that the predicted severity of impairment was proportional to the network "hubness" of the virtually lesioned area in the task-evoked directed connectivity network, rather than in the anatomical network determined from tracer studies. These results suggest that the prefrontal cortical areas dynamically shape a functional hub-centric network to reallocate the lesion-effective site depending on the cognitive processes, apart from static anatomical hubs.

12.4 Brain Mechanism of Long-Term Memory with Regards to Space

As mentioned above, one important aspect of episodic memory is the spatial context. It is well known that one of the responsible cells for spatial context is a place cell, first discovered specifically in the hippocampus (O'Keefe and Dostrovsky 1971). The place cell fires when an animal is located at a particular space (place) in the environment. This particular place termed the place field. Place fields are similar to the receptive fields of neurons that respond to other sensory input, in that the firing region corresponds to a region of sensory information in the environment (e.g., the visual receptive field). A given place cell has only one or a few place fields in a typical small laboratory environment, but usually more in a larger region. Place cells fired more rapidly when rats ran past places (in the place fields) in the environment, when a new item was added to the environment, or when an item that was usually there was not present (O'Keefe 1978).

Other neurons with specific pattern of firing are related to place cells. One example is a head direction cell, which was first identified in the dorsal presubiculum near the hippocampus (Taube et al. 1990a, b). Head direction cells fire when the animal's head is in a specific direction. The place cells and head direction cells are complementary in the spatial context; the place cells are mostly orientation-invariant and location-specific, while head direction cells are mostly orientation-specific and location-invariant. Although robust head direction cells were found in the hippocampus, substantial numbers of head direction cells were recently found in the entorhinal cortex located adjacent to the hippocampus.

Another neuron type related to place cells is a grid cell, located in the entorhinal cortex that provides a dense anatomical projection to the hippocampus (Bush et al. 2015; Fyhn et al. 2004; Moser et al. 2014; Sanders et al. 2015). Grid cells have a sharply defined firing field but fire at multiple locations. Strikingly, the arrangement of the firing fields shows regularity, i.e., a hexagonal grid-like pattern, which is different from place cells in the hippocampus (Hafting et al. 2005). Grid cells have been found in all layers of the medial entorhinal cortex (Burgalossi and Brecht 2014). However, grid cells in different layers of the entorhinal cortex differ in their firing; pure grid cells, which fire equally regardless of the direction an animal traverses in a grid location, are located mainly at layer II, while grid cells in the deep layers are intermingled with conjunctive cells and head direction cells (Sargolini et al. 2006). Thus, the deep layers contain cells with a grid-like pattern that fire when the animal is directed in a particular location. Taken together, the representation of place, distance, and direction are implemented in the same network of medial temporal cortical neurons, allowing the computation of a continuously updated metric representation of the animal's location (Giocomo et al. 2011). The putative function of grid cells might be in the mechanism whereby a place code is computed in cells in the entorhinal cortex and then fed into the hippocampus where associations between places and events occur to form memories of the spatial environment (Hafting et al. 2005).

It is widely accepted that the hippocampus and surrounding brain areas in the medial temporal lobe constitute a neuronal network for memory of the spatial context, with the place cells, head direction cells, and grid cells playing key roles. The hippocampus receives anatomical inputs via the medial entorhinal cortex from regions that encode spatial information, such as location and head direction. The medial entorhinal cortex receives anatomical input from the postrhinal cortex (parahippocampal cortex) that receives input from visuospatial regions. In primates, for example, the parahippocampal region includes the parahippocampal place area where neurons respond to the visual images of scenes (Epstein et al. 1999). The medial temporal cortex is also interconnected with the presubiculum, parasubiculum, and retrosplenial cortical areas, which contain head direction cells, place cells, and grid cells. This stream appears to use strategies such as path integration by updating a representation of the animal's present spatial position and direction of heading (McNaughton et al. 2006; Sargolini et al. 2006). On the other hand, the hippocampus receives anatomical inputs via the lateral entorhinal cortex from regions that encode items (Bussey and Saksida 2005; Hargreaves et al. 2005). The lateral entorhinal cortex receives anatomical input from the perirhinal cortex that is involved in the processing of visual objects (items). The perirhinal cortex receives input from various sensory areas (Burwell 2000).

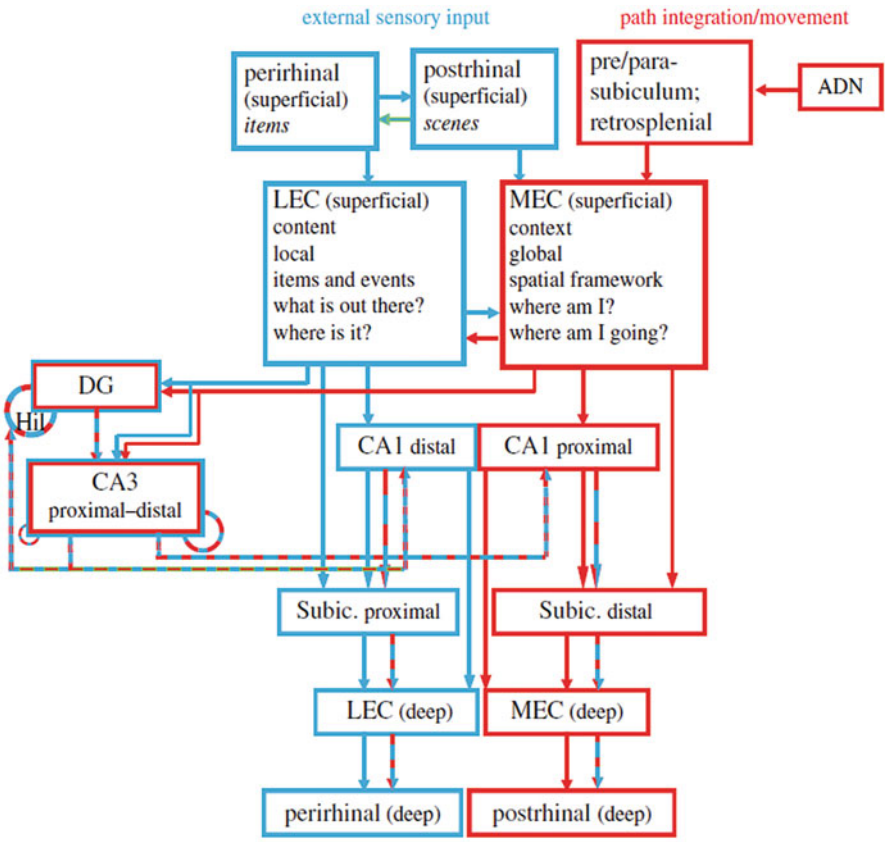

Fig. 12.5 Parallel processing streams into the hippocampus for memory. The lateral entorhinal cortex (LEC) and medial entorhinal cortex (MEC) connect to distinct regions of CA1 and subiculum, segregated along the transverse axis of the hippocampus. CA1 and subiculum send return projections to the deep layers of the entorhinal cortex. Note that there is crosstalk along these pathways, both prior to their entry into the hippocampus and especially in the convergent projections to the DG and CA3. Specific mnemonic properties of the DG and CA3 regions are thought to be supported by the recurrent feedback loops represented by the *dashed circles*. *ADN* anterior dorsal nucleus of the thalamus, *DG* dentate gyrus. *Hil* hilus, *Subic.* subiculum (Adapted from Knierim et al. 2013)

These medial and lateral processing streams anatomically converge at the dentate gyrus and CA3 region in the hippocampus (Fig. 12.5). Thus, neurons in the hippocampus combine information from these regions into a conjunctive representation of the "what" and "where" of one's own memory (Eichenbaum et al. 2007; Ranganath 2010). It is noteworthy that these two streams are also thought to be substrates for the functional processing related to other aspects such as "self" and "other" (Knierim et al. 2013; Manns and Eichenbaum 2006).

12.5 Neuronal Circuits for Long-Term Memory at the Multi-scopic Scale

To date, the brain mechanism involved in how we memorize items or events within a specific context in time and space, and how we retrieve them from long-term memory is poorly understood. However, several recent studies have revealed the precise neuronal circuits for the retrieval of visual information from long-term memory. Pair-association memory in the perirhinal cortex is one of the most intensively investigated systems. The primate perirhinal cortex is located within the medial temporal lobe memory system, where it receives information from the ventral visual pathway and contributes to the storage and retrieval of visual long-term memory (Miyashita 2004; Squire et al. 2007; Suzuki 2009; Suzuki and Naya 2014). Using the pair-association task, previous studies have identified several types of perirhinal neurons that are active during the retrieval of visual associative memory. One type exhibits sustained activity that continues from the presentation of a cue stimulus (cue-holding neurons) (Naya et al. 2003), and a second type exhibits gradually increasing activity toward the presentation of the paired associate (pair-recall neurons) (Naya et al. 2001, 2003; Sakai and Miyashita 1991), of which the neuronal response dynamically appear or disappear on demand for the retrieval of a learned paired-associate (Naya et al. 1996).

However, the functional microcircuitry and neuron-to-neuron information flow during the retrieval of visual associative memory still remains to be elucidated. A recurrent cortical network model with Hebbian plastic synapses was proposed to explain theoretically the neuronal circuit for pair association memory (Mongillo et al. 2003). In the first stage of the model, the learning of image pairs led to the emergence of neuronal activity during the delay period, representing individual images ("retrospective" activity). As the learning proceeded, the same learning mechanism used retrospective delay activity together with choice stimulus activity to potentiate synapses connecting neural populations representing associated images. As a result, the neural population corresponding to the pair-associate of the image presented was activated prior to its visual stimulation ("prospective" activity). The probability of the appearance of prospective activity was governed by the strength of the inter-population connections, which in turn depended on the frequency of pairings during training (Fig. 12.6).

Recently, the microcircuit in A36 of the perirhinal cortex that retrieves visual information from long-term memory was identified (Hirabayashi et al. 2013a). In that study, the authors conducted simultaneous recordings of multiple single units in the monkey perirhinal cortex (area 36, A36) using tetrodes while they performed a pair-association memory task. Using Granger causality analysis for the signal flow between neurons, the authors observed the emergence of directed couplings during the delay period predominantly from cue-holding neurons to pair-recall neurons, especially in the gamma frequency band (Fig. 12.7). Moreover, these interactions coincided with a unidirectional signal flow from the recipient recall

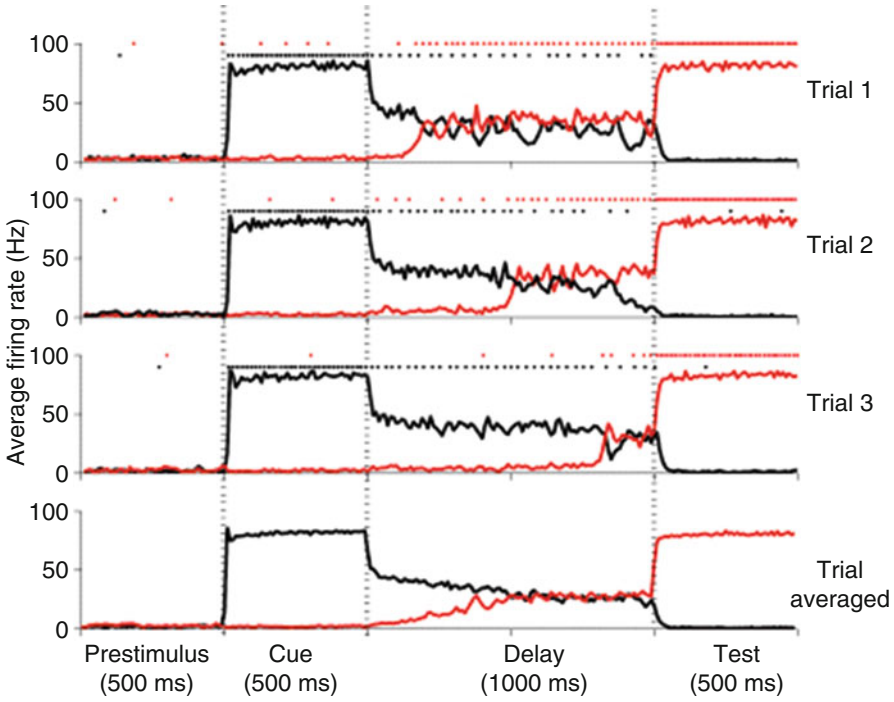

Fig. 12.6 Prospective activity in the delay interval proposed by a recurrent cortical network model. The bottom panel depicts the epochs of the trial (prestimulus: 0–500 ms; cue presentation: 500–1,000 ms; delay period: 1,000–2,000 ms; test presentation: 2,000–2,500 ms). *Black curve*: average rate in the predictor population. *Red curve*: average rate in the choice population. Top three panels: single-trial examples of transition at different times during the delay period. At the top of each panel, a spiking activity of one representative neuron belongs to the predictor population (*black*) and one to the choice population (*red*). Note that retrospective activity can either persist (Trials 1 and 3) or die out (Trial 2). Bottom: predictor and choice population activity averaged over 100 trials. The average delay activity in the pair-associate population shows a continuously increasing activity during the delay period (Adapted from Mongillo et al. 2003)

neuron to another recall neuron. These results suggest that there is cascade-like signal propagation among the memory cell assembly in A36 for memory retrieval (Fig. 12.8).

In the hierarchy of occipitotemporal cortical areas, neuronal representations of visual objects are elaborated, and the recognition of a feature as "novel" is commonly thought to emerge and become prevalent at a cortical area because of local signal processing. Hirabayashi et al. (2013b) tested another possibility that a feature representation becomes prevalent in a given area because a microcircuit creates a small number of precursor representations in a prior area in the cortical hierarchy, and the representations then become prevalent through proliferation in the subsequent area (Hirabayashi et al. 2013b). Previous studies have demonstrated

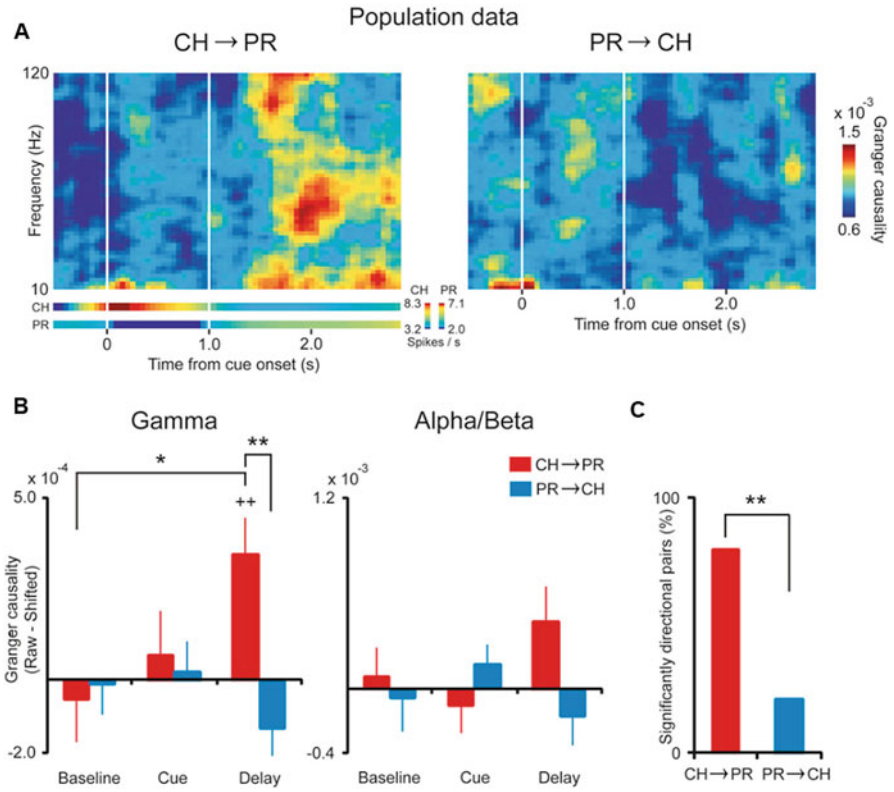

Fig. 12.7 Population Granger causality between Cue-holding (CH) and Pair-recall (PR) neurons. (**a**) Spectral dynamics of population Granger causality in the direction from CH to PR (*left*) and PR to CH (*right*). Time courses of spike firings for both CHs and PRs are depicted below. (**b**) Time courses of Granger causality in the gamma (*left*) and alpha/beta (*right*) frequency ranges. Trial-shifted control was subtracted. (**c**) Proportions of cell pairs showing a significantly directional causal influence (Adapted from Hirabayashi et al. 2013a)

that single neurons representing associations between two object images (pair-coding neurons) (Miyashita 2004; Naya et al. 2003; Sakai and Miyashita 1991) become prevalent in A36, although the pair-coding neurons only constitute a small minority in area TE (Miyashita 2004; Naya et al. 2003), a hierarchically prior cortical area (Saleem and Tanaka 1996; Suzuki and Amaral 1994). It is unknown whether activities of the small number of neurons in area TE merely reflect the potential variability of response selectivity or whether they emerge as a result of specific computations in a convergent microcircuit. Microcircuits that generated pair-coding neurons in areas TE and 36 were investigated by simultaneous recording from multiple single neurons in each of these areas in monkeys performing a pair-association memory task. They found the areal difference in functional

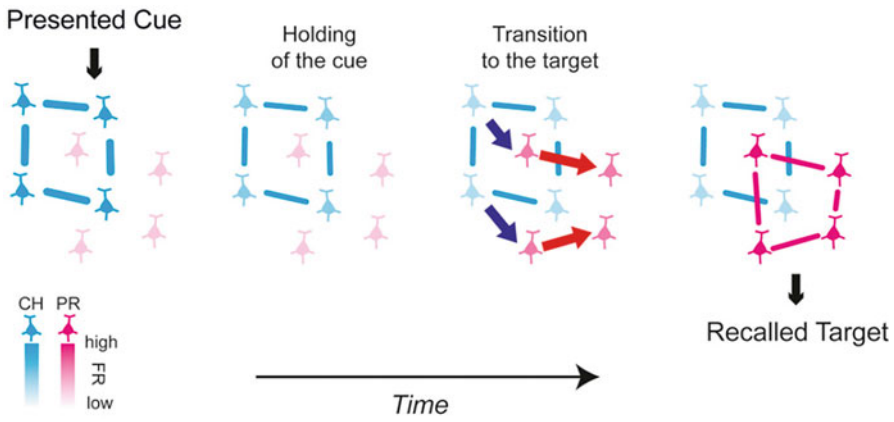

Fig. 12.8 Schematic diagram of the functional microcircuitry in the perirhinal cortex in retrieval of object association memory. Cyan and magenta neurons, CH and PR neurons. *Blue and red arrows* between neurons depict directed interactions identified in the present study. Lines between neurons represent functional couplings. This model shows that cue information is transmitted from the CH cell assembly to the PR cell assembly to convert the representation in the microcircuit from the cue to the sought target (Adapted from Hirabayashi et al. 2013a)

connectivity by cross-correlogram (CCG). As shown in previous studies, the pair coding index (PCI) values were significantly greater in area 36 than in area TE, and significant associative representations were observed only in area 36 but not in area TE as a population (Miyashita 2004; Naya et al. 2003). However, PCI values of the target units, but not the source units, in area TE were indistinguishable from those of area 36 neurons. These results suggest that the prototype of associative representations can be generated in area TE as a result of microcircuit processing and then transferred to area 36, where the representations become prevalent.

Evidence from the primary sensory cortices suggests that local circuits extending across cortical layers are crucially involved in sensory processing (Douglas and Martin 2004; Nassi and Callaway 2009). This raises questions about how the interlaminar circuitry in the temporal cortex is differentially recruited to process presented visual objects and to retrieve visual long-term memory. Miyashita and his colleagues used two strategies to investigate interlaminar signal flow (Takeuchi et al. 2011). First, they utilized current source density (CSD) analysis as a tool for layer estimation in each electrode penetration because the CSD reflects the gross transmembrane current flow in the local neuronal ensemble and is used to estimate the cortical layers that receive afferent inputs (Csicsvari et al. 2003). Second, they utilized cross-correlation analysis of spike trains to infer the functional interactions across cortical layers: asymmetry or peak lag of the CCG reflects the direction of functional connectivity between neurons (Alonso and Martinez 1998; Hirabayashi

et al. 2013b). For neuron pairs between the granular layer and supragranular layer, individual CCGs during the cue period showed a shifted peak to the feed-forward direction, from the granular to supragranular layer. However, during the delay period, this directional bias was not significant. Regarding neuron pairs between the supragranular layer and infragranular layer, CCGs showed a shifted peak in the direction from the supragranular to the infragranular layer during the cue period. However, during the delay period, CCGs exhibited a bias in the opposite direction, from the infragranular to the supragranular layer. These results demonstrated the dynamic signal flow during the performance of the pair-association task was from the granular to the supragranular layer and from the supragranular to the infragranular layer during the cue period as in the canonical feed-forward processing. However, during the delay period, the direction of the signal flow reversed, suggesting the recruitment of a "feed-back" pathway. In the rat primary auditory cortex, the direction of the interlaminar signal flow depends on the cortical state; sensory-evoked responses were initiated in the thalamorecipient layers and then propagated to the superficial and deep layers, whereas in spontaneously active up-states, neuronal activity was initiated in the deep layers and then propagated to the superficial layers (Sakata and Harris 2009). These state-dependent changes in the interlaminar signal flows in rats are consistent with the aforementioned results obtained in monkeys performing a memory task. Together, these findings highlight the flexibility of cortical laminar circuits.

Anatomical evidence suggests that reciprocal processing occurs throughout the subareas of the medial temporal lobe and connected association cortices (Lavenex and Amaral 2000). The distinct inter-areal connection pattern indicates specific roles for subareas in the medial temporal lobe, which is supported by both lesion and physiological studies (Murray et al. 2007). Thus, the medial temporal lobe memory system is not a unified memory pipeline leading to and from a singular memory store in the hippocampus, but rather a system with distributed but interacting components (Xia et al. 2015). One plausible model is that during the performance of the pair-association task, visual inputs propagate forward through the ventral visual pathway, while the learned association signal spreads from the perirhinal cortex back to visual area TE, with biasing neuronal activity to the sought target. One method to examine the inter-areal interactions underlying retrieval of visual objects from long-term memory is to conduct simultaneous multi-site recordings to quantify the temporal relationship between the output signal (spikes) of an upstream area and the input signal local field potentials of a downstream target (Pesaran et al. 2008). Moreover, combining inter-area multi-site recording with inter-laminar analysis is a natural extension to this approach because the anatomical wiring between areas follows general patterns of laminar organization, and these appear differently for feedforward and feedback connections (Felleman and Van Essen 1991). However, the functional connectivity for feedback signals and its impact on intra-laminar processing during memory retrieval has not been investigated. Takeda et al. (2015) used this approach to investigate the laminar-specific feedback signal from A36 to TE of monkeys during the delay period of a pair-association

task (Takeda et al. 2015). In this study, spike recordings in A36 were combined with multicontact laminar recordings of local field potential (LFP) in TE. They found that, during memory retrieval, coherence between spiking in A36 and the low-frequency band LFP in TE was increased. A36 spikes led the trough of TE LFP, and these results were consistent with the signal transmission delay between two cortical areas in previous studies (Gregoriou et al. 2009). The directionality and timing of the observed A36 to TE coherence suggest a coordination of activity between spikes in A36 and LFP signals in TE. In addition, they found two distinct streams of information flow; one group of A36 neurons fired coherently with the LFP in the supragranular layers of TE, while other group fired coherently with the LFP in the infragranular layers (Fig. 12.9). The two distinct streams of feedback information flow may reflect the multiple anatomical connections between the two areas (Suzuki et al. 2000). They also investigated whether and how each stream affected the local ensemble activity in TE, as approximated by A36-spike-triggered gamma oscillations that were most pronounced in the supragranular layers. They demonstrated that spikes of neurons that were coherent with the low-frequency LFP in TE infragranular layers were coupled with the gamma power in TE. Moreover, this coupling was behaviorally relevant and significantly larger in correct trials than in error trials. These results suggest that only the signal flow from A36 to the infragranular TE may modulate the neural activity in supragranular TE and thus facilitate memory retrieval during the pair-association task.

As mentioned above, at the level of single neurons, recordings within macaque TE and A36 during visual pair-association tasks revealed a class of neurons exhibiting discharges selective for learned associations, neuron-to-neuron interaction, and inter/intra areal interactions (Hirabayashi et al. 2013a, b; Naya et al. 2003; Takeda et al. 2015, 2005). However, little is known about the entire picture of the cortical memory representation that is distributed across brain regions in the temporal lobe. Thus, whether memory formation accompanies the area-wide reorganization of collective neural ensembles or just local microcircuit-level neuronal plasticity remains elusive because of a lack of recording methods with high temporal resolution as well as wide spatial coverage. To investigate this possibility, Nakahara and his colleagues devised a novel high-density electrocorticographic (ECoG) electrode grid to acquire multi-site LFP recordings on the cortical surface of the medial temporal lobe of monkeys performing a visual pair-association task (Nakahara et al. 2016). They investigated whether ECoG local field potentials evoked by one item of a learned pair shared spatiotemporal patterns to those evoked by the other item of the pair. An ultrathin, 128-channel electrode grid over the anterior middle temporal sulcus was subdurally implanted to the monkey brains. They found that the majority of channels distributed from TE to the medial temporal lobe showed significant stimulus selectivity in the theta-frequency band. In addition, similar spatial patterns of the theta activity were elicited by both members of the learned paired associate. Then, using a multivariate machine-learning approach, trial-by-trial robustness and specificity of theta pattern similarity was assessed. A machine-learning decoder was first trained on theta activity patterns evoked by one member of a particular pair that

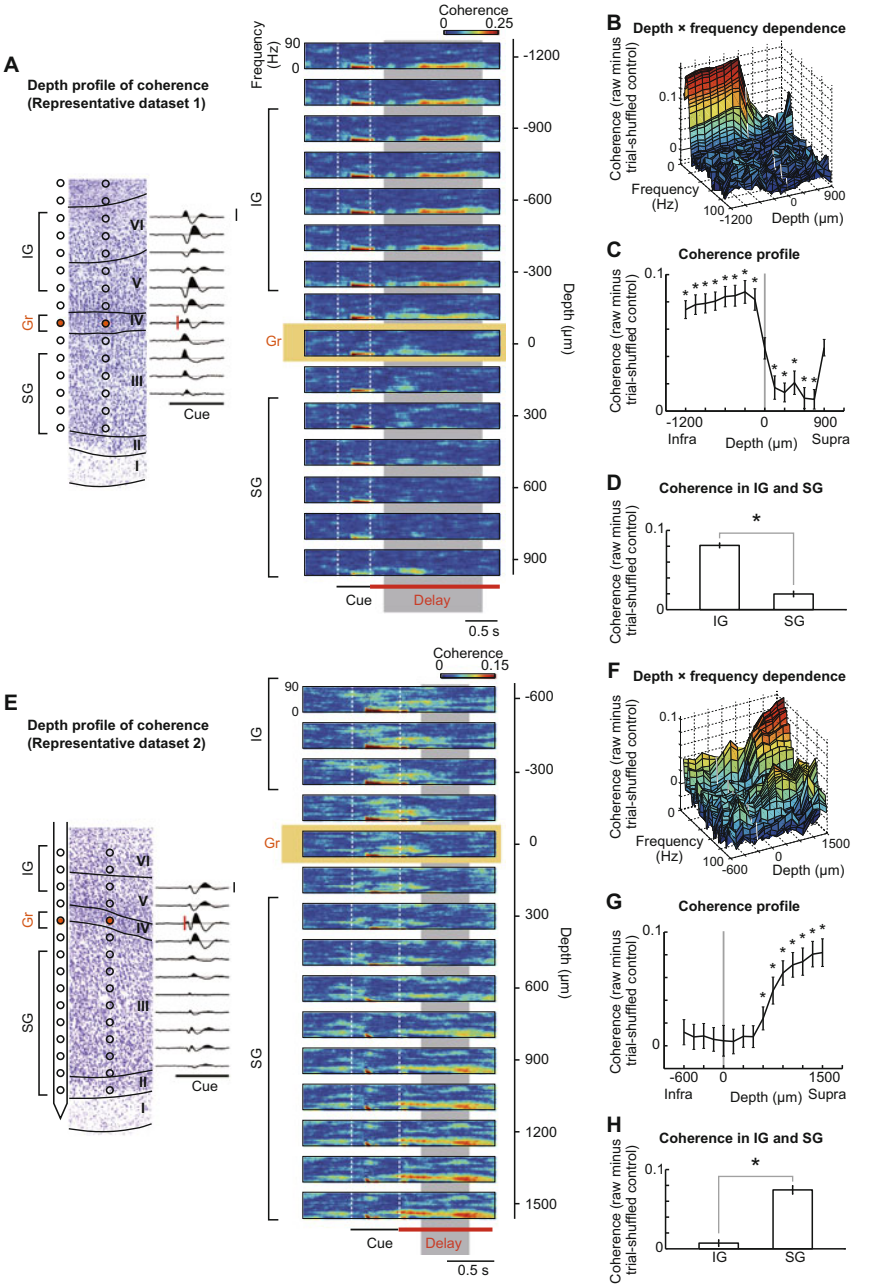

Fig. 12.9 Representative depth profiles of inter-area coherence. (**a**) *Left*: Nissl-stained histological section and CSD profile. The channel showing the earliest current sink (*red line*) was defined as the granular layer (Gr). Right: depth profile of inter-area coherence between the A36 single unit

was presented as a cue, and this decoder was then tested as to determine whether it correctly predicted the identity of theta patterns evoked by the other member of the pair. They demonstrated that the pair-decoding accuracy was significantly higher than chance level after the cue onset, especially in A36 and TE. These results indicate that the theta activity patterns elicited by associated visual stimuli are similar and suggest that the formation and sharing of specific spatial patterns of theta activity are involved in the mechanisms of associative memory representation in the temporal cortex.

12.6 Future Perspective

As discussed above, the neuronal mechanisms for memory in the temporal and spatial context has been intensively investigated. Our current knowledge suggests that the memory system is not a unitary stream of information processing, but is rather underlined by multiple interactive streams of information processing. However, several issues remain to be elucidated. First, the behavioral paradigm of episodic memory for animals needs to be designed. To do this, some "gimmicks" have to be included in the behavioral task to prove the consciousness of animals for memory in the spatial/time context. Second, it is necessary to expand our understanding of memory mechanisms at the single neuron level to the brain-wide network level. To achieve this, several recently developed methodologies might be of benefit, such as fMRI for animals, multi-site recording, and laminar analysis. Third, it is necessary to show not only a correlation of neuronal activity with memory but also a causality between them. This might be achieved by using optogenetics, one of the most beneficial techniques available. Using such methodologies with a new behavioral paradigm for episodic memory might allow elucidation of the neuronal machinery of brain-wide networks for memory in the spatial and time context in the near future.

Fig. 12.9 (continued) activity (SUA) and the TE local field potential (LFP). Recording depth relative to Gr (0 μm) is shown on the right side. Shaded gray depicts the time window for calculating the depth profile of coherence in (**b**–**d**). (**b**) Three-dimensional plot of coherence as a function of frequency and recording depth. The trial-shuffled control was subtracted from the raw coherence data. (**c**) Coherence profile at 9–25 Hz (mean ± SEM) after subtracting the trial-shuffled (100 times) control. *Comparison with coherence at Gr (*t*-test, $p < 0.01$, corrected for multiple comparisons across channels). (**d**) Comparison of coherence between infragranular (IG) and supragranular (SG) layers after subtracting the trial-shuffled control. *Paired t-test, $p < 0.001$. (**e**–**h**) Another representative data set in which the coherence profile showed higher coherence in SG of TE than that in IG and Gr. Figure configuration is the same as in (**a**–**d**) (Adapted from Takeda et al. 2015)

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Chapter 13
Holographic Memory: A Novel Model of Information Processing by Neuronal Microcircuits

Alexey Redozubov

Abstract In the proposed model, each cortical minicolumn possesses a complete copy of the memory characteristic of the entire cortical zone to which it belongs. Hence, the cortex has holographic properties, where each fragment of an information carrier contains not just a part of the information but a complete copy. It is argued that each minicolumn encodes the new information using its own interpretation. Such transcoding is equivalent to considering the source information in a particular context. The model suggests that the cortex zone is a space of possible contexts for interpretation. The presence of a full copy of the memory at each minicolumn allows to determine which context is most suitable for interpreting the current information. Possible biological mechanisms are discussed that could implement the model components, including information processing algorithms that enable high computing power.

Keywords Holographic memory • Microcircuits • Information waves • Hippocampus • Meaning of information • Membrane receptors • Cluster of receptors • Cerebral cortex • Dendrites • Combination of neurotransmitters

13.1 The Propagation of Information Waves

13.1.1 Waves at Cellular Automaton

A cellular automaton (Von Neumann and Burks 1966) is a discrete model, which describes the regular lattice of cells, the possible states of the cells and the rules of changes between those states. Each cell can be in a finite number of states, for example, 0 or 1. For each cell, we define an area that contains its neighbors. The current state of the cell and the states of its neighbors determine the next state of the

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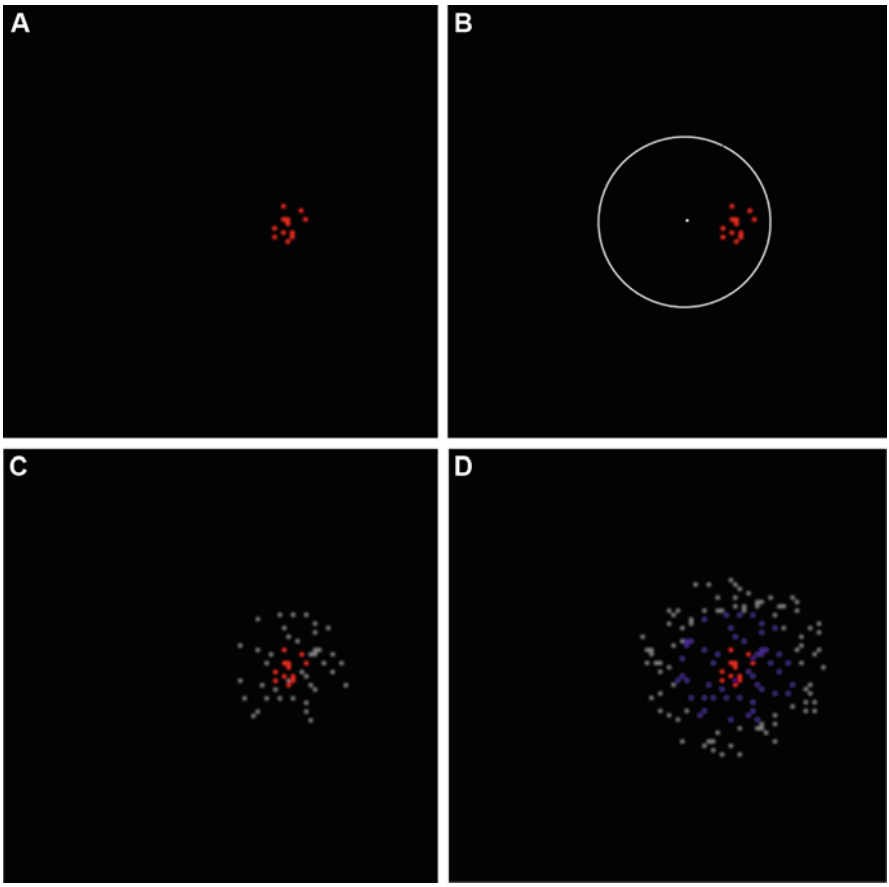

Fig. 13.1 Patterns of propagation. (**a**) the pattern of the initial activity. Only the active elements are shown. Elements are depicted tightly without a gap. Each pixel of the image corresponds to a single element. (**b**) the tracking field of an element and active elements within. (**c**) the first step of the simulation. The wave activity (*gray*) in front of the initial activity (*red*). (**d**) the second step of the simulation. The wave front propagation. Elements in the state of relaxation are painted in *blue*

cell. The most famous example of cellular automata is the "Life" game (Gardner 1970). Potentially, during the selection of a next state, cells can consider not only neighboring states and the transition rules, but their previous state changes too. In this case, we consider cellular automaton with memory.

Let us consider cellular automata with memory. Let's place its elements (automata cells) on a regular grid. For each element, we define its neighborhood that is the tracking zone of this element. Suppose that a compact pattern of activity appeared somehow on the automaton plane (Fig. 13.1a). The compactness of a pattern means here that all active elements fall in space within the size of tracking zone.

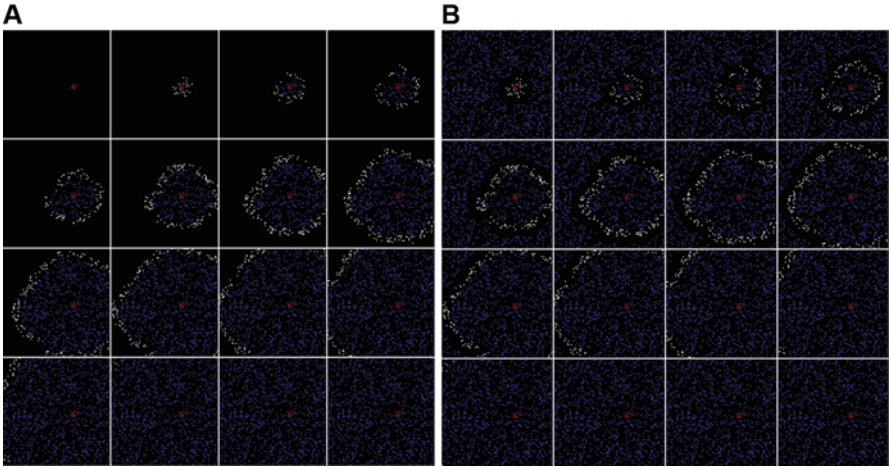

Fig. 13.2 (**a**) a series of initial cycles that propagate the wave activity pattern. *White dots* are the active elements forming the wave front. *Blue dots* are the elements in the state of relaxation against the spreading signal. (**b**) wave propagation on already trained automaton

Now we count how many active elements fall in the tracking field of each elements (Fig. 13.1b). Let's define some small probability p_{in} (roughly 3 % for the provided model). For each element in the quiet state, to count the number of active elements within the tracking field that exceeded a certain threshold, we perform the following procedure. Let's force an element to switch into an active state randomly, with the probability p_{in}. Accordingly, an element remains in an inactive state with probability $1 - p_{in}$. For that element, let's remember its choice and active elements in its tracking field. As the result of this procedure, a randomly generated pattern of activity forms around the pattern of initial activity (Fig. 13.1c). For reasons that will soon become clear let's define this emerged activity as wave-like. On the second step of the simulation, the elements located on the perimeter of the wave activity zone, will "observe" significant activity in their tracking fields. For those ones with the activity exceeded the threshold we repeat the previously described activation procedure. The elements activated on the previous step, using the parameter p, we transit to the state of relaxation. We deactivate them and block for a certain amount of time $\mathbf{T_{relax}}$ their ability to be activated by the pattern that caused their activity before (Fig. 13.1d).

By repeating the simulation steps, we get activity propagating across the automaton with a certain unique randomly generated pattern (Fig. 13.2a).

By changing the initial pattern, we scatter the wave front with its randomly generated internal pattern. Wherein the machine elements to be remembered what patterns have already ran through them. Due to this memory can be made so that the repetition of the initial pattern will be repeated, and the wave pattern. Now let us introduce the rule of the wave excitation. Since each element has a high level of activity around it, we need to check whether there is a pattern of activity in his

memory. If there is a pattern, then the element being excited or not will depend on the choices made in the beginning. The resulting logic of the automaton can be described as follows: if an element encounters an unknown signal, it either triggers or not on a random basis, and it stores the signal and the choice it has made; if the signal is known, it repeats its initial choice. The set of triggered elements generates the wave front, diverging from the pattern of the initial compact activity. The relaxation ensures unidirectional wave propagation from the places where activity occurred in the directions where it did not happen yet. This way we defined, constructed and have got an automaton that memorized a unique wave pattern, unambiguously corresponding to the original activity pattern. Repetition of the initial activity will not require elements to randomly determine their states. The elements "recognize" pattern they encountered before and propagate it further, thus, in the end, propagation of a wave happens with the same pattern as initially (Fig. 13.2b).When a different compact activity pattern appears, the automaton will generate the propagation front wave of activity exactly the same way. However, importantly, the new wave pattern will be unique and different from the previous wave pattern. Any compact combination of active elements will generate a unique wave pattern. For each emitting pattern, the propagating wave, firstly, will have a unique pattern different from all other wave patterns and, secondly, this pattern would always be the same for the same initial activity. It means that, if we define a glossary where each item is encoded by a compact pattern, then we will be able to transmit the information about activity of that item (i.e. its encoding pattern) across the plate of a cellular automaton. Indeed, as each initial pattern creates a unique wave pattern, it is possible to judge what notion the wave propagates in any arbitrary location of a cellular automaton plate. The Fig. 13.3 shows how patterns of wavefronts differ in the same location of a cellular automaton plate for two different initial patterns.

13.1.2 Properties of Information Waves

If a signal is encoded by a rather small percentage of activity across elements, then several waves can propagate through the automaton simultaneously without losing their individuality and not interfering with each other. During simultaneous spreading of several waves, the wavefronts of these waves can pass through each other keeping their pattern intact.

A binary vector can describe the activity of the automaton in each area. The crossing of signals forms a binary vector as the logical sum of each signal's binary vectors. It is equivalent to a Bloom filter (Bloom 1970). Accordingly, the false positive rate can be calculated the way it is for the Bloom filter. It is worth mentioning that the signals encoded by such an automaton gain a property of duality that corresponds to the wave-particle duality. Same as quantum-scale objects may be partly described in terms not only of particles, but also of waves, an informational signal in the simulation described acts as a pattern that triggers a wave, and a wave

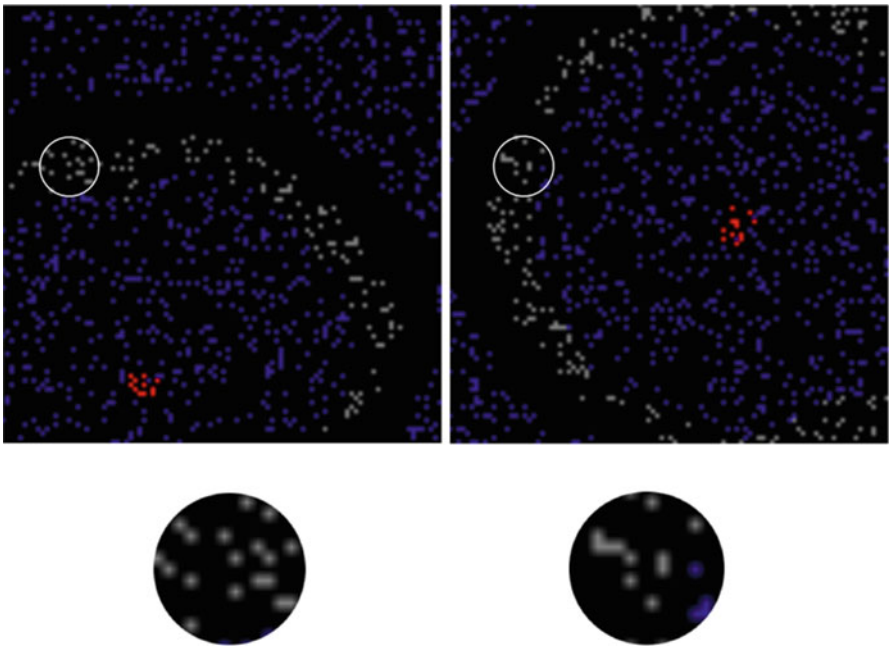

Fig. 13.3 The wave patterns from different initial patterns emerging at the same position of the cellular automaton

itself. In each phase of its propagation this wave forms a pattern which in turn propagates the wave further. The Huygens-Fresnel principle is applicable to the spreading of an information wave where each point reached by the wavefront could be considered as an independent source of emission of a spherical wave.

Let us pick an item known to the automaton. That item would match a wave with a unique pattern. If a fragment of this pattern is reproduced anywhere in the plane of the automaton, then this area will spread a wave reproducing the same unique pattern on all the way through its repetition. For example, if a specific pattern is created in the automaton in the area encircled by the line 1 (Fig. 13.4a), then the wave front will create a unique pattern for this wave reaching the area 2 (Fig. 13.4b). If a new wave is being emitted from the area 2 (Fig. 13.4c) by the pattern that was a part of the original wave then wave front reaching the area 1 re-creates the original pattern there (Fig. 13.4d).

This way the full connectivity of the automaton plate is achieved. Potentially, any area can store in memory any wave information and play it back later, all areas on the automaton plate reached by the corresponding wave, will have access to this information. The cellular automaton described here was modeled on a computer and showed stable operation over a wide range of parameters (Redozubov, Programs. [Online] http://www.aboutbrain.ru/programs/).

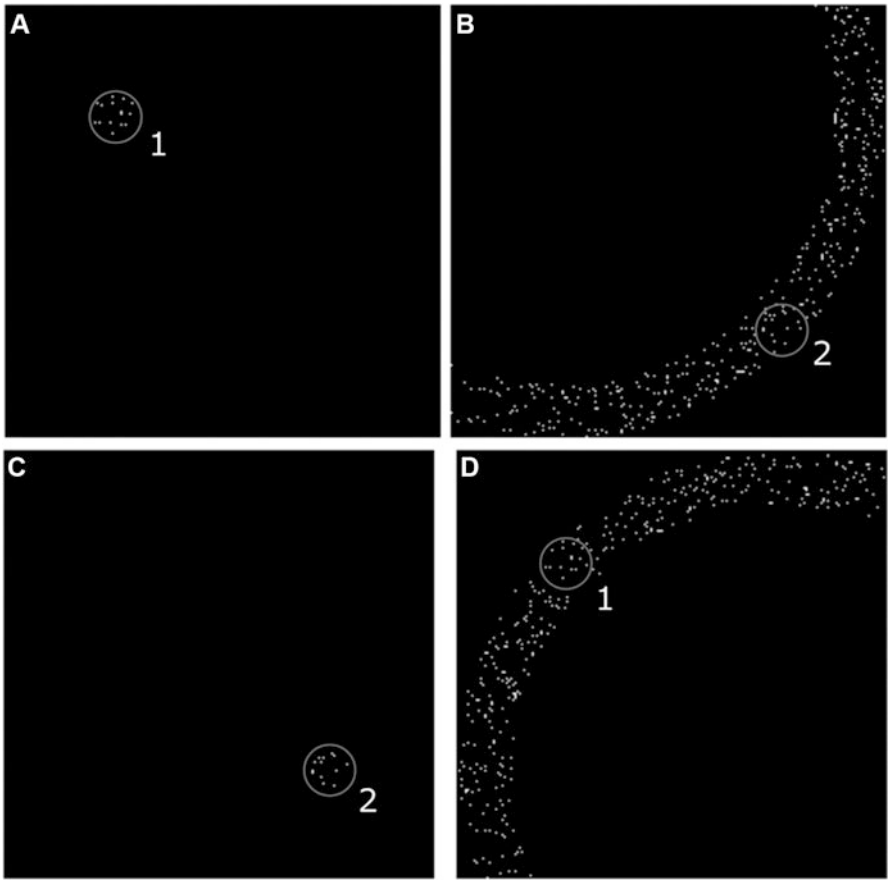

Fig. 13.4 A pattern emits a wave from the area 1 and, reaching the area 2, creates a unique pattern there (*top* figures). A new wave is being emitted from the area 2 by the pattern that was a part of the original wave. The wave front reaching the area 1 re-creates the original pattern there (*bottom* figures)

13.1.3 Brain Cortex Patterns

What structures in the cortex can act as elements of a cellular automaton? Such a structure should meet the following requirements:

- The structure can have at least two different states;
- There should be the capacity to transmit information about the state to the neighbors;
- There should be a mechanism to allow the structure under the influence of the pattern of neighbors to change its status;

- There should be a mechanism to selectively respond to different surrounding patterns;
- Transfer of information should be fast enough to match the rhythms of the brain;
- Since it is assumed that the pattern-wave mechanism should involve for every time transfer a large number of elements, the energy cost of each item should be minimal.

Thin branches of the dendritic trees are the most suitable candidate for these functions. According to neuron doctrine, the branches of the dendritic tree contribute to the functions performed by the neurons to which they belong. However, they can also have individual properties and act in some situations as autonomous elements. It has been shown that dendrites have cable properties (Wilfrid 1959). A branch of a dendrite can be compared with a cable, which has an internal resistance, leakage resistance and capacity of the surface. Although dendrite resistance very large and significant leakage, nevertheless currents that arise from excitatory postsynaptic potentials can have a significant impact on the overall state of the neuron. It can be assumed that the role of these currents is especially high at short distances, for example, within single dendritic branches of the tree.

A detailed mechanism of how the dendritic sections can act as carriers of information waves is described in (Redozubov 2016).

It can be assumed that the spread of dendritic activity patterns is accompanied by the appearance of spontaneous activity in certain neurons. This spontaneous activity can be interpreted as the calculation by local neuronal groups of the hash functions from the dendritic signals. Such spontaneous activity of neurons is very similar to the "neural avalanches" observed in the monkey cortex (Petermanna et al. 2009).

In the described model, all information arriving at any area of the cortex can be read by analyzing the state of any of it small fragments. This view on cortical processing suggests the possibility of brain-machine interfaces based on cortical microcircuits (Lebedev and Opris 2015).

13.2 Holography Memory

13.2.1 Patterns Interference in a Cellular Automaton

As described above, the cellular automaton wave activity, while spreading, creates a unique pattern on the automaton plate. A unique feature of our automaton is that reproducing a fragment of this wave anywhere in the automaton will cause the wave propagation from this point with exactly the same pattern as the original wave had. This means that the information encoded by a wave can be stored anywhere on the automaton plate by memorizing the pattern that occurs at that location when the information wave passes through. The elements of the described automaton have memory. The memory of an element is its ability to store certain patterns of activity

within its field tracking area and then respond with its own activity whenever any of the stored patterns reappears.

The memory of elements can be used as a universal cellular automaton storage device that implements an associative array. The associative array is a storage of "key-value" pairs. To be able to manipulate the stored data, an associative array must support the following operations: to add a pair, to search for pairs (by key or data), and to remove the pair. For closer analogies to the cortex, let us turn from the flat cellular automata to the 3D by replacing the flat tracking field with volumetric. Let's place the elements in the nodes of a regular lattice. We assume that the automaton thickness is substantially smaller than its surface. Let's allocate for observations a cylindrical volume with dimensions comparable to the tracking field of the automaton elements (Fig. 13.5a). We call this the unit volume size, meaning that this is the minimum space that would guarantee a wave propagation, if a fragment of this wave is reproduced inside this volume.

Suppose that two information waves were sequentially emitted. The first wave carries a value that we want to store. The second wave is a unique key that will serve

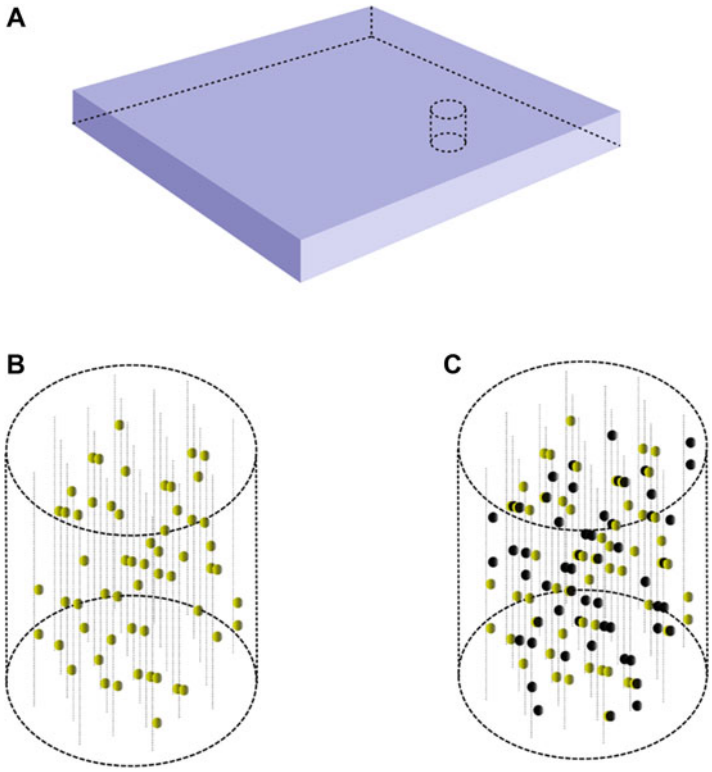

Fig. 13.5 (**a**) a spatial cellular automaton and the marked cylindrical fragment of a size comparable to the size of the tracking field of an element. (**b**) the trace of the information wave, carrying the value that will be remembered. (**c**) the trace of two waves. Elements that encode value are in *yellow*. Elements that encode key are painted *black*

as the identifier for the information stored. Each wave will propagate its pattern over the entire automaton space, that is, each area will contain two patterns formed by the first and the second waves, respectively. In the observed fragment, the first wave will leave a trace, as shown in the figure (Fig. 13.5b). The second wave will leave its trace in the same place. Let's mark elements of each waves with a different color, while some elements can receive two colors at once (Fig. 13.5c).

Now let's consider memorizations. For this purpose all yellow elements remember the pattern of the black elements. As a result of this kind of "interference", this area will memorize a "key-value" pair. Since we have chosen the volume comparable to the tracking area, the pattern enclosed therein can propagate its own wave if necessary. That is, if we subsequently reproduce the wave encoding key (the black wave), then the yellow items activate, because the pattern of black elements is the signal that causes their activity. As a result, a pattern encoding the value for the corresponding key arises in this volume. This pattern emits a wave that will spread the information retrieved from the memory space along the automaton. Actually, the described above is the implementation of store-and-search the information by a key.

If all keys are unique, the key propagation will cause a unique responding information wave corresponding to the paired value for that key. If the values are also unique, it is possible to do a reverse search of a key by its value. To store a single information element (a "key-value" pair), memorizing in a unit volume is enough. However, nothing prevents to store information "redundantly" distributed across the automaton. This means that the information is stored not in one place, but in the entire volume of a cellular automaton. Both local and distributed memory, as shown below, are extremely important for the implementation of information processes.

Interference of two waves of information and distributed storage makes the described mechanism extremely similar to optical holography (Gabor 1948). The main property of optical holograms is that each section of a hologram contains all the information about the entire light beam. The same property is incorporated in our memory model.

13.2.2 Special Dendrites Points

The pyramidal and stellate neurons constitute the main percentage of cortical neurons (Braitenberg and Schuz 1998). The axons of these neurons are characterized by highly branching collaterals. Most of the synaptic axon contacts falls on the volume of a size comparable to the size of the dendritic tree. This axon geometry ensures that the axon signal becomes available in almost all dendritic branches, located in a neighborhood (radius of the order of 50–70 microns) of the neuron.

The availability of a signal means that any dendritic branch in a proximity of a neuron has a segment close to the axon of this neuron. Accordingly, in a moment of activity of the neuron, when each synapse of its axon releases neurotransmitters, a portion of these neurotransmitters can reach the dendritic branch due to spillover.

The synapses surrounding a dendritic branch, both its own and external, are the sources of the extrasynaptical neurotransmitters for this branch.

In reference (Redozubov 2016) it is shown that with a probability close to 1 on any dendrite segment for each selected surround neurons signal will be a place in which will meet a minimum 5 of active axons of neurons. This place on the dendrite can be considered as the favorite in relation to the selected signal. To recall exactly which axons (synapses) had been active, it will subsequently with high accuracy detect repetition of the same signal.

13.2.3 Coding Signal in Selected Place by a Combination of Neurotransmitters

For the majority of synapses, at the time the activity is allocated a "basic" neurotransmitter, and in addition to one or more of the neuropeptide (Lundberg 1996; Bondy et al. 1989). The presence a large number of neurotransmitters and neuromodulators let us suggests, that the primary function of such a manifold – is the creation in time of synchronous neuronal activity in each point in space a unique combination of neurotransmitters and modulators. It can be assumed that the additional substances in synaptic vesicles distributed throughout the synapses so as to provide at each location a maximum space diversity among neighbors. If so, the detection of a particular combination of synaptic activity reduced to determining that the corresponding synapses unique set of emitted substances.

Thus, if in a location selected against a specific dendrite signal to place the detector, sensitive to the combination of substances, characteristic of this signal, the operation of the detector is very likely to represent the repetition of the original signal.

13.2.4 Receptors Neurons as Storage Elements

In addition to direct transfer mechanisms, there exist indirect mechanisms, which is activity-related metabotropic receptors. These receptors are not ion channels and, therefore, do not participate directly in the polarization or depolarization. The metabotropic receptors act indirectly by modifying the activity of ion channels, ion transporters and receptor proteins. Impact on the neuron's membrane potential metabotropic receptors is exerted through G-proteins (Dunlap et al. 1987).

Neighbor receptors can be connected, creating dimers. Dimers, in turn, unite to form clusters of receptors. The receptors cluster suitable for such role are neighbors synapses specific combination activity detectors. However, in order to use these receptors as universal memory elements, there must be mechanisms transform those

receptors from sensitive state to insensitive state and back. Such mechanisms are detailed in (Radchenko 2007).

Therefore, there is a possibility to describe a hypothetical mechanism of memorizing that's based on patterns interference Assume in a local capacity of the crust we have two patterns of activity which sequentially replace by each other The first pattern describes an information, a second is an id. The both patterns consist of the great amounts of active dendritic elements. After performing hashing for the first pattern we've got a pattern of spikes synchronous activity of neurons. Active elements by the second pattern indicate dendritic segments, which have to memorize a pattern of neurons activity. On each segment, that has to memorize an image of volume activity, will found a favorites location relative to the signal. In favorite's location either through a random combinatorics already exists a ready cluster of receptors corresponding to the chemical composition by spillovers, or perhaps, such a cluster can be dynamically generated. The cluster's receptors are changing their conformation that brings the cluster into the sensitive state.

In this way, a pair of identifier pattern and its informational description in form of "hash" is memorized. Swapping of the information description and identifier, will result in memorization of the information description pattern in conjunction with the identifier "hash code".

Passage of such processes throughout the cortex will result in a "holographic" memory, where the same information is stored in each element.

It turns out that the clusters are receptive, sensitive to certain surround signals, potentially, may be memory elements that form a memory trace called engrams. Memory, created in such a way is time-dependent. The conformation of the receptor has hysteresis properties (Radchenko 2007). This means that receptors can stay in sensitive mode until external stimulus returns them to their original state. Such exposure may be, for example, a strong change in membrane potential. In this state, the memory status is short-term. That is the latest recording readily available for the memories, but the availability is reduced over time as going receptors reset. Engrams can be stored for long time. Adhesion and polymerization processes can fix receptor conformational changes. This is transforming memory into a state of sustainable storage. This memory can be stored until the end of life.

In a spatial structure that interlaces axons and dendrites, and which employs the principle of "favorite locations", the memory elements could include various types of receptors. This means that, most likely, the majority of membrane receptors are associated with any working memory systems. Furthermore, glial cells of the cortex have the same sets of receptors as neurons (Halassa et al. 2007), and thus can participate in mechanisms of memory. Astrocytes are able to both enhance the reaction of the synapse due to release of the corresponding mediator, and to weaken it by its absorption or release of the neurotransmitter binding proteins. In addition, astrocytes are capable of releasing signaling molecules that regulate the release of the neurotransmitter axon. Concept signaling between neurons that takes into account the effect of astrocytes, is called tripartite synapse (Fields and Stevens-Graham 2002). It is possible that the tripartite synapse is the main element that implements the mechanisms of mutual work of the various memory systems.

13.2.5 The Hippocampus Role. IDs for Information

In 1953, bilateral hippocampus resection was made as anti-epilepsy therapy for patient that is known as H.M. (Henry Molaison) (Scoviille and Milner 1957). As a result, H.M. had lost ability to memorize anything. He remembered all that were happened to him before the operation. However, new memories became completely lost on his attention switch. H.M. case is unique. In other cases of hippocampus resection, without full both sided destruction memory corruption were not so well presented of were not existed at all (Scoviille and Milner 1957). Full hippocampus resection makes forming new memories impossible. Hippocampus dysfunction may lead to Korsakov syndrome, which appears as impossibility to fix current events while old memory is safe.

The widely known hippocampus role is holding current memories and reorganization later within cortex space of this memories. In the describing model hippocampus have different role. It is memories unique keys creation. The keys created by the hippocampus are distributed to the corresponding cortex zones through projection system. Interference of hippocampus identifiers and information descriptions creates the memory. Thus, memory forms "in its own place" and does not move between the hippocampus and cortex. Such representation agrees with the experimental data quite well. Hippocampus removal makes new memories formation impossible because of memories keys lack. Old memories stays untouched as they are independent of hippocampus. Their identifiers may be extracted and used without hippocampus action.

But the main arguments in favor of described hippocampus role connected with functions found in hippocampus and have no direct relationship with memory mechanism. In 1971 John O'Keefe discovered place cells in hippocampus (O'Keefe and Dostrovsky 1971). These cells act as inner navigation system. If a rat is placed in long hall, then it is possible to determine rat particular place from particular cells activity. What is more that cells activity is independent of way rat is come in particular place.

Hippocampal formation contains neurons that encode spatial location using grid-like coordinates (Hafting et al. 2005). In 2011, it was revealed that there are cells in hippocampus that code time intervals in the same way. Their activity forms rhythmic patterns even if there is nothing happening around (MacDonald et al. 2011).

Storing data in form of key-value pairs creates associative array. In an associative array, key has two functions. It is unique identifier, which lets differ one key-value pair from another. In other side key may hold information that can make search simpler. As example, PC file system may be considered as associative array. Value is information in the file; key is information about file. Information about the file is the path that defines storage place, name of the file, date of creation. For photos additional information – geotags, place where picture was taken, may exists. For music files there are album name and performer name. All this data about files forms complex keys that is identifies file uniquely but at the same time lets perform

searching by any key field or its combination. The more key details, the more flexible search ability is.

As brain implements the same informational tasks as computer systems, it is reasonable to make an assumption that storing data in key-value pairs by a brain will lead to creation of the keys which will be more convenient for searching.

For human memories it is reasonable to have the following key descriptors:

- Scene designation;
- Position in space designation
- Time designation
- Number of concepts that is related to what is happening. Something like article keywords which describes article content.

It looks like the hippocampus not just works with the scene, position in space and time, but uses it for composing complex informational keys for the memories. At least this explains why such different functions came together in one place that is responsible for memory formation.

Time encoding is of special interest. Human memory let remember not only static images, but a sequence of scenes with their chronology. So, memory coding system must contain such ability. It was shown that the hippocampus has time cells that creates rhythmic patterns (MacDonald et al. 2011). Patterns cyclicity suggests that hippocampus may use the same principles for creation identifiers time fields as humans do for time measuring.

13.3 Algorithmic Model Based on the Meaning of Information

13.3.1 Cryptography and Meaning

Consider an example from the field of cryptography. Suppose that we have a stream of encrypted messages. The encryption algorithm is based on substituting characters of the original message with another according to rules, which are defined by encrypting mechanism and key. With something like that has dealt Alan Turing, hacking the code of the German "Enigma". Suppose that there is a finite set of keys and that we know the algorithm of the encrypting mechanism. Then, to decrypt the current message you need to iterate over all the keys, decode messages and try to find meaningful among them.

To determine the meaning of the message, it is necessary to have a dictionary with words that may appear in the message. As soon as the message will take the form in which the message words coincide with the words from the dictionary, it will be possible to say that we found the right key and decrypted received message. If we want to speed up key search, then we will have to parallelize the decoding process. Ideally, you can take as much parallel processors as number of

different keys. Allocate keys on the processors and run on each transformation reverse conversion with his key. Then check the result for the meaning. In one passage of the calculations, we will be able to check all the possible hypotheses about the key used to find out which one is most suitable to decrypt the message.

To test the meaningfulness each of the processors should have access to a dictionary of possible words in the message. Another option – each processor must have a copy of the dictionary and turn to it for checking. Let us consider the second option. Now, make the task more interesting. Suppose that we know only a few words for meaningfulness test, which constitute our dictionary. Then in the message stream, we can find the key only to those in which there is at least one of the known words. There may be situations when multiple keys will show words in the decoded message, which we have in the dictionary. Then, you can either ignore such messages as undeciphered, or select the key that gives a greater match of words in the dictionary. When we find out the right code for these few messages, we will get the correct spelling for the other previously unknown to us words. These words can supplement vocabulary of the processor, which had found the right answer. Furthermore, new words can be transferred to all other processors in addition to their local dictionaries. As you gain experience, we will decrypt greater percentage of messages until we get a complete dictionary and close to one hundred percent decryption effectiveness.

The resulting cryptographic system is interesting because it allows us to introduce the notion of "meaning" and give an algorithm that allows to work with it. Sense for such system is a property of the encoded message that appears in the selection of such a code, which creates a decoded message, interpreted on the existing dictionary. For described cryptographic task the meaning of the encoded message can be called the couple "key-decrypted content." A proper understanding of the meaning of the message – is the selection of the same code, and obtaining the same messages that were laid by the sender. The algorithm for determining the meaning – is to check all the possible interpretations and the selection of one that looks the most plausible in terms of memory, which stores all previous experience of interpretations.

13.3.2 The Meaning of Discrete Information. Frames

Interpretation of the meaning and the algorithm of its determination imposed for cryptographic tasks can be extended to the more general case of arbitrary information messages composed of discrete elements. We introduce the term "concept" – c (concept). We assume that we have N available concepts. A set of all available concepts forms a dictionary.

$$C = \{c_1 \cdots c_N\}$$

We define information message as set of concepts length k

$$I = (i_1 \cdots i_k), \text{where } i_j \in C$$

We assume that the message can be associated with his treatment I_{int} (interpretation). The interpretation of messages – it is also an informational message, consisting of concepts from set C. We introduce the rule for interpretations producing. We believe that any interpretation is obtained by replacing each concept of the original message with some other concept or with itself. Assume that exists a system for performed replacements, which is generally not known to us.

Let us introduce the notion of "subject" S. We define subject's memory as an array of information known to him, received interpretation. Information with the interpretation can be written as a couple

$$m = \left(I, I^{int}\right)$$

Then, the memory can be represented as:

$$M = \{m_i | \, i = 1 \cdots N_M\}$$

Determine the first stage of subject's learning. Perform supervised learning. We submit informational messages and their correct interpretation. Memorize all the information received. Based on the memory, formed supervised, we can try to find a system in comparison concepts and their interpretations.

Firstly, we can draw up a range of possible interpretations for each concept. To do this, for each concept we need to collect all its interpretations that are stored in memory. By the way, the frequency of using a particular interpretation can give the appropriate estimate of the interpretation probability. Secondly, we can use any reasonable method to solve the problem of clustering and divide m_i objects into classes, according to how the same concepts are interpreted in the class. We will try to make sure that all objects within the class use the same interpretation rules for the constituent concepts. Let us call classes resulting from a clustering – "contexts".

The set of all contexts for the subject S forms the space of contexts $\{Cont_i\}$. For each context i, you can specify a set of rules for interpretation of concepts

$$R_i = \left\{ \left(c^{orig}, c^{int}\right)_j \middle| \, j = 1 \cdots N_{Context} \right\}$$

After finishing supervised learning, we can introduce the new algorithm that allows us to interpret new information. We distinguish memory M^{int} from M, consisting solely of interpretations

$$M^{int} = \left\{ I_i^{int} \middle| \, j = 1 \cdots N_M \right\}$$

We introduce a measure of coherence of interpretation and memory of interpretations. In the simplest case, this may be the number of matches interpretation and memory elements, i.e. the number of times it occurs in such an interpretation in interpretations memory

$$\rho(I) = \sum_i \begin{cases} 1, I = I_i^{int} \\ 0, I \neq I_i^{int} \end{cases}$$

Now for any new information I for each context $Cont_j$ we can get an interpretation I_j^{int}, applying to the original data transformation rules R_j. For each of the resulting interpretations can determine its consistency with interpretations memory

$$\rho_j = \rho\left(I_j^{int}\right)$$

The scheme for the calculations of the context is shown in Fig. 13.6a.

We introduce the probability of interpretation the information in the context j.

$$p_j = \begin{cases} 0, \rho_j = 0 \\ \rho_j / \sum_i \rho_i, \rho_j \neq 0 \end{cases}$$

As a result, we will get the interpretation of the information I in each of the K possible contexts and the probability of this interpretation

$$\left(\left(I_1^{int}, p_1\right) \cdots \left(I_K^{int}, p_K\right)\right)$$

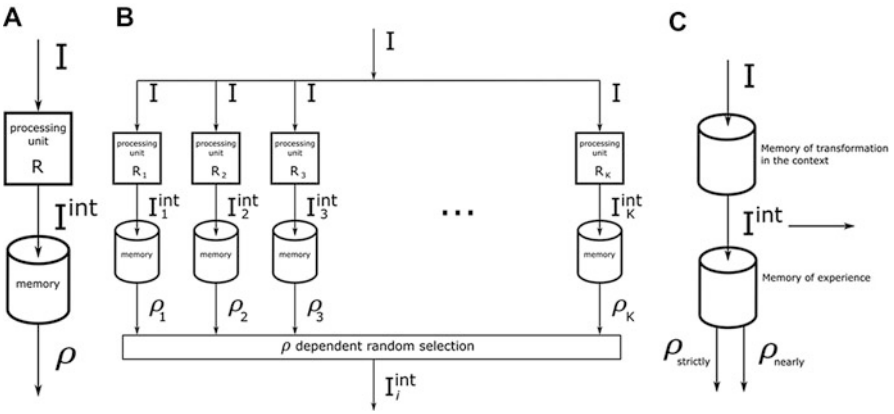

Fig. 13.6 (**a**) computational scheme of the context module. (**b**) computational scheme for determining one of the meanings in the system with K contexts. (**c**) diagram of basic computing functions for minicolumn of cortex

If the probability is zero, we can state that the information is not understood by the subject and has no meaning for him. If there is a probability different from zero, then the corresponding interpretation form a set of possible meanings of the information. If we decide to determine the one main information interpretation for the subject, you can use context with the maximum probability value. As a result, the notion of "meaning" can be described as follows. The meaning of the information I to the subject S is a set of interpretations that the subject finds during context matching, which was built on the determination of the conformity of interpretations that have arisen in different contexts and memory. General computational diagram associated with the meaning determining can be represented as a set of parallel working contextual computing modules (Fig. 13.6b). Each module performs the interpretation of the original description by its own transformation rules. The memory of all the modules has identical content. Comparison with memory provides the conformity assessment of the interpretation and experience. Meaning selection is based on the probabilities of interpretations. The procedure is repeated several times to retrieve the set of possible interpretations.

Once the meaning of the information is defined, memory can be supplemented by new experience. This new experience can be used for determining the interpretation of subsequent information and to clarify the context of space and transformation rules. Thus, you should not allocate a separate stage of primary education, but simply accumulate experience, while improving the ability to retrieve the meaning.

Described semantic approach to data contains a few key points:

- Information descriptions to which this approach is applicable are built from discrete (nominal) terms. This is determined by the ideology of the concepts comparison and their interpretations in a certain context. Descriptions of different nature, for example, quantitative indicative descriptions can be used only after conversion of the quantitative variables to their approximate discrete representation.
- Experience allows you to create the space of contexts and interpretation rules in these contexts. Accordingly, the meaning can be determined by the subject only with a certain experience.
- Since experience of different subjects can vary and different meanings can be obtained as a result of perception of the same information;
- Information can be specially prepared by the sender so as to maximize the probability of the specific meaning for recipient;
- Needless to say that the information contains meaning regardless of the perceiving subject.

Meaning is the result of "measurement" of the information made by the subject. Prior to determining the meaning, for a specific subject information contains interpretations in all contexts for which was a non-zero probability of these interpretations. Each "measurement" allows you to see one of the possible meanings.

Described context meaning model, in many respects, solves the same problem as the concept of Marvin Minsky's frames (Minsky 1974). Common challenges, that models are facing, will inevitably lead to similar realizations. Describing the frames, Minsky uses the term "microworlds", meaning by them situations in which there is a certain consistency of definitions, rules and actions. These microworlds can be compared with the contexts in our definition. Selection of the most successful frame from the memory, and adaptation to the real situation, the same can be largely matched to the procedure of determining the meaning.

When using frames to describe visual scenes frames are treated as different "points of view". In this case, different frames have a common terminal that allows you to coordinate information between frames. This corresponds to the way, how in different contexts interpretation rules may lead different initial description to the same descriptions-interpretations.

Popular in the programming, object-oriented approach is directly related to the theory of frames. It uses the idea of polymorphism, when the same interface when applied to objects of different types causes different actions. It is close enough to the idea of interpretation the information in context.

Despite the similarity of approaches associated with the need to answer the same questions, context-semantic mechanism differs significantly from the theory of the frames, and, as will be seen below, cannot be reduced to it.

The main value of the context-semantic approach is that it is equally well applicable to all kinds of information faced by the brain and operates. All the zones of the real cerebral cortex extremely similar in terms of the internal organization. It makes one think that they all use the same principle of information processing. It can be assumed that the semantic context approach is that general principle.

13.3.3 Semantic Information

Words that build speech can be interpreted in different ways depending on the overall context. However, for every word is possible to make a range of values described in other words. Consistent variation of interpretation of the words allows to allocate the available set of contexts. Contexts can be associated with time, number, gender, subject area, topics and so on. Determining the meaning of the phrase – is the choice of the context and interpretation that the most plausible, based on the experience of one who tries to understand the meaning. There may be a situation where the same phrase in different contexts create different interpretations, but these interpretations will be allowed on the basis of previous experience. If the task is to determine the only meaning of this phrase, it is possible to choose the interpretation that has higher match to memory and, respectively, the calculated

probability for it. If the phrase was originally formulated as ambiguous, it is appropriate to accept each of the senses individually and establish the fact that the author of the phrase intentionally or unintentionally managed to combine them in a single statement.

Natural language is a powerful tool for expression and conveying meaning. However, this power is achieved due to ambiguities and interpretations of probabilistic nature, depending on the experience of the perceiver. When the meaning of the phrase is rather complicated, as it happens often enough, for example, when discussing the scientific or legal matters makes sense to switch to the use of special terms. Transition to terminology is the choice of the interlocutors a coordinated context in which the terms are treated equally by interlocutors. For this context to be available to both interlocutors each of them needs some relevant experience. In order to interpretations were similar its require a certain similarity of experience (learning).

For the natural language, it is possible to use a measure of consistency of the context and memory based not only on complete coincidence of descriptions, but also on their similarity. Then becomes available a larger number of possible meanings and there is a possibility of additional interpretations of phrases. For example, so you can correctly interpret phrases containing errors or internal contradictions. In determining the meaning is easy to take into account the overall context. For example, if the phrase allows interpretation in different contexts, preference is given to contexts that were active in the previous sentences and established the general context. If the phrase allows interpretation only in the context different from the main, it will be taken as shifting to another topic.

13.3.4 Auditory and Visual Information

Analog audio signal can be easily converted into a discrete form. First the discretization of time when a continuous signal is replaced by measurements performed with a sampling frequency. Then, quantization of the amplitude is done. Wherein signal level is replaced by the number of the nearest quantization level. The resulting recorded signal can be divided into time intervals and for each applied windowed Fourier transform. The result is a sound encoded as a series of spectral measurements.

Let's define a cyclic identifier with period N_T for time intervals The first N_T intervals will then be numbered from 1 to N_T. The N_{T+1} interval will then be numbered 1 again, and so on. Thus, interval numbers will be repeating every N_T intervals. Let's assume that a Fourier transform contains N_F frequency intervals. Then, any spectral measurement will consist of N_F complex values. Let's replace every complex value with its respective amplitude and phase and apply quantization. Number of quantization levels is N_A for amplitude and N_P for phase. Within the range of N_T time intervals each spectral record element may be described with the following set: (time interval code, frequency value, amplitude value, phase value).

Let's introduce the set of concepts C, allowing us to describe the sound within the period of the cyclic identifier. This set will include all the possible combinations of type

$$(n_T, n_F, n_A, n_P)$$

Total number of such concepts will

$$N = N_T N_F N_A N_P$$

The set of concepts C will then contain N elements

$$C = \{c_1 \cdots c_N\}$$

Any sound signal not longer than N_T time intervals can thus be recorded as the sequence of concepts.

$$I = (i_1 \cdots i_k), \text{where } i_j \in C$$

In practical applications, e.g. in speech recognition, the signal may be transformed according to some set of rules, while still retaining its original meaning, i.e. the words it represents.

The simplest signal transformations are:

- Time shift
- Frequency shift
- General volume change
- Time scale change (reproduction speed change)

Let's introduce the context space, covering all possible transformation combinations. For each context transition rules can be defined, i.e. we can describe how each of the source concepts will look like in the context of the appropriate transformation. E.g. for the context, shifting the frequency one position up all the concepts will get interpretation, shifting their frequency one position down. Pure 1 kHz tone is equal to 900 Hz tone in the context of common frequency shift 100 Hz up. The same applies to other transformation types. After the transition rules for different contexts are described it becomes possible to recognize words regardless of how they are transformed. The moment of pronunciation, loudness, voice pitch and speed will not affect the possibility to compare current information with the memorized one. Current sounding will be transformed to different interpretations, corresponding to all possible contexts. In the context, corresponding to the appropriate transformation, description will result in an interpretation that could be easily recognized as being heard earlier.

In practice, while working with complex signals, like speech, single processing step is not sufficient. Initially, it is useful to separate simple phonemes. Contexts

will then contain rules for transformations of simple sounds, as shown above. Then we can compose a description, consisting of phonemes. Here phonemes are complex elements, identifying not only the sound form, but also it's pitch, timing and pronunciation speed. Information consisting of phonemes can then be further processed on the space of own contexts and own memory. Sophisticated contexts may be constructed, not just limited by simple transformations. The definition of appropriate context in itself creates additional information. For example, in case of speech different intonations and language accents are contexts. Not only intonation and accent contexts increase the precision of speech recognition, but also give additional information on how the phrase was told.

Similar considerations are valid for visual information (Redozubov 2016). The visual description may correspond to a certain binary code. Different image transformations are the rules for changing this code. A set of various transformations, for example, horizontal and vertical displacements, and rotations creates a space of visual contexts.

The basic idea of this approach lies in the fact that for the invariant representation of an object is not necessarily to spend a lot of time for training, showing the object from different angles. It's much more efficient to teach the system the basic rules of geometric transformations inherent in this world and common to all objects. Partially the described approach is implemented in a well-proven convolutional network (Fukushima 1980; LeCun and Bengio 1995).

13.4 Cortical Minicolumns

13.4.1 The Memory Capacity of One Minicolumn

The cerebral cortex is composed of minicolumns. Minicolumn is a vertically spaced group of 80–120 neurons.

Previously it was shown the formation of a memory circuit, built on the interference of two wave patterns. The first pattern defines the elements (dendritic section), which should keep the memory. The second pattern defines a memory key. Hash conversion from the second pattern creates a short key of memories (spiking activity of neurons). In special places receptor clusters that are specific to the combination of neurotransmitters has arisen, fixed memory. In (Redozubov 2016) show that with this approach, one mini-column of the cortex can store about 300 MB of information.

The approach based on the plasticity of synapses provides a much more modest result as the main memory element. The minicolumn contains about 800,000 synapses. Even assuming that the synapse due to changes in the level of plasticity encode multiple bits of information, obtained value will total only the hundreds of kilobytes. Increasing memory capacity three orders of magnitude gives a qualitative leap in information capabilities minicolumns. Since the nature of information stored

in minicolumn, is close to the semantic information, the 300 MB capacity are quite sufficient to save, for example, all human memories that accumulate in the course of life.

The book of 500 pages in the uncompressed form is about 500 KB. A one minicolumn allows to store memories library consisting of 600 volumes. Approximately one book per month of life, or 15 pages per day. It seems that it is enough to hold the semantic description of everything that happens to us.

Three hundred megabytes of memory minicolumns should not be compared with the gigabyte range photographic libraries or film libraries. When the image stored in the memory, it not stored in photographic form. It can be stored in the form of short semantic description consisting of concepts corresponding to the image. At moment of memories image is not reproduced, it reconstructed anew, creating the illusion of photographic memory. This can be compared with the way the human portrait can be restored close enough to photograph only according to his verbal description.

At the first moment the idea that only 100 minicolumns neurons can store the memories of a lifetime seems absurd, especially for those who are accustomed to believe that memory is distributed over the entire space of the cortex. Moreover, the duplication on many millions of minicolumns of the same information in the traditional approach seems pointless waste of resources. However, the meaning approach allows us to take under such an architecture of cortex serious justification.

13.4.2 The Basic Computing Functions of Cortical Minicolumns

The basic idea of defining the operation of a minicolumn, is quite simple (Fig. 13.6c). Consider one operating cycle of cortex. The information which carrying the current description, is distributed by zone of cortex consisting of a plurality of minicolumns. Each minicolumn sees this information as patterns passing therethrough defined activity (presumably activity of dendritic segments). Each minicolumn keeps the memory of transformations. Each of the minicolumn is responsible for its own perception of the information context. Each context implies its own, distinct from others, rules of transformation source descriptions in their interpretation. Minicolumns memory of transformations – a mechanism for the transformation of patterns of basic concepts, that constitute the description, in the patterns of concepts relevant in the context of the interpretation of a particular minicolumn.

As a result of the transformation of concepts constituting present description, in their context-dependent interpretation in each minicolumn appears own hypothesis of interpretation of this description. This hypothesis is a description, composed of corresponding interpretations. Physically, it most likely, looks like accumulated over clock cycle the activity of dendritic segments. This activity can be associated with a binary array, composed on the basis of Bloom filter. It can be assumed

that there are mechanisms that allow the transformed information and the original description co-exist without interfering with each other. It is possible that for a separate processing correspond to different layers of the cortex. The combination of the activity of dendritic segments leads to spike activity of minicolumns neurons. The code compiled from the activity of neurons, can be interpreted as a hash function of information description, corresponding to the interpretation of the original information.

Previously, it has been shown that the combination of neuronal activity may be the key to which the memory can be retrieved previous experience with the same or such like him the key. Memory of each minicolumn stores all the events previously. Previous experience, supposedly, stored as pairs "hash of information description – the identifier" and pair "hash of identifier – information description" Cloning the same memory on all minicolumns necessary so, that each minicolumn could compare own interpretation of information with all previous experiences.

It can be assumed that the result of comparing the current interpretation of the description and the memory is the calculation of the compliance functions. The first function of compliance indicates the presence of an exact match interpretation and some memory elements. The second function evaluates the overall similarity of interpretation and experience stored in the memory.

Signals compliance functions potentially can be encoded changes in the membrane potential of individual neurons or groups of neurons.

Matching functions allow to judge about how minicolumns context appropriate for the interpretation of the current information, that is, how much interpretation received in this context, in line with earlier experience. Making a comparison between minicolumns, you can select a minicolumn-winner.

The interpretation received at a winning minicolumn is based on the concepts common to the entire cortex. The winning treatment can be pattern-wave method distributed throughout cortex area and memorized by all cortical minicolumns.

The above description of the interference information and the identifier will allow to fill up the memory of each minicolumns "correct" interpretation of the new experience. New information will be comparing with that interpretation.

Winning minicolumns elements can, depending on what is required, to reproduce the relevant interpretation or current information or the most appropriate under the current description memory of past experience or even any information stored in the minicolumn. Reproduced information can spread on cortex area or can be projected to other areas for further processing.

If the initial information allows for multiple interpretations, all of them can be produced in succession. To do this, after the determination of the first interpretation suppress the activity of the relevant context and repeat the context selection procedure. So one by one, you can single out all the possible semantic interpretation of the analyzed information.

A cortical minicolumn in our approach is a universal module that performs and the autonomic computing, and interaction with others minicolumns. However, different areas face different information tasks. In some tasks more important is number of contexts and less important volume of internal memory of minicolumn.

In others, conversely, more important is volume of internal memory and as a consequence an increase of internal bit hash code, i.e., the number of neurons in the minicolumn. The optimal setting of universal computing modules for task specific areas of the cortex can go two ways. Firstly, the number of neurons in the minicolumn may vary for different areas of the cortex. Second, the potentially possible to combine several vertical columns of neurons in one computation module. The scope of axonal and dendritic trees of neurons, constituting a diameter on the order of 150 microns, can combine multiple columns into a single computer system without altering the above general principles of work.

In addition, it can be assumed that a full copy of the memory cannot fit into one minicolumn and be distributed in the space of a few neighboring minicolumns. Since dendritic tree diameter is about 300 microns, this space is potentially available for minicolumn for operation with memory.

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Chapter 14
Factors Influencing Opposing Effects of Emotion on Cognition: A Review of Evidence from Research on Perception and Memory

Florin Dolcos, Yuta Katsumi, Ekaterina Denkova, and Sanda Dolcos

Abstract Recent research emphasizes the intimate relationship between emotion and cognition, and shows that emotions can have complex influences on various cognitive processes. The present chapter examines emerging evidence regarding factors that can modulate opposing effects of emotion on visual perception and memory, and the associated neural correlates. First, we introduce evidence regarding enhancing and impairing effects of emotion on visual perception and episodic memory. Then, we discuss evidence regarding the role of specific factors (emotion regulation strategies and individual differences: age and sex) in modulating these opposing effects, and also point to emerging evidence highlighting the roles of other factors (emotional states, personality traits, and clinical status) in these effects. The chapter concludes with a summary emphasizing the need to consider various factors that can influence the opposing effects of emotion on cognition, and identifies new avenues for future investigations. Elucidation of the mechanisms underlying emotion-cognition interactions in healthy functioning has relevance for understanding alterations in emotional disturbances, where these opposing effects of emotion tend to be exacerbated and deleterious.

Keywords Affect • Memory • Emotion-cognition interactions • Emotion regulation • Amygdala • Prefrontal cortex • Brain imaging • fMRI

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14.1 Introduction

. . .And suddenly the memory returns. The taste was that of the little crumb of madeleine which on Sunday mornings [. . .] my aunt Léonie used to give me, dipping it first in her own cup of real or of lime-flower tea (Marcel Proust, *In Search of Lost Time*)

The distraction of our mind is result of our blind surrender to our desires, our incapacity to control or moderate our passions (Francois Boissier de Sauvages, *Nosologie Methodique, 1772*[1])

Emotion-cognition interactions are reflected in virtually every aspect of human behavior, from basic motivations to satisfy our physiological needs to the driving forces of passions and desires that fuel our greatest accomplishments. Optimal interactions between emotional and cognitive processes allow us to lead "*happy and productive lives*", whereas non-optimal interactions may lead to dramatic changes in behavior and functioning that are associated with emotional disturbances, such as anxiety and depression. During the last decades, the topic of emotion-cognition interactions has gained considerable interest from psychologists and neuroscientists, and hence left the domain of philosophers. This is also reflected in an increasing number of reviews (e.g., Banich et al. 2009; Barrett and Satpute 2013; Braver et al. 2014; Davidson 2004; Joëls et al. 2011; LeDoux 2012; McGaugh 2004; Okon-Singer et al. 2015b; Pessoa 2013; Phelps 2006), including from us (Dolcos and Denkova 2008, 2014, 2015, 2016; Dolcos et al. 2011, 2012, 2017, in press), as well as in recent Special Issues (Dolcos et al. 2015; Okon-Singer et al. 2015a) discussing emotion-cognition interactions at different levels of analysis. This effort testifies the need to investigate cognitive processes not as encapsulated entities, but to consider how they are modulated by emotional/motivational processes, which can provide insights into the complexity of psychological functioning in everyday life.

As also illustrated by the quotes above, emotions can enhance or hinder various aspects of our cognition and behavior, and are susceptible to cognitive control. Indeed, emotions may affect both lower level (e.g., perceptual) and higher level (e.g., mnemonic) cognitive processes, and their effects can be either beneficial/enhancing or detrimental/impairing. Importantly, these enhancing vs. impairing effects of emotion on cognition are also susceptible to cognitive influences typically exerted in the form of emotion regulation/control, which can be engaged transiently by experimental manipulations and may also reflect individual differences in chronically activated affective states, both in healthy functioning and in clinical conditions. While tremendous progress has been made to clarify the interplay between emotion and cognition, research is now moving toward understanding the situations in which emotion can benefit or hinder cognitive processing, and toward elucidating the factors that can modulate these opposing effects of emotion on cognition. Clarification of the role of modulating factors in these effects is of particular importance, because it is often a combination of such factors that can determine if the immediate (e.g., perceptual) and long-term (e.g., mnemonic) impact of emotion

[1] As quoted by Michel Foucault, *Madness and Civilization, 1965, p. 77.*

is beneficial or detrimental to cognitive functioning. Moreover, elucidating these factors and the associated neural mechanisms is also essential for furthering our understanding of alterations associated with affective disorders, in which emotion-cognition interactions are dysfunctional.

The emphasis of the present chapter is on emerging evidence from investigations examining factors that influence the neural mechanisms of enhancing vs. impairing effects of emotion, as derived from evidence provided by studies of healthy groups. The first section summarizes basic behavioral and brain imaging evidence for the enhancing and impairing effects of emotion on *visual perception* and *episodic memory*. The second section discusses in detail evidence that provides insight into specific factors that can contribute to these opposing effects, with a focus on the role of (1) *emotion regulation strategies,* and of individual differences related to (2) *age* and (3) *sex*, and other factors, such as (4) *emotional states, personality traits,* and *clinical status*. The chapter ends with concluding remarks and a presentation of open issues and future directions.

14.2 Basic Evidence Regarding Opposing Effects of Emotion on Cognition

Available evidence shows that emotional stimuli can benefit from enhanced perceptual processing due to their ability to "capture attention", and hence through this prioritized processing they can be better encoded and remembered (Dolcos and Denkova 2008; Dolcos et al. 2006, 2012; Phelps 2006; Pourtois et al. 2013; Vuilleumier 2005). In addition, there is evidence that emotion can not only enhance various cognitive processes (Dolcos and Denkova 2014; Dolcos et al. 2011, 2012), but also impair them (Johnson et al. 2005; Most et al. 2005; see also Oaksford et al. 1996; Seibert and Ellis 1991; Shackman et al. 2006), as demonstrated by previous studies documenting detrimental effects of emotion on both perceptual and mnemonic processing (e.g., Iordan et al. 2013b; Kensinger 2009; Mather and Sutherland 2011; Shafer et al. 2012). This topic has been the focus of extensive discussions and debate in the current literature (see Dolcos and Denkova 2014, 2015; Dolcos et al. 2014b, 2015). Here we will provide a summary of the available evidence demonstrating opposing effects of emotion on *visual perception* and *episodic memory*.

14.2.1 Opposing Effects of Emotion on Visual Perception

Enhancing Effects

There is abundant evidence of facilitated perceptual processing of emotional information, as reflected in enhanced detection of emotional compared to neutral

stimuli (Carretie 2014; Okon-Singer et al. 2015b; Pourtois et al. 2013). At the neural level, these facilitating effects have been linked to increased engagement of the amygdala (AMY), an almond-shaped group of nuclei located within the medial temporal lobe (MTL) (Anderson and Phelps 2001; Lim et al. 2009; Mather and Sutherland 2011). Activity in the AMY was also found to correlate with activity in perceptual brain regions, typically according to the category of the stimuli (e.g., lateral extrastriate cortex for visual stimuli in general, fusiform gyrus [FG] for faces, superior temporal sulcus for voices) (Grandjean et al. 2005; Vuilleumier et al. 2001). Although traditionally the AMY has been associated with processing of negatively-valenced emotions, particularly fear (Adolphs et al. 1995; Calder et al. 2001; Morris et al. 1996; Whalen et al. 1998; Zald 2003), a number of functional neuroimaging studies involving both positive and negative stimuli, equated for emotional arousal, have also reported AMY responses to various positively-valenced stimuli, including verbal (Garavan et al. 2001; Hamann and Mao 2002; Kensinger and Schacter 2006b), pictorial (Dolcos et al. 2003; Hamann et al. 2002; Kensinger and Schacter 2006b), olfactory (Anderson et al. 2003b; Winston et al. 2005) and gustatory (Small et al. 2003) stimuli. Thus, the attention capturing effect of emotion can be triggered by both positive and negative stimuli, although their subsequent effects (e.g., on memory) may differ, with both types producing similar beneficial effects on episodic memories) (for reviews, see Dolcos et al. 2012; Dolcos and Denkova 2008; Dolcos et al. 2017, in press), but with negative stimuli being more effective in producing detrimental effects when presented as task-irrelevant distracters (Iordan and Dolcos 2017).

Impairing Effects

An important factor in determining the impact of emotion on perception and attention is whether emotional stimuli serve as targets (task-*relevant*) or distracters (task-*irrelevant*). When an emotional stimulus is task-relevant, the prioritization of processing resources for affective information results in task-enhancement, whereas when it is task-irrelevant, emotion processing can lead to depletion of resource availability and result in task-impairment (e.g., Hur et al. 2016). This suggests that when emotional stimuli act as distracters (e.g., when they are task-irrelevant), they can impair perceptual processing of goal-relevant information. Previous studies, including those discussed above in the section on enhancing effects of emotion, identified the involvement of the AMY in processing emotional information presented as task-irrelevant distracting stimuli (Anderson et al. 2003a; Grandjean et al. 2005; Vuilleumier 2005; Vuilleumier et al. 2001), which could impair performance on ongoing cognitive tasks (Vuilleumier et al. 2001). A previous investigation from our group using a perceptual orientation-discrimination task with emotional distraction (Shafer et al. 2012) showed that emotional distraction can impair lower-level perceptual processing, because it detracts attention from the goal-relevant information. Specifically, this study investigated the impact of emotional distraction by manipulating both the degree of emotional charge of the distracting information (*high emotionally negative, low emotionally negative, neutral*, and *absolute neutral*)

and the attentional demands by varying the time of presentation (*short vs. long duration*) and task difficulty (*low vs. high perceptual load*). Behavioral findings revealed impaired performance by emotional distraction reflected in longer reaction times (RTs) for negative than for neutral items, regardless of manipulations of attentional demands. However, the detrimental effect of emotional distraction was strongest when the difference in emotional content was the greatest (highly emotional vs. absolute neutral), there was more time for distraction (long duration), and the attentional resources were most available (low load), hence suggesting that emotional information is also susceptible to attentional modulation (Fig. 14.1). It should be noted, however, that the detrimental impact on ongoing task-relevant perceptual processing occurred in the context of enhanced perceptual processing of the emotional information itself. At the neural level, areas known to be involved in affective processing (including AMY, portions of the medial prefrontal cortex [mPFC], insula), as well as perceptual areas that are sensitive to affective modulation (FG, lateral occipital cortices), showed greater activation to emotional compared with neutral distracters.

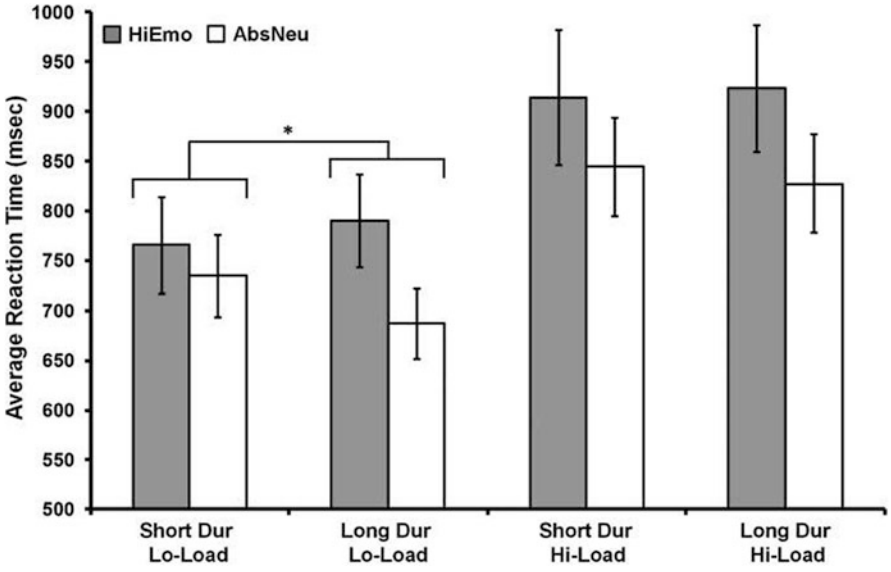

Fig. 14.1 The impact of emotional distraction on perception, as a function of attentional load. The figure illustrates average reaction times (RTs) for correctly identified rectangles in a perceptual orientation-discrimination task with emotional distraction. First, there was a detrimental impact on ongoing task-relevant perceptual processing produced by enhanced perceptual processing of the emotional information: i.e., trials with highly emotional (*HiEmo*) distractors resulted in longer RT than those with absolutely neutral (*AbsNeu*) distractors, in all conditions. However, the results also revealed an interaction between emotional content and stimulus duration that was driven by the condition with low cognitive load (Lo-Load). This indicates that the impact of emotional distraction was augmented when more attentional resources were available to be engaged in processing emotional distraction (From Shafer et al. 2012 with permission)

Paralleling these behavioral effects, and consistent with the traditional view regarding the automaticity of emotion processing (Vuilleumier 2005), activity in basic emotion-related regions (AMY) was found in response to emotional stimuli, regardless of manipulations of attentional demands. However, the engagement of higher-level (cortical) emotion processing regions (i.e., mPFC and ventro-lateral PFC [vlPFC]) showed susceptibility to modulation by attention with increased engagement when there was more time to process distraction and attentional resources were most available. Hence, depending on the circumstances, emotional information can be processed automatically but is also susceptible to modulations linked to the availability of attentional resources. Overall, these findings provided reconciling evidence regarding the automaticity of emotion processing, which has been the focus of a long-term debate in the literature (Pessoa 2013; Pessoa et al. 2002, 2005; Pourtois et al. 2013; Vuilleumier 2005; Vuilleumier et al. 2001).

In sum, available evidence suggests that emotion can have both enhancing and impairing effects on visual perception, and these opposing effects are related to the way emotional information is presented (task-relevant or task-irrelevant). At the neural level, these effects are linked to differential engagement of and interplay among basic emotion- (AMY) and perception-related (FG) brain regions and higher-level brain regions (PFC) that are susceptible to/exert modulatory influences affecting emotion processing.

14.2.2 Opposing Effects of Emotion on Episodic Memory

Enhancing Effects

In his masterpiece, *In Search of Lost Time* (1913), the French novelist Marcel Proust discusses an instance of involuntary memory recollection, which is now famously known as the "madeleine episode". As illustrated in the text cited above, upon tasting a piece of a madeleine cake steeped in a cup of tea, Proust experiences sudden and vivid recollection of his childhood memories. This example shows how even brief exposure to a memory cue can evoke vivid recollection of an event associated with personal and emotional significance, even though the event might have originally occurred in a distant past. Consistent with this idea, previous empirical studies have provided strong evidence that emotional events are typically better and more vividly remembered than neutral ones (Dolcos and Denkova 2008; Dolcos et al. 2006, 2012; McGaugh 2005; Phelps 2004). The enhancing effects of emotion on episodic memory (EM) have been investigated at various stages of memory, from the early stages of memory formation (encoding and early consolidation of memory traces) to their later retrieval, and typically by considering the two orthogonal affective dimensions: arousal and valence (Lang et al. 1993; Russell 1980). To eliminate potential confounding effects of general perceptual

processing and to specifically identify the enhancing effects of emotion on memory, the typical procedure used in brain imaging studies is to calculate the so-called *difference in memory* (*Dm)* effect – i.e., the difference between brain activity for remembered vs. forgotten items (Dolcos et al. 2012; Shafer et al. 2011).

In general, the extant research primarily emphasizes the role of two main mechanisms involved in the memory-enhancing effect of emotion – one based in the MTL (i.e., AMY and memory-related MTL regions) and the other outside of the MTL, involving the PFC, among other regions (e.g., parietal cortex) (see Fig. 14.2) (Dolcos and Denkova 2008; Dolcos et al. 2006, 2011). On the one hand, the AMY and memory-related MTL regions (e.g., hippocampus [HC]) interact through direct/bottom-up neurohormonal mechanisms that contribute to the memory-enhancing effect of emotion during encoding (e.g., Dolcos et al. 2004b; Kensinger and Corkin 2004; Kensinger and Schacter 2006a; Ritchey et al. 2008; Sergerie et al. 2006), consolidation (Ritchey et al. 2008), and retrieval (e.g., Dolcos

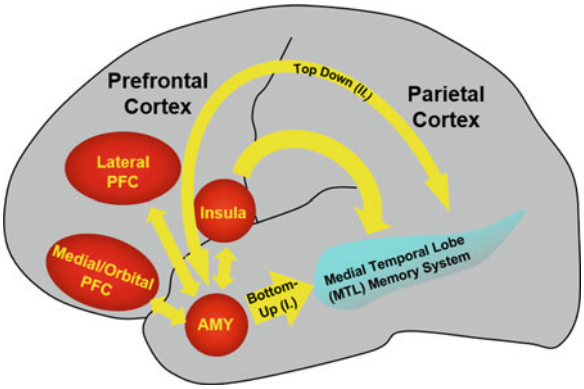

Fig. 14.2 Diagram summarizing the neural correlates of the memory-enhancing effect of emotion, as resulted from brain imaging studies. Two main basic mechanisms involved in the memory-enhancing effect of emotion were identified, one based in the MTL (AMY and MTL Memory System) and the other outside of the MTL, involving the prefrontal cortex (PFC), among other regions (parietal cortex). The AMY and the MTL memory regions interact through direct neurohormonal mechanisms that contribute to the memory-enhancing effect of emotion (*bottom-up* mechanism), whereas PFC is part of a mechanism that has an indirect/mediated involvement in emotional memories, by enhancing strategic, semantic, working memory, and attentional processes (*top-down* mechanism). Investigation of emotional memory for social aspects (e.g., Tsukiura 2012) identified valence-specific engagement of other brain regions that contribute to enhanced emotional memories in social contexts – i.e., memory for socially-relevant information involves activity in and interactions between orbital PFC and MTL, in the case of items with positive connotations, and Insula and MTL, for items with negative connotations. Moreover, as also discussed later in the chapter, investigation of the impact of emotion regulation on emotional memory identified bidirectional relationships between MTL and PFC regions associated with specific emotion regulation strategies, involving (i) the lateral and medial PFC in top-down modulation of the AMY-MTL mechanisms in emotional memory encoding and retrieval, and (ii) the AMY signaling medial PFC the need to exert control over emotional stimuli, resulting in overall reduced emotional experience, during autobiographical retrieval (Adapted from Dolcos et al. 2012, with permission)

et al. 2005; Kensinger and Schacter 2005) of emotional memories. On the other hand, the PFC as part of an indirect/top-down mechanism also seems to be involved in the formation of emotional memories, by enhancing semantic, working memory, and attentional processes (Dolcos and Denkova 2008; Dolcos et al. 2011; LaBar and Cabeza 2006).

Regarding the role of basic emotional properties of stimuli, previous research showed that the bottom-up AMY-MTL mechanisms are maily modulated by arousal, whereas the top-down mechanisms involving the PFC regions seem to also be influenced by valence (Dolcos et al. 2004a; Kensinger 2004; Kensinger and Schacter 2006b). Additionally, there is also evidence suggesting that successful encoding of positive vs. negative information depends on different mechanisms. For instance, Ritchey et al. (2011) showed that intrinsic AMY-HC interaction is stronger for encoding of negative stimuli, whereas the extrinsic interactions between HC and PFC are stronger for encoding positive stimuli (see also Mickley Steinmetz et al. 2010). Other studies have shown that successful encoding of positive information is associated with activity in specific PFC subregions (Botzung et al. 2010), probably due to more elaborative processing requiring cognitive resources, whereas encoding of negative information is associated with temporo-occipital regions (Mickley and Kensinger 2008), probably due to increased sensory processing. Finally, there is also emerging evidence showing that encoding and retrieval of emotional memories with *social relevance* is associated with the engagement of additional regions, such as mPFC, orbital PFC, and insula, as well as their interaction with the bottom-up AMY-MTL mechanism (Dolcos et al. 2012, see also Dolcos et al. 2017, in press).

Taken together, available research provides evidence that the enhancing effects of emotion on EM involve two mechanisms: (1) *bottom-up/direct* involving AMY-MTL interactions, assumed to be relatively automatic and modulated primarily by emotional arousal, and (2) *top-down/indirect* mechanisms, involving modulatory influences to and from outside of the MTL (PFC and other cortical regions) and assumed to be sensitive to emotional valence and the social significance of stimuli.

Impairing Effects

Despite strong evidence concerning the enhancing effect of emotion on EM discussed above, there is also evidence that not all aspects of an event benefit from the enhancement of memory by emotion (Kensinger 2009). More specifically, the enhancing effect of emotion on EM has been typically observed for isolated emotional items and their intrinsic properties, whereas memory for other extrinsic aspects or contextual details of the emotional event tends not to be enhanced and can be even impaired (Kensinger 2009; Mather 2007; Yonelinas and Ritchey 2015). In a similar vein, Chiu et al. (2013) suggested that the enhancing vs. impairing effects of emotion can be linked to the dissociation between memory for isolated items vs. memory for relations among items (i.e., relational or associative memory), respectively. This notion is based on available evidence from memory

research (Cohen and Eichenbaum 1993; Cohen et al. 1999; Eichenbaum and Cohen 2001) revealing that memories for items vs. associations are subserved by different memory-related regions within the MTL. Specifically, whereas the perirhinal cortex (PRC) is important for encoding individual items or objects from an experience, the HC is important for binding distinct item representations into memory (Brown and Aggleton 2001; Davachi et al. 2003; Ranganath et al. 2004; Tubridy and Davachi 2011).

Further evidence also revealed that the PRC may also contribute to some simpler forms of associative learning (Staresina and Davachi 2010), based on unitization (Graf and Schacter 1989). Unitization involves assembling together different aspects of an object into a single representation (e.g., association between an object and its color). Therefore, memory for isolated and unitized items can be mediated by similar PRC-based mechanisms, whereas memory representations involving more complex associations of different and diverse components of an event, as well as associations between temporally separate events, are mediated by HC-dependent mechanisms (Ezzyat and Davachi 2014). In the context of the impact of emotion on EM, Chiu et al. (2013) proposed that emotion leads to memory enhancement of separate as well as unitized items, but to impairment of more complex HC-dependent memory representations. In support of this hypothesis, recent studies provided direct evidence that emotion can enhance item memory but can impair associative memory (Bisby and Burgess 2014; Guez et al. 2015; Mao et al. 2015). In particular, enhanced item memory was linked to increased engagement of AMY, while impaired associative memory was linked to decreased engagement of HC (Bisby et al. 2016). Consistent with this evidence, Yonelinas and Ritchey (2015) have recently put forth the *emotional binding* model of emotional memory, which also emphasizes the dissociable involvement of AMY and HC in emotional item vs. associative memory, respectively. Specifically, the emotional binding account posits that item-emotion associations are dependent on the AMY (particularly through its interactions with the PRC) and are relatively more resistant to forgetting, whereas item-context associations are dependent on the HC, and are forgotten more rapidly (Yonelinas and Ritchey 2015) (Fig. 14.3).

In sum, these findings highlight the complex interactions between emotion and EM and suggest that differential engagement of regions within the direct MTL mechanisms may explain the opposing effects of emotion on memory, when considering the distinction between memory for isolated items vs. complex associations between an item and its context (Chiu et al. 2013; Yonelinas and Ritchey 2015). Other accounts explaining opposing effects of emotion on memory have also been proposed, including those emphasizing a trade-off between the *central vs. peripheral* aspects of stimuli (e.g., objects vs. backgrounds) (Kensinger 2009; Kensinger et al. 2007a, 2007b; Kensinger and Schacter 2006a; Mickley Steinmetz et al. 2012; Waring and Kensinger 2009; Waring et al. 2010), or the *level of priority (high vs. low)* of emotional information (Lee et al. 2012, 2014; Mather and Sutherland 2011; Sakaki et al. 2014; Sutherland and Mather 2012; see also Weymar et al. 2013, 2014) (for recent reviews, see Dolcos and Denkova 2015, 2016; Dolcos et al. 2017, in press).

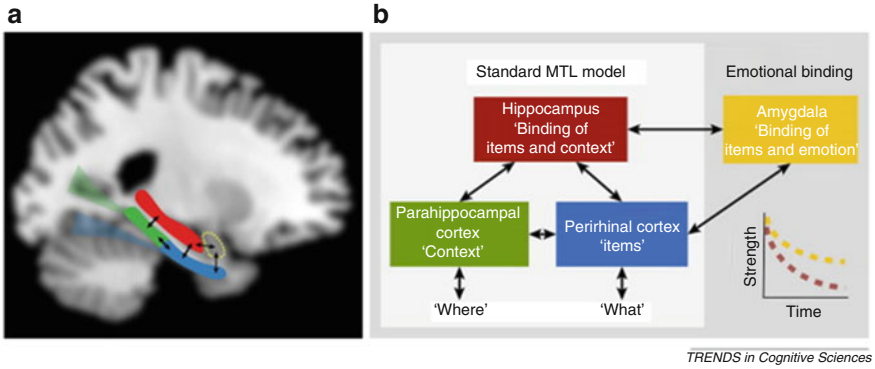

Fig. 14.3 The emotional binding model of emotional episodic memories. (**a**) The medial temporal lobe (MTL) regions involved in episodic memory (EM). (**b**) Overview of the standard model of MTL function and the emotional binding model. In the standard model, the perirhinal cortex (PRC) receives projections from the ventral 'what' stream and is thought to play a role in identifying and processing the items and objects in the environment. The parahippocampal cortex (PHC) receives projections from the dorsal 'where' stream, and is thought to play a role in processing contextual information such as the ongoing spatial and temporal context. The hippocampus (HC) receives information from the PRC and PHC via entorhinal projections, and binds the item and context information together to form EMs. The emotional binding model subsumes the standard MTL model, but in addition assumes that the amygdala (AMY) forms item–emotion bindings that are forgotten more slowly than the item–context bindings supported by the HC (From Yonelinas and Ritchey 2015, with permission)

Overall, available evidence based on previous studies of enhancing and impairing effects of emotion on cognition discussed here suggests that emotion can exert beneficial or detrimental effects on visual perception and memory. These opposing effects have been linked to the involvement of and interactions between neural systems associated with bottom-up and top-down processing of emotion. Regarding the opposing effects on perception, enhanced perception of emotional vs. neutral stimuli seems to be subserved by the AMY and its modulatory influences on activity in the lower-level perceptual processing regions, such as the FG and occipital cortices. Processing of task-irrelevant emotional distraction is similarly associated with increased activity in these bottom-up affective regions, and further engages other emotion-related regions (mPFC, vlPFC) when attentional resources are available. Regarding the effects on EM, the bottom-up and top-down systems have been described as part of direct vs. indirect mechanisms involving mainly the MTL (AMY, HC) and PFC regions, respectively, which have joint contribution to the beneficial effects of emotion on EM. The impairing effects of emotion on EM, as revealed by investigations of item vs. associative memory, seem to be mediated by differential engagement of regions within the direct MTL mechanisms (AMY/PRC vs. HC, respectively).

It is important to note that, although these findings have been identified based on previous research independently examining the enhancing and impairing effects

of emotion on cognition, perception and EM are highly interactive cognitive processes that do not usually occur independently of one another. This idea has been demonstrated by evidence from recent within-subject investigations linking the immediate/impairing (perception and WM) vs. long-term/enhancing (EM) impact of emotion, mediated by overlapping and dissociable neural systems, involving both top-down and bottom-up mechanisms (Dolcos and Denkova 2014; Dolcos et al. 2013; Shafer and Dolcos 2012). Additionally, it is also important to note here that the impairing effects of emotion are not limited to perception and EM, but also to other types of memory, such as working memory (WM), and these effects also involve bottom-up and top-down mechanisms (Dolcos et al. 2007, 2008; Dolcos and McCarthy 2006) (for reviews, see Dolcos et al. 2011; Iordan et al. 2013b). Moreover, evidence also points to specific neural mechanisms linking and dissociating opposing effects of emotion on cognition at different levels (Dolcos and Denkova 2015, 2016).

14.3 Factors Influencing Opposing Effects of Emotion on Cognition

Building on the extant evidence regarding the basic mechanisms of enhancing/impairing effects of emotion on cognition summarized above, recent research has begun to show that these opposing effects can also be modulated by several factors, such as the engagement of emotion control/regulation (Hayes et al. 2010) and current emotional states, as well as by individual differences in personality traits, age, and gender (Hooker et al. 2008; Meyers-Levy and Loken 2015; Reed and Carstensen 2012). As we will see in this section, these factors can exert modulatory influences on both automatic/bottom-up and controlled/top-down mechanisms involved in the enhancing and impairing effects of emotion on perception and episodic memory.

14.3.1 Emotion Regulation

> *Anybody can become angry, that is easy; but to be angry with the **right person**, and to the **right degree**, and at the **right time**, for the **right purpose**, and in the **right way**, that is not within everybody's power and is not easy* (Aristotle (Nicomachean Ethics, II.9, 1109a27))

The above quote by the Greek philosopher suggests that adaptive emotion processing, expression, and manifestation require one's ability to control his/her emotional responses, depending on the context or circumstances, and that such control can be effortful and demanding. More than two millennia later, the topic of emotion regulation (ER) has gained considerable interest in cognitive and affective neuroscience, as it is established that the ability to cope adaptively with

emotionally challenging situations is vital for physical and mental health (Gross 2008, 2015). Relevant for the present discussion, the engagement of ER, either spontaneously or instructed, can affect the impact of emotion on both perceptual and mnemonic processes. Although various ER strategies can be used to modulate the impact of emotion, the two most widely studied ER strategies are *cognitive reappraisal*, which involves attempts to change the meaning of stimuli/situations (by thinking, for instance, that a given situation is not real), and *expressive suppression*, which involves attempts to decrease emotionally-expressive behavior (Gross 2008). Studies comparing reappraisal and suppression in healthy participants suggest that these strategies are not equally effective (see review by Gross 2008), indicating an advantage of reappraisal over suppression in reducing the subjective emotional experience (Eippert et al. 2007; Kalokerinos et al. 2015; Olatunji et al. 2017; Tull et al. 2010), which was linked to differential engagement of emotion- and control-related brain regions (e.g., Cutuli 2014). This advantage has been observed not only in the case of instructed, transient engagement of ER (i.e., in which participants are explicitly told to regulate their emotional experiences), but also in the case of habitual use of ER strategies (i.e., which reflects participants' tendency to spontaneously use specific ER strategies to regulate emotions in daily life). Indeed, evidence regarding the differential impact of reappraisal and suppression is coming from two complementary lines of research: one examining how instructing participants to use a given ER strategy affects their emotional perception and experience, and the other examining how individual differences in the habitual use of ER strategies without any explicit instructions to do so may contribute to differential emotional responses. Below, we summarize evidence highlighting the impact of ER on the effects of emotion on perception and memory.

Impact of ER on Opposing Effects of Emotion on Visual Perception

There has been a tremendous progress in clarifying the impact of ER on the processing of various emotion-eliciting material (Gross 2015; Sheppes et al. 2015) and the associated neural correlates (Buhle et al. 2014; Kohn et al. 2014a; Ochsner et al. 2012; Wager et al. 2008). The effect of emotion control has been typically investigated through experimental paradigms that manipulate ER in response to the presentation of visual stimuli, such as pictures, faces, and films containing emotional vs. neutral content, and the impact is measured in terms of emotional responses to visually perceiving such materials. On the one hand, participants may be instructed to either up-regulate or down-regulate their emotional response while processing emotional stimuli, without being provided instructions regarding specific ER strategies to use. Findings from previous studies involving these general ER strategies revealed that regulatory goals (up *vs.* down regulation) can differentially modulate AMY engagement, with increased AMY activity linked to up-regulation and decreased AMY activity linked to down-regulation (Ochsner et al. 2004). On the other hand, participants can be instructed to use specific ER strategies, with reappraisal and suppression being so far the two most widely studied strategies (for

other types of ER strategies, see Dorfel et al. 2014; Kanske et al. 2011; McRae et al. 2010). Findings from studies examining the neural correlates of instructed reappraisal and suppression revealed differential patterns of activity in and/or connectivity between basic emotion processing (AMY) and emotion/cognitive control (PFC) brain regions, even though both strategies can be effective in reducing the transient experienced emotional responses. In particular, reappraisal has been associated with decreased activity in the AMY and early increased activity in the PFC, whereas suppression was associated with increased activity in the AMY and late increased activity in the PFC (Goldin et al. 2008), and these opposing patterns of activity in emotion *vs.* cognitive control brain regions have also been confirmed in a recent meta-analysis (Buhle et al. 2014). Interestingly, the dissociation in the AMY response (decreased vs. increased), when engaging reappraisal vs. suppression, and the timing of increased response in the PFC (early vs. late, respectively), is consistent with the proposed differential timing of engaging these ER strategies, with reappraisal being conceptualized as *antecedent-focused* whereas suppression is seen as *response-focused*, relative to the occurrence of the triggering emotional stimulus (Gross 1998, 2008).

Although the extant research on ER has primarily explored instructed forms of ER, there has also been an increasing interest in understanding how habitual use of ER strategies modulates processing of emotional information. One way of assessing the habitual the use of ER strategies is by using the Emotion Regulation Questionnaire (ERQ) (Gross and John 2003), which assesses the relative engagement of cognitive reappraisal and expressive suppression in daily life experiences. Noteworthy, opposing effects in the habitual engagement of reappraisal vs. suppression are reflected in their long-time consequences on well-being (Llewellyn et al. 2013). Specifically, there is evidence pinpointing that habitual use of reappraisal is associated with increased psychological well-being (Gross and John 2003), whereas habitual use of suppression is associated with increased vulnerability to symptoms of emotional dysregulation (Aldao and Nolen-Hoeksema 2012; Llewellyn et al. 2013; Werner et al. 2011). At the neural level, available evidence suggests that greater habitual use of reappraisal is associated with decreased engagement of the AMY and increased activity of the PFC and parietal cortices during perception of negative facial expressions (Drabant et al. 2009; see also Moore et al. 2016), whereas greater habitual use of suppression is associated with increased engagement of the AMY (Vanderhasselt et al. 2013) and greater volume in the dorso-medial PFC (Hermann et al. 2014; Kühn et al. 2011). These findings are overall consistent with those reported in previous studies using instructed ER, and further suggest that the dispositional tendency to use a given ER strategy in everyday life may differently modulate how emotional stimuli or events are perceived, experienced, and/or remembered, as also discussed in the next sections.

Overall, the available evidence regarding the impact of ER on emotion perception shows that various regulatory goals (up- vs. down-regulate) and ER strategies are associated with differential patterns of activity in basic emotion processing and emotion/cognitive control brain regions. These findings also show that the transient and habitual engagement of ER can differentially modulate emotion processing and

the time-scale of its effects (immediate vs. long-term), and thus may help explain why in some circumstances ER strategies can heighten processing of emotional stimuli and well-being, whereas in others they can hinder them.

Impact of ER on Opposing Effects of Emotion on Episodic Memory

Although important progress has been made in understanding the impact of ER on how a stimulus/event is initially perceived (e.g., Lieberman et al. 2011; Ray et al. 2010), only a few studies have started to clarify how the engagement of various ER strategies affects the long-term impact of emotion on memory (Ahn et al. 2015; Dillon et al. 2007; Richards and Gross 2000), and the underlying neural substrates (Binder et al. 2012; Erk et al. 2010; Hayes et al. 2010). Overall, available research reveals that cognitive reappraisal during memory encoding enhances subsequent memory for the reappraised information (Dillon et al. 2007; Liu et al. 2015; Richards and Gross 2000), even after longer intervals (Ahn et al. 2015; Kim and Hamann 2012), whereas suppression tends to impair memory for the suppressed items (Richards and Gross 2000). One potential explanation that has been put forward to explain the enhancing effects of reappraisal on memory is linked to semantic elaboration processes involved during reappraisal, which might lead to a deeper level of encoding of the reappraised items (Dillon et al. 2007).

Regarding the neural correlates of these opposing effects of reappraisal and suppression on memory, recent neuroimaging studies point to differential neural engagement for successfully encoded emotional items that were reappraised or suppressed (Binder et al. 2012; Hayes et al. 2010). Specifically, Hayes et al. (2010) showed that the memory enhancement by reappraisal was linked to the increased engagement and co-activation of the HC and left lateral PFC (Fig. 14.4), whereas Binder et al. (2012) revealed that memory impairment by suppression was associated with decreased engagement and co-activation of the HC and lateral PFC. These findings suggest that the core memory region (HC) and the higher-level cognitive processing region (PFC), as well as their interplay during memory formation of

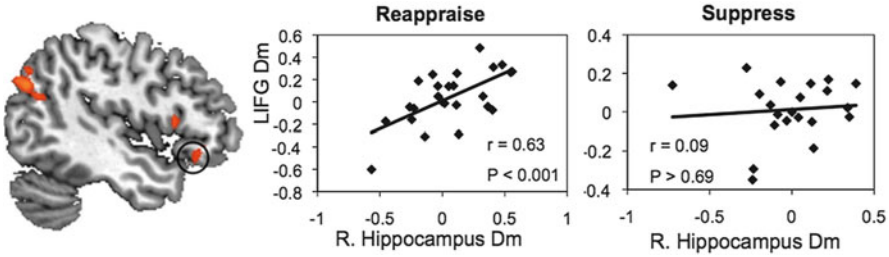

Fig. 14.4 Correlations between memory-related activity in the left inferior frontal gyrus and hippocampus, as a function of ER strategy. Stronger positive correlation was identified between the left inferior frontal gyrus (LIFG) and hippocampus (HC) when using cognitive reappraisal compared to suppression during encoding of pictorial stimuli. **Dm = Difference due to memory** (Adapted from Hayes et al. 2010, with permission)

"regulated" emotional items, are differently affected by the engagement of these ER strategies, which results in different effects on the subsequent emotional memory.

In sum, while still in its infancy, available research investigating the impact of ER on emotional memory suggests that using different ER strategies (reappraisal vs. suppression) while encoding or retrieving emotional information may be associated with opposing effects on subsequent memory (enhanced vs. impaired). Interestingly, these effects seem counterintuitive when compared with the long-term effects of habitual engagement of reappraisal and suppression on well-being (increased vs. decreased, respectively), given that affective disturbances, such as anxiety and depression, are typically associated with increased focus on memories for distressing events. Clarification of these issues is an important focus of future research in the impact of ER strategies on emotional memory (see also Conclusions and Future Directions below).

14.3.2 Age-Related Differences

Aging is associated with well-known co-morbidities and losses, but also with relatively high levels of emotional well-being. In the context of overall preserved emotional functioning, considerable evidence supports the idea of an age-related *positivity effect* in emotional perception, attention, and memory, by which older adults tend to (1) pay greater attention to and remember more positive information (Charles et al. 2003; Isaacowitz et al. 2006; Knight et al. 2007; Mather and Carstensen 2003), and (2) show reduced processing of negative information (Grühn et al. 2007; Wood and Kisley 2006), compared to younger adults (see also Mather 2016; Reed and Carstensen 2012; Reed et al. 2014). According to the Socioemotional Selectivity Theory (SST) (Carstensen et al. 2003; Reed and Carstensen 2012), an influential account of the age-related positivity effect, older adults' preference for positive over negative information is driven at least in part by their prioritization of more present-focused motivational goals related to emotional meaning and satisfaction, which in turn enhances their well-being. This implies that age-related differences in emotion processing occur as a function of differential engagement of the top-down mechanisms, such as ER strategies, that allow older adults to spontaneously cope with emotional challenges (Dolcos et al. 2014a; Mather and Carstensen 2005). As we will see below, available evidence regarding the neural correlates of age differences in the enhancing vs. impairing effects of emotion on cognition points to preserved bottom-up (AMY) mechanisms and enhanced top-down (PFC) mechanisms.

Impact of Age-Related Differences on Opposing Effects of Emotion on Visual Perception

Supporting the idea that age differences in emotion processing are primarily linked to modulation of top-down/controlled mechanisms, there is evidence suggesting that bottom-up/automatic processing of emotional (especially high arous-

ing/threatening) stimuli is relatively preserved in aging (Dolcos et al. 2014a; Kensinger and Leclerc 2009; Mather and Knight 2006; St Jacques et al. 2010). Such preservation of sensitivity to basic emotional information in aging has been most consistently linked to a similar engagement of the AMY in younger and older adults, which also seems to show less structural decline as a function of age compared to other brain regions (Jiang et al. 2014; Li et al. 2014). In the context of overall preserved AMY functioning in aging, there is also evidence showing age differences in AMY sensitivity to the valence of emotional stimuli. For instance, previous studies of emotional perception identified decreased AMY response to negative stimuli (Erk et al. 2008; Gunning-Dixon et al. 2003; Iidaka et al. 2002; Mather et al. 2004; Tessitore et al. 2005), whereas others observed increased AMY response to positive stimuli (Kehoe et al. 2013; Leclerc and Kensinger 2011; Mather et al. 2004), in older compared to younger adults.

Furthermore, the studies of emotional perception reviewed above and others have also identified increased engagement of the PFC and ACC regions during the viewing of negative vs. neutral and positive vs. negative stimuli, in older adults (Dolcos et al. 2014a; Gunning-Dixon et al. 2003; Leclerc and Kensinger 2008; Nashiro et al. 2012; St Jacques et al. 2010; Williams et al. 2006). These findings, along with evidence for chronic activation of ER goals in aging (Dolcos et al. 2014a; Gross et al. 1997; Mather and Knight 2005), suggest that greater activity in the PFC/ACC regions observed in aging linked to emotional perception may reflect enhanced habitual engagement of ER strategies in older adults, which may further exert modulation of activity in basic emotion processing regions (e.g., AMY). Consistent with this idea, there is evidence for increased functional connectivity between the ACC and AMY in healthy older adults, who also show overall reduced emotional ratings of negative stimuli (St Jacques et al. 2010) (Fig. 14.5a). Of note, age differences in the ACC-AMY interactions were also associated with changes in the perceived emotional content of negative stimuli, reflected in older adults' overall reduced emotional ratings of the negative stimuli (due to a "negative-to-neutral-shift" in rating some of the negative stimuli) (St Jacques et al. 2010), thus suggesting a role of this region in reducing AMY activity when regulation is successful. This idea was further supported by recent evidence identifying activity in similar ACC areas showing a negative correlation with subjective emotional ratings for negative stimuli in older adults (Dolcos et al. 2014a), thus confirming a role of this region in effective spontaneous regulation of negative emotions in aging (Fig. 14.5b). Notably, this latter study also clarified that the observed effects were specific to processing of low arousing stimuli, thus highlighting the importance of taking into consideration the level of emotional charge when investigating emotion processing in aging.

Consistent with the notion that older adults experience negative emotions to a lesser extent, compared to younger adults, older adults also show impairments in recognizing faces displaying negative emotions such as fear and sadness, but not so much in recognizing happy faces (Ruffman et al. 2008). These findings appear consistent with the positivity effect in aging, but recent evidence shows that older adults' ability to recognize disgust may be better than that of younger adults (Mather 2016), thus suggesting that these effects may be driven by specific emotions, rather

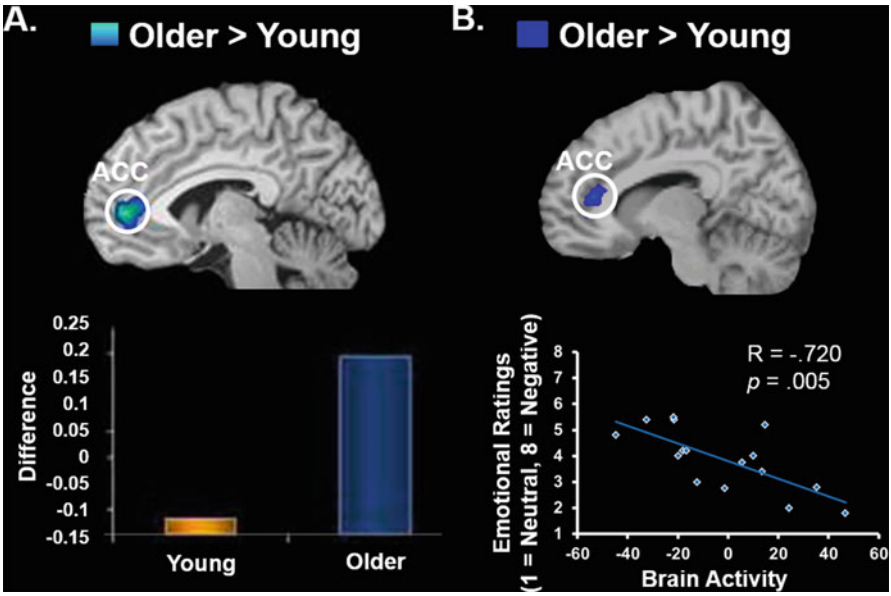

Fig. 14.5 Role of the anterior cingulate cortex in "spontaneous" emotion regulation in healthy aging. (**a**) Older adults show greater functional connectivity between the anterior cingulate cortex/medial prefrontal cortex (ACC/mPFC) and right amygdala (AMY), during the evaluation of negative pictures; the y-axis of the bar graph represents the difference in correlations between negative and neutral conditions. (**b**) Activity in the ACC is also negatively correlated with the emotional ratings of negative pictures, in older adults. Together, these findings point to a role of the ACC/mPFC in effective spontaneous regulation of negative emotions in aging (Adapted from St Jacques et al. 2010; Dolcos et al. 2014a, with permission)

than simply by positive vs. negative valence. Further research is needed to clarify the mechanisms underlying these age-related selective impairments in emotion recognition, possibly focusing on the interaction between the bottom-up (AMY) and top-down (PFC) mechanisms, as well as on the possible role of other regions that may mediate the interaction between the two in processing specific emotions (e.g., insula) (see also Dolcos et al. 2017, in press).

Impact of Age-Related Differences on Opposing Effects of Emotion on Episodic Memory

In the memory domain, numerous studies have provided evidence for similar valence-related opposing effects in memory, linked to the positivity bias observed in healthy older adults. This is reflected in their tendency to spontaneously recall fewer negative autobiographical memories (Schlagman et al. 2006) and reappraise them in a more positive way (Comblain et al. 2005), to remember personal memories in a more positive manner (Kennedy et al. 2004), and to remember more positive than negative personal memories and pictorial stimuli (e.g., Charles et al. 2003;

Ebner and Johnson 2009; Fernandes et al. 2008; Spaniol et al. 2008). Regarding the neural correlates of the memory-enhancing effect of emotion, the role of AMY-MTL and PFC mechanisms has been identified, with the PFC regions playing a pivotal role (reviewed in Dolcos et al. 2012). For instance, St Jacques et al. (2009) and Murty et al. (2009) both identified decreased connectivity between the AMY and HC, coupled with increased connectivity between the AMY and lateral PFC, linked to successful encoding of negative information in older compared to younger adults. In addition, studies of effective connectivity during emotional encoding observed both (1) stronger positive modulation of MTL activity by PFC in older than younger adults, and (2) enhanced *intra*-regional connectivity within PFC (e.g., medial, lateral, and orbital), during the encoding of positive information in older adults (Addis et al. 2010; Waring et al. 2013). Finally, Sakaki et al. (2013) found that those older adults who showed enhanced connectivity between AMY and mPFC *at rest* also showed (1) greater medial PFC activity during the encoding of emotional faces, and (2) a stronger positivity effect in a subsequent memory recognition test (i.e., more likely to remember positive vs. negative faces), whereas these effects were not observed in younger adults. Taken together, these findings suggest that age-related increase in AMY-PFC connectivity is overall associated with enhanced emotional memory encoding, and also linked to the positivity effect in older adults.

Regarding the impairing effects of emotion on EM, available behavioral evidence suggests that older adults are more susceptible than younger adults to the trade-off effect between emotional/central vs. non-emotional/peripheral features of an event (Kensinger et al. 2005, 2007c; Nashiro and Mather 2011). These age differences have been linked to older adults' relatively reduced ability to employ specific encoding strategies (e.g., broad allocation of attention to contextual aspects of stimuli) that would otherwise help younger adults alleviate the negative impact of the trade-off effect. This suggests that older adults may be particularly impaired in disengaging attention from emotionally salient aspects of stimuli (Kensinger et al. 2005, 2007c). In addition, there is also evidence that emotional arousal helps remember information about intrinsically-linked contextual features (e.g., stimuli and their location) through memory binding only in younger adults, hence suggesting that limited cognitive resources in older adults may lead them to only remember the gist but not the associated details (Nashiro and Mather 2011). These findings are consistent with previous studies documenting age-related deficits in efficient inhibition and attentional control (Fabiani 2012), as well as various forms of associative memory (Old and Naveh-Benjamin 2008). Although evidence regarding the neural correlates of age-related impairments in associative memory is still limited, a recent large-scale investigation of the impact of age on memory processes identified a significant association between older adults' associative memory performance and HC volume, consistent with the involvement of this region in representations of item-context relations (see also section "Enhancing effects" above) (Henson et al. 2016).

In sum, available evidence on the role of age-related differences points to general and valence-related opposing effects of emotion on perception and memory, and highlights the involvement of both bottom-up (AMY) and top-down (PFC/ACC)

neural mechanisms. Regarding the enhancing effects of emotion, older adults seem to maintain increased sensitivity to processing emotional information, in general, and this is linked to similar engagement of AMY in younger and older adults in emotional perception and memory encoding. Older adults, however, also tend to show a preference toward positive over negative information in perception and memory processes, and also experience less negative emotions, compared to younger adults. Extant evidence regarding this positivity effect points to a pivotal role of increased engagement of the PFC/ACC regions in older adults, allowing them to chronically activate ER goals to cope with emotional challenges. It seems, however, that this habitual engagement of ER in healthy older adults tends to particularly affect low-arousing emotional stimuli. Previous studies also point to age-related impairments in correctly identifying some negative facial expressions, but further research is needed to clarify the underlying neural mechanisms of their impaired emotion recognition. Finally, aging also seems to be associated with a pronounced impact of the trade-off effect in remembering central vs. peripheral features, which may be related to reduced involvement of the HC in associative memory in older adults.

14.3.3 The Role of Sex Differences

In our society, it is commonly believed that women perceive, experience, and express emotions to a greater extent than men do (Briton and Hall 1995; Meyers-Levy and Loken 2015). This section discusses scientific evidence pointing to both beneficial and detrimental aspects related to the role of sex differences in emotion processing. Consistent with beneficial aspects, there is evidence pointing to *enhanced emotional competence* in women. However, consistent with detrimental aspects, there is evidence highlighting *increased vulnerability* to affective disorders in women. At the neural level, available evidence identifies both general and specific sex differences in the patterns of brain activations during emotion processing. For instance, evidence from brain imaging studies highlights dissociable engagement of the AMY, in women and men, both in general emotion processing (Andreano et al. 2014; Stevens and Hamann 2012) and in emotional memory (Andreano and Cahill 2009; Cahill 2003; Hamann 2005).

Role of Sex Differences in Opposing Effects of Emotion on Visual Perception

Consistent with the idea of enhanced emotional competence in women (Collignon et al. 2010; Hall and Matsumoto 2004; Montagne et al. 2005), there is evidence that, compared to men, women identify and decode others' emotional expressions more accurately (Collignon et al. 2010; Hall and Matsumoto 2004; Montagne et al. 2005), are more emotionally expressive (Kring and Gordon 1998), and

display more extensive knowledge of emotional experience (Barrett et al. 2000). However, consistent with increased vulnerability to affective disturbances, there is also evidence pointing to a *negative bias* in emotion processing. Specifically, women are known to exhibit enhanced reactivity to emotional stimuli (particularly negative ones) (Hamann and Canli 2004; Lang et al. 1993; Shields 1991; Spalek et al. 2015), tend to be more cautious and show avoidance-focused motivations (Meyers-Levy and Loken 2015), which may be linked to nearly two times higher lifetime prevalence of mood and anxiety disorders than in men (Bekker and van Mens-Verhulst 2007; Kessler 2003; Nolen-Hoeksema 2001).

Brain imaging studies provide further emerging evidence consistent with a *negative affective bias* and valence-related sex differences in emotion processing. For instance, a recent meta-analysis of brain imaging studies examining sex differences identified a sex × valence interaction in emotion processing, such that women are more likely to show greater AMY response to negative information, whereas men tend to show greater AMY response to positive information (Stevens and Hamann 2012). Moreover, a subsequent study by Andreano et al. (2014) showed that AMY response to negative stimuli tends to be "persistent" over multiple repetitions in women, whereas AMY response to negative stimuli in men is only sensitive when the stimuli are novel (as opposed to familiar). Importantly, the difference in AMY response to novel vs. familiar negative stimuli was negatively associated with self-reported measures indexing symptoms of anxiety and depression across men and women, thus lending support to the idea that reduced habituation of the AMY response to negative stimuli may be linked to the greater incidence of affective disorders in women (Andreano et al. 2014).

Additional support consistent with the notion of enhanced emotional reactivity in women comes from studies investigating the impact of emotional distraction. For instance, processing of novel task-irrelevant distracters in a negative emotional context was associated with slower response time and decreased hit rates in a visual perception task in women, compared to men (Garcia-Garcia et al. 2008). This finding, coupled with a larger P3 response (typically associated with attentional orientation, among others, Bradley et al. 2012) for novel distracters in the negative context in women, suggests heightened sensitivity and hence greater allocation of attentional resources to potential threat in women (Garcia-Garcia et al. 2008). Furthermore, other studies examining sex differences in the basic response to task-irrelevant emotional distraction identified increased activity in brain regions involved in emotion processing such as the AMY, FG, and subgenual ACC in women (Iordan et al. 2013a), consistent with enhanced bottom-up impact of negatively-valenced emotional distraction in women (Fig. 14.6a, b). Interestingly, activity in the left FG, a perceptual area susceptible to modulation by emotional information, was negatively correlated with performance in a concurrent WM task only in women (Fig. 14.6b) (Iordan et al. 2013a). This evidence further supports the idea that women's greater sensitivity to emotional stimuli is linked to increased engagement of bottom-up emotion processing regions and which leads to detrimental impact on ongoing cognitive processing (see also Iordan et al. 2013b).

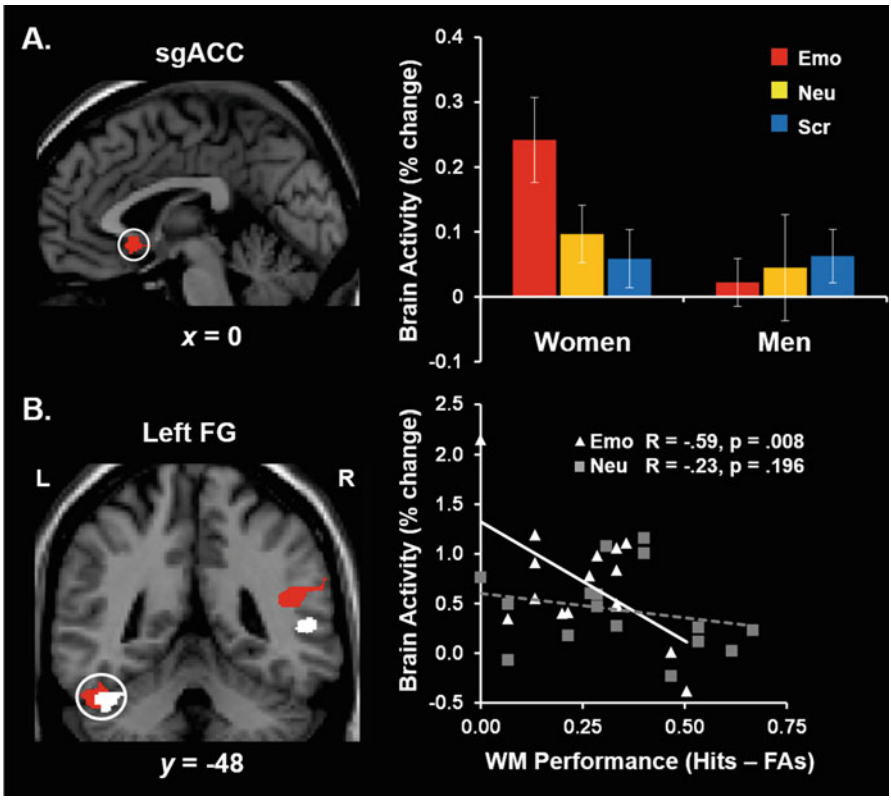

Fig. 14.6 Increased sgACC and FG activity to emotional distraction in women. (**a**) *Left panel*: women showed an increased response to emotional distraction in the subgenual anterior cingulate cortex (sgACC, BA 25). The area indicated by the white circle illustrates the difference in activation in response to emotional distracters (angry faces) in women versus men. *Right panel*: the bar graph illustrates the fMRI signal, as extracted from the sgACC region corresponding to the difference in activation between women and men. (**b**) *Left panel*: the left fusiform gyrus (FG) also showed similarly increased sensitivity for emotional distracters in women than in men (*red cluster*). *Right panel*: interestingly, the overlapping area in the FG (*white cluster*) also showed a negative covariation between brain activity and WM scores for trials with emotional distracters, in women. *Emo* emotional distracters, *Neu* neutral distracters, *Scr* scrambled distracters *BA* Brodmann area (From Iordan et al. 2013a, with permission)

Role of Sex Differences in Opposing Effects of Emotion on Episodic Memory

Evidence consistent with the discussion above regarding sex differences in emotional competence vs. increased vulnerability to affective disturbances, linked to valence-related differences in processing emotional information between women and men, also comes from studies of emotional memory. For instance, compared to men, women recall more emotional autobiographical memories (Davis 1999;

Seidlitz and Diener 1998) and show increased overall brain activity during encoding of emotional memories (Canli et al. 2002a). Previous studies of sex differences in the neural correlates of emotional memory also point to a hemispheric asymmetry in the involvement of AMY, such that the left AMY is associated with successful emotional memory encoding in women, whereas the right AMY is associated with successful encoding in men (Cahill et al. 2001; Canli et al. 2002a; but see Fischer et al. 2007). There is evidence that consolidation of emotional memory is also modulated by sex differences (Mackiewicz et al. 2006), and that the gender-related lateralization in the AMY linked to emotional memory encoding seems to also depend on sex differences in the stimuli to be encoded. Specifically, there is evidence that the left AMY is preferentially involved in successful encoding of female emotional faces in women, whereas the right AMY is correlated with successful encoding of male emotional faces in men (Armony and Sergerie 2007).

The finding showing women's preferential processing of same-sex stimuli is consistent with evidence that women tend to have greater preference for socially-relevant items, in general (e.g., faces and people vs. scenes) (Proverbio et al. 2008a, b). This led to the suggestion that feminine and masculine roles as established by the society, rather than the sex per se, influence the differences in emotional memory (Cahill et al. 2004) between women and men. This interpretation is also supported by evidence for sex differences in the AMY linked to opposing effects in memory for central vs. peripheral details. Specifically, activity in the right and left AMY was linked to enhanced consolidation of central vs. peripheral aspects of emotional events in men and women, respectively (Cahill and van Stegeren 2003). Moreover, a subsequent study by these authors showed that those participants who showed greater masculine traits also remembered more the central aspects, whereas those who showed greater feminine traits remembered more the peripheral aspects of emotional information (Cahill et al. 2004). Taken together, these findings show that femininity is associated with relatively impaired vs. enhanced recall of central vs. peripheral features of emotional information, respectively, with evidence for the latter being subserved by the engagement of the left AMY.

Similar to the studies on emotion perception discussed above, evidence consistent with a *negative affective bias* in women, possibly linked to increased vulnerability to affective disturbances, also comes from studies of memory investigating sex differences in the recollection of emotional autobiographical memories (AMs) (Denkova et al. 2012; Young et al. 2013). Consistent with the aforementioned negative bias, the study by Denkova et al. (2012) showed that women recalled more negative and fewer positive AMs than men, although women and men did not differ in the appraisal of phenomenological properties (e.g., arousal, vividness) of their AMs (Young et al. 2013). Furthermore, the same study also showed that retrieval of emotional AMs and post-retrieval affective mood was differently influenced by habitual use of ER strategies, in women and men. Specifically, engaging suppression as a habitual ER strategy in women may be inefficient and could come with the cost of also being associated with overall enhanced retrieval of negative AMs and increased post-retrieval negative affect (Denkova et al. 2012). At the neural level, recollection of emotional AMs has been linked to both common and dissociable

engagement of brain regions in women and men. Specifically, whereas women and men similarly engaged the PFC, AMY, and memory-related MTL regions during recollection of emotional AMs, recalling negative AMs was also associated with increased activity in various regions, including the AMY, in women compared to men (Young et al. 2013).

In sum, available evidence concerning sex differences in the enhancing vs. impairing effects of emotion on cognition points to women's enhanced sensitivity to emotional stimuli in general, and to negative stimuli in particular. Although women generally exhibit enhanced emotional competence in emotion processing, they are also more likely to show a negative affective bias in perception and memory. At the neural level, this processing bias has been linked to increased sensitivity in bottom-up emotion processing regions, including the AMY and FG, which may in turn be linked to heightened vulnerability to emotional disturbances in women. It remains unclear, however, the seemingly paradoxical co-occurrence of both beneficial (increased emotional competence) and detrimental (increased vulnerability to emotional disturbances) aspects regarding emotion processing in women.

14.3.4 Other Factors Modulating the Opposing Effects of Emotion on Cognition

Besides the factors discussed above, emerging evidence points to other factors that can also modulate effects of emotion on cognition. For instance, one's emotional states (Biss and Hasher 2011; Biss et al. 2012; Cohen et al. 2016; Fitzgerald et al. 2011) or personality traits influencing emotion processing (Hamann and Canli 2004; Hooker et al. 2008) can influence the way emotion interacts with cognition. Consideration of these factors can contribute to further insight into alterations associated with dysfunctional emotion-cognition interactions in affective disorders.

Mood/Emotional States

There is anecdotal and empirical evidence that longer-lasting (mood) and transient emotional states can affect one's cognition and behavior (Biss and Hasher 2011; Blaney 1986; Cohen et al. 2016; Fitzgerald et al. 2011). The effect of mood is typically investigated through mood induction procedures, using for instance recollection of emotional AMs or viewing affect-laden movie clips or images (Kohn et al. 2014b; Wagner et al. 2012; Young et al. 2012; Zhang et al. 2014). In laboratory studies, participants' current emotional states are usually assessed before and after the study, using measures such as the state scale of the Positive and Negative Affective Schedule (PANAS-S) (Watson et al. 1988). In the case of mood, for instance, available evidence suggests that positive *vs.* negative mood can

have opposing effects on focusing attention during visual processing. Specifically, it has been suggested that positive mood may broaden the focus of attention (Fredrickson and Branigan 2005; Grol and Raedt 2014; Wadlinger and Isaacowitz 2006), whereas negative mood may narrow the focus of attention (Gasper and Clore 2002). However, emerging evidence suggests that the effects of positive *vs.* negative mood are more complex, and may also depend on other factors, such as motivation (Gable and Harmon-Jones 2010) or context (Hunsinger et al. 2012).

In the memory domain, it has been shown that mood can lead to differential effects depending on its congruency with the emotional information to encode and remember, a phenomenon known as the *mood congruent memory* (Blaney 1986). Specifically, memory can be enhanced when the valence of the mood during encoding or retrieval is congruent with that of the information to encode or remember (Fitzgerald et al. 2011; Leppanen 2006), and these effects have been linked to the engagement of PFC mechanisms (Fitzgerald et al. 2011; Lewis et al. 2005). Also relevant to the present chapter, there is behavioral evidence that, although older adults overall showed a typical positivity effect in memory recall (i.e., reduced recall of negative words independently of mood induction), they were also more sensitive to negative mood induction, showing mood congruence effects during induced sadness on more tasks than younger adults (Knight et al. 2002). Interestingly, mood seems to impact not only attention, perception, and memory, but also cognitive control processes (Cohen et al. 2016; Frober and Dreisbach 2014; Vanlessen et al. 2015). While this emerging evidence highlights the impact of mood on memory and provides insights into the associated neural underpinnings further investigations are needed to elucidate the role of mood in the impact of emotion on cognition. This is of particular importance for understanding the interplay between emotion and cognition in mood disorders, such as depression, which is characterized by an overall negative affective bias (affecting attention, perception, and memory) coupled with impaired cognitive control (Drevets 2001; Koster et al. 2005). Hence, clarifying the impact of mood on various aspects of cognition is an important avenue of research on emotion-cognition interactions.

Personality Traits

Available research suggests that valence-related opposing effects of emotion on perception and memory are also influenced by individual variations in personality traits linked to general emotion processing, such as extraversion and neuroticism (Rubin et al. 2008; Young and Martin 1981). For instance, traits associated with positive affect, such as extraversion (Costa and McCrae 1980; John and Srivastava 1999), are associated with enhanced recollection of positive memories (Rusting 1999), whereas personality traits associated with negative affect, such as neuroticism, are linked to enhanced recollection of negative memories (Mayo 1983; Ruiz-Caballero and Bermudez 1995). We recently identified such relations in the case of retrieving personal memories for real-life events (Denkova et al. 2012). More specifically,

we showed that extraversion contributed to remembering more positive personal experiences and to maintaining a positive state, whereas neuroticism predicted the phenomenological characteristics of negative AMs; interestingly, the latter trait was also linked to sex differences. Moreover, there is also evidence for similar interactions between personality traits and age differences. In particular, older adults with high levels of neuroticism do not seem to experience decreases in negative affect, unlike the patterns exhibited by their same-age peers (Charles et al. 2001; Griffin et al. 2006); there is also evidence that older adults may even be more sensitive and reactive to negative stressors (see also Dixon et al. 2012; Mroczek and Almeida 2004; Mroczek et al. 2006). Taken together, these findings highlight the importance of considering concomitantly individual differences in personality traits and sex/age in order to achieve a comprehensive understanding of the factors or combinations of factors that may influence the opposing effects of emotion on cognition.

Furthermore, it has been shown that extraversion and neuroticism can influence the neural correlates associated with the impact of emotion on a range of cognitive processes, including perception, attention, and memory (Canli et al. 2002b; Hamann and Canli 2004; Hooker et al. 2008; Touryan et al. 2007). It has also been suggested that individual differences in emotional biases linked to specific personality traits might be rooted in an attentional network driven primarily by the AMY reactivity during the encoding of emotional stimuli (Haas and Canli 2008). Moreover, there is also evidence that activity in the AMY and HC during fear learning positively correlates with the level of neuroticism (Hooker et al. 2008). These findings suggest that neuroticism, which has also been linked to heightened vulnerability to affective disorders (Bienvenu et al. 2004), is associated with increased sensitivity of the AMY and HC to negative stimuli, leading to enhanced encoding of negative associations (see also below), which in turn can also influence the negative affective bias during retrieval. Overall, available evidence suggests that individual differences in personality traits can play a pivotal role in modulating the impact of emotion on cognition, and provides insights into understating factors of vulnerability to affective disorders.

Clinical Status: Affective Disorders

The valence-related opposing effects of emotion on cognition tend to be particularly exacerbated in affective disturbances. For instance, mood, anxiety, and stress-related disorders (e.g., depression, generalized anxiety, and PTSD, respectively) are characterized by increased negative affective bias (e.g., *hypervigilance* toward potential threats in the environment) and reduced responsiveness to positive affect, coupled with impaired executive control and ER (Brown and Morey 2012; Drevets 2001; Hayes et al. 2012; Mayberg 1997; Mayberg et al. 1999; Rauch et al. 2006; Shin and Liberzon 2009). Increased sensitivity to negative material can impair attention, memory, and cognitive control in depression and PTSD, and this is typically associated with altered activity in emotion-related (AMY, rostral ACC) and control-related brain regions (PFC, dorsal ACC) (Dolcos 2013; Foland-Ross

and Gotlib 2012; Hayes et al. 2012). In the case of PTSD, there is evidence pointing to a possible link between the impact of emotion on episodic memory for trauma-related material (enhanced gist-based memory) (Hayes et al. 2011) and the impact of such material as task-irrelevant distraction presented concurrently with a cognitive task (non-specific response of trauma compared to non-trauma material) (Morey et al. 2009). We proposed that the non-specific (gist-based) effects produced by trauma-related materials on episodic memory is due to hyperarousal during initial encoding, which leads to functional disorganization of the memory-related AMY-HC mechanisms. In turn, the gist-based memories produce non-specific responses when cues for such memories are presented as trauma-related distraction. This further leads to enhanced hypervigilance that contributes to the maintenance of a hyperarousal state and non-specific (re)encoding of traumatic memories, hence restarting and maintaining this dysfunctional cycle (Dolcos 2013).

Overall, separate lines of investigations reviewed above suggest that several factors may impact the interplay between emotion and cognition and the directionality of these interactions. While there has been steady progress during the last decades in understating the mechanisms of emotion-cognition interactions, further investigations specifically targeting concurrent examination of these factors are needed to gain a comprehensive picture of how they interact in influencing the opposing effects of emotion on cognition.

14.4 Conclusions and Future Directions

The overarching goal of the present chapter was to discuss emerging evidence from investigations examining factors that modulate the neural mechanisms of enhancing vs. impairing effects of emotion, with a particular emphasis on the role of *ER strategies* and individual differences linked to *age* and *sex*, as well as additional factors including *emotional states, personality traits*, and *clinical conditions*. Overall, available evidence regarding the basic enhancing vs. impairing effects of emotion on visual perception and episodic memory points to the involvement of and interactions between *bottom-up*/direct mechanisms, mainly involving the AMY, MTL, and perceptual regions (e.g., FG), and *top-down*/indirect mechanisms, mainly mediated by the PFC and other cortical regions (e.g., ACC, insula, parietal cortices). Emerging evidence from investigations examining various factors linked to individual differences also identifies valence-related opposing effects of emotion (e.g., typically, reflected in a relative *positive* affective bias in older adults and linked to high extraversion scores vs. increased relative *negative* bias in women compared to men, and linked to high neuroticism scores and affective disturbances), and this shift in sensitivity to emotional valence has been associated with differential engagement of both the bottom-up and top-down mechanisms in emotion processing. Moreover, the deployment of specific ER strategies and their impact on visual perception and memory also seem to vary as a function of individual differences, and dysfunctional ER (or emotion dysregulation) has been linked to affective disturbances, such as anxiety, depression, and PTSD. The main

conclusions of the present chapter are summarized below, and then followed by open questions for future research.

Evidence regarding the opposing effects on visual-perceptual processes points to an important role of AMY in exerting modulatory influences on bottom-up perceptual regions, such as the FG and lateral temporo-occipital cortices, allowing enhanced detection and processing of emotional compared to neutral stimuli. Furthermore, in the context of processing task-irrelevant emotional interference, increased AMY sensitivity to emotional stimuli seems to not only influence low-level perceptual brain regions, but also modulate activity in other affective processing regions, including portions of the PFC, possibly suggesting the sensitivity of these higher-order cortical regions to the motivational significance of stimuli (Shafer et al. 2012). Similarly, regarding the effects on EM, the enhancing effects of emotion have been linked to the involvement of two separate yet highly interactive neural systems, namely, bottom-up/direct mechanisms involving the AMY/MTL, and top-down/indirect mechanisms involving the PFC and other cortical areas (e.g., parietal cortices). The bottom-up mechanisms are particularly sensitive to the emotional arousal of the stimuli. The top-down mechanisms – through their involvement in semantic, working memory, and attentional processes – aid in the formation of emotional memories, and are sensitive to the valence as well as social relevance of emotional stimuli. Within the MTL regions involved in the bottom-up mechanisms of emotional memory, there also seems to be functional dissociation between the PRC and HC, whose activity has been linked to memories for isolated or unitized items vs. complex associations between a given item and its context, respectively.

Evidence from investigations examining the effects of ER strategies and individual differences in healthy populations provides insight into the role of these factors in modulating the enhancing vs. impairing effects of emotion on visual perception and EM. Regarding the role of *ER strategies*, available research shows that instructed deployment of different regulatory goals (up *vs.* down regulation) or ER strategies (i.e., cognitive reappraisal vs. expressive suppression) can differently affect processing of and memory for emotional information, as reflected in differential patterns of activity in basic emotion (i.e., AMY) and cognitive control (i.e., PFC) brain regions. For instance, using reappraisal to down-regulate emotional responses has been associated with decreased activity in the AMY and increased activity in the PFC during processing of emotional stimuli. In addition, it is suggested that the increased engagement of the PFC regions coupled with the increased engagement of the HC may explain enhanced memory for "reappraised" emotional items. By contrast, the opposite pattern is observed for suppression where decreased engagement and co-activation of PFC and HC may explain impaired memory for "suppressed" emotional items. In addition, available evidence also identifies functional and structural alterations in the AMY and PFC regions linked to the habitual engagement of reappraisal vs. suppression. While emerging evidence coming from separate lines of investigations suggests opposing effects of ER strategies on perceptual and mnemonic processing of emotional information, further research is needed to directly address how different ER strategies can lead to enhanced vs. impaired impact of emotion on perception and memory.

Regarding the role of *age* differences, available evidence highlights age-related modulation of bottom-up and top-down mechanisms involved in the impact of emotion on cognition. In the context of overall preserved sensitivity to emotional information subserved by the AMY in aging, older adults tend to show increased attention to and memory for positive information, or attenuated processing of negative information, compared to younger adults. This so-called *positivity effect* seems to occur as a result of enhanced and habitual deployment of ER, which in turn is subserved by greater engagement of the ACC/mPFC regions in older adults, particularly in the context of processing low-arousing emotional stimuli. Similarly, PFC regions also play an important role in older adults' emotional memory, showing greater connectivity with the AMY linked to successful emotional encoding, relative to younger adults. Aging also seems to selectively impair aspects of emotional perception and memory, as reflected in older adults' reduced sensitivity to some negative emotions and increased sensitivity to the central vs. peripheral memory trade-off. However, further research is needed to elucidate how aging modulates the bottom-up and/or top-down mechanisms involved in these processes, as well as the interaction between the two, particularly with respect to the role of ER and positivity effect as discussed above.

Regarding the role of *sex* differences, extant evidence identifies women's increased sensitivity to emotional stimuli, in general, and to negative information (i.e., *negativity bias*), in particular, compared to men. Whereas women's greater emotional sensitivity, subserved by the AMY, may contribute to their enhanced emotional competence, sustained AMY response to negative stimuli may also be linked to their increased susceptibility to affective disturbances. Greater activation of the bottom-up perceptual regions in response to task-irrelevant emotional distraction is also linked to greater interference of ongoing cognitive processing, thus underscoring the detrimental impact of women's heightened sensitivity to emotional stimuli. Similarly, while women's successful emotional memory encoding has been linked to activity in the left AMY, women's negativity bias in recollecting AMs is also associated with greater response in both the AMY and ER-related regions such as the PFC and ACC. There is also evidence that femininity may be associated with relative impairment in recalling the central aspects (compared to peripheral aspects) of emotional information.

Finally, there is emerging evidence that other factors, such as *emotional states* and *personality traits* can also modulate the opposing effects of emotion on cognition. Similar to the other factors discussed above, these factors also seem to be associated with differential sensitivity to the valence of emotional stimuli, which in turn is mediated by both bottom-up and top-down processes involved in the impact of emotion on cognition. Of note, these valence-related opposing effects of emotion tend to be particularly exacerbated in affective disturbances, thus suggesting the importance of considering these additional factors to gain better understanding of vulnerability to affective disorders.

Despite a growing body of literature elucidating the role of various factors in modulating the enhancing vs. impairing effects of emotion on perception and memory, a number of issues still remain unclear. Regarding the role of *ER strategies*,

further investigations are needed to clarify how various ER strategies can modulate not only perception but also memory. Given that emerging research highlights the effectiveness of attentional deployment strategies (e.g., distraction, focused attention) (Denkova et al. 2015; Dolcos et al. 2015; Depue et al. 2007; Hur et al. 2016), future investigations of the impact of ER on memory should include more elaborated practices and training that rely on attentional control. Moreover, while progress has been made in elucidating the impact of explicit ER strategies, further research is needed to clarify the impact of implicit (e.g., priming) or habitual engagement of ER strategies not only at the level perceptual processing of emotional events, but also at the level of mnemonic processing. For instance, whereas habitual engagement of reappraisal and suppression is associated with increased vs. decreased psychological well-being, respectively (Gross and John 2003; Llewellyn et al. 2013), the explicit instructed use of these strategies in laboratory studies is also associated with enhanced vs. impaired subsequent memory for emotional items (Dillon et al. 2007; Richards and Gross 2000). Hence, better understanding of the mechanisms underlying the impact of explicit vs. implicit/habitual ER on perception and memory would provide valuable insight into affective disorders, which are characterized by inefficient ER.

Regarding the role of *age* differences, it remains less understood how age differences might mediate the impact of emotion on various aspects of perception and memory, particularly with respect to the differential engagement of top-down mechanisms involved in emotion processing. For instance, although converging evidence suggests enhanced ER in healthy aging, older and younger adults prefer different ER strategies in effectively regulating the impact of emotion. Compared to young adults, older adults seem to favor strategies that may depend less on cognitive resources, such as situation selection or distraction (Etxeberria et al. 2016; Scheibe et al. 2015; Urry and Gross 2010), and this age-related shift in the preference toward specific ER strategies is linked to increased affective well-being in older adults (Scheibe et al. 2015). However, only a few studies so far have examined and directly compared the mechanisms of different ER strategies in older vs. younger adults (Allard and Kensinger 2014a, b). In addition, although there is emerging evidence that older adults' deployment of different ER strategies depends on the level of arousal and valence of stimuli (Dolcos et al. 2014a; Martins et al. 2016), the neural mechanisms associated with such interactions between ER strategies and emotional properties of the stimuli remain unclear. Future research taking into consideration these aspects would be helpful in elucidating the flexible and adaptive nature of ER strategy choice across the lifespan.

Regarding the role of *sex* differences, it remains unclear the paradoxical co-occurrence of both beneficial (increased emotional competence) and detrimental (increased vulnerability to emotional disturbances) aspects of emotion processing in women, compared to men, and the associated neural mechanisms linking these two phenomena. One possibility is that women's hypersensitivity to emotional cues may interfere with disengagement from processing negative stimuli, resulting in chronically activated negative emotional states. This notion is consistent with available evidence showing that women are more likely than men to attend to

detailed characteristics in emotion processing (Heisz et al. 2013), and that such sex differences are most pronounced when processing negative stimuli, particularly ambiguous ones (see also Andreano et al. 2014; McClure et al. 2004; Montagne et al. 2005). Moreover, as discussed in the preceding section, women's habitual engagement of suppression is associated with increased recollection of negative memories and experience of the associated emotional response (Denkova et al. 2012). However, sex differences in the neural mechanisms mediating these effects are still unclear. Future studies investigating the role of sex differences in enhancing vs. impairing effects of emotion on cognition might consider the impact of differential engagement of ER strategies on both the immediate and long-term impact of emotion, and clarify how these effects might translate to the mechanisms of affective disturbances that disproportionately affect women and men, such as mood and anxiety disorders.

Additionally, future investigations of the role of age and sex differences should also consider targeting the potentially dissociable impact of specific negative emotions. Regarding age, although older adults tend to show impairments in recognizing some negative emotions, such as sadness, fear, and anger, their ability to recognize and experience disgust seems to be preserved or even improve as a function of age (Mather 2016). While this implies that the perception of various negative emotions may engage different neural processes, and that they may be differentially impacted by aging, the mechanisms underlying such selective impairment/enhancement in recognizing specific emotions still remain unclear (see also Mather and Ponzio in press). Moreover, sex differences also exist in the processing of specific negative emotions, such that women are more likely to perceive and experience sadness or fear, whereas men are more likely to perceive and experience anger (Fischer et al. 2004; Glenberg et al. 2009; Kret and De Gelder 2012). At the neural level, there is evidence that processing of angry faces under a stressful situation is associated with an increase in functional connectivity among regions involved in emotional perception (e.g., AMY, FG, insula) in women compared to men (Mather et al. 2010). Overall, these findings suggest that future studies need to acknowledge the importance of considering and separating specific categories of negative emotions in studying the role of individual differences, as these emotions may be associated with differential behavioral and/or neural responses across participant groups.

Finally, future studies examining the role of individual differences in modulating the opposing effects of emotion should emphasize the importance of considering concomitantly individual differences in multiple domains, given the highly interactive nature of their effects on these phenomena. For instance, as discussed above, neuroticism but not extraversion was related to sex differences in the recollection of emotional memories and the associated post-retrieval emotional states (Denkova et al. 2012). Moreover, neuroticism at older ages is associated with elevated levels of negative affect (Mroczek et al. 2006), as well as an increased risk of developing mild cognitive impairment (Wilson et al. 2005). At the neural level, neuroticism has been shown to interact with both sex and age in influencing the volume of brain

regions involved in emotion processing (e.g., AMY, FG) (Jackson et al. 2011; Nostro et al. 2016). Thus, concomitant consideration of multiple domains of individual differences, such as personality, sex, and age, would be essential in gaining a comprehensive understanding of the mechanisms involved in the enhancing vs. impairing effects of emotion.

Overall, the present chapter emphasizes the need to consider the various factors that can influence opposing effects of emotion on cognition, and identifies new avenues for future investigations of emotion-cognition interactions. These issues have relevance for understanding mechanisms of emotion-cognition interactions in healthy functioning and in emotional disturbances, where such opposing effects of emotion tend to be exacerbated and deleterious.

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Part III
Disorders of the Mind

Chapter 15
Neural Correlates of Normal and Impaired Consciousness

Andrea E. Cavanna

Abstract Consciousness is notoriously difficult to conceptually define and measure, despite being central to human experience in both health and pathology. In recent years, the combined efforts of researchers working in the fields of philosophy, psychology and neuroscience have led to the development of a level-versus-contents bi-dimensional theoretical framework to assist the scientific study of consciousness. According to the bi-dimensional model of consciousness, conscious states are characterised by the general level of arousal (clinically tested as responsiveness) and the awareness of specific contents of consciousness (clinically tested as first-person reports of subjective experiences). This model allows clinical researchers to systematically explore the neural correlates of consciousness across a range of healthy and altered conscious states. In addition to physiological states, such as the different sleep stages, both chronic and transient pathologies of consciousness have been the subject of high-quality neurological research conducted over the last few years. Chronic pathologies of consciousness include coma, vegetative state, and minimally conscious state, whereas the different types of epileptic seizures are the most extensively investigated neurological conditions associated with transient alterations of consciousness. Multidisciplinary approaches to consciousness studies offer promising avenues to reach the dual goal of shedding some initial light on the so-far elusive neural correlates of consciousness and improving health-related quality of life in patients with chronic and transient neurological conditions affecting consciousness.

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15.1 Defining Consciousness

Consciousness has proven a surprisingly difficult concept to define, despite being experienced so intimately by all humans (Chalmers 1995). In time, multiple definitions have been proposed to capture this ambiguous term (Zeman et al. 1997; Zeman 2001). With the turn of the new millennium, neuroscientific publications on consciousness have seen an unprecedented increase, often overlapping with psychological and philosophical research (Cavanna and Nani 2014). In the second edition of the classical neuroscience textbook 'Human brain function' (2004), the authors of the chapter titled 'The neural correlates of consciousness' explicitly stated that '*In the first edition of this book there was a final chapter on the future of imaging in which use of the word consciousness was strictly avoided until very last sentence. Now that we have moved into a new millennium it has no longer been so easy to resist the* Zeitgeist*. That single sentence has become a whole chapter*' (Portas et al. 2004a). This statement reflects the availability of novel clinical and experimental approaches to the investigation of the neurobiological underpinnings ('neural correlates') of human mental states, including consciousness the ultimate *sancta sanctorum* of our mental life (Cavanna et al. 2011a, 2013a). The following section will introduce the theoretical bi-dimensional model of consciousness, based on the identification of the two main components of arousal and awareness, whereas the remaining sections of this chapter will provide an overview on the clinical and neurobiological correlates of neurological conditions associated with chronic and transient alterations of consciousness.

15.2 The Bi-dimensional Model of Consciousness: Level and Contents

In medical textbook as well as clinical practice, consciousness is typically mentioned in the context of conditions characterised by its impairment, ranging from physiological states (sleep-wake cycle from dreamless sleep through drowsiness to alert wakefulness) (Portas et al. 2004b) to acute (seizures, black-outs) or chronic (coma, vegetative state, minimally conscious state) brain pathologies (Laureys et al. 2004). Subjects in these conditions share the characteristic of being unresponsive, suggesting that the ability of an individual to respond to stimuli in the integrated manner expected in the waking state can be used an objective measure of arousal (i.e. wakefulness, alertness, or vigilance) (Zeman 2001).

It has long been known that arousal is maintained by the activation of the so-called 'ascending reticular activating system', a functional module of the complex

neuronal network within the reticular formation of the upper brainstem. The ascending reticular activating system contains two major components: the reticulo-thalamo-cortical pathway and extrathalamic pathways. Activation of the reticulo-thalamo-cortical pathway promotes widespread cortical activation by facilitating thalamo-cortical processing of sensory information conveyed to the intralaminar and reticular nuclei by upper brainstem cholinergic projections (Laureys et al. 2004; Mesulam 2000; Posner et al. 2007). The extrathalamic pathways contribute to the direct functional activation of the cortical structures through parallel projections originating in the brainstem and basal forebrain (Laureys et al. 2004).

In healthy subjects, varying degrees of arousal correspond to different patterns of cortical electrical activity, which have traditionally been investigated by electroencephalography recordings (Mesulam 2000). Analysis of the number of electrical waveforms per second (hertz, Hz) has revealed four basic electroencephalographic patterns across different arousal stages: beta activity, which is associated with mental exertion, is characterised by low amplitude and fast activity, occurring at frequencies of 13–30 Hz. The predominant background activity during relaxed wakefulness with eyes closed is alpha activity (frequencies of 8–13 Hz). Lower arousal states of drowsiness are characterised by theta activity, a slower rhythm of 4–7 Hz. Slower frequencies of less than 4 Hz are seen in delta activity, associated with deep sleep and pathological states of abolished arousal. Overall, increasing levels of arousal are known to be associated with increasing frequency of electrical activity in the cerebral cortex, which in turn correlates with a reduction in the extent and degree of cortical synchronisation.

Arousal is not the only component of consciousness, as it is common knowledge that when we are awake our consciousness populates with a wide range of subjective experiences: awareness of the environment and the self, as well as sensations, emotions, thoughts, memories, and other familiar psychological processes (Zeman 2001). Subjective experiences are associated with activation patterns within specific cortical areas. For example, awareness of visual movement is associated with activity in visual area V5, whereas awareness of colour correlates with activity in visual area V4 (Zeki et al. 1991). Clinical observations have consistently shown that focal cortical lesions in these areas result in akinetopsia and achromatopsia (Zeki 1990, 1991). The structural and functional connections between these areas and other regions, especially within the limbic system, plays an important role in determining the emotional salience of both externally- and internally-generated experiences.

The identification of two different components of consciousness (arousal, or level of consciousness, and awareness, or contents of consciousness) prompted a multidimensional approach to the scientific study of consciousness, through the development of a bi-dimensional theoretical model for the assessment of conscious states (Cavanna et al. 2011a; Laureys et al. 2004). In most physiological and pathological conditions there is a direct correlation between the level and the contents of consciousness, which can be graphically represented as a biaxial diagram with a linear correlation between arousal and awareness (Fig. 15.1). As

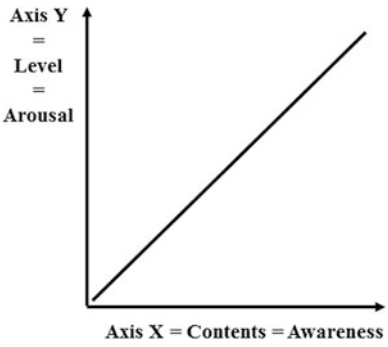

Fig. 15.1 Bi-dimensional model of consciousness: level of arousal (axis Y) *versus* contents of awareness (axis X)

it can be expected, decreased levels of arousal result in a corresponding decrease in the extent and vividness of the subjective contents of consciousness.

However the interaction between the level of arousal and the subjective contents of consciousness is more complex than expected, as there are a few instances in which subjects can report vivid experiences despite being unresponsive (absent level of consciousness). This is a common occurrence, for example, in the dream-state seen in 'rapid eye movement' (REM) sleep (Frith et al. 1999), which clearly demonstrates that the contents of consciousness can vary independently of the level of consciousness (Zeman 2001; Portas et al. 2004b; Laureys 2005). Interestingly, functional neuroimaging studies have shown that regional cerebral blood flow during REM sleep increases at the level of the rostral brainstem, thalamus and limbic regions, whereas it decreases in the prefrontal and posterior cingulate cortices, as well as in some regions of the parietal cortex (Maquet et al. 1996). The opposite situation, whereby relatively high levels of arousal are associated with poor awareness (decreased contents of experience), has been reported, for example, in limbic status epilepticus (Monaco et al. 2005), a condition which resembles somnambulism or sleepwalking. Both patients in limbic status epilepticus and sleepwalkers are known to be able to carry out simple actions like walking in a 'zombie-like', automatic fashion while showing no awareness of their behaviours (Broughton 1968).

The assessment of consciousness has crucial implications in terms of diagnosis, treatment and prognosis for patients with neurological conditions which result in chronic or transient alterations of consciousness. The clinical relevance of understanding the neurobiological mechanisms responsible for the specific alterations of consciousness induced by different pathologies cannot be underestimated, and it is not surprising that the international neuroscientific community has developed a particular interest in consciousness studies. Over the last few years, the level-*versus*-contents bi-dimensional model has increasingly been used to assist the clinical assessment of patients affected by pathologies of consciousness. Specifically, the implementation of the bi-dimensional model facilitates the standardised assessment of the different components of consciousness and the identification of correlations with neurobiological substrates.

15.3 Chronic Alterations of Consciousness: Coma, Vegetative State, and Minimally Conscious State

15.3.1 Coma

Patients in coma are in a state of complete unconsciousness characterised by absent arousal and lack of awareness of themselves or their surroundings (Young 2009). The clinical assessment relies on the use of specific instruments, such as the Glasgow Coma Scale, which conventionally defines coma as a failure to open eyes in response to verbal command, perform no better than weak flexion, and utter only unrecognisable sounds in response to pain (Bateman 2001). Coma is caused by structural brain lesions at the level of the ascending reticular activating system or brain pathologies resulting in widespread cortical dysfunction (bilateral hemispheric or white matter injuries, focal lesions affecting the ponto-mesencephalic tegmentum or paramedian thalami) (Laureys et al. 2004). Functional neuroimaging studies have consistently shown a marked (50–70 %) reduction in grey matter glucose metabolic rate in patients who suffered severe hypoxia or traumatic brain injuries resulting in a coma (Bergsneider et al. 2000; Hattori et al. 2003).

15.3.2 Vegetative State

The transition from coma to vegetative state, a state of 'wakeful unawareness', is typically marked by restoration of the sleep-wake cycle. Vegetative state is often clinically described as loss of cortical function with preserved activity of the brainstem and connected subcortical structures (Adams et al. 2000). The functional preservation of these structures is thought to maintain arousal and autonomic functions (Maquet et al. 1997). Patients in vegetative state may be aroused by painful or salient stimuli and present with stereotyped responses such as grimaces, in the absence of conscious perception or deliberate action (Zeman 2001; Maquet et al. 1997). Despite the presence of the hallmarks of arousal, patients who receive a correct diagnosis of vegetative state show no signs of being aware of themselves or their environment (Owen and Coleman 2008). In fact, Jennett and Plum's original definition of vegetative state referred to '*an organic body capable of growth and development but devoid of sensation and thought*' (Jennett and Plum 1972). Medical care, including artificial hydration and nutrition, can allow prolonged survival, as in 'permanent vegetative state' (Laureys 2005). Functional neuroimaging studies of patients in vegetative state have shown global brain metabolic activity decreases to around 50 % of normal levels (Laureys et al. 1999), a similar decrease to that seen in subjects under general anaesthesia or in deep sleep. Direct comparisons of brain activity levels between patients in vegetative state and healthy controls in a resting conscious state have identified metabolic dysfunction in a wide fronto-parietal network, encompassing higher-order associative cortices: lateral and medial frontal

regions, parieto-temporal and posterior parietal areas, including key mesial regions such as the posterior cingulate and precuneal cortices (Laureys 2005). Compared to healthy controls, patients in vegetative state demonstrate impaired functional connectivity in both cortico-cortical and cortico-thalamo-cortical pathways (Laureys et al. 1999, 2000a). Interestingly, the results of a functional neuroimaging study showed that pain stimuli from electrical stimulation resulted in activation in the midbrain, contralateral thalamus, and primary somatosensory cortex of patients in vegetative state (Laureys et al. 2002). However, in contrast to control subjects, higher-order areas of the pain matrix (secondary somatosensory, insular, posterior parietal and anterior cingulate cortices) did not show any activation (Laureys 2005). Similar results were seen with Studies of the brain correlated of auditory stimulation in patients in vegetative state yielded similar findings: the stimulation resulted in activation of the primary auditory cortices, whereas higher-order associative areas remained silent and functionally disconnected (Hattori et al. 2003; Laureys et al. 2000b; Boly et al. 2004; Bernat 2006).

15.3.3 Minimally Conscious State

Patients in minimally conscious state can show similarities to patients in vegetative state, with the important distinguishing feature that they show limited yet clear evidence of awareness, on a reproducible or sustained basis. Specifically, a number of behaviours can be demonstrated by patients in minimally conscious state, ranging from the ability to follow simple commands to the expression of gestural or verbal yes/no responses, or even intelligible speech and simple, yet purposeful, actions which are qualitatively different from reflex actions. Recovery from the minimally conscious state is defined as the ability to communicate or use objects functionally (Giacino et al. 2002). Contrary to vegetative state, in minimally conscious state a limited level of awareness can be demonstrated, though not at a level that would be expected from a healthy individual at the same level of arousal. Although the overall cerebral metabolism in minimally conscious state is comparable to the one observed in vegetative state (Maquet et al. 1997), the precuneus and posterior cingulate cortex of patients show a level of metabolism which is higher than in vegetative state (Phillips et al. 2011). In fact, auditory stimulation to patients with minimally conscious state results in activation of auditory associative areas, in addition to primary auditory cortices, suggesting the occurrence of more complex information processing (Boly et al. 2004).

15.4 Transient Alterations of Consciousness: Epileptic Seizures

15.4.1 Generalised Seizures

Transient alterations of consciousness characterise the clinical phenomenology of different types of epileptic seizure, and are of crucial importance for the clinical assessment of the ictal state. Specifically, the degrees of alterations in both the level and contents of consciousness depend on the differential involvement of brain structures. Over the last decade a set of psychometric instruments have been specifically developed to assist the clinical assessment of alterations of consciousness during epileptic seizures (Johanson et al. 2011; Nani and Cavanna 2014). Instruments like the Ictal Consciousness Inventory, Consciousness Seizure Scale, and Responsiveness in Epilepsy Scale have proven useful in assisting clinicians in the difficult task of systematically assessing the ictal conscious state across different seizure types (Cavanna et al. 2008a; Arthuis et al. 2009; Yang et al. 2012).

Generalised seizures (convulsive seizures, including generalised tonic-clonic seizures, and absence seizures) result in complete 'black-outs', with simultaneous impairment of the both the level and the contents of consciousness (Cavanna and Monaco 2009; Cavanna et al. 2009; Cavanna and Ali 2011a; Mann and Cavanna 2011; Blumenfeld 2012). The dramatic clinical phenomenology of generalised tonic-clonic seizures is characterised by a tonic phase (rigid stiffening of the limbs), followed by a clonic phase (the actual convulsions), lasting for up to two minutes and typically followed by post-ictal confusion and complete amnesia. The results of ictal electroencephalographic studies have shown widespread, low-voltage, fast or polyspike activity during the tonic phase, followed by polyspike-wave activity in the clonic phase, and generalised suppression in the post-ictal phase. Neuroimaging studies using single-photon emission computerised tomography and positron emission tomography in patients with either focal seizures with secondary generalisation or tonic-clonic seizures induced by electroconvulsive therapy have shown substantial blood-flow changes. These include bilateral increases in blood flow in the lateral fronto-parietal cortex, medial parietal cortex, thalamus and upper brainstem, coupled with ictal decreases in the activity of the medial frontal cortex and anterior cingulate cortex (Cavanna and Monaco 2009; Cavanna et al. 2009; Cavanna and Ali 2011a; Mann and Cavanna 2011; Blumenfeld 2012; Paige and Cavanna 2013; Takano et al. 2007).

Similarly to convulsive seizures, absence seizures are characterised by complete loss of consciousness in terms of both level and contents. Patients typically display staring and unresponsiveness, with occasional eyelid fluttering or mild myoclonic spasms, lasting for a few seconds. Both onset and termination are abrupt, and patients tend to be amnestic for their transient 'loss of contact' with the external environment (Bayne 2011). This seizure type is most commonly seen in childhood absence epilepsy and its electroencephalographic correlates are generalised spike-wave discharges at the frequency of 3–4 Hz, lasting for up to 10 s (Gibbs et al. 1935).

Most studies with simultaneous electroencephalography and functional magnetic resonance imaging during absence seizures have shown characteristic changes in brain activity in association with ictal loss of consciousness: increased activity in the thalamus and decreased activity in the medial frontal cortex, medial parietal cortex, anterior cingulate cortex, posterior cingulate cortex and lateral parietal cortex, as well as a mixture of increased and decreased activity in the lateral frontal cortices (Cavanna and Monaco 2009; Cavanna et al. 2009; Cavanna and Ali 2011a; Mann and Cavanna 2011; Blumenfeld 2012; Seri et al. 2011; Bagshaw et al. 2014). Of note, regional activations can begin in the medial frontal and parietal cortex up to 10 s before the electroencephalographic onset of the absence seizure, and can be followed by complex changes in both cortical and subcortical activity, which cannot be measured by the standard haemodynamic-response function used for conventional functional magnetic resonance imaging (Bai et al. 2010).

15.4.2 Focal Seizures

Among various focal (or partial) seizure types, temporal lobe seizures are known to be associated with qualitative changes in the contents of ictal consciousness, encompassing a wide range of experiential phenomena (Picard and Craig 2009). The level of ictal consciousness, as measured by patients' responsiveness, can also change: the traditional distinction between complex and simple partial seizures depends on whether the level of consciousness is compromised ('complex partial seizures') or not ('complex partial seizures') (Cavanna and Ali 2011b; Ali et al. 2012). The investigation of the neurophysiological and neuroimaging correlates of ictal experiential phenomena induced by temporal lobe seizures has shed initial light on the neural correlates of seizure-induced alterations of the contents of consciousness, the so-called 'epileptic qualia' (Monaco et al. 2005; Alvarez-Silva et al. 2012; Hanoğlu et al. 2014). 'Qualia' is a Latin word used by philosophers of mind to refer to the qualitative features of subjective experiences, i.e. 'what it feels like' to have a particular experience, such as a perception, a memory, an emotion. Philosopher of mind Daniel Dennett famously described the concept of qualia as '*an unfamiliar term for something that could not be more familiar to each of us: the ways things seem to us*' (Dennett 1988).

The most commonly reported alterations of the contents of consciousness during temporal lobe seizures include perceptual, dysmnesic, affective and cognitive phenomena (Johanson et al. 2008a, b; McCorry and Cavanna 2010; Mula and Monaco 2011). Structured visual hallucinations, memory flashbacks, déjà-vu, and ictal fear are among the most commonly reported ictal subjective experiences (Picard and Kurth 2014; McCrae and Whitley 2014). Patients with temporal lobe epilepsy sometimes report ictal dissociative symptoms (transient derealisation and/or depersonalisation), occasionally accompanied by autoscopy and out-of-body experiences (Medford 2014). Ictal and peri-ictal cognitive changes often go unrecognised, despite their relevance to focal seizure classification: for example,

Fig. 15.2 Neurosurgeon Wilder Penfield (1891–1976), pioneer of consciousness studies in epilepsy

forced attention and ictal dysphasia can affect the assessment of the patients' responsiveness during seizures, whereas ictal and post-ictal amnesia can affect their retrospective recall of ictal experiential phenomena (Zeki 1990; Johanson et al. 2003). Electroencephalographic recordings during temporal lobe seizures associated to altered contents of consciousness are characterised by epileptiform discharges over the temporal lobe and the relationship between temporo-limbic activity and experiential phenomena was first documented by Wilder Penfield's pioneering work in epilepsy surgery (Fig. 15.2). Specifically, Penfield's experiments showed that subjective experiences similar to 'epileptic qualia' could be elicited by electrical stimulation of temporal lobe structures (Penfield and Rasmussen 1950).

An altered level of consciousness (arousal), assessed as impaired responsiveness, is the defining feature of complex partial seizures, which have been recently reconceptualised as 'focal seizures with impairment of consciousness' in a report from the International League Against Epilepsy (Berg et al. 2010). Ictal behavioural changes associated with complex partial seizures encompass arrest of voluntary behaviour, staring, and possible automatisms, such as chewing and lip smacking, typically lasting for a few minutes. Post-ictal confusion and amnesia are commonly reported (Mula 2014).

The results of neurophysiological and neuroimaging studies have consistently shown that alterations of consciousness during temporal lobe seizures correlate with large-amplitude slow electroencephalographic activity and neuroimaging signal decreases in fronto-parietal association networks (Cavanna et al. 2011b; Bagshaw and Cavanna 2011; Englot et al. 2010). These observations suggest an important role for extra-temporal structures in determining the nature and extent of ictal impairment of the level of consciousness in complex partial seizures of temporal origin ('network inhibition hypothesis') (Englot and Blumenfeld 2009). The abnormal neuronal discharges characterising temporal lobe seizures originate in the temporal lobe and can spread along both cortical and subcortical networks. The complex alterations of ictal consciousness caused by temporal lobe seizures can also be understood within the theoretical framework of the 'global workspace' theory of consciousness, according to which information processing accesses consciousness through the synchronised activity of neuronal modules linked to widespread brain

networks. According to this model, thalamo-cortical functional connectivity plays a crucial role in this dynamic system, as the deactivation of thalamic structures, along with fronto-parietal associative cortices, can impair conscious processing of information by preventing it from entering the global workspace (Bartolomei and Naccache 2011; Bartolomei et al. 2014).

15.5 The 'Consciousness System' and the 'Default Mode Network'

Multiple lines of evidence show that the neural correlates of the pathologies of consciousness converge on an overlapping set of interconnected cortical-subcortical networks, which have been collectively referred to as the 'consciousness system' (Blumenfeld 2011, 2012; Cavanna et al. 2013b). The cortical components of the consciousness system include the medial frontal, anterior cingulate, posterior cingulate, and medial parietal (retrosplenial and precuneal) cortices on the medial surface, and the lateral frontal, orbitofrontal, and lateral temporo-parietal association cortices on the lateral surface, possibly plus from portions of the insula. The subcortical components of the consciousness system are the basal forebrain, hypothalamus, thalamus, and upper-brainstem activating systems, with a possible contribution from portions of the basal ganglia, cerebellum, and amygdala.

Findings from neurophysiological and neuroimaging studies of pathologies of consciousness have consistently shown that involvement of the main components of the consciousness system result in alterations in the level of consciousness, whereas temporo-limbic structures appear to be involved in the processing of emotional aspects of the contents of consciousness. Of note, there is a considerable overlap between the consciousness system and the so-called 'default mode network', a highly integrated network that appears to sustain the level of consciousness and is characterized by selective deactivations in both chronic and transient alterations of consciousness (Danielson et al. 2011; Bagshaw and Cavanna 2013; Di Perri et al. 2014; Vanhaudenhuyse et al. 2010). A leading role in coordinating patterns of activation and deactivation within the default mode network seems to be played by the posteromedial parietal cortex (Cavanna and Trimble 2006; Cavanna 2007; Cavanna et al. 2008b; Cauda et al. 2010; Koch et al. 2016). As per the ongoing search for the neural correlates of consciousness (conceptualised as the minimum neural mechanisms sufficient for any one specific conscious percept), recent findings point towards a posterior cortical hot zone that includes sensory areas, rather than a fronto-parietal network involved in task monitoring and reporting.

The current goal of consciousness research is to reveal the neural basis of subjective experiences or qualia, which has traditionally relied on first-person perspective reports. More recent research approaches attempt to dissociate neural activity that gives rise to consciousness from the activity that enables the report: in particular, so-called 'no-report paradigms' have been implemented to study conscious experience

in the full absence of any report. Arguably, no-report paradigms have the potential to bring us closer to understanding the true neural basis of consciousness (Tsuchiya et al. 2015). Thus, despite conceptual difficulties and theoretical uncertainties, the last few years have seen neuroscientists entering the arena of consciousness studies to offer a key contribution towards the search for the neurobiological mechanisms underlying the whole spectrum of qualitative features of subjective experience (Searle 1998; Orpwood 2007; Monaco et al. 2011; Loorits 2014). For example, the 'integrated information theory' developed by neuroscientist Giulio Tononi provides a principled account of both the quantity and the quality of an individual experience (a quale, singular of qualia), and an algorithm to evaluate whether or not a particular physical system is conscious and of what (Tononi and Koch 2015). Beyond its theoretical appeal, the field of consciousness studies sheds light on aspects of brain function which can inform researchers and clinicians about the most promising avenues to develop effective treatments to improve health-related quality of life of patients with pathologies of consciousness.

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Chapter 16
EEG Assessment of Consciousness Rebooting from Coma

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Abstract The bi-dimensional arousal-awareness operational framework of defining consciousness assumes a graded level of both arousal and awareness. At the lower end of both the arousal and awareness scales is coma, defined as a state of unresponsiveness, in which a patient cannot be awaken. Recovery from coma following brain injury occurs through a sequence of disorders of consciousness (DOC) ranging from unresponsive wakefulness syndrome (UWS)/vegetative state (VS) which shows no signs of awareness to minimally conscious states (MCS) from which consciousness can emerge. The graded consciousness recovery parallels scales of brain injury severity suggesting that consciousness recovers by "turning on" hierarchical services. This sequence resembles a computer "booting" process, which may "hang" at a specific "intermediate levels of consciousness" such as

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UWS/VS or MCS. The recovery sequence can be assessed by electroencephalography (EEG), a large-scale measure of fluctuations in electrical activity of the brain. Resting state EEG assesses the graded recovery of brain oscillations from isoelectric line to burst-suppression (BS) to EEG slowing to wakefulness alpha activity and faster rhythms. Given that some degree of "connectivity" is required for consciousness, the assessment of DOC can be improved by testing the EEG in controlled stimulation paradigms addressing either the event related potential (ERP) or the event related changes in background EEG rhythms referred to as reactivity, which can be evoked even in BS. This grading of EEG changes provides the rationale for developing EEG indexes for monitoring the "booting process" during coma recovery to improve the diagnosis and prognostication of DOC.

Keywords Coma recovery • Disorders of consciousness • Resting state EEG • ERP • EEG reactivity • Burst-suppression • Perturbational complexity index • Bispectral index

16.1 Consciousness Recovery from Coma as a "Rebooting" Process

The bi-dimensional arousal-awareness operational framework of defining consciousness (Cavanna et al. 2011) assumes both a graded level of arousal – considered to reflect cortical "activation" towards wakefulness by the subcortical structures comprised in the "ascending reticular activating system" (ARAS) (Moruzzi and Magoun 1949) – as well as a lesser defined "graded level of awareness" clinically testable by the degree of behavioral "cooperative command following". At the lower end of both the arousal and awareness scales is coma (meaning "deep sleep" in Greek language), defined as a state of unresponsiveness, in which a patient cannot be awaken. Anatomically and physiologically ARAS has a redundancy of pathways and neurotransmitters which may explain why in patients surviving their brain injury, coma is usually transient (seldom lasting more than 3 weeks) (Young 2009). Recovery of arousal (eye opening) with partial recovery in awareness generates a broad spectrum of potentially evolving disorders of consciousness (DOC). The most severe form of DOC is the unresponsive wakefulness syndrome (UWS) – previously known as "vegetative state" (VS), thereafter referred to as UWS/VS (Laureys et al. 2010) – where patients show no overt signs of awareness. UWS/VS can be persistent or transition to minimal conscious states (MCS) (Giacino et al. 2002) ranging from simple behavioural evidence of awareness (such as ocular fixation) to voluntary behaviour (command-following) referred to as MCS minus and MCS plus respectively (Bruno et al. 2011). Patients can emerge from minimally conscious state (EMCS) while regaining communication abilities or object use.

The graded recovery from coma is comprised in neurological scales such as the "Glasgow Coma Scale" (GCS) and its variants (Teasdale and Jennett 1974; Chou

et al. 2017) designed to assess the severity of brain injury (both traumatic and non-traumatic – i.e. brain ischemia) by scoring impairment in eye, verbal, and motor responses. More recently, Coma Recovery Scale-Revised (CRS-R) aids prognostication by scoring arousal, auditory, visual, motor, oromotor and communication functions (Giacino et al. 2004). The proven diagnostic and prognostic value of the GCS and CRS-R provide the conceptual proof that the degree of consciousness impairment is related to the extent of brain dysfunction. Thus, the graded recovery from coma (deep to superficial) to UWS/VS to MCS (MCS minus to MCS plus) to EMCS suggests that components of hierarchical increasing complexities (decreasing redundancies) must be "activated" so that a conscious experience can emerge (Gerrard et al. 2014).

Experimental observations of recovery from unconsciousness not resulting from brain injuries such as general anaesthesia (Brown et al. 2011; Hudson et al. 2014), sleep (Massimini et al. 2009) and even epileptic absence seizures (Guo et al. 2016) corroborate the view that the consciousness recovers as a result of the "turning on" hierarchical services, a sequence much like a computer "booting" process. As such, in context of a brain injury/dysfunction, the boot process could theoretically "hang" at specific "intermediate levels of consciousness" (Bayne et al. 2016). This proposed computer booting analogy agrees with "information integration theory of consciousness" (Tononi 2004, 2008) which proposes that conscious experiences crucially depend on the brain's ability to integrate information, which is reflected by the extent of functional connectivity among different brain modules and thus allows for intermediate levels of consciousness. Nevertheless, other models of consciousness favor the view that consciousness is an "all-or none" phenomenon and question the existence of "levels of consciousness" (Bayne et al. 2016). Among those models, the "global neuronal workspace model of consciousness" proposes that the neural basis of consciousness is a "sudden self-amplifying process leading to a global brain-scale pattern of activity that occurs once ignited", i.e. when threshold has been crossed (Dehaene and Naccache 2001; Sergent and Dehaene 2004). As some theoreticians point out, the views may not necessarily be exclusive and it is quite possible that at the lower end of the scale, the recovery is graded (e.g. recovery of arousal systems) whereas at some threshold along the recovery the conscious awareness is ignited (Windey and Cleeremans 2015).

The graded recovery of consciousness can occur over several months and years. Although some time limits have been defined – e.g. UWS/VS is considered persistent when no improvement can be clinically detected for more than 3 or 12 months following non-traumatic or traumatic brain injury, respectively (Multi-Society Task Force on PVS 1994) – the poor predictability of recovery over such an extended time-span has important socio-economic consequences (Wijdicks and Wijdicks 2006). This fuels the quest for improving the early diagnosis, monitoring and prognostication of the comatose states. Although positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) are increasingly used in coma research, the most used neuroimaging method remains quantitative electroencephalography (EEG) (Bagnato et al. 2015; Blume et al. 2015; Gosseries et al. 2016; Koch et al. 2016). This chapter focuses on reviewing established and emerging EEG

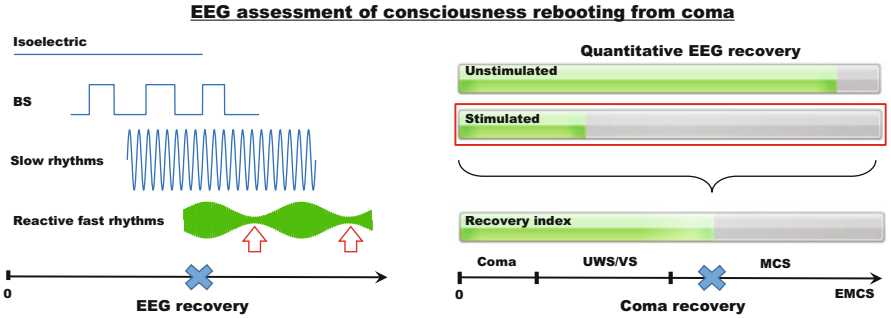

Fig. 16.1 EEG assessment of consciousness rebooting from coma. Recovery from coma following brain injury occurs through a sequence of disorders of consciousness (DOC) ranging from unresponsive wakefulness syndrome (*UWS*)/vegetative state (VS) which shows no signs of awareness to minimally conscious states (*MCS*) from which consciousness can emerge (*EMCS*). The graded consciousness recovery parallels scales of brain injury severity suggesting that consciousness recovers by "turning on" hierarchical services, a sequence much like a computer "booting" process, which may "hang" at a specific "intermediate levels of consciousness" such as UWS/VS or MCS. The recovery sequence can be assessed by electroencephalography (EEG), a large-scale measure of fluctuations in electrical activity of the brain. As illustrated in the left panel, resting state EEG recovers from isoelectric line to "binary" burst-suppression (*BS*) patterns to slow rhythms (i.e. <4 Hz) to fast rhythms which are reactive to external stimulation (*arrows*). The panel at right illustrates the assessment of a specific time-point of recovery (*X*) using quantitative EEG methods, in both unstimulated (i.e. resting-state) and stimulated paradigms (i.e. ERP and reactivity). Progress bars (top) indicate that stimulated EEG methods may be more sensitive to detect consciousness recovery than unstimulated methods. In the future, such paradigms may be combined in a single EEG index for monitoring the "booting process" during coma recovery (lower progress bar) to improve the diagnosis and prognostication of DOC

measures which showed clinical value in assessment of coma recovery, and pleads for the rationale of deriving a unique EEG index of coma recovery, equivalent to a progress indicator of the "booting process" in the presented computer analogy (Fig. 16.1).

16.2 Brain's Electrical Activity Assessed by Quantitative EEG

EEG is a non-invasive neurophysiological imaging technique that permits to record with millisecond temporal resolution the electrical potential fluctuations resulting from brain activity. The EEG signal results predominantly from synaptic activity (Buzsaki et al. 2012) of specially organized populations of cortical neurons (pyramidal cells) which extend a long (apical) dendrite perpendicular to the cortex (Lopes da Silva 2010). Excitation of the dendrites creates an extracellular voltage that is more negative (sink) than the cell body sitting deeper in the cortex (source) and this spatial separation generates an electrical dipole. The potential recorded by

a surface EEG electrode results from volume conduction through the brain, skull and scalp of a "source dipole" resulting from the summated activity of a network of thousands of parallel neuronal dipoles that are activated simultaneously i.e. in synchrony (Jackson and Bolger 2014). It should be noted that fluctuations in the momentary dipoles recorded by EEG result from relative changes in activation of different excitatory and inhibitory neurons within the brain although it is not per se an indication of either excitation or inhibition so that EEG description focuses on synchronizing/desynchronizing features which imply a certain degree of connectivity. Furthermore, it should also be noted that the electro-magnetic field is defined in terms of the force it exerts, like the other three fields in nature physics uses to describe reality (gravitational, strong, and weak). The presence of a time-varying electro-magnetic force associated with the brain activity has spawned various interest for electro-magnetic mind theories (Liboff 2016), surges of EEG in near-death experiences (Borjigin et al. 2013) or deep levels of coma "beyond the isoelectric line" (Kroeger et al. 2013). These interesting phenomena are considered outside the scope of this review since EEG oscillations persist in unconsciousness.

The resting scalp EEG voltages typically oscillate with amplitudes up to about 100 μV and frequencies up to about 80 Hz, although higher frequency waveforms such as ripples and high frequency oscillations can be recorded in pathologic situations (Usui et al. 2010; Worrell 2012; Zelmann et al. 2014). The oscillatory nature of the EEG reflects synchronous rhythms at preferred frequencies within thalamocortical networks (Steriade et al. 1993) arising from cooperation of both network and membrane intrinsic properties (Buzsaki et al. 2012). Nevertheless, attempting to localize the cortical oscillatory "source" from surface EEG is mathematically difficult, because even with "high density" EEG recordings (Klem et al. 1999) the "inverse problem" remains poorly specified (Grech et al. 2008) leading to multiple probable solutions (Uhlirova et al. 2016). In addition, experimental work in animals, and, more recently intracortical EEG recordings in humans, revealed that different sources may oscillate at similar frequencies and may have different significance in wakefulness and sleep (Lopes da Silva 2010). Although the reinstatement of sleep-wake cycles is characteristic for the emergence from coma to VS/UWS, the sleep-related EEG changes in DOC remain poorly understood (Cologan et al. 2010; Blume et al. 2015). Therefore, studies on resting EEG in DOC are typically carried out in states of behavioral wakefulness, although fluctuations in vigilance during wakefulness of MCS patients are not typically distinguished (Piarulli et al. 2016).

For operational simplicity, the human EEG rhythms have been summarized in five canonical frequency bands: delta (<4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz) and gamma (30–80 Hz) which are applied to both physiologic wakefulness and sleep as well as pathologic states. The typical analysis of EEG rhythmicity relies on quantification of band "powers" in the frequency domain, resulting from power density spectra of selected "stationary" epochs estimated by fast Fourier transform methods (Muthuswamy and Thakor 1998). This approach became known as "quantitative EEG" (Azabou et al. 2017) for distinction with the standard EEG, which relies on visual recognition of specific "EEG patterns" – e.g. "rhythmic delta waves" (Brenner 2005) from which graded scales can also be

derived (Synek 1988; Young et al. 1992) with good prognostic value, especially in the early stages of coma (Azabou et al. 2015). The distinction is important because numerical methods have their own limitations, i.e. in spectral analysis, even when using advanced multi-taper methods (Babadi and Brown 2014; Prerau et al. 2017), the delta power may be non-zero even when no "delta waves" can be identified in the EEG. Furthermore, coma and post-comatose states occurring in context of brain lesions could occasionally lead to localized pathologic rhythmic delta frequency activities both epileptic and non-epileptic (Trinka and Leitinger 2015) which may not necessarily abolish consciousness (Vuilleumier et al. 2000).

This chapter concentrates on assessing large-scale oscillations, which offer a global representation of consciousness processes (Schiff et al. 2014). Apart from spectral quantification of rhythmicity, other signal processing methods have been used for quantitative analysis of EEG. One example is the "microstate" analysis which considers the global brain EEG as a sequence of a few non-overlapping classes that persist in the sub second-range (Koenig et al. 1999) and could potentially reflect "atoms of thought" (Van De Ville et al. 2010). Changes in microstate occurrence and duration were found with loss of consciousness in sleep (Cantero et al. 1999) and DOC (Fingelkurts et al. 2012) although their potential in coma recovery remained largely unexplored as the primary research interest in microstates has been directed to neuropsychiatric disorders (Khanna et al. 2015). Other analysis strategies that aim to describe physical/statistical properties of the signals and their relationships gain increasing attention in DOC, such as the information dynamics, symbolic dynamics, measures of causal relationships, and measures of network dynamics derived from graph theory (Rapp et al. 2015). These EEG "complexity" measures have been extensively investigated in connection with monitoring general anaesthesia i.e. decreasing entropy measures with increasing anaesthetic concentration (Palanca et al. 2009; Liang et al. 2015) showing some clinical value (Chhabra et al. 2016), and are now investigated in DOC (Gosseries et al. 2011).

Conceptually, the EEG represents the summated activity of stimulus processing and default activities. As such, the EEG can be assessed in either resting state EEG paradigms (unstimulated) or stimulation paradigms in which external stimuli (of different complexities) are used to evoke controlled changes in EEG (Fig. 16.1).

16.3 Recovery of the Resting (Unstimulated) EEG

Resting wakefulness EEG, typically recorded with eyes closed, is characterized by a predominant oscillation in the alpha band, especially over the visual cortex – possibly reflecting cortical inhibition of visual input for favoring performance of internal tasks (Klimesch et al. 2007). "EEG slowing" (with increasing amplitude due to increased synchrony) from alpha to theta and then to delta rhythms occurs in transition from wakefulness to slow-wave sleep (SWS) where consciousness is lost (Siclari et al. 2013). In fact, EEG recording of repeated high-amplitude (>75 μV) delta waves remains an effective indicator of loss of consciousness in humans

(Murphy et al. 2011). Experimental studies suggested that synchronized delta waves emerge with occurrence of "slow oscillation" of cortical neurons between depolarized up-states and hyperpolarized down-states about every second (Timofeev et al. 2000) which coalesce the subcortical delta bursts resulting from a hyperpolarized thalamus (Nita et al. 2003; Steriade 2006) e.g. due to excessive subcortical inhibition (Schiff 2009), a decreased arousal drive though the ARAS (Moruzzi and Magoun 1949) or deafferentation in comatose states (Fernandez-Espejo et al. 2011).

At extreme levels of cortical deafferentation, such as following thalamectomy, undercutting, and complete gyrus isolation in experimental animals (Kristiansen and Courtois 1949) and after a variety of lobotomy operations in man (Henry and Scoville 1952), when the connectivity within the cortical networks falls below a certain threshold (Timofeev et al. 2000; Lukatch et al. 2005), the oscillatory EEG pattern is replaced by a discontinuous pattern comprised of bursts of high-amplitude EEG oscillations on a "flat" background referred to as burst-suppression (BS) (Swank and Watson 1949). The bursts emerge from cortical "generators" (Hughes 1986) and are limited by metabolic availability (Ching et al. 2012). Similar BS patterns can be observed as a result of a "functional" deafferentation during anaesthesia. With increasing concentrations of general anaesthesia, the suppression periods become increasingly longer progressing to isoelectric line (Fig. 16.1). The process is fully reversible at cessation of anaesthesia (Rampil et al. 1988). In comatose patients after cerebral ischemia/hypoxia, persistence of BS or isoelectric line at 24 h is considered a predictor of poor outcome without false positives (Hofmeijer and van Putten 2016) although this may change with increasing use of therapeutic hypothermia (Greer et al. 2014). Nevertheless, it should be noted that even in the context of brain insults, BS and even isoelectric EEG are potentially reversible conditions e.g. as indicated by recovery from ischemic electrocortical suppression (Niedermeyer et al. 1999; Ilie et al. 2006b). In this case, the underlying functional disconnection was attributed, at least in part, to alterations in synaptic transmission by accumulated adenosine (Ilie et al. 2006a, 2009) which also contributes to EEG slowing after continuous EEG oscillations are restored (Constantinescu et al. 2011). It should be noted that both BS and delta EEG, although distinct physio-pathologically, are associated with loss of consciousness at different levels.

Although altered alpha rhythms have been found in cognitive impairment (Huang et al. 2000), alpha EEG does not directly reflect awareness, as it can occur in unconscious patients with severe post-anoxic coma – "alpha coma" (Westmoreland et al. 1975), a variant of "theta coma" (Berkhoff et al. 2000) which is more commonly associated with MCS (Schiff et al. 2014). Thus, recovery from BS to slow continuous EEG to alpha (Fig. 16.1) clinically correlates with recovery of arousal from coma to UWS/VS, however, it remains in itself a poor indicator of awareness in MCS (Schiff et al. 2014).

The recent search for a "consciousness rhythm" is being directed towards rhythms faster than alpha. The beta rhythm, at least its lower frequency components, is the prominent rhythm of the corticospinal system where it probably serves an inhibitory function. As the occipital alpha rhythm is desynchronized during attentive wakefulness (e.g. at eye-opening) – historically known as "EEG activation"

attributed to ARAS (Moruzzi and Magoun 1949) – also the beta rhythm is desynchronized during voluntary movements, or even cues that predict the need for a voluntary movement (Pfurtscheller and Lopes da Silva 1999). Cortical beta activity also synchronizes with electromyographic (EMG) oscillations, as evidenced in the "EEG-EMG coherence" (Chakarov et al. 2009). In addition, specific EMG changes were found in loss of consciousness associated with seizures (Conradsen et al. 2013; Beniczky et al. 2014, 2015). As such, occurrence of the beta rhythm could be useful in assessing motor recovery after brain lesions (Tecchio et al. 2005) although it is less informative about recovery of consciousness, even when present in MCS (Schiff et al. 2014). In recent years, gamma synchronization around 40 Hz (Gold 1999), which is increased by visual hallucinogens (Don et al. 1998), was proposed as a marker of conscious processes based on experiments on visual consciousness in cats (Gray et al. 1989) as well as in humans (Rodriguez et al. 1999; Melloni et al. 2007). Nevertheless, due to its small amplitude, recording gamma EEG is technically challenging in awake human studies. Furthermore, studies under general anesthesia could also reveal synchronous gamma activity (Murphy et al. 2011) which casts doubts on its specificity to conscious processes (Koch et al. 2016).

Different neurobiological models of consciousness such as the "global neuronal workspace model" (Dehaene and Naccache 2001; Sergent and Dehaene 2004) and the "information integration theory" (Tononi 2004, 2008) agree that a certain level of brain connectivity is necessary for conscious experiences. It is thus reasonable to suspect that "connectivity" within a certain EEG frequency band would bring additional value to the band power measurements in assessing recovery of consciousness, providing a unified insight into both arousal and awareness. Measuring connectivity between different EEG electrodes by spectral coherence is, however, technically questionable due to volume conduction artefacts. To account for this, more sophisticated methods like the imaginary part of coherency (Nolte et al. 2004) or phase lag index (Stam et al. 2007) were proposed. As such the MCS patients were found to have a larger connectivity in the alpha-theta bands than UWS/VS patients (Lehembre et al. 2012). Nevertheless, other studies in persistent UWS/VS patients have suggested a larger than normal alpha connectivity which could reflect a network reorganization years after the lesion (Varotto et al. 2014). More promise show EEG complexity measures that assess the directional information flow, like symbolic transfer entropy (STE) a surrogate marker of connectivity, which is theoretically better suitable to evaluate consciousness (Lee et al. 2015). Consistently, a recent study, found that STE was more decreased in UWS/VS than in MCS (Thul et al. 2016). The relevance of alpha/theta connectivity measures remains to be clarified especially that these frequencies seem to reflect the EEG activity of the default mode network (Fomina et al. 2015), which was found in neuroimaging studies to be the brains most globally connected network (Cole et al. 2010) while it's deactivation reflects impaired consciousness (Crone et al. 2011).

16.4 Recovery of the Stimulated EEG

Stimulation EEG paradigms have the potential advantage of assessing the brain function in controlled conditions. By mathematical averaging (Dawson 1954) of sufficient EEG changes time-locked to a repeating stimulus presentation, event related potentials (ERP) can be extracted with good signal-to noise ratio. The ERP is a sequence of positive (P) and negative (N) peaks, typically with amplitudes below 10 μV. For example, following presentation of the visual stimulus, the visual evoked potential (VEP) presents a large positive peak after around 100 ms, referred to as P100, which roughly corresponds to the arrival of the stimulus to primary visual processing areas in the occipital cortex. Similarly, ERPs evoked by other stimulus modalities like the somatosensory evoked potentials (SSEP) in response to peripheral nerve stimulation, and the brainstem auditory evoked potentials (BAEPs) show their first cortical components within 100 ms, and they are conventionally referred to as "short latency evoked potentials", or simply "evoked potentials" for distinction with later ERP components reflecting early cognitive processing which share similarities among different stimulus modalities and stimulus complexities (Chiappa and Ropper 1982a, b). Following brain injury, impairment of SSEP, the EP with the shortest latency to the cortex, is one of the strongest indicators of bad prognosis (Koenig et al. 2006; Oddo and Rossetti 2011; Endisch et al. 2015). Although in routine ERP studies, the focus is on EEG <100 Hz, it should also be noted that peripheral nerve stimulation also elicits high frequency oscillations >400 Hz, referred to as SEP-HFOs (Klostermann et al. 1999) which reflect both subcortical and cortical generators. These potentials were found to be attenuated during sleep (Halboni et al. 2000; Klostermann 2005) and enhanced by arousal (Gobbele et al. 2000; Restuccia et al. 2004). Although their persistence in resuscitated cardiac arrests appears to increase the prognostic value of SSEP in hypoxic encephalopathy (Endisch et al. 2015, 2016), the relationship between SEP-HFOs and consciousness remains poorly investigated.

In contrast to the simple repetitive stimulation required for EP, recording of "cognitive" ERP components relies on designing sequences of different types of stimuli, either in "passive" paradigms (without the need for subject's cooperation) or "active" task-based paradigms (i.e. requiring subject to mentally count a specific type of stimulus or press a button) which can potentially assess awareness (consciousness content). The contingent negative variation ERP (Walter et al. 1964), an electro-cortical sign of sensori-motor association (Walter 1968) as well as the motor readiness potential (Deecke et al. 1976; Schultze-Kraft et al. 2016) which fuels debates about the conscious "free will" and agency (Libet et al. 1983; Klemm 2010) proved little utility in DOC assessment. Two components received most attention: the mismatch negativity (MMN) typically occurring at 150–200 ms (Naatanen et al. 1978; Kremlacek et al. 2016) and the P300 (Sutton et al. 1965; Picton 1992; Polich 2007). Both MMN and the early component of the P300, referred to as P3a, can be evoked passively when odd stimuli are presented in a sequence (many to one) referred to as the "odd ball" paradigm i.e. such as a higher pitch tone in a low pitch

tone series (Ritter and Vaughan 1969). While the MMN occurs "automatically" in conditions of an unexpected deviant – distractor- (novelty) (Khouri and Nelken 2015), some degree of attentive discrimination (typically associated to wakefulness) is required for P300, although this does necessarily require subjects cooperation, as it is the case of the early P3a component (Polich 2007). Detection of MMN and P3a were found to be good predictors of recovery (Daltrozzo et al. 2007). Nevertheless, studies in DOC using salient stimuli, like the subject's own name (SON) (Perrin et al. 2006; Fischer et al. 2008) indicated that P3a does not in itself reflect recovery of consciousness and that some level of "automatic" semantic processing is at least partially preserved in non-communicative brain-damaged patients.

The utility of passive stimulation paradigms to reflect conscious attributes that differentiate between MCS and VS/UWS patients remains unclear, because the stimuli used (i.e. SON or simpler odd stimuli in a sequence of identical ones) might as well elicit automatic or even conditioned responses (i.e. automatic semantic processing or a conditioned orienting response to SON). The scientific attention has been directed to "active paradigms" aiming to detect "willful" modulations of EEG alone or in combination with passive stimulation paradigms. For example, in a SON task, the P300 responses were found to be larger when MCS patients were instructed to count their own name – regardless of behavioral confirmation – which improved distinction from VS/UWS (Schnakers et al. 2008b). Such changes could be attributed to the amplification of the late component of P300, referred to as the P3b (the "classical" P300) which is task-specific in conscious subjects (Polich 2007). Nevertheless, task-irrelevant stimuli do not trigger a P3b even when participants are clearly conscious of them, whereas stimuli that are not consciously detected can trigger a P3b questioning the value of P3b as a signature of consciousness (Koch et al. 2016).

A different approach than the ERP is to measure the changes induced by a stimulus in the "background" EEG rhythms, either stimulus time-locked or not (Fig. 16.1). Traditionally this was referred to as event-related desynchronization (ERD)/event-related synchronization (ERS) with research focus on the alpha rhythm and slower beta rhythms related respectively to integration of sensory information and motor behavior (Pfurtscheller and Lopes da Silva 1999). Such changes, falling now under the broader term of "EEG reactivity" (Admiraal et al. 2017) bear important similarity with "responsiveness" assessed in clinical coma recovery scales (Giacino et al. 2004), although it should be noted that un-responsiveness is not equivalent with unconsciousness (Sanders et al. 2012). This was apparent from fMRI studies showing that even a patient that was behaviourally diagnosed with VS/UWS was able to imagine to "play tennis" or "navigate through a house" upon instruction (Owen et al. 2006) leading to a non-behavioral MCS classification – abbreviated as MCS* (Vogel et al. 2013; Gosseries et al. 2016). By analogy, the same "active" stimulation principle (requiring subjects participation) was able to distinguish EEG spectral desynchronization in response to mental imagery in noncommunicative brain injured patients (Goldfine et al. 2011). In fact, assessment of reactivity by simple spectral methods was found to be sensitive enough to discriminate between SON uttered by unfamiliar and familiar voices (del Giudice

et al. 2014) whereas more advanced time-frequency analysis was able to distinguish among DOC (Fellinger et al. 2011). As such, there is a growing interest for further developing EEG reactivity measures for assessment of coma beyond spectral analyses (Hermans et al. 2016) to entropy measures (Thul et al. 2016).

16.5 Towards an EEG Index of Coma Recovery

EEG measures reviewed here support a graded recovery from BS to continuous EEG slowing to reactive alpha activity, which provides the rationale for developing an index of consciousness recovery (Fig. 16.1). Furthermore, the presence of a hierarchy indicates that such an index could be used as a surrogate measure of global brain impairment, although particular situations where small lesions in critical network hubs have a major impact on the recovery process cannot be excluded.

The feasibility of deriving a simple numerical index based on resting EEG to assess coma recovery was proven by the bispectral index (BIS). The EEG bispectrum analysis is developed to account for the fact that different brain oscillatory sources are not independent (e.g. are "phase coupled") (Schack et al. 2002) in agreement with the rhythm coalescence hypothesis (Steriade 2006), a view that is not comprised in the simple power spectrum analysis. Mathematically, EEG bispectrum quantifies non-linearities in the EEG due to interactions between frequency components, hence it is a function of 2 frequencies. BIS was introduced in an attempt to simplify the interpretation of the EEG bispectrum in monitoring of general anaesthesia (Sigl and Chamoun 1994). BIS index integrates a series of EEG parameters (features) to describe a specific EEG state: bispectral features at low frequencies, spectral features at high frequencies as well as time-domain methods to detect low-voltage suppressions (e.g. in BS) (Sigl and Chamoun 1994). Using multivariate statistical methods on EEGs of more than 5000 anaesthetised patients, a 100 point BIS scale was derived and implemented for monitoring the "depth of hypnosis during anaesthesia and sedation" (Sennholz 2000). Awake, unsedated individuals typically have a BIS value >97 while unconsciousness occurs when BS falls below 60. BIS below 30 signals linearly increasing burst suppressions towards a BIS of 0 at the isoelectric line (Bruhn et al. 2000). The BIS monitor was primarily intended to provide a simple sedation monitor for the EEG non-specialist (Riker et al. 2003). Subsequently, it became apparent that BIS could also be used to assess coma recovery after brain injury, where an empirically defined BIS cut-off value of 50 differentiated unconscious patients (coma or UWS/VS) from conscious patients (MCS/EMCS) with limited prognostic value (Schnakers et al. 2005, 2008a). As a purely statistical analysis method of resting EEG, the generalization of BIS, as well as of other resting EEG monitoring indexes (Kreuer et al. 2004, Kreuer and Wilhelm 2006) beyond "depth of anaesthesia" (Musizza and Ribaric 2010) sparks little enthusiasm (Zetterlund et al. 2016).

Theoretical models (Dehaene and Naccache 2001; Tononi 2004) agree that a global connectivity "glow" spread within the brain is required for conscious

experience (Noy et al. 2015). As previously discussed, resting connectivity methods cannot be readily applied to EEG. The "effective connectivity" (Friston 2011; Donos et al. 2016) of the brain can be assessed by quantification of passive perturbations in high-density EEG after transcranial magnetic stimulation (TMS) (Rosanova et al. 2012) as introduced in PET-TMS studies (Paus 2005). Briefly, the number of independently significant EEG "sources" contributing to the average artefact-free TMS-evoked potentials (over 300 ms) were estimated by inverse source modelling using the minimum norm estimate (Ilmoniemi et al. 1997) at significant changes in the global field power (Skrandies 1990) as employed in "microstate-analysis" (Lehmann et al. 1987). In patients in UWS/VS, TMS evoked local response involving few sources, similar to previous observations of unconscious sleeping or anaesthetized subjects. In contrast, in MCS patients, TMS triggered activations involved multiple sources over distant ipsilateral and contralateral cortical areas (Rosanova et al. 2012). Such a measure independent of the integrity of subcortical afferent and efferent pathways is particularly important in assessing non-communicative MCS/"locked-in" conscious patients (Bruno et al. 2011). The perturbational complexity index (PCI) (Casali et al. 2013) was introduced as a unique numerical index to quantify the number and distribution of sources contributing to the TMS-EEG responses, ultimately reflecting the brain's ability to integrate activity patterns. PCI is calculated by first compressing the TMS-EEG evoked spatiotemporal binary matrix of significant sources by the Lempel-Ziv algorithmic complexity index (Lempel and Ziv 1976) – a symbolic analysis distinct from STE – and subsequent normalization by source entropy (Kaspar and Schuster 1987) reflecting the total amount of significant activity. Although theoretically the PCI should be 1 for maximally complex patterns in the data, PCI measures in awake subjects could be as low as 0.4. In unconscious sleep, general anaesthesia and UWS/VS patients, PCI is typically below 0.3, while MCS patients typically have an intermediate PCI of 0.3–0.4 (Casali et al. 2013; Sarasso et al. 2014, 2015). In a recent validation study a PCI cut-off of 0.31 was found to distinguish consciousness irrespectively of behavioural responsiveness, age, gender, stimulation site, and presence of brain lesions (Casarotto et al. 2016).

While BIS and PCI proved useful for assessing "recovery of consciousness" they are not directly comparable with clinical coma assessment and prognostication scales such as GCS (Teasdale and Jennett 1974) or CRS-R (Giacino et al. 2004) which rely on behavioural reactions to different somatosensory stimuli. An early assessment of the extent of brain injury is particularly important in deep coma. Nevertheless, a BIS of 10 cannot distinguish between general anaesthesia and a terminal post-ischemic BS. Furthermore, PCI, although it has not been so far validated in BS coma, is designed to bypass the somatosensory pathways whose integrity assessed by SSEP was found to be most prognostic of critical injuries (Koenig et al. 2006).

It has been long known that SSEP evoked by peripheral nerve stimulation can still be recorded in BS anaesthetic coma (Allison et al. 1963) suggesting that in spite of the profoundly depressed level of consciousness, somatosensory stimuli may reach the cortex. Subsequent studies indicated that stimuli of different

modalities could reorganize the BS patterns in anaesthetic coma (Hartikainen et al. 1995a, b; Hudetz and Imas 2007). More recently it was suggested that BS may even represent a hyperresponsive brain state (Kroeger and Amzica 2007) during which even subliminal stimuli are able to evoke bursts (Yli-Hankala et al. 1993; Kroeger and Amzica 2007). Nevertheless, with stimulus repetition not all stimuli were able to evoke bursts (Jantti et al. 1998; Kroeger and Amzica 2007) even at nociceptive stimulation intensity (Rytky et al. 1999; Huotari et al. 2004) indicating that the "reactivity" of BS patterns reflected changes in brain function. These studies provided the rationale for developing a standardized "BS reactivity" measure for assessing the comatose brain. At surface EEG resolution, the BS patterns appear synchronous (Lewis et al. 2013; Moldovan et al. 2016) and therefore a representative binary BS pattern can be derived from multichannel EEG by global field power (Skrandies 1990) amplitude "thresholding" (Nita et al. 2016). The binary BS signal could then be used in calculation of EEG suppression ratios (SR) – measuring the fraction of time spent in suppression over 1 min epochs (Rampil et al. 1988, Rampil and Laster 1992) from 0% in continuous EEG to 100% in isoelectric line. A "BS reactivity" could therefore be calculated as the change in SR during repetitive stimulation (SR_{Stim}) from the corresponding SR prior to stimulation (SR_{Pre}) (Calin et al. 2014; Nita et al. 2016). Most encouragingly, a standardized index of BS reactivity by SR_{Pre}, measured using a routine photic stimulator setup, was correlated with the GCS scores in comatose patients of different aetiologies, thus being able to distinguish between injury severities at the same SR_{Pre} (Nita et al. 2016). This provides proof of concept that measures of EEG reactivity are also informative even in the deepest levels of coma. It is possible that the BS state provides access to the most basic, and thus most critical level of brain functioning, equivalent to the basic input/output system (BIOS) in the presented computer booting analogy. Further studies should be carried out to assess the prognostic value of BS reactivity measures.

Thus, EEG measures here strongly support that measures of stimulated brain reactivity, as an indicator of global rather than local connectivity (Donos et al. 2016) within the brain can be used to index consciousness recovery from very deep levels of coma such as BS. The quest for a unique EEG reactivity index of coma recovery that can monitor the whole "consciousness rebooting sequence" (Fig. 16.1) from the BIOS level reflected by BS to conscious wakefulness rhythms remains, however, open. A future neurophysiological index may combine different EEG reactivity metrics (Hermans et al. 2016) as well as other neurophysiological reactivity indexes derived from EMG (Beniczky et al. 2015) or electrocardiography (ECG) i.e. the analgesia nociception index derived from ECG heart rate variability (Ledowski et al. 2013; Constant and Sabourdin 2015). Furthermore, monitoring trends of change in such an index (i.e. speed of recovery), could hold more prognostic information than its value at any point in time (Swisher and Sinha 2016; Azabou et al. 2017).

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Chapter 17
Role of Feed-Forward Inhibition in Neocortical Information Processing: Implications for Neurological Disorders

Oleg V. Favorov, Olcay Kursun, and Mark Tommerdahl

Abstract A major well-documented feature of cortical functional organization is the presence of prominent broadly tuned feed-forward inhibition in the input layer 4, in which local layer 4 inhibitory cells receive direct thalamocortical input and in turn suppress responses of neighboring layer 4 excitatory cells to their thalamocortical drive, thereby sharpening their receptive field properties. Here we review the evidence that the presence of broadly tuned feed-forward inhibition in layer 4 turns local layer 4 domains into functional analogs of Radial Basis Function networks, enabling layer 4 to contribute importantly to sensory information processing as a *pluripotent function linearizer*: i.e., it performs such a transform of afferent inputs to a cortical column that makes possible for neurons in the upper layers of the column to learn and perform their complex functions using primarily linear operations.

Feed-forward inhibition is subserved by fast-acting basket cells and slow-acting neurogliaform cells, which rely on $GABA_A$ and $GABA_B$ receptor-mediated inhibition, respectively. Their respective contributions can be observed by measuring tactile stimulus detection threshold using step vs. ramp vibrotactile stimuli. The static (step) threshold reflects basket-mediated inhibition, whereas the difference between the static and dynamic (ramp) thresholds reflects neurogliaform-mediated inhibition. Our feed-forward inhibition metric, which is based on the static and dynamic detection thresholds, can provide significant insight about the neurological health of the cortical circuitry, given that neurogliaform cells are engaged in on-demand energy homeostasis of cortical networks through their local release of insulin. For example, we have found this metric to be below normal in adolescents with autism spectrum disorder, but highly elevated in type 2 diabetes. Maladaptive feed-forward inhibition can have significant downstream implications for cortical information processing, and our metric can potentially be an effective means for evaluating a number of cortical abnormalities.

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Keywords Cerebral cortex • Layer 4 • Feedforward inhibition • Basket cell • Neurogliaform cell • Simple cell • GABAB receptor • Insulin • Autism • Diabetes

17.1 Contribution of Layer 4 to Cortical Information Processing as a Pluripotent Function Linearizer

Cortical areas comprising the neocortex are organized anatomically and functionally into multiple intertwined information-processing streams (Felleman and Van Essen 1991). These streams build their functional properties incrementally, with the hierarchically higher-level cortical areas building their more complex functional properties on the simpler properties developed by the lower-level cortical areas (Iwamura 1998; Rauschecker 1998; Grill-Spector and Malach 2004). As a part of this functional elaboration, each successive cortical area receives its afferent input from the lower-level cortical areas and/or the thalamus and computes certain higher-order nonlinear functions over that input (Fig. 17.1a). The computed nonlinear functions are not predefined, but are learned from experience (Sur and Rubenstein 2005).

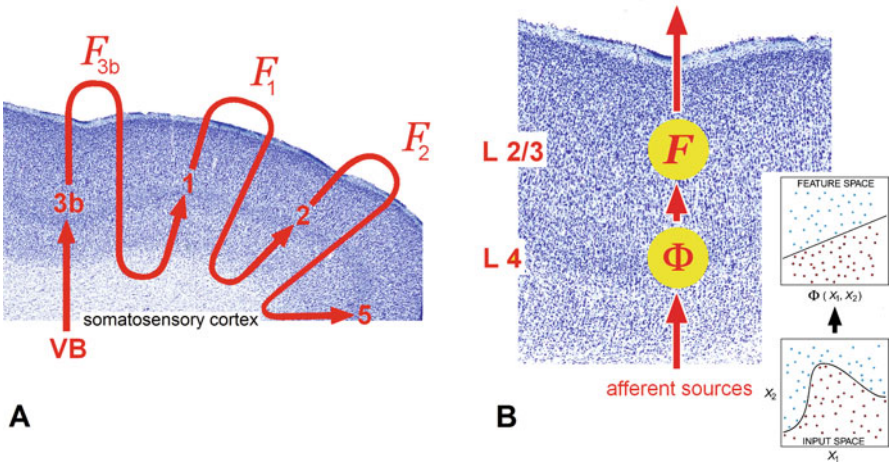

Fig. 17.1 Stages of cortical forward information processing. (**a**) Peripheral sensory input, delivered to the cortex via the thalamus, is passed through a series of cortical areas. Each area transforms its input from the preceding stage by computing a certain nonlinear output function *F* over it. This processing flow is illustrated on an example of the somatosensory cortex, comprising Brodmann cytoarchitectonic areas 3b, 1, 2, and 5, as well as somatosensory ventrobasal (VB) thalamic complex. (**b**) In each cortical area, the afferent input is first preprocessed in the input layer 4, which performs a function-linearization transform Φ, and then the output function *F* is computed in the upper cortical layers 2 and 3. The insert illustrates the function linearization strategy of transforming the input space into a "feature" space on an example of a classification problem. The curved decision boundary separating two classes of data samples (*little red* and *blue squares*) in the input space is made linear – and thus easier to learn – by mapping the data samples into a nonlinear transform of the input space

In the field of machine learning and pattern recognition, it is well appreciated that learning nonlinear functions is much more difficult than learning linear functions. To overcome such difficulties, in 1990s a highly effective strategy emerged for dealing with nonlinear problems, according to which the problem's input space should be transformed into a new higher-dimensional "feature" space, in which the problem becomes linear and thus more readily solvable with efficient linear techniques (Schölkopf and Smola 2002). The proven success of this "problem-linearization" strategy in machine learning naturally raises a question whether such a strategy might also be used by neocortex in its experience-driven development, during which it acquires its unrivaled ability to recognize in its sensory input patterns the perceptually and behaviorally significant features of high degrees of nonlinear complexity and abstraction (Kourtzi and DiCarlo 2006; Freedman and Miller 2007).

All cortical areas face essentially the same task of learning to compute their nonlinear functions over their afferent inputs and all of them can benefit from doing their own function linearizations. The principal initial recipient of the afferent input to a cortical area is its Layer 4 (L4). L4 converts that input into a new form and outputs that new form to the upper layers (Layers 2 and 3, or L2/3) of the same cortical area for further processing (Fig. 17.1b). The product of that L2/3 processing is then sent to L4 of the next cortical area, where the two-stage information processing operation is repeated (Fig. 17.1a), but on a higher level, building on the advances made by the preceding cortical area (Rockland and Pandya 1979; Felleman and Van Essen 1991). The division of tasks between L4 and L2/3 does suggest that a function-linearization strategy might be implemented in L4 for the benefit of L2/3.

According to this strategy, the task of L4 cells would be to enable the L2/3 cells to learn and perform advanced nonlinear functions over the afferent inputs (i.e., their "target" functions) using fundamentally linear operations. This task is accomplished by transforming the afferent inputs in L4 in such a nonlinear manner that makes linear the relations between the outputs of the L4 cells and the target L2/3 functions. In their transformation of the afferent inputs, L4 cells in a cortical column will have to "linearize" target functions for the large number of cells comprising L2/3 of the column. Furthermore, since the L2/3 target functions are not specified a priori, but are developed by L2/3 cells gradually in a process of experience-driven self-organization and without providing any significant feedback to L4, the L4 cells will have to linearize the potential L2/3 target functions "blindly." This means that the L4 transform has to be "pluripotent." That is, the L4 transform should be optimized so as to make linear as broad a repertoire of potential functions over the afferent inputs as possible. The L2/3 cells will then select their target functions from this repertoire.

Although at a first glance such a pluripotent function linearization transform might seem daunting, its mathematically abstract elaboration under very basic cortically imposed constraints does readily produce a computational system that closely resembles the real cortical L4 in its structure and functional properties (Favorov and Kursun 2011). Such a biologically realistic and highly effective pluripotent function linearizer has the following ingredients (Fig. 17.2): (1) the output of each

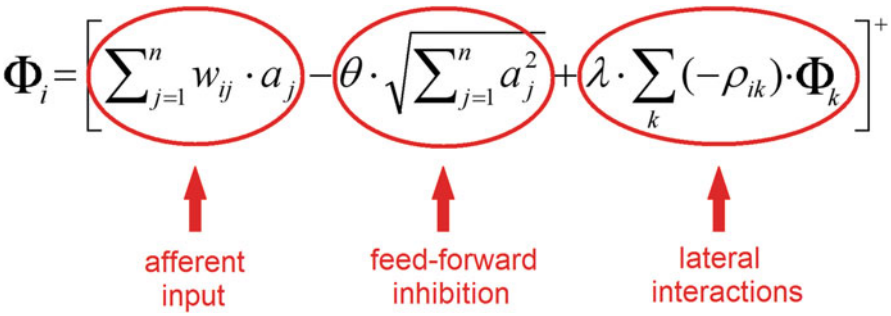

Fig. 17.2 Mathematical representation of the functional structure of macrocolumnar layer 4 domains. Output of excitatory L4 cell i is computed as a function of its afferent inputs $a_1 \ldots a_n$ and lateral inputs from neighboring cells $\Phi_1 \ldots \Phi_k$; w_{ij} and ρ_{ik} are connection weights (Favorov and Kursun 2011)

excitatory L4 cell is computed, in part, as a weighted sum of its afferent inputs, which are Hebbian; (2) lateral interconnections among L4 cells are used to diversify the afferent connectional patterns among L4 cells in a cortical column and give them a rich variety of receptive field properties; and (3) feed-forward inhibition makes L4 cells behave similarly to radial basis function (RBF) units and is principally responsible for function linearization capabilities. Importantly for the L4 linearizer's pluripotency, RBF networks are recognized as highly capable universal function approximators (Park and Sandberg 1991; Kůrková 2003).

Feed-forward inhibition is a prominent property of the real L4 functional architecture (Miller et al. 2001; Alonso and Swadlow 2005). Feed-forward inhibition of L4 excitatory cells (which include spiny stellates, pyramidal cells and star pyramids) is mediated by L4 inhibitory cells that are directly driven by the afferent inputs to the neighborhood (Porter et al. 2001; Hirsch et al. 2003; Swadlow 2003; Sun et al. 2006; Cruikshank et al. 2007; Hull et al. 2009). While this feed-forward inhibition is broadly tuned, comparable to the tuning of the afferent input, it effectively sharpens tuning of excitatory L4 cells by suppressing the weaker thalamic drive evoked by non-preferred stimuli (DeAngelis et al. 1992; Kyriazi et al. 1996; Bruno and Simons 2002; Swadlow 2002).

When the above computational model of L4 is developed on natural images and LGN-like input patterns and optimized for maximal pluripotency in linearizing arbitrary functions over natural images, it acquires structural and functional properties that closely match the properties of L4 of the cat primary visual cortex (Favorov and Kursun 2011). The list of nontrivial parallels, which are described in detail in Favorov and Kursun (2011), includes the following:

(a) Presence of inhibitory cells with strong direct thalamic inputs (Cruikshank et al. 2007) and unoriented RFs (Hirsch et al. 2003), which implement feed-forward inhibition;

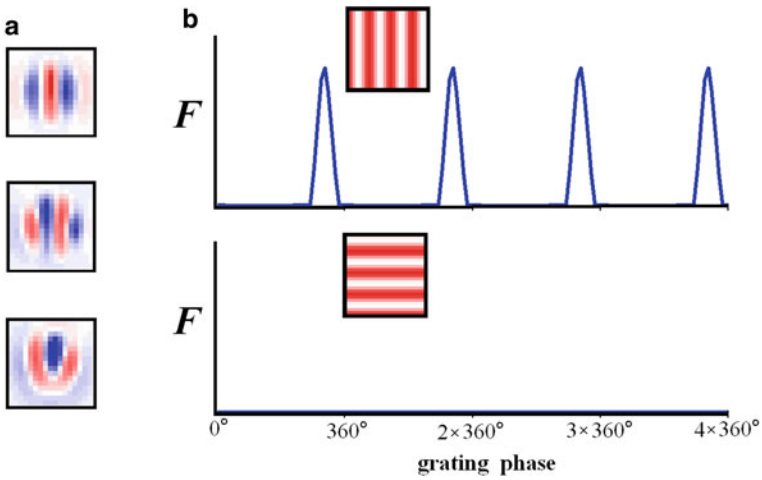

Fig. 17.3 The pluripotent function-linearizing L4 model, trained on natural images, develops receptive fields closely matching those of the simple cells in the visual cortex. (**a**) Two examples of simple-cell receptive fields and an end-stopping receptive field developed by the L4 model. (**b**) Simple-cell property of prominent phase modulation of a model cell's response *F* to a moving grating stimulus at the optimal orientation vs. no response to the same grating at the orthogonal orientation

(b) High density of excitatory interconnections among the cells in the L4 network (Anderson et al. 1994; Tarczy-Hornoch et al. 1999);
(c) Anti-Hebbian plasticity of lateral excitatory connections among cells in the L4 network (Egger et al. 1999; Sáez and Friedlander 2009);
(d) Self-organization of LGN connections to L4 cells into narrow parallel ON-center and OFF-center strips, producing simple-cell receptive fields (Fig. 17.3a; Hubel and Wiesel 1962; Alonso et al. 2001);
(e) Comparable numbers of receptive field subfields and aspect ratios (Jones and Palmer 1987; DeAngelis et al. 1993; Gardner et al. 1999);
(f) Emergence of end-inhibition receptive fields/hypercomplex cells (Fig. 17.3a; Hubel and Wiesel 1962; Dreher 1972; Tolhurst and Thompson 1981);
(g) Prominent phase modulation of cells' responses to grating stimuli of optimal orientation (Fig. 17.3b; Skottun et al. 1991);
(h) Narrow orientation tuning of comparable half-width at half-height (Fig. 17.4; Rose and Blakemore 1974);
(i) Contrast invariance of orientation tuning (Fig. 17.4; Sclar and Freeman 1982);
(j) Comparable average optimal spatial frequency of grating stimuli (Movshon et al. 1978);
(k) Narrower orientation tuning for grating stimuli of higher spatial frequencies (Vidyasagar and Siguenza 1985);
(l) Narrow orientation tuning of LGN inputs to L4 cells, close to orientation tuning of their outputs (Ferster et al. 1996; Chung and Ferster 1998);

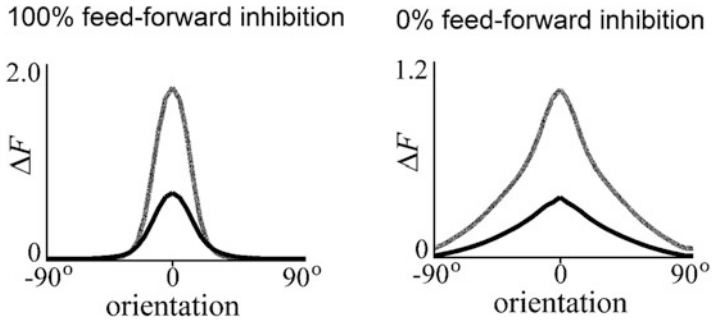

Fig. 17.4 Orientation tuning of the model L4 cells is contrast invariant and highly, but not fully, dependent on feed-forward inhibition. (*Left*) Average orientation tuning of all L4 cells with simple-cell receptive fields (*gray curve* – maximally contrasted grating stimuli; *black curve* – grating stimuli at 1/3 of the maximal contrast). Note that, just as in the real visual cortex, stimulus contrast does not change the tuning width. (*Right*) Average orientation tuning of all the simple cells with feed-forward inhibition turned off

(m) Presence of iso-orientation inhibition (Ferster 1986);
(n) Suppressive effects on cells' responses to optimally oriented grating stimuli by orthogonally oriented superimposed gratings (plaid-like stimuli; Bonds 1989; DeAngelis et al. 1992).

The presence of both feed-forward inhibition and anti-Hebbian lateral connections (which are unique to L4; see Egger et al. 1999; Sáez and Friedlander 2009) is required in order for L4 cells in the model to develop the biologically accurate diversity of multi-subfield receptive fields and acquire orientation tuning matching in sharpness that of real L4 neurons.

In conclusion, the fact that an efficient pluripotent function linearizer, designed on a few generic neurally-guided principles, exhibits emergent structural and functional properties that closely resemble those of cortical L4 strongly suggests that L4 has effective function-linearization capabilities and that its major function is to perform a transform of its afferent input enabling the upper layers to learn and compute complex functions using operations that are to a large degree linear.

17.2 Temporal Stimulus-Evoked Dynamics of L4 Feed-Forward Inhibition

Feed-forward inhibition in L4 is produced by basket cells and neurogliaform cells residing there. Both cell types receive strong afferent input, but basket cells act via fast $GABA_A$ receptor-mediated synaptic transmission, whereas neurogliaform cells release GABA as a volume transmitter and produce more slowly developing $GABA_A$ and very slow $GABA_B$ receptor-mediated inhibition (Tamas et al. 2003; Olah et al. 2009). As a result, feed-forward inhibition can be expected to have

fast and slow temporal components, associated with basket and neurogliaform cells, respectively. This means that in response to a stimulus application, feed-forward inhibition in L4 develops gradually and, if the stimulus is continuing, feed-forward inhibition reaches its maximum a few hundreds of milliseconds after the stimulus onset. The initial – and only partial – stimulus-evoked feed-forward inhibition is generated exclusively by the basket cells, but then it is gradually augmented by the slowly developing contribution from the neurogliaform cells. Given our understanding (see above) that feed-forward inhibition contributes greatly to sharpening receptive field feature extracting properties of L4 cells (Fig. 17.4), we can expect that the initial response of L4 cells to a stimulus will be less feature selective (and thus the stimulated individual less discriminative) than after a short period of continuing exposure to the stimulus.

Another aspect of somatosensation where fast vs. slow feed-forward inhibition should be clearly observable is in sensory testing of tactile stimulus detection threshold. The cells responsible for feed-forward inhibition are more responsive to weak afferent drive than are the excitatory L4 cells. Thus, sub-threshold or weak stimulus inputs should have the effect of raising the threshold at which excitatory L4 cells begin to respond to peripheral stimuli. Therefore, the sensory detection threshold should reflect the effectiveness of feed-forward inhibition: the stronger the feed-forward inhibition in a tested individual, the higher his/her detection threshold.

One sensory testing method that we have developed to examine feed-forward inhibition in human subjects involves the measurement of two independently collected values: (1) a "static" detection threshold, defined as the weakest 0.5 s duration vibrotactile stimulus an individual can detect; and (2) a "dynamic" threshold, defined as the weakest slowly ramping vibrotactile stimulus an individual can detect (Fig. 17.5). The **static threshold** is measured using a 20-trial Two Alternative Forced Choice (2AFC) Tracking protocol. During each trial a 25 Hz vibrotactile test stimulus (lasting 500 ms) is delivered to the tips of either index (D2) or middle (D3) fingers. Following each stimulus, the subject is prompted to select the skin site (D2 or D3) that was perceived to be stimulated. After a 5 s delay the stimulation is repeated until the completion of the 20 trials. The stimulus amplitude starts at 15 μm and is modified based on the subject's response in the preceding trial. During the **dynamic threshold** protocol, a 25 Hz vibrotactile stimulus is delivered to either D2 or D3. The amplitude of the stimulus starts from zero and is increased at a rate of 2 μm/s. The subject is instructed to indicate the skin site receiving the stimulus as soon as the vibration is detected. Multiple trials are conducted and the results from those trials are averaged for each subject.

In our interpretation of these two tests, in the static threshold test the subject detects the presence of the threshold stimulus right at its onset, when feed-forward inhibition is coming only from fast basket cells but not from slow neurogliaform cells, allowing excitatory cells to respond with spike discharges to the stimulus-evoked afferent drive. In contrast, during the dynamic threshold test the stimulus starts at zero amplitude and grows in strength at a slow rate that is sufficient to engage slow-acting neurogliaform cells. By the time the stimulus amplitude reaches the static threshold (typically 4–5 s into the stimulus), the feed-forward inhibition

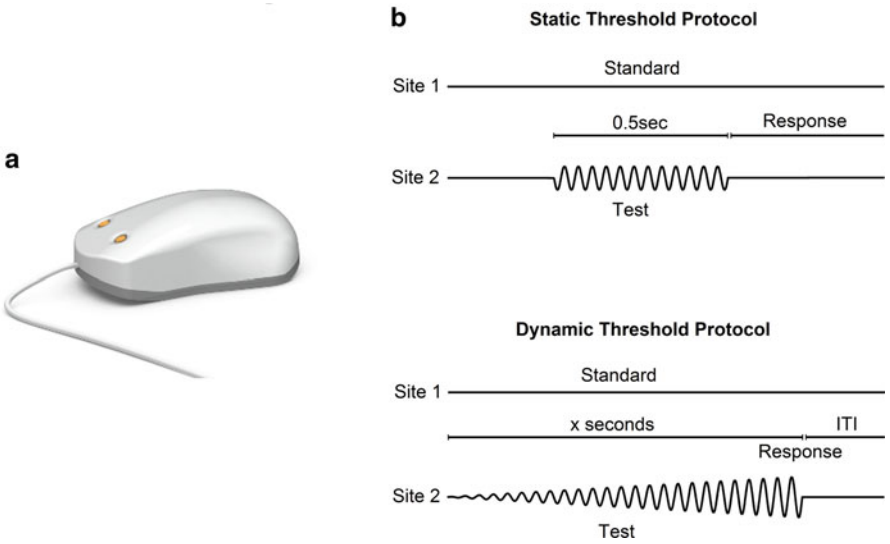

Fig. 17.5 Sensory testing of human vibrotactile detection threshold. (**a**) Tactile stimulator. (**b**) Two vibrotactile detection thresholds are measured using static and dynamic threshold protocols

is stronger than during the static threshold test, coming now from both basket and neurogliaform cells, and it prevents excitatory cells from firing their spike discharges. Instead, the stimulus amplitude will have to be raised higher in order for the afferent drive to overcome feed-forward inhibition in the excitatory cells, so that they will finally emit spike discharges and evoke conscious perception of the stimulus. Computer simulation of this phenomenon is illustrated in Fig. 17.6.

Consistent with this interpretation, dynamic thresholds have been demonstrated to be significantly elevated relative to static thresholds in healthy individuals across the age spectrum (Fig. 17.7; Zhang et al. 2011). The plot in Fig. 17.7 shows that although the static detection threshold rises with age (due to age-related changes in the skin), the dynamic threshold rises as well and continues to exceed the static threshold. This difference in the two measures can most parsimoniously be accounted for by feed-forward inhibition: i.e., the dynamic threshold is higher than the static threshold because the initial sub-threshold stimulus that is delivered during the dynamic testing increases the detectable threshold via feed-forward inhibition mediated by the neurogliaform cells.

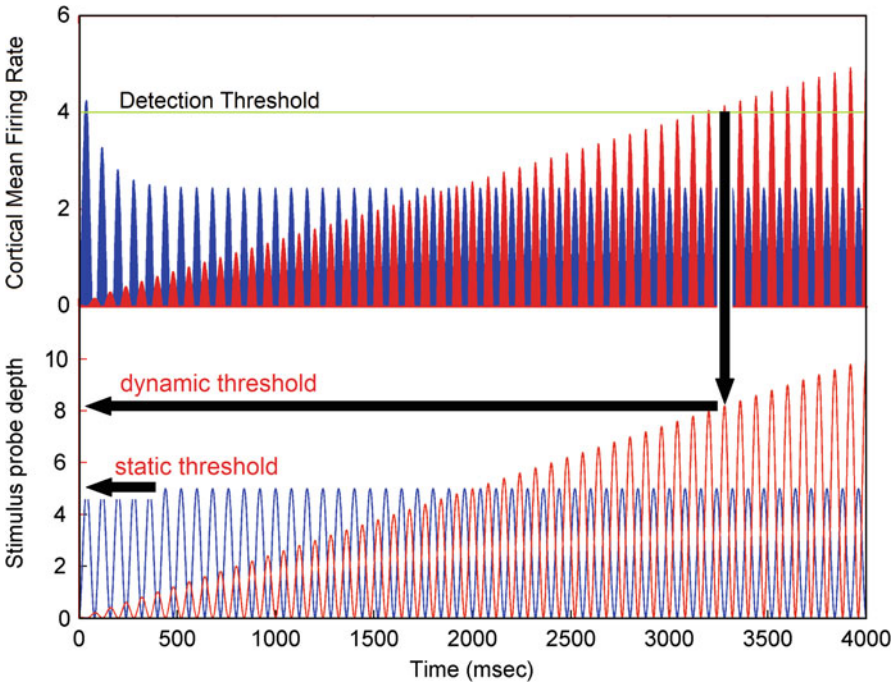

Fig. 17.6 Computer simulation of L4 response to static and dynamic threshold stimuli. The pluripotent function-linearizing model of a macrocolumnar L4 domain (Favorov and Kursun 2011) was used for simulation. The *top plot* shows the time-course of the mean L4 population firing rate during static (*blue curve*) and dynamic (*red curve*) sinusoidal skin stimulation. A hypothetical perceptual stimulus detection threshold is indicated by the *green horizontal line*. The *bottom plot* shows the time-course of the stimulating probe's skin indent. The step stimulation pattern (*blue*) evokes L4 response that barely exceeds the detection threshold and therefore its amplitude is taken as the static threshold. The ramp stimulation pattern (*red*) evokes a gradually rising L4 response, which crosses the detection threshold at a much higher stimulus amplitude, which is taken as the dynamic threshold

17.3 Feed-Forward Inhibition in Neurological Disorders

17.3.1 Autism Spectrum Disorder

A number of populations with some type of neurological disorder have demonstrated a reduction in the difference between the static and dynamic thresholds. One of the most studied is autism spectrum disorder (ASD). Multiple lines of evidence point to GABA deficiencies as a problem in ASD (for review, see Purkayastha et al. 2015; Brondino et al. 2016) and it is clearly established that there is an imbalance in excitation and inhibition in this population. When measures of static and dynamic threshold were obtained in multiple studies in adolescents with ASD, there was little or no difference found between the two metrics, suggesting depressed neurogliaform

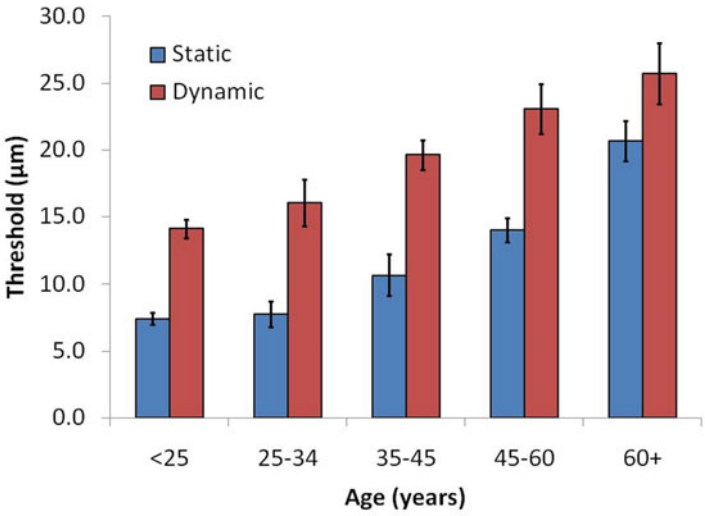

Fig. 17.7 Average vibrotactile detection thresholds measured in groups of healthy subjects of different ages using static and dynamic threshold protocols (Fig. 17.5)

cell-mediated feed-forward inhibition (Francisco et al. 2013; Puts et al. 2014, 2016; Tavassoli et al. 2015). Given the reliance of neurogliaform cells on $GABA_B$ receptor-mediated inhibition, this finding suggests that ASD might be associated in particular with reduced $GABA_B$ involvement in cortical operations.

In one of the studies (Puts et al. 2016), the same individuals with ASD who were found to have similar static and dynamic thresholds, were also found to have lower GABA levels based on their magnetic resonance spectroscopy (MRS) imaging. Figure 17.8 compares the test performance of 37 typically developing children (TDC) with 35 children with ASD studied by Puts et al. (2016). It shows no significant difference between static and dynamic thresholds in children with ASD, suggesting very little involvement of $GABA_B$ inhibition by neurogliaform cells in feed-forward inhibition. At the same time, the dynamic thresholds are very similar also between ASD and TDC groups ($p = 0.55$), indicating that their fully expressed feed-forward inhibition has comparable effectiveness. This indicates that $GABA_A$ inhibition by basket cells must be enhanced in the ASD group in order to compensate for the loss of $GABA_B$ inhibition. This inference is supported by the finding that $GABA_A$-specific static detection threshold in the ASD group is elevated relative to the TDC group ($p = 0.03$). The last inference to make from the collected data is that the reduced GABA levels in the ASD group, detected by MRS imaging, is likely to be due predominantly to reduction of GABA produced by neurogliaform cells.

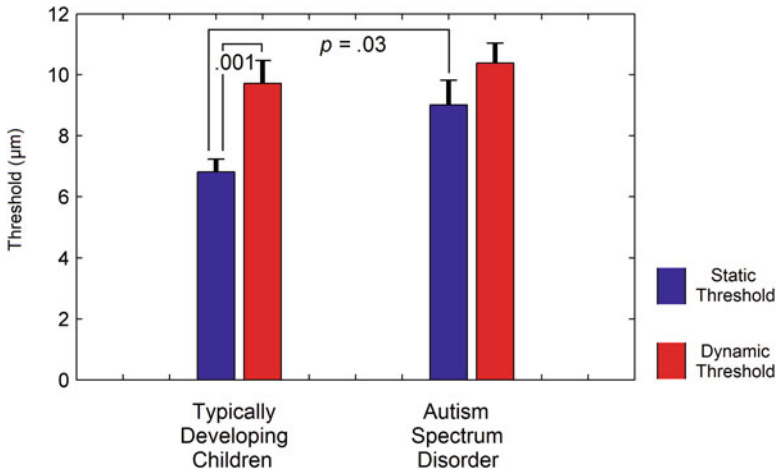

Fig. 17.8 Average vibrotactile detection thresholds measured in 37 typically developing children and 35 children with ASD using static and dynamic threshold protocols (Based on Puts et al. 2016)

17.3.2 Diabetes

Since we view depressed activity of neurogliaform cells as playing a major role in reducing dynamic detection threshold, we sought to study a population in which neurogliaform cells might be hyperactive. These cells happen to be the only known cells in the neocortex that produce and release insulin (Molnár et al. 2014). According to Csajbok and Tamas (2016), the function of neurogliaform cells is to regulate on-demand energy homeostasis of local cortical networks, and they respond to transient elevation of neural activity in local circuits during periods of information processing in three complementary ways. First, they release insulin, which increases transport of glucose into active neurons, thus satisfying their transient energy demands. Second, neurogliaform cell-released insulin suppresses excitation in cortical neurons. And third, neurogliaform cells release GABA, which also suppresses local neural activity via $GABA_B$ receptor-mediated inhibition. The second and third actions together curtail further energy demands of the local circuit.

In Type 2 Diabetes, insulin resistance impacts CNS and is associated with cognitive impairments (McNay and Recknagel 2011). We hypothesized that such insulin resistance in cortical networks could lead to chronic increase in insulin demand and consequently to hyperactivity in neurogliaform cells, which will manifest itself in elevated neurogliaform cell-mediated feed-forward inhibition. Based on this consideration, we measured static and dynamic detection thresholds in 37 Type 2 diabetic patients and found that the difference in dynamic and static thresholds in this group was significantly larger than in healthy control subjects (Fig. 17.9). Even patients who were in the early stages of diabetes and had not yet developed peripheral neuropathy already had dynamic detection threshold

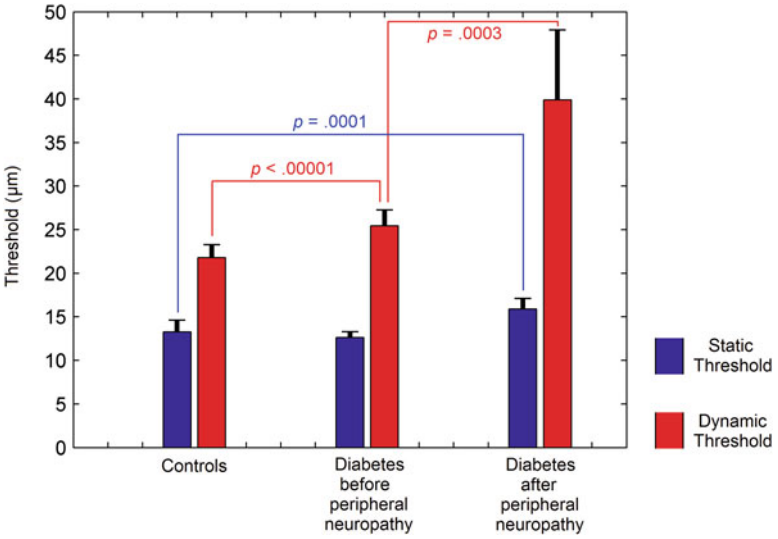

Fig. 17.9 Average vibrotactile detection thresholds measured in 17 healthy control subjects, 28 type 2 diabetes subjects without peripheral neuropathy, and 9 type 2 diabetes subjects with developed peripheral neuropathy using static and dynamic threshold protocols. Note that in the first two groups the static threshold is the same, but it is statistically higher in the third group, presumably due to their peripheral neuropathy

statistically higher than the control population. Thus, this sensory testing metric (i.e., the difference between the static and dynamic detection thresholds) could serve as a sensitive indicator of insulin resistance in neocortex and its impact on CNS information processing.

17.3.3 Could Maladaptive Feed-Forward Inhibition Play a Significant Role in Neurodegenerative Processes?

Cortical insulin is important for development of dendritic arbors and maintenance of excitatory and inhibitory synapses, thus contributing to the balance of excitation and inhibition in cortical networks (Csajbok and Tamas 2016). It is not inconceivable that altered activity of neurogliaform cells might play a role in the development of some neurodegenerative disorders, particularly those that have been linked with altered insulin activity. For example, a wide range of studies have implicated high levels of stress as playing a role in the development of PTSD (reviewed by Delaney 2013). Stress increases cortisol levels in the blood, which then damages brain cells by inhibiting insulin production, which leads to lower than normal glucose uptake. Thus, long-term stress leads to long-term metabolic problems in the CNS, which in turn results in a neuroinflammatory response. PTSD has been described in multiple

studies as being the result of chronic neuroinflammation (Furtado and Katzman 2015). Additionally, there is a significant association of diabetes with PTSD (Egede and Dismuke 2012) and some success has been demonstrated with intranasal insulin treatment of acute psychological stress (Bohringer et al. 2008) as well as a variety of other neurocognitive disorders such as Alzheimer's disease (Chapman et al. 2013; de la Monte 2013). Thus, there does appear to be some relationship between stress, CNS metabolism, neuroinflammation and insulin and the development of some neurodegenerative disorders.

It is also possible that local CNS insulin levels (which can be 10–100 times plasma insulin levels) play a role in the development of diabetes as a consequence of a neurodegenerative process. Impaired or excessive feed-forward inhibition mediated by neurogliaform cells could lead to altered CNS insulin levels, which would in turn modulate hypothalamic activity that has a downstream effect on pancreatic insulin production. In other words, impaired feed-forward inhibition, which would undoubtedly result in both sensory and cognitive deficits, and could be the result of an imbalance of excitation and inhibition, could lead to alterations in neurogliaform activity that impact CNS insulin levels.

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Chapter 18
Cortical Microstructures: Lateralization, Ageing, and Disruption Across the Lifespan

Steven A. Chance

Abstract The present review considers the evidence for microstructural cell assemblies as a form of neuroanatomical module, constituting building blocks for functional differentiation and processing specialisation (Chance 2014). Their organisation confers subtle differences between the hemispheres in the typically developed human brain and reveals anomalies of development associated with altered processing in some neuropsychiatric conditions. In the mature brain the same structures may be seen to undergo changes as a result of acquired functional specialisation and, in later life, they may be measured as an index of loss of differential function in ageing and neurodegeneration.

Keywords Dementia • Autism • Schizophrenia • Dedifferentiation • Neurodevelopment • Category learning • Cognitive reserve • Lateralisation • Modularity • Minicolumn

18.1 The Rise and Fall of Modules

During the Nineteenth Century, Paul Broca and Carl Wernicke made some landmark observations concerning the brain localisation of different aspects of language function, based on the associations between the type and location of brain injury and the symptoms of aphasia. For some time previously, doctors and natural philosophers had commented on the way our apparently coherent mental faculties may be composed of, and, subsequently, broken down into component parts. Whilst, in the era of modern brain imaging, few would argue against a degree of localisation in brain function, much of the continuing debate concerns the extent to which components of brain function can be identified, separated and considered to be 'modules'.

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Some prominent challenges to the received view of modularity have arisen in the forms of neuroconstructivism, evolutionary developmental ('evo-devo') accounts, connectionist learning and Bayesian statistics. Several of these accounts emphasize the developmental emergence of modules with 'fuzzy' boundaries of information processing, as a difficulty for the orthodox Fodorian account. Certainly, broadly increased awareness of the neuroplasticity of the brain and the widespread bi-directional connectivity of even primary sensory processing areas under the top-down influence of polymodal associative cortex sit uncomfortably with a relatively static model of the mature brain consisting of encapsulated modules. So far the challenges have focused on development during the early stage of the lifespan. However, there is increasing evidence that the later stage of life also presents a challenge through the apparent erosion of aspects of modularity. This view extends the notion of 'emergent modularity' towards a dynamic model which potentially includes a later decline and therefore a peak in its trajectory. The concept of fluctuating or dynamic modularity with a peak level at some point in the lifespan (perhaps in mid-life) opens up questions concerning the genetic regulation of this trajectory and its evolutionary and clinical significance.

Some ecological consequences may follow – fluctuating modularity may exaggerate the mis-match between optimal cognitive age and optimal physical or fertile period, it may create a different trajectory from a hyperbolic curve (which reaches a plateau) to a parabolic curve (which declines again). Ageing effects on cognition are not unique to humans (Cruz et al. 2004), however the decline in humans appears to be more extreme. Consequently, an evolutionary shift to a steeper parabolic trajectory of cognitive ability and, in particular, of modular differentiation may create a more sharply defined temporal window with fitness consequences related to environmental adaptability, mate selection and social competition among other things.

An interdisciplinary approach offers further complication. There are different kinds of requirements for the definition of modularity depending on whether the emphasis is on psychological, neuroanatomical, developmental, genetic or evolutionary independence. In addition, several hurdles in the way of consensus relate to questions about the relationships between these levels of analysis, such as whether all genetic modules encode a psychological module while not all psychological modules require a genetic module.

The present review considers the evidence for microstructural cell assemblies as a form of neuroanatomical module, constituting building blocks for functional differentiation and processing specialisation (Chance 2014). Their organisation confers subtle differences between the hemispheres in the typically developed human brain and may reveal anomalies of development associated with altered processing in some neuropsychiatric conditions. In the mature brain the same structures may be seen to undergo changes as a result of acquired functional specialisation and, in later life, they may be measured as an index of loss of differential function in ageing and neurodegeneration.

18.2 Microstructural Asymmetries in Language and Face Cortex

The simplest models of hemispheric asymmetry have often been based on the principle that a larger brain region on one side of the brain denotes dominance for a lateralized function (Galaburda 1995). However, the correspondences between structures within the same individual and between structural asymmetry and functional lateralization are often inconsistent. In humans, the superior temporal gyrus (STG) contains perhaps the most prominently asymmetrical brain area: the auditory association cortex of the planum temporale (PT). This region plays a key role in phonological processing and forms part of the receptive language region often identified as Wernicke's area. Geschwind and Levitsky (1968) found leftward asymmetry (greater size on the left than the right) of the PT in two-thirds of individuals. However, it has been found that PT asymmetry and language laterality may not be correlated, even though they are both significantly left-hemisphere biased. (Eckert et al. 2006). Meanwhile, the right hemisphere dominance for music perception, located in the homologous region of the right hemisphere, is primarily found in untrained listeners and lateralization depends on the degree of expertise and ability (Ono et al. 2011). Therefore, the evidence suggests that the lateralization of functions often depends on the interplay of multiple components, both cognitive and structural. The search for the link between structure and function leads therefore to the small-scale modular components that underpin the functions of interest.

The horizontal expansion of cortical surface during development (within individual brains), and across evolutionary time (between species), is largely due to the proliferation and spacing of radial minicolumns of cells that form the cortex (Rakic 1995). These structures, comprising cell bodies and their axonal and dendritic connections, persist throughout the mature brain Although the human minicolumn asymmetry is not large (Buxhoeveden et al. 2001; Hutsler 2003), it is estimated to account for a surface area asymmetry of 8–9% of the PT region's size (Chance et al. 2006). Notably, this asymmetry of minicolumn spacing is absent in the equivalent area of the brains of other apes (Buxhoeveden et al. 2001). The microscopic asymmetry in humans is also detected at the slightly larger scale of inter-connected "macrocolumn" patches (approximately 500 μm diameter) which are more widely spaced in the left than in the right auditory association cortex (Galuske et al. 2000). Recent single-unit electrophysiological recordings have demonstrated that cells within the same minicolumn share greater similarity of stimulus sensitivity than with cells in neighboring columns (Opris et al. 2012). The combination of stimulus-sensitive columns in a region presumably confers at least part of its functional specialization.

In terms of function, two underlying processing biases are apparent at a basic level that may contribute to language laterality. First, the left hemisphere is biased toward processing short temporal transitions in the sound signal which is especially suitable for recognizing speech (Efron 1963; Tallal et al. 1993; Zatorre et al. 2002). Conversely, the right hemisphere is biased for spectral sound processing

(Zatorre and Belin 2001) which may form the basis of the dominance of music perception in the right hemisphere in untrained listeners. Second, evidence supports the concept that in the generation of "meaning" the left parieto-occipito-temporal junction (Wernicke's area) is associated with the activation of more discrete, narrow, semantic associations, whereas the right hemisphere activates more distributed semantic fields appropriate to its greater sensitivity to context (Rodel et al. 1992).

Minicolumn organization in the PT has been found to correlate with cognitive scores (tests such as the Mini Mental State Exam which covers a range of tasks including object naming and simple sentence construction; Chance et al. 2011a). The relationship with cognition was specific to minicolumn measures and was not found for neuron density, as also reported in monkeys (Cruz et al. 2009). It has been suggested that greater spacing of minicolumns in human association cortex results in less-overlapping dendritic trees and allows more independent minicolumn function (Seldon 1981a, b). This is consistent with the association between the greater surface area and the wider spacing of evoked electrophysiological activity peaks in the superior temporal plane of the left hemisphere compared with the right (Yvert et al. 2001). Harasty et al. (2003) have developed the notion that widely spaced minicolumns function as discrete units facilitating computational processing of more independent components, whereas densely spaced minicolumns permit greater overlapping co-activation and therefore confer more holistic processing. In Jung-Beeman's (2005) model, the basal dendrites of right-hemisphere pyramidal neurons have longer initial branches and more synapses further from the soma than left-hemisphere neurons where the more widely spaced minicolumns have more dendritic branching within their territory. Wider minicolumn spacing is therefore associated with higher resolution processing across less-overlapping basal dendritic fields whereas dense minicolumn spacing is associated with lower resolution, holistic processing due to relatively greater distal sampling of more overlapping fields (Jung-Beeman 2005).

A similar analysis may be applied to face processing which is another highly evolved lateralised ability. However, it is biased towards the right hemisphere in humans (Kanwisher et al. 1997). In particular, the holistic analysis of faces is biased to the right hemisphere whereas individual facial features are detected in the left hemisphere (Rossion et al. 2000). The face processing area is found in the mid-fusiform region This local specialization and the high heritability of face processing (Zhu et al. 2010) make it plausible that there is a detectable neuroanatomical correlate in this region, although the extent to which the neural structure depends on genetic contribution or early social learning is unresolved.

In humans, cells have become large and less densely packed in the evolution of mid-fusiform cortex compared to the chimpanzee and this is accentuated in the left hemisphere with the result that there is an inter-hemispheric asymmetry that is not found in chimpanzees (Chance et al. 2013). Consequently, in humans, the wider minicolumns and larger neurons are found in the hemisphere opposite to the one that is dominant for face perception. Therefore, unlike auditory language processing, it appears that the arrangement of minicolumns that confers dominance for face processing is the thinner, denser spacing that is found in the right hemisphere

(Chance et al. 2013). The human asymmetry is relatively confined to the mid-posterior fusiform region, as a previous study that included the more anterior fusiform (area 20) reported a minicolumn asymmetry that was not statistically significant (Di Rosa et al. 2009). It has been suggested that the wider minicolumn spacing in the mid-posterior fusiform of the left hemisphere may relate to its role in visual word recognition in humans in addition to its role in face processing (Chance et al. 2013).

Therefore, in the visual domain, it is possible that wider minicolumn spacing may be associated with detailed feature processing, whereas thin minicolumns facilitate holistic, configural processing of the type usually associated with face processing. In such a scheme, face processing is similar to music processing. Holistic, configural processing for face recognition benefits from the computational overlap generated by densely spaced minicolumns in the fusiform gyrus, just as, in the auditory domain holistic, music processing is supported by thin, dense minicolumns in the right PT. The wider minicolumn spacing in the left STG facilitates fine temporal discrimination because minicolumns function as more discrete computational elements. This suggests that minicolumn width is dissociated from "dominance," per se, and instead relates to the type of processing: featural or holistic (Van Veluw et al. 2012).

18.3 Mechanistic Models and Functional Specialisation

It is recognized increasingly that many tasks combine elements of both holistic and featural processing (Rossion et al. 2000). Thus, two streams of processing occur in parallel – global processing in broad-activation fields of the right hemisphere and local processing in focused fields of the left hemisphere. By cross-referencing the differences between the active fields of the two hemispheres via the corpus callosum the relationship of local features to global features may be encoded. Cytoarchitectural asymmetries have been found in normal auditory cortex that correlate with the number of axons passing through the connecting regions of the corpus callosum (Chance et al. 2006). The emergent hierarchy of features within features is a recursive structure that may functionally contribute to generativity – the ability to perceive and express layers of structure and their relations to each other. Gabora (2002) has proposed a model of the evolutionary enhancement of cognitive processing capacity in humans through the cross-referencing of different levels of conceptual organization. Gabora (2002) described this as a process of widening and narrowing the "activation function" and, although Gabora's (2002) "activation function" was not clearly defined, its physical instantiation may be interpreted as a field of activated units such as the overlapping minicolumns.

Gabora's (2002) model suggests the evolutionary advantage of variable focus is to expand the capacity of conceptual space by interpolation between concepts. In statistical terms, it is equivalent to the generation of continuous data rather than categorical data. In psychological terms, it may be described as the contrast between

dimensional and categorical processing. Taylor et al. (1999) found that the right hemisphere uses more dimensions than the left hemisphere to represent the semantic map in healthy control subjects. More diffuse activation of the network in response to a linguistic stimulus, consistent with the model of holistic, overlapping activation described above, has been proposed to explain the lesser discrimination between primary and secondary word meanings that is also typically found in the right hemisphere (Weisbrod et al. 1998). This lower resolution discriminative capacity in the right hemisphere is found for face processing even as the right hemisphere is also dominant for making categorical (face vs non-face) distinctions (Meng et al. 2012).

In many cases the acquisition of expertise may be seen as an increase in discriminative capacity in a given domain of perception or motor control. One debate about the nature of the fusiform face area concerns whether or not it should be understood to be a unique module for face processing (Kanwisher et al. 1997) or the consequence of a general emergence of object-recognition expertise which happens to be suited to faces in this region because of its local cytoarchitecture and connectivity (Gauthier et al. 1999). Although the two models have been portrayed in opposition to each other they reflect potentially complementary aspects of functional fine-tuning. Seen in terms of the hemispheric differences in discriminative processing described above, they may be co-existent parallel levels of discrimination within a domain, one at a coarse, categorical level that is relatively easily specified innately, and one at a more fine-grained level that could be more dependent on experience.

Clearly, there has to be room for learning and acquisition of expertise in any account of brain function, even allowing for a high degree of innate specification of modules. Therefore the two models may also reflect a chronological change in emphasis which emerges from the dynamic process of development. Modular specialisation is enhanced when a low level of innately specified expertise becomes transformed with practice and/or learning, into a high level of expertise. This suggests that the processing requirements for a function will shift from a low level of discrimination to a high level over time, which may be associated with a fluctuation between categorical or dimensional discrimination, and in functional terms, between featural or holistic processing. In the mechanistic-anatomical description of minicolumns presented here this requires that either the separation of units (minicolumns) in the cortical region underlying this expertise changes over time or that the location of dominance for a function itself can change over time by becoming assigned to another brain region with more suitable unit separation.

There is preliminary evidence for both effects. The process of training and practise is associated with expansion of the cortical grey matter in the brain region associated with a function (Draganski et al. 2004). The effect of training on minicolumn morphology has not been measured directly but it is reasonable to estimate, given the unlikelihood of entirely new minicolumns growing, that cortical expansion is due to increased synapse and neurite growth from existing cells, expanding the space amongst the minicolumns. Although this may have some permanent effect on the size of the cortical region (Maguire et al. 2006), it must ultimately be limited by physical constraints on intracranial space, and data indicate that a large part of the grey matter enlargement is transient (Driemeyer et al. 2008).

It is likely that the restructuring involves not only expansion, but also fine-tuning, perhaps in the form of synaptic down-scaling during sleep (Tononi and Cirelli 2003), which enables a return to a less expanded total regional volume while retaining specifically enhanced synaptic connections. The second effect is complementary to this as it appears that the acquisition of expertise may be associated with a relocation of dominance for the function to a different area. For example, expert musicians tend to depend more on the PT of the left hemisphere for the judgement of musical differences, whereas in naïve listeners the brain activity is greater in the right hemisphere (Ohnishi et al. 2001; Elmer et al. 2011). This finding is correlated with the amount of training of the participants so it appears to be a result of acquired expertise rather than a predisposition.

Rosenzweig (2002) has reviewed the range of mechanisms of neuroplasticity across the lifespan, and Gopnik (2010) describes a contrast in learning strategies and plasticity in childhood compared to adulthood. The development of more separated conceptual dimensions during childhood (e.g. disambiguating concepts such as big, bright, high and tall) is associated with more sophisticated cognitive discriminative ability (Carey 1978; Goldstone and Barsalou 1998). Aspects of brain structural maturation and plasticity presumably relate to this process of cognitive maturation. The increase in discrimination associated with separable dimensions is similar to the acquisition of expertise, which is often associated with left-hemisphere specialization for fine-grained difference judgements, e.g., for faces, word meaning and music. The process, extended over childhood, is also likely to be influenced by the social and cultural environment, including the requirements of social integration and communicative pressure for shared conceptual frameworks. Appropriately, it is the same hemisphere (the left) that is associated with the acquisition of expert discrimination and dominance for the communicative faculty of language that facilitates social reinforcement.

In addition, a shift to increased influence of prefrontal executive brain regions is seen with the development of expertise in many functions (e.g. chess experts). This is described as a greater emphasis on top-down processes associated with a concomitant alleviation of demand (or effort) on the bottom-up contribution of primary sensory regions (Bilalic et al. 2012; Cardin et al. 2011). Accordingly, prefrontal regions are generally associated with greater neuropil expansion and wider minicolumn spacing than primary sensory areas (Van Veluw et al. 2012).

18.4 De-differentiation and Decline

Shifts in cognitive processing are therefore accompanied by structural changes and occasional, subtle shifts in functional localisation. Such changes form part of an over-arching trajectory of change in structure across the lifespan (Sowell et al. 2003). Older adults are capable of counteracting age-related neural decline through plastic reorganization of neurocognitive networks. At the small scale, on the structural level, several aspects of neuroplasticity occur in adult brains, including alterations of dendritic arborisation, synaptic remodelling, axonal sprouting, neurite extension, synaptogenesis, and neurogenesis (Mesulam 1999). The PFC,

for example, is a relatively dynamic structure in the brain, capable of adaptive neuroplastic response to changes or damage, perhaps reflecting its extended period of development during childhood and adolescence. However, its subsequent decline in adulthood in humans (Giedd et al. 1999) forms part of a long arc of change that seems to involve an 'undoing' of several aspects of structural and functional specialisation that have been acquired in earlier life.

The process of 'dedifferentiation' has been defined in functional terms previously; for example, reduced face discrimination ability in old age resulting from a gradual loss of specialisation for this function (Goh et al. 2010). An indication that this functional specialization is associated with minicolumn structure arises from the marked minicolumn alteration that occurs in fusiform cortex in old age (Di Rosa et al. 2009). The process of dedifferentiation has also been reported for areas of frontal cortex (Cabeza et al. 2002). Structurally, it has been observed previously that minicolumn thinning in normal ageing is greater in areas of association cortex which have relatively expanded minicolumn width, as in prefrontal cortex (PFC), whereas there is little or no change in primary sensory areas where the minicolumns are already relatively narrow (Chance et al. 2006).

Based on known anatomy, the units of function across the cerebral cortex seem to be largely the same in terms of cell types and basic architecture. Following the neuroconstructivist account (Karmiloff-Smith 2009), the differences between modules are mainly emergent properties – differences of processing and connectivity. Clearly gross cortical connectivity at the level of major white matter tracts is not likely to be lost on sufficient scale in a living person as to become fully undifferentiated. However, given that the cellular architecture is fundamentally similar and the differences between modules are largely emergent properties (such as connections and 'wiring') it seems highly likely that any process which erodes the fine-tuning through the loss of connections will erode the emergent properties of the modules first, effectively winding back the modules to their relatively undifferentiated architecture. There is evidence for this: in the microanatomy of normal ageing the minicolumns thin less in areas where they are already narrow and more in areas where they are wider, to the extent that the previously different areas come to have similarly narrow minicolumns – they appear to have returned to a 'baseline'. There is some functional evidence for a loss of later acquired (more 'specialised') knowledge, before knowledge that was acquired earlier in life during the progression of semantic memory decline associated with dementia. The neuroplasticity hypothesis therefore offers a mechanism to help explain differential regional vulnerability in neurodegeneration during old age (Arendt 2003; Esiri and Chance 2006) and links the time course of development in early life with vulnerability in late life.

In some respects, the maturation of modules may be seen as the accumulation of constraints. Certainly the refinement of information processing and the acquisition of expertise is associated with a loss of plasticity during development. Many academic colleagues, despite the wealth of their accumulated knowledge, have bemoaned the loss of their juvenile ability to learn. However the loss of this cognitive receptivity with maturity may be more than an unfortunate consequence of

ageing, it may be a necessary, perhaps defining, feature of mature cognition. It may be precisely that the systematic processing of mature cognition depends on the loss of immature plasticity. Consequently the often wished for coupling of a youthful ability to learn with an adult clarity of thought would be a contradiction in terms.

The structural and functional shifts associated with the acquisition and loss of differential processing specialisation suggests that the neuroconstructivist account (Karmiloff-Smith 2009) of the emergence of modularity in early life is only part of the story and that modular specialisation should be seen as dynamic in a profound sense, not only as the rise but also the fall of specialisation across the long arc of an individual's lifespan, as well as potentially fluctuating between an incipient and emergent state for any given functional specialisation even in adult life.

18.5 Neurodegeneration and Cognitive Reserve

It has become clear from unselected epidemiological studies linked to neuropathology that there is surprisingly frequently a mismatch between pathological changes found post-mortem and the recorded cognitive performance of a person before they died (Savva et al. 2009). In some cases cognitive performance was below the level expected for the amount of pathology found but more often someone with a substantial load of pathology had nonetheless performed cognitively within the normal range before death. A recent large study found that careful quantification of neuropathology and brain weight accounted for only between a third and a half of the variance in cognitive performance in a relatively unselected group of elderly people, leaving the rest unaccounted for (Dowling et al. 2011). Cognitive reserve is the concept that has been developed to deal with this discrepancy (Stern 2009).

The development, through education and training, of alternative problem solving strategies likely to be associated with PFC function, has been linked to enhancement of cognitive reserve (Steinerman 2010). There is evidence that individuals with high IQ are better able to cope with pathological aging, enabling preservation of cognitive abilities (Lindenberger and Baltes 1994; Tucker and Stern 2011), probably due to plastic reorganization of neurocognitive networks. Therefore, one hypothesised basis for cognitive reserve is a well-nourished, well-developed brain with healthy neurons and synapses. This fits with the fact that longer years of education protect against dementia and, conversely, that enhanced risk of dementia is experienced by those who have had a serious head injury. This concept particularly links cognitive reserve to grey matter regions of the brain and to the cortical plasticity inherent in these. Not all forms of reserve are the same, and they depend on the forms of brain insult and neuroplasticity that may be involved. Stern (2002) has compared neural compensation, neural reserve, and cognitive reserve. Compensation is a response to pathologically altered processing, whereas reserve refers to differences, or potential flexibility, in processing without pathology. Stern considers all three to be 'neural mechanisms' in the sense that they are attributed to interactions within neural

networks. However, the relationship between cognitive reserve and its architectural neural basis is not clear.

Estimates of cognitive reserve use the mis-match between level of pathology and level of cognitive dysfunction, however, such estimates depend on the presence of pathology and therefore do not offer insight into the potential reserve that exists prior to the onset of pathology. As an alternative, an appropriate measurement of intact architecture should provide a neuroanatomical index that precedes pathology, changes with normal ageing, and correlates with cognitive ability (Chance et al. 2012). In previous work (Chance et al. 2011a) we have drawn attention to a distinction in the neuroanatomical domain – between the markers of molecular neuropathological processes, such as plaques and tangles, and measurement of the remaining, intact cortical architecture that is presumably the basis for ongoing cognitive function. Synapse loss (Terry et al. 1991) and minicolumn change (Chance et al. 2011a) have shown some of the clearest structural relationships with functional deficits in ageing and dementia. In the context of identifying a neural basis for cognitive reserve, pathological molecular markers may be identified with deficit, whereas measures of intact cortical microstructures (i.e. minicolumns) may correspond to reserve.

Previously, Chance et al. (2011a) reported that the minicolumnar spacing of neurons in the cerebral cortex related to cognitive ability, and that minicolumn thinning was a sensitive biomarker of Alzheimer's disease. In particular, it was found that there is a correspondence between minicolumn thinning in the medial temporal lobe and MMSE (mini-mental state score) and between dorsolateral prefrontal cortex and IQ decline in Alzheimer's disease (van Veluw et al. 2012). In similar studies of cognitively impaired monkeys, Cruz et al. (2009) showed that the relationship with cognition is specific to the region of cortex associated with the function being tested, whereas a neighboring region that is not thought to contribute to the function showed no correlation. Analysis of cortical minicolumn structure has also been applied to dementia with Lewy bodies which revealed that minicolumn changes were more sensitive to the presence of disease than other common histological measures such as cell density (Buldyrev et al. 2000).

Larger, cognitively healthier brains appear to have a greater range of cytoarchitectural differentiation between brain regions, perhaps associated with greater functional differentiation, enabling greater cognitive reserve (Esiri and Chance 2012). These regional specialisations appear to be lost in ageing and dementia – in post-mortem studies of elderly brains the greatest regional differentiation between measures of cortical minicolumn width is found in aged control cases, slightly less differentiation in mild cognitive impairment, and most reduced differentiation in cerebrovascular disease and fronto-temporal dementia, with the greatest changes in the regions with wider minicolumns and almost no change in primary sensory regions such as auditory cortex. Furthermore, the different patterns of change in modular cytoarchitecture that are identified in different dementias may reflect the selective loss of functional specialisations that are characteristic of the different disorders.

18.6 Alternative 'Models' of Development: Schizophrenia and Autism

Testing the mechanistic significance of cytoarchitectural variations in minicolumnar morphology is challenging because the aspects of cognitive function that are affected may be relatively subtle and human-specific. For example, the lateralized functions discussed above appear to be confined to humans and, debatably, few other animals. However, disruptions of both minicolumnar structural organization and lateralized function are found in human neuropsychiatric disorders which provide further insight.

Altered cerebral asymmetry has been found in schizophrenia (Bilder et al. 1994; DeLisi et al. 1997; Chance et al. 2005) and the prominent role of language anomalies in schizophrenia also implicates lateralization (Crow 1990). The auditory region offers one of the clearest associations between psychotic symptoms and brain structure, as it is activated during auditory hallucinations (Shergill et al. 2000; Ropohl et al. 2004). The loss of left-hemisphere ERP mismatch responses to anomalous words at the end of a sentence, based on incongruous word meaning (Spironelli et al. 2008), provides a link between the sensory, phonological abnormalities and linguistic meaning. Reduced gray matter in this area, including the PT, is one of the most replicated structural changes in the disorder. Minicolumn asymmetry of this region is also altered in male patients (in whom illness is usually more severe) in such a way that both hemispheres are configured more like the typical right hemisphere (Chance et al. 2008).

Word generation (semantic fluency) tests the integrity of the semantic network that encodes basic knowledge about the meanings of words. Patients with schizophrenia have been shown to have networks that are less organized than those of control subjects (Paulsen et al. 1996; Rossell et al. 1999). If increased number of dimensions is taken to be indicative of more diffuse activation in the right-hemisphere network in normal subjects (as described above; Taylor et al. 1999), then the hypothesis that patients have unusually diffuse semantic associations in the left hemisphere as well as the right hemisphere (Weisbrod et al. 1998) predicts that patients use more, poorly discriminative dimensions overall. This is supported by several studies which reported less effective mapping of semantic space in low dimensions for schizophrenia, indicating the requirement for more dimensions (Paulsen et al. 1996; Rossell et al. 1999). The evidence that semantic category boundaries are less clear in schizophrenia (Paulsen et al. 1996) raises the prospect that the normal city-block cognitive metric may not provide a best fit for patients. In adolescent onset schizophrenia it has been found that the city-block metric did, indeed, provide a less beneficial data fit than in controls (Chance et al. 2011b). Therefore, alterations in the dimensions of conceptual space, consistent with disruption of lateralized cognitive processing biases, accompany abnormal anatomical structure of the cortex, including altered asymmetrical cytoarchitecture in schizophrenia.

The developmental shift from the Euclidean cognitive metric to the more separable dimensions of the city-block metric proposed by Gardenfors (2000) may be relevant in the neurodevelopmental context of schizophrenia. Although there is a clear genetic component in the etiology of schizophrenia, onset of illness is not identified until adolescence or early adulthood. It has been proposed that, structurally, this may be linked to the time course of myelination (Crow et al. 2007; Chance et al. 2008). Functionally, it may be linked to the shift in cognitive metric and as dimensionalization matures the anomalies associated with psychosis are exposed, leading to the recognition of "onset" and diagnosis.

Schizophrenia patients sometimes have difficulty in recognizing their own face (Kircher et al. 2003) and minicolumns have also been shown to be altered in the fusiform gyrus in patients (Di Rosa et al. 2009). In another neuropsychiatric condition, people with autism have a selective deficit in perceiving facial expressions categorically (Teunisse and de Gelder 2001) which affects activation of the fusiform gyrus (Pierce et al. 2004). One of the few neuropathological features of the disorder is altered minicolumn organization (Casanova et al. 2006) accompanied by altered neuron density in layer III of the fusiform gyrus (Van Kooten et al. 2008). Although it is not, so far, apparent that the effect in autism is asymmetrical between the hemispheres, it is clear that these alterations present a risk of disruption to the very structures that support lateralized face processing and are consistent with atypical processing in that functional domain. Indeed, attempts to characterize the deficits in ASD at a broader level led to the "weak central coherence" hypothesis (Frith 1989) which proposes that the core difference in ASD involves poor integration of "featural" information into a coherent whole.

In contrast to autism, schizophrenia is associated with over-interpretation of word meaning at the semantic level and over-interpretation of relevance at the level of pragmatic competence. Altered interhemispheric connections have been found to be correlated with minicolumn asymmetry in auditory language cortex in schizophrenia suggesting a link to language-processing anomalies that occur in the disorder (Chance et al. 2008; Simper et al. 2011). In terms of language and theory of mind, autism is associated with excessively literal interpretation of word meaning and under-interpretation of social relevance at the pragmatic level. Both appear to emerge from a disruption of the ability to interpret layers of meaning and their relations to each other. Therefore, autism and schizophrenia may involve a contribution from disequilibrium in the processing of local and global features related to the disorganization of minicolumnar units of processing.

Altered processing of semantic categories has been implicated in autism (Gastgeb et al. 2006; although further studies have suggested that the effects are often subtle). More broadly, in visual categorization tasks, deficits in prototype formation have been indicated (Gastgeb et al. 2012) and altered influence of categorical knowledge in autism has been interpreted as a reduction of top-down influence on perceptual discrimination (Soulières et al. 2007). In the context of altered minicolumn structure, these effects are consistent with the mechanistic model of minicolumn organisation – relatively wide minicolumns in primary sensory perceptual brain regions may limit the influence of top-down modulation from the

prefrontal cortex which normally comprises wider minicolumns itself. A coherent interpretation of the wider minicolumns in ASD, reported especially for younger subjects, is a bias towards processing the features of a stimulus rather than global, holistic processing.

Wider spacing of minicolumns, with less overlap of the dendritic trees associated with the constituent neurons (Seldon 1981) may result in less co-activation of neighbouring minicolumns allowing them to function more independently and so facilitate the processing of individual features as seen in ASD (Harasty et al. 2003; Chance et al. 2013). In addition, a number of theories have suggested that there may be disruption of the excitation-inhibition ratio in ASD towards a relatively increased level of excitation (Rubenstein and Merzenich 2003; Polleux and Lauder 2004; Pizzarelli and Cherubini 2011); a disruption which, if occurring as the primary change, has been shown to bias towards the formation of wider minicolumns (Gustafsson 1997, 2004).

18.7 Conclusion

Modularity of the brain at a cytoarchitectural level develops from early migration of cells into columnar arrays as they form the cerebral cortex. As this organisation matures in different brain regions its structure reflects differences in cognitive processing biases between those regions. Within an overall trajectory of expansion and then erosion, differences in these structural modules are found between cerebral hemispheres and between top-down modulatory and bottom-up perceptual brain regions, reflecting fluctuating levels of specialisation and acquired expertise. The location of functional dominance for a given domain may change and will reflect the information processing biases of changing minicolumn width and separation. The emerging picture is one, therefore, which consists of a varying degree of modularity with changing characteristics across the lifespan. The underlying architecture of information processing confers particular biases and constraints on cognition which, if sufficiently atypical, may be identified as particular neuropsychiatric conditions. The basis of cognitive reserve, which is neuroprotective against some disorders, is not understood, however cytoarchitectural modules in the cerebral cortex may provide an index of brain health. Dedifferentiation, in the form of reduced modular specialisation, appears to be a marker of vulnerability which occurs in late life.

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Chapter 19
Building Elements of the Adaptive and Pathological Pain Neural Networks

Maria-Luisa Flonta and Violeta Ristoiu

Keywords Nociception • Neural network • Inflamatory pain • Neuropathic pain • Chronic pain • TRP-channels • Microglia • Chemokines • Dorsal root ganglia • Endophenotypes

Everybody try to avoid pain, but pain is required for survival and maintaining the integrity of the organism. Pain has evolved as a physiological function which is lifesaving. The brief, acute, nociceptive pain is useful in order to signal tissue damage. The tonic ongoing pain which follows, helps to protect the wounded place, facilitating the healing process. As such, pain is an adaptive phenomenon, but dysfunctional pain which persists long time after healing of the initial injury or can appear also in the absence of an obvious trigger, can be life destroying. This chronic pain results only in a marked decrease in people's quality of life. Chronic pain is a disease in its own right and big efforts are made in order to understand the molecular, cellular and neural mechanisms of pain generation, temporal development and persistence, with the aim of finding therapies to reduce people's suffering (Scholz and Woolf 2002). The adaptive role of pain perception is even more illustrated by cases of congenital analgesia, when distinct channelopathies eliminate the ability to feel pain. The affected persons have high rates of early mortality due to repetitive fractures and self-mutilation (Peirs and Seal 2016). As such, pain motivates decisions to act, in order to escape or remove a noxious stimulus.

Trials to explain pain are old. We find already in Descartes book *L'Homme* (1664) (Descartes 1677) an explanatory schema (Fig.19.1). In his vision, the fire pulled on "delicate threads" that opened pores in the common sense center, which he located in the pineal gland. Descartes was visionary because, much later, sensory fibers were identified as thick, myelinated Aβ fibers, involved in transmission of tactile information, and thin, myelinated Aδ fibers or unmyelinated C fibers, involved in transmission of information about noxious events. The postulated pores were,

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Fig. 19.1 Descartes'picture of the pain pathway from *L'Homme* (1664). The fire pulled on "delicate threads" that opened pores in the common sense centre (F), which he located in the pineal gland. (http://gallica.bnf.fr/ark:/12148/bpt6k57486b/f1.planchecontact#)

centuries later, discovered as ionic channels in the neuronal membranes, acting as generators of the nerve impulse which transmits information.

Nowadays, there is an extraordinary dichotomy in the pain research field. Exciting progresses are made in dissecting the mechanisms which generate neural signals that we ultimately interpret as pain, but for many patients pain continues to produce severe distress, dominating and disrupting their lives. The clinical treatment is only partially effective, has disturbing side effects and abuse potential. This situation is due to the very complex characteristics of the pain phenomenon and the great diversity of mechanisms which generate different types of pain in various physiological and pathological conditions. Generalizing, pain is an *"unpleasant sensory and emotional experience, associated with actual or potential tissue damage, or described in terms of such damage"*, as it was defined by the International Association for the Study of Pain (Loeser and Treede 2008).

Pain, as a sensory experience, appears in physiological conditions, the so called **nociceptive pain,** when it transduces noxious stimuli in useful information and act as a protective mechanism, or in pathological conditions when inflammation produced by tissue damage or lesions in the nervous system generate **inflammatory pain** and respectively, **neuropathic pain**.

19.1 Nociceptive Pain

The nociceptive pain is a multimodal experience involving peripheral nerves, the spinal cord and higher brain centers (Fig.19.2). Sensory neurons of the peripheral nervous system have their cell body in distinct population of sensory ganglia. These neurons send peripheral afferent to the somatic, visceral and craniofacial regions, transmitting the nociceptive signals to the spinal cord and to the brain.

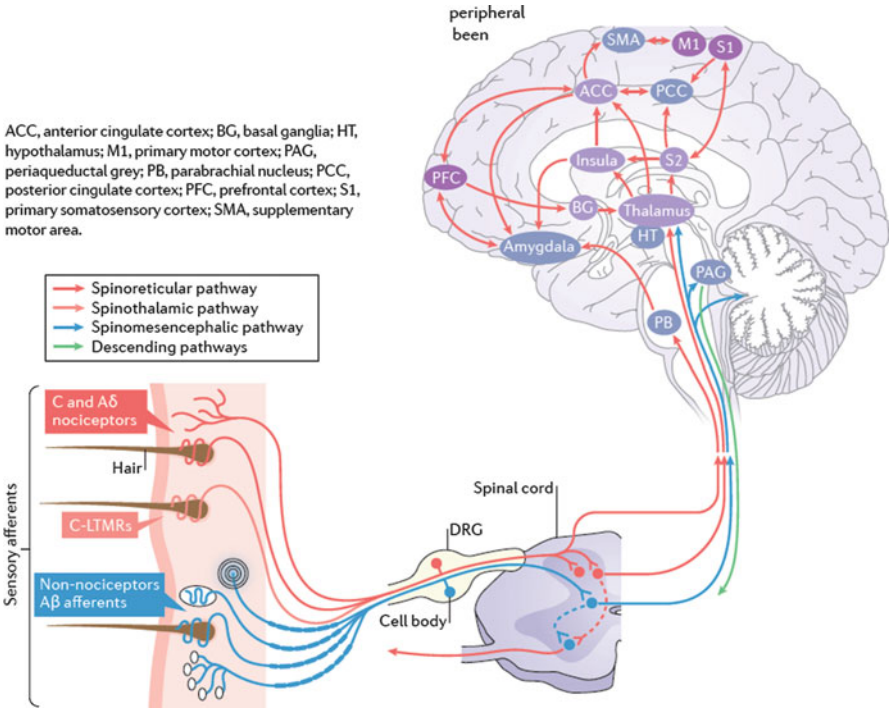

Fig. 19.2 Nociceptive pathways from the periphery to the brain. The energy of the innocuous or noxious stimuli is transduced in the peripheral nerve terminals of the dorsal root ganglia neurons. The nociceptive signal is conducted through thinly myelinated Aδ fibers or unmyelinated C fibers to the lamina I and II of the dorsal horn in the spinal cord, the non-nociceptive signal is transmitted through thick, myelinated Aβ fibers to the lamina III. A loss of this segregation results in intractable forms of chronic pain, as allodynia. Nociceptive stimuli stems either from internal tissues, or from the external world. Information is further distributed to neural circuits in the spinal cord and in the brain. Second order projection neurons reach the thalamus and from there, third order neurons transmit the signal to different cortical and subcortical regions, enabling the sensory-discriminative processing, the emotional-motivational and the cognitive-evaluatory processing. A descending modulatory pathway influences the nociceptive ascendant transmission (Kuner and Flor 2017)

Nociceptive pain allows early warning of noxious stimuli, an accurate differentiation between innocuous and noxious stimuli. The adaptive character of nociception is even more illustrated by the capacity to increase the sensitivity of the nociceptive system after a first exposure to a damaging stimulus, in order to allow healing of the injured tissue. This is the phenomenon of **sensitization**, which enables organisms to evoke escape responses, readily and with a reduced threshold, protecting the organism from further injury. An optimal threshold to elicit pain has to be high enough in order not to interfere with normal activities, and low enough, in order to be evoked before tissue damage occurs (Scholz and Woolf 2002).

The specific receptive properties of nociceptive neurons are determined by the membrane-inserted ionic channels present on sensory nerve endings, which transduce the energy of noxious stimuli into a propagating change of the membrane

potential. The nociceptor ionic channels are gated by temperature variations, by chemical stimuli or by mechanical forces and after activation transduce the external stimulus into a transient receptor potential (TRP). The resulting electrical depolarization of the neuronal membrane triggers the activation of Na^+ channels, which will generate the propagating action potential. Channels involved in transduction are thermosensitive TRP-channels, acid sensing ionic channels (ASIC) for free protons, P2X3 purinergic channel activated by ATP released by damaged or inflamed cells, a calcium gated chloride channel (Ca^{2+} -gated Cl^{--}) ANO1 or PiezoType 1 or 2 mechanosensitive channels for mechanical sensation (Gangadharan and Kuner 2013).

The major group of molecular detectors/transducers are the transient receptor potential (TRP) channels, non-selective cation channels with a high Ca^{2+} – permeability, expressed on the plasma membrane and also on intracellular organelles membranes. (Venkatachalam and Montell 2007; Wu et al. 2010). They share the same overall membrane topology with tetramers of 6-transmembrane segment polypeptide subunits and a central ion conducting pore, which is similar to voltage-gated K^+ channels (Mickle et al. 2016). Three TRP sub-families, TRPV, TRPA and TRPM are involved in nociception.

The major polymodal nociceptive TRP channel, **TRPV1** is directly activated by noxious temperatures (>43° C) and an acidic extracellular environment (pH 6.0 or less) (Caterina et al. 1999; Tominaga et al. 1998; Jordt et al. 2000; Julius 2013), as well by a basic intracellular environment (pH 7.8 or more) (Dhaka et al. 2009). Some endovanilloids and endocanabinoids produced by the lipid metabolic pathways also directly activates TRPV1 (Hwang et al. 2000; Zygmunt et al. 1999; Julius 2013). The most used activator of this channel in experimental settings is the vanilloid capsaicin, which gives also the name of this subfamily. Activation of the TRPV1 channel leads to a Ca^{2+} and Na^+ influx, through the channel pore (Chung et al. 2008; Mohapatra et al. 2003), which produces the neuronal plasma membrane depolarization, than subsequent opening of voltage gated Na^+/Ca^{2+} channels to initiate action potentials propagation. Following activation the TRPV1 channel undergoes rapid Ca^{2+} -dependent desensitization, resulting in diminished action potentials firing (Mohapatra et al. 2003, Loo et al. 2012). TRPV2 channels are activated only by higher noxious temperatures (>52 °C), no endogenous ligand was found so far (Vriens et al. 2009). Similarly other thermosensitive channels form a thermal receptor scale, covering the whole physiologically relevant temperature interval. TRPV3, TRPV4, TRPM2, TRPM4, TRPM5 sense innocuous warm temperatures (Fig.19.3).

On the lower side of the thermal scale, the **TRPM8** channel is activated by innocuous cooling (26–15° C) to noxious cold temperatures (15–8° C) (Reid and Flonta 2001; Yudin and Rohacs 2012). TRPM8 is activated also by menthol, a compound found in pepper mint, explaining the refreshing effect of menthol containing food (Fig. 19.4). In addition, it can be directly activated by testosterone in human prostate cell lines and in rat dorsal root ganglia neurons (Asuthkar et al. 2015a, b).

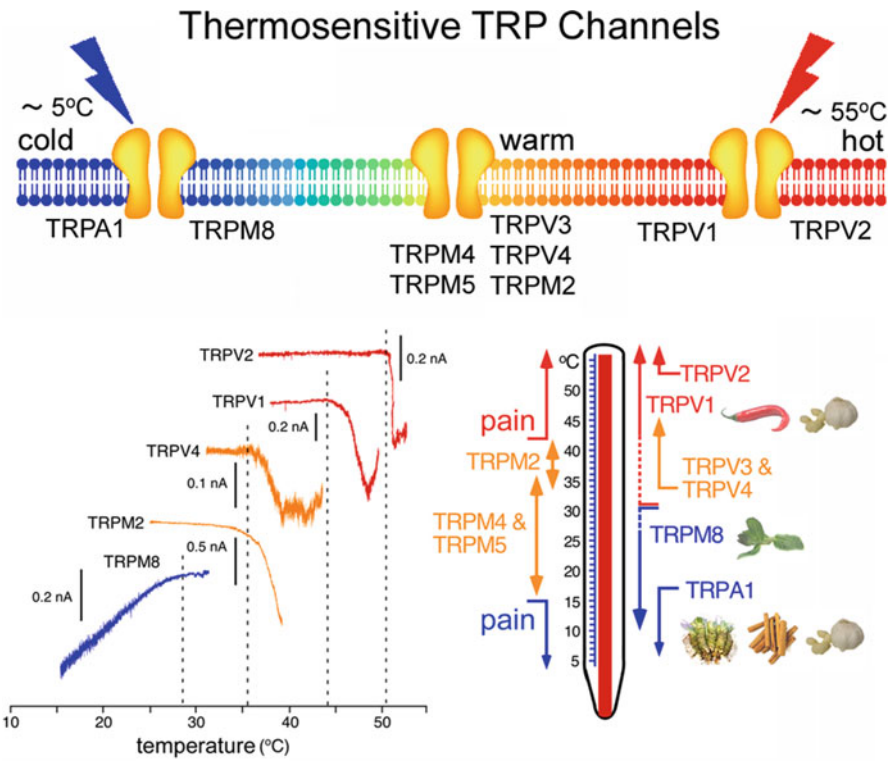

Fig. 19.3 A temperature scale is sensed by the TRP transducers of thermal energy detected on objects at physiologically relevant temperatures. Down left: the transient receptor currents generated by the different TRP channels at specific temperature intervals are recorded using the patch clamp method. (M. Tominaga, personal communication!)

TRPA1 was initially described as a noxious cold sensing ionic channel (Karashima et al. 2009). More recently it was shown that human TRPA1 exhibits an U-shaped temperature – activation curve (Moparthi et al. 2016). It is activated at noxious cold temperatures (>15 °C), shows a relative inactivity at mild cooling temperatures (20–25° C), again opens the channel at neutral to warm temperatures (25–35° C), and finally shows a decreased open probability at noxious warm temperatures (Moparthi et al. 2016). Other noxious factors can also activate the TRPA1 channel: pungent natural compounds as allicin, mustard oil, cinnamaldehyde, environmental irritants as acrolein, noxious mechanical stimuli, oxidant agents as H_2O_2, inflammatory peptides as bradykinin and various lipid peroxidation products that are produced in states of oxidative stress (Kistner 2016).

Upon activation, all these thermosensitive channels generate a transient receptor potential due to Na^+ and Ca^+ entry into the neuron; which depolarize the neurons and initiate action potentials which transmit farther away the nociceptive information (Mickle et al. 2016). The transient potential is even more amplified

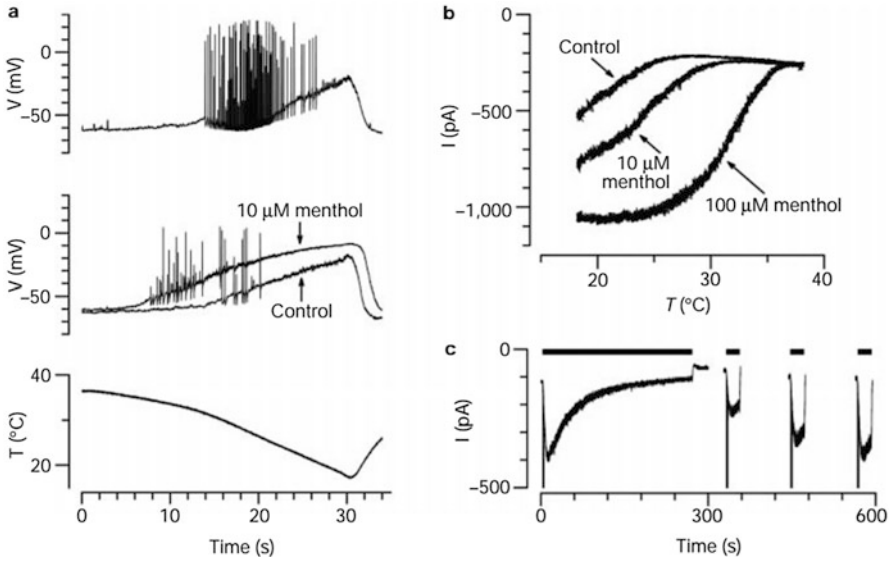

Fig. 19.4 Cold sensitivity and cold-induced inward current in primary sensory neurons from dorsal root ganglia (DRG). (**a**) *Top*, depolarization and action potentials during cooling in a rat DRG neuron; middle, sensitization by 10 μM (−) menthol in the same neuron (10 μM bupivacaine was added to reduce action potential frequency); *bottom*, thermal stimulus; (**b**) Current-temperature relationship of cold-induced current during ramp similar to those in (**a**), and the senitization induced by 10 μM and 100 μM (−) menthol; (**c**) Adaptation of the cold-induced current during prolonged cooling to 15 °C (*horizontal bars*) and recovery at 32 °C. (Reid and Flonta 2001)

in the form of a "regenerative potential" by voltage gated Na^+ channels, $Na_v1.8$ and $Na_v1.9$ (Raouf et al. 2010). Finally, the activation of the voltage gated Na^+ channels $Na_v1.7$ triggers the action potentials which carries nociceptive information from the periphery to the spinal cord and higher brain centers for interpretation. The generated signal is proportional to the degree of damage. After activation, the TRP channels undergo rapid Ca^{2+} -dependent desensitization, resulting in diminished action potentials firing (Fig. 19.4). A loss- of function mutation in the human $Na_v1.7$ gene leads to complete insensitivity to pain, the congenital analgesia. Affected people are victims of fractures and wounds which cannot heal, because the protection of the damaged parts of the organism is behaviorally missing (Cox et al. 2006). In contrast, a gain of function mutation of $Na_v1.7$ causes a congenital paroxysmal pain disorder as erithromelalgia. This is a vascular peripheral pain disorder in which blood vessels, usually in the lower extremities or hands, are episodically blocked (frequently on and off daily), and become hyperemic and inflamed, accompanied by a severe burning pain and skin redness (Fertleman et al. 2006).

After transduction of painful stimuli into neuronal electrical activity, the action potentials are conducted to the central nervous system. The nociceptive signal is transmitted to the central synapse in the spinal dorsal horn by releasing a variety of

neuromediators, such as glutamate, substance P or calcitonin gene related peptide (CGRP). Glutamate activates postsynaptic AMPA (α-amino-3 hydroxi-5-methyl-4-isoxazole-propionic acid) and kainate receptors on the second order nociceptive projection neurons. The nociceptive signal can be modified at this level by activation of GABA (gamma-amino-butyric acid)-ergic or glycinergic inhibitory interneurons. The spinal second order neurons projects to the thalamus, and from there, third-order neurons distribute the nociceptive signal to different cortical and subcortical regions, producing the multidimensional experience of pain with its sensory-discriminative, emotional-motivational and cognitive-evaluative components (Fig. 19.2). The spinal cord second-order neurons can be further modulated by the descending serotonergic and noradrenergic pathways, which can modify the perception of pain and the response to it (Grace et al. 2014).

19.2 Inflammatory Pain

Tissue damage can happen mechanically, by infection, burn, ischemia, tumor growth, chemical irritants or autoimmune processes. Inflammation is the immune response that occurs as a reaction to all these types of injuries, in order to remove the harmful agent and to promote tissue healing. Inflammation has two phases: *the acute phase*, when the recruitment of neutrophils, granulocytes and macrophages happens, and *the chronic phase*, when inflammatory mediators are synthesized and released by the damaged tissue, the recruited immune cells and by the affected sensory nerve terminals into the extracellular space. This mixture of substances is called the "inflammatory soup" and contains and ever-growing list of chemicals: H^+, ATP, histamine, proteases, serotonin, bradykinin, kallicrein, prostaglandins, lipid mediators, substance P, calcitonin gene related peptide (CGRP), growth factors, nitric oxide (NO), cytokines and many others (Linley et al. 2010). The effect of these algogenic substances is to sensitize or to directly excite the peripheral part of the nociceptive neurons via three types of receptors: (1) G protein coupled receptors as the histamine receptor H_1, the bradykinin receptor B_1 or B_2 or the protease-activated receptor PAR1-3; (2) tyrosine kinases receptors as the growth factor receptors, TrkA or TrkB; (3) ionotropic receptors, the ionic channels (Linley et al. 2010). The outcome of these inflammatory mediators is depolarization of the sensory neuron, lowering of the threshold for the activated channels and for action potential firing and a delayed repolarization, which all leads to the hypersensitization of the nociceptive neuron. Hypersensitization means pain response to normally innocuous stimuli (allodynia), or an exaggerated response to weak noxious stimuli (hyperalgesia) (Fig. 19.5).

All ionic channels active in transducing noxious stimuli are subject either to sensitization by increasing the amplitude of the receptor potential, or to reduced desensitization by prolonging the transient receptor potential. Hypoxia was shown to induce TRPV1 channel sensitization, which involves activation of hypoxia-inducible factor-1 alpha and protein kinase C (PKC) (Ristoiu et al. 2011). In contrast

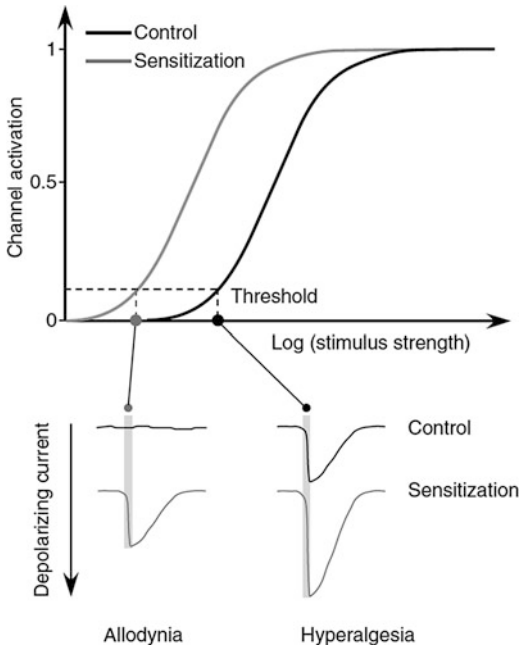

Fig. 19.5 Inflammatory hypersensitization of the ionic channels located in the peripheral nociceptors. The curve describing the relation of the channel activation to the stimulus strength is shifted to the left when sensitization occurs. That means that a weaker stimulus produces a higher channel activation. In allodynia, a stimulus which in normal conditions is unable to elicit any measurable current, produces a depolarizing current, when acting on sensitized nerve terminals. In hyperalgesia, a weak noxious stimulus induces a much higher depolarization, as in control conditions. (Linley et al. 2010)

catecholamines reduce TRPV1 desensitization, mediated by α_1, α_2 and β_2 receptors (Ribeiro et al. 2000; Filippi et al. 2016). TRPV1 and TRPA1 channels were shown to be photosensitized (an exaggerated sensitivity to harmless light) by ultraviolet and blue light. This fact explains the burning pain which affect thecutaneous porphyria patients. These two channels act as cellular sensors to detect the oxidative stress produced by UV and blue light. These radiations generate singlet oxygen, which oxidizes and activates TRPV1 and TRPA1 (Babes et al. 2016). A clinical relevant fact concerning TRPA1 sensitization is that the anti-diabetic drug, glibenclamide, is an agonist of the TRPA1 channel, thus explaining some of the adverse effects of the drug (Babes et al. 2013). In contrast, a systemic desensitization of the TRPA1 channel by capsazepine and mustard oil, may guide the development of a new class of analgesics (Kistner 2016).

The concept of metabolically driven hyperalgesia is illustrated by data showing that the $Na_v1.8$ channel, which is essential for sensing pain at low temperatures (0 °C) (Zimmermann et al. 2007), is post-translationally modified in the presence of a glycolytic metabolite – methylglyoxal, which is present in higher concentrations in the diabetic patients which manifest painful diabetic neuropathy (Bierhaus et al. 2012). Another group of detectors of noxious states are the acid sensing ionic channels (ASIC), which are activated by low extracellular pH and thus are sensors of tissue acidosis, which often accompanies inflammation (Wemmie et al. 2006). ASIC3 was suggested to mediate pain during inflammation produced by low pH (Deval et al. 2008).

Hyperalgesia results also when purinergic P2X receptors, the ligand-gated Ca^{2+} channels, are activated by extracellular ATP. During tissue injury or inflammation, ATP is released from the damaged cells or from the skin keratinocytes which were exposed to mechanical injury or inflammation (Koizumi et al. 2004).

Histamine, serotonin and bradykinin are, since long time, known as pain inducing endogenous compounds (Keele 1967). Cytokines, with some of its subtypes like interleukins (IL), chemokines and tumor necrosis factors, have only recently started to be considered as important for both inflammatory and chronic pain (Ren and Dubner 2010; Marchand et al. 2005). Under *inflammatory conditions*, resident immune cells like **mast cells and macrophages** which are activated within minutes of injury, release pro-inflammatory mediators including IL-6, IL−1β, IL-8 and tumor necrosis factor-α (TNF-α) which contribute to pain (Aich et al. 2015; Huygen et al. 2004). In addition, hematogenous immune cells like **neurotrophils, monocytes, circulating macrophages and lymphocytes** adhere to the vessel walls, extravasate and accumulate at the site of injury where they contribute to peripheral nociceptive sensitization by releasing soluble pro-inflammatory mediators or by interacting directly with the nociceptors. The cytokines secreted by neutrophils are similar with those secreted by monocytes and macrophages, and include pro-inflammatory cytokines (i.e. TNF-α, IL-1β, IL-1α, IL-6, IL-7, IL-18, etc.), and both CC and CXC chemokines (i.e. CCL2-4, CCL17-20), CXCL1-6, CXCL8-13) (Tecchio et al. 2014). Baicalin, a flavone glicozide, reduces pain in carrageenan-induced inflammation by inhibiting neutrophil accumulation and their pro-inflammatory mediators overproduction, including cytokines (Chou et al. 2003). **Lymphocytes** are better known for their contribution to neuropathic pain development, which will be discussed below in the neuropathic pain section, while for inflammatory pain they are known for IL-17 secretion and contribution to pain resolution (Rajakariar et al. 2008). In addition, some components of the **complement syste**m also contribute to inflammatory hyperalgesia. C5a and C3a, two proteins formed by the cleavage of complement components 5 and 3, contribute to inflammatory pain via increasing neurotrophil attraction to the lesion site (Ting et al. 2008) or by directly interacting with nociceptors. Application of C5a or C3a proteins to peripheral nerves *ex vivo* sensitizes C fiber nociceptors, possibly by a direct binding to C5a receptors (similarly structurally homologous to C3aR), normally expressed by primary sensory neurons (Jang et al. 2010).

The downstream effectors of many of the above mentioned pro-inflammatory cytokines are TRPV1 and TRPA1 channels, which thus contribute to inflammatory pain.

TNF-α, which was strongly associated with inflamatory pain (Cunha et al. 2005), acts through its receptors TNFR1 and TNFR2 which are coexpressed with TRPV1 in both DRG and trigeminal sensory neurons to alter its functioning. The mechanism are either a rapid sensitization of TRPV1 mediated by p38/mitogen-activated protein kinase, c-jun N-terminal kinase pathway or protein kinase C phosphorylation (Russell et al. 2009, Devesa et al. 2011), or a long-term increase in TRPV1 expression via extracellular signal-regulated kinase pathway (Khan et al. 2008, Hensellek et al. 2007). In addition, it was shown that TNF-α can induces IL-1β secretion which subsequently sensitize TRPV1 receptors (Russell et al. 2009).

TNF-α can also activate the TRPA1 receptors and increase mechanical hyperalgesia after inflammation (Fernandes et al. 2011), possibly by increasing its co-transport with TRPV1 to the plasmalemma via VAMP1-containing vesicles in the subset of trigeminal and dorsal root ganglion neurons that co-express TRPV1 and TRPA1 receptors (Kobayashi et al. 2005, Meng et al. 2016).

IL-1β induces thermal hyperalgesia in arthritic pain by increasing TRPV1 expression via a mechanism independent of SNARE-dependent exocytosis (Camprubi-Robles et al. 2009) or by PKC phosphorylation (Obreja et al. 2002). For TRPA1 there are no available data about an IL-1β modulatory effect.

IL-6 together with its soluble receptor (sIL-6R) induces and maintains thermal hyperalgesia by fastly modulating TRPV1 receptors in rat dorsal root ganglia neurons via p130/Jak/PKCdelta signalling pathway (Obreja et al. 2005) and it is involved in mechanociception by modulating TRPA1 expression (Malsch et al. 2014). In addition, it was also suggested that together with other cytokines, IL-6 might mediate the monosodium urate crystals-induced inflammation and joint pain by acting on TRPA1 receptors (Moilanen et al. 2015).

IL-17 which is secreted by lymphocytes T-helper, sensitizes joint nociceptors to mechanical stimuli and contributes to arthritic pain through neuronal interleukin-17 receptors whose downstream effector is not very well known (Richter et al. 2012), although it was suggested it could be due to amplification of TNF-α, IL-1β, CXCL1, endothelin-1 and prostaglandins, and therefore, indirectly, to TRP channels (Pinto et al. 2010).

Recent studies have shown that the epithelial cell-derived atopic dermatitis cytokine thymic stromal lymphopoietin (**TSLP**) activates a subset of sensory neurons that express TSLPRs and TRPA1 to promote inflammation and itch associated with atopic dermatitis (Wilson et al. 2013). TSLP leads to TRPA1 activation downstream of TSLPR possibly by PLC or JAK/STAT pathways, although it is not clear yet how. This is another example of TRP channels modulation by cytokines associated with inflammation, although not necessarily with pain, too.

Chemokines, a group of chemotactic cytokines, are also involved in regulating inflammatory processes. Although their receptors are expressed in both central and peripheral nervous system (Ubogu 2011; Cartier et al. 2005), there are not so many data about the influence of chemokines on TRP channels. Preincubation with ***MCP-1/CCL2*** (Monocyte Chemoattractant Protein-1/CC chemokine ligand 2), an endogenous ligand for CCR2 receptors, up-regulates the current density and expression of TRPV1 channels in nociceptive DRG neurons by activating the PI3K/Akt signaling pathway, and activates TRPV1 receptors in spinal neurons (Kao et al. 2012, Spicarova et al. 2014). These mechanisms are considered important for both inflammatory and neuropathic pain. Pretreatment with ***MIP-1α/CCL3*** (Macrophage-inflammatory protein-1/ CC chemokine ligand 3), an endogenous ligand for CCR1 receptors, sensitize TRPV1 receptors most likely by removal of PI(4,5)P2, a TRPV1 endogenous inhibitor, and phosphorylation by PKC (Zhang et al. 2005). Intraplantar injection of CCL3 into the footpad of a mouse induces thermal hyperalgesia, supporting the in vitro observations. Recently we have shown that intracerebroventricular (ICV) administration of ***MIF*** (Migration Inhibitory Factor), an endogenous ligand for CXCR2 receptors, increased painful responses to a sub-

cutaneous injection of formalin in the rat hind paw, mainly flexing, licking and paw-jerk behaviors (Deftu et al. 2016). Knowing that TRPV1 receptors are also expressed in the central nervous system (CNS), it is possible that they could also be a downstream effector for MIF, but there are not clear data about this so far. We also investigated in our lab the effects of two other chemokines ***GROα/CXCL1*** (growth related oncogene α/C-X-C motif ligand 1 chemokine), and ***MIP-2/CXCL2*** (macrophage inflammatory protein 2/C-X-C motif ligand 2 chemokine) which are members of the ELR(+) CXC chemokine family, with a 78% homology of their sequence and which act specifically through CXCR2, a G protein-coupled receptor. Our data showed that after overnight incubation with 1.5 nM CXCL1 or CXCL2, only CXCL2 significantly decreased the TRPV1 current and increased its desensitization rate, whereas CXCL1 had no effect (Deftu et al. 2017). Knowing that a reduction in desensitization rate is associated with TRPV1 sensitization (Ristoiu et al. 2011), any molecule that would increase TRPV1 desensitization and therefore reduce its ability to respond to subsequent stimuli would be a very good candidate for pain treatment. In our study, only CXCL2 increased the desensitization rate of TRPV1 expressed in cultured DRG neurons, while CXCL1 had no effect, suggesting that on long term, CXCL2 might have analgesic effects, mainly by reducing TRPV1 activation.

19.3 Neuropathic Pain

Both nociceptive and inflammatory pain are protective and adaptive, warning the organism to remove the pain producing stimulus and to protect the damaged tissue until healing. Sometimes pain can extend long time after healing of the initial injury. In this case chronic pain develops, but in most cases is maladaptive. The most common type of chronic pain is the neuropathic pain. Neuropathic pain arises as a result of nerve injury such as diabetic neuropathy, HIV neuropathy, post-herpetic neuralgia, drug-induced neuropathy and traumatic nerve injury. The mechanisms associated with neuropathic pain are often studied on animal models in rodents, almost all of which involve partial injury of the sciatic nerve (Ristoiu 2013). An important characteristic of these models is that both lesioned and unlesioned axons have dysregulated gene expression and generate intense, repeated or sustained discharges which results in a pain-facilitatory state in the spinal dorsal horn synapse which is known as central sensitization or windup. This state is associated with phosphorylation of receptors as NMDA (N-methyl-D-aspartate), AMPA and/or kainate receptors, which increases synaptic efficacy by changing the channel open time, the burst firing or by removing the Mg^{2+} block in NMDA channels and promoting receptors trafficking to the post-synaptic membrane. In these conditions, Aβ fibers which are usually activated by innocuous stimuli, can activate the nociceptive C fibers, either because of their higher excitatory input, or because of the lowered threshold of the nociceptive projection neurons (Grace et al. 2014). Desegregation of touch and pain information can arise in the spinal cord through two types of mechanisms: remodeling of the spinal circuitry which results in new physical links (new synapses) between the non-nociceptive and nociceptive neurons (Fig. 19.6a), or disinhibition of the existing physical links (Fig. 19.6b, c).

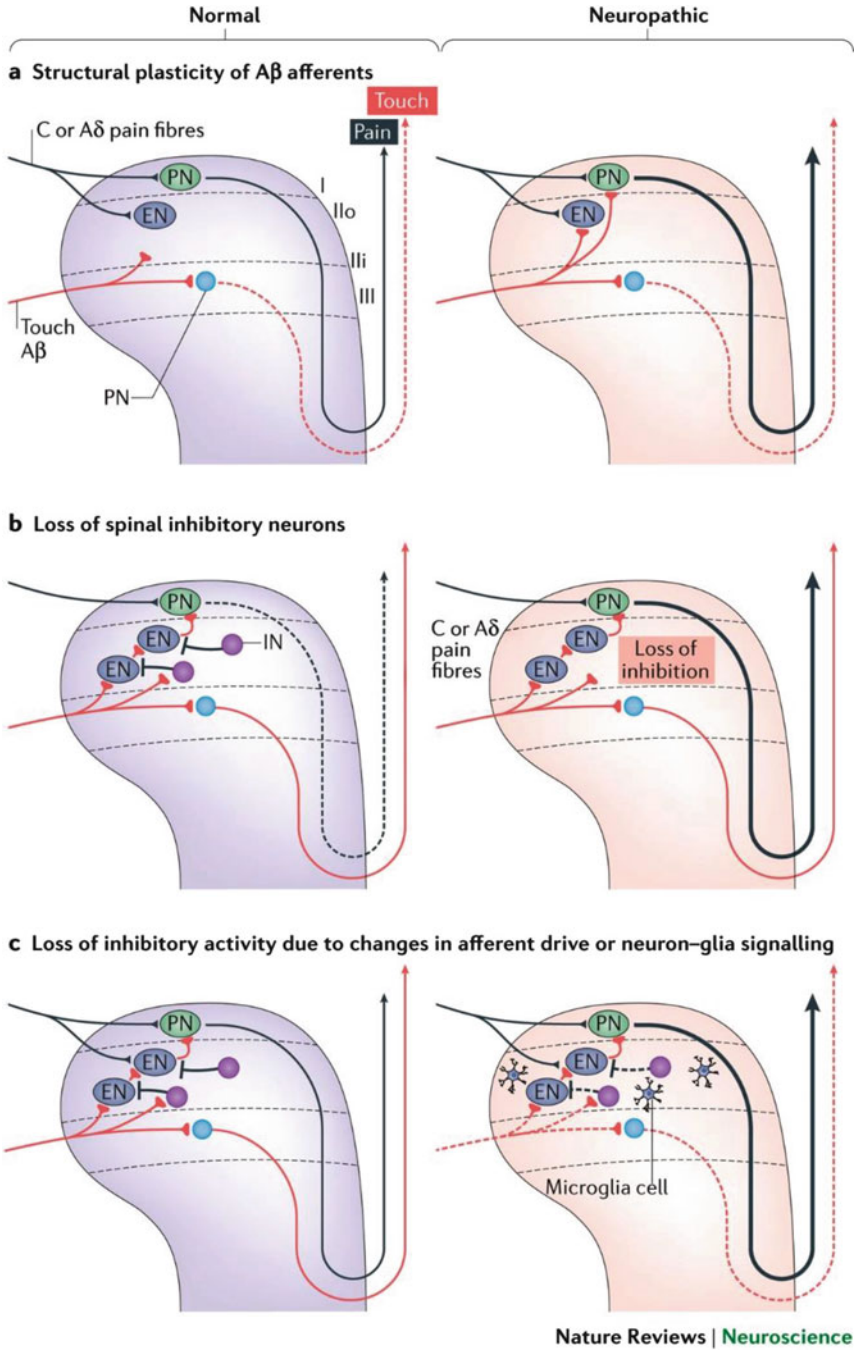

Fig. 19.6 Changes which may occur in the spinal circuitry, located in the dorsal horn, resulting in allodynia, when pain and touch pathways are no longer segregated. (**a**) Under neuropathic conditions, touch-sensitive Aβ, that normally terminate in deep spinal laminae IIi and III, sprout

Disinhibition happens either by loss of inhibitory neurons (Fig. 19.6b), or by the action of brain derived neurotrophic factor (BDNF) released by activated microglia which down-regulates a K-Cl cotransporter 2 in the spinal neurons and as such decreases the chloride-mediated inhibition (Fig. 19.6c).

But neurons are not the only players in generating the neuropathic pain. A "triad" of actors produces and maintain the neuropathic, chronic pain: neurons, immune cells and glial cells (Scholz and Woolf 2007). The highly coordinated temporal pattern of immune and glial cells activation in the periphery, in the dorsal root ganglia and in the spinal cord is adaptive in nociceptive or inflammatory conditions, but can be dysregulated to produce transition to neuropathic pain. Peripheral nerve damage induces a reaction of the immune system and glial cells at different levels in the nervous system.

In **the periphery**, near the injured nerve, **mast cells** contribute by recruiting neutrophils and monocytes to hyperalgesia. Stabilization of mast cells with sodium cromoglycate and treatment with histamine receptor antagonists suppressed the development of hyperalgesia associated with partially ligated sciatic nerve pain model (Zuo et al. 2003). **Neutrophils** have also been shown to significantly accumulate at the site of injury after partial transection of sciatic nerve. Depletion of circulating neutrophils at the time of nerve injury, but not days later, significantly attenuated hyperalgesia suggesting that endoneurial accumulation of neutrophils at the site of peripheral nerve injury is important in the early genesis of pain (Perkins and Tracey 2000). Recently it has been shown that peripheral keratinocyte-derived chemokine contributes to pathogenesis of partial sciatic nerve ligation-induced pain by stimulating neutrophil infiltration into the sciatic nerve and increasing the production of pro-inflammatory mediators (Manjavachi et al. 2014). At the lesion site **Schwann cells and macrophages** initiate the Wallerian degeneration in the distal part of the axotomized fiber, but can also contribute to pain development. After partial sciatic nerve ligation in mice, a persistent ipsilateral upregulation of high-mobility group box-1 (HMGB1) detected in both infiltrating macrophages and proliferating Schwann cells was associated with mechanical hypersensitivity. Perineural treatment with anti-HMGB1 antibody significantly ameliorated pain, suggesting that Schwann cells are important not only for the myelination process, but also for neuropathic pain development (Zhang et al. 2015). In addition, depletion of **hematogenous macrophages** with liposome-encapsulated clodronate leads to a reduction of hyperalgesia and allodynia after traumatic or metabolic nerve

Fig. 19.6 (continued) into the superficial laminae I and IIo that receive the nociceptive input. This new synapses produce an enhanced activity in the pain pathway. (**b**) The polysynaptic connections between the touch and pain pathways are subject to strong inhibition. Physical loss of inhibitory interneurons, can promote the cross-talk between the touch and pain circuits, increasing the activity of the pain pathway. (**c**) lesions or defects on the Aβ fibres activates spinal microglia which modulates, via secreted mediators, the balance between excitatory and inhibitory neurons. An imbalance in the spinal circuitry will increase activity in the pain pathway and decrease activity in the touch pathway (Kuner and Flor 2017).

injury (Liu et al. 2000; Mert et al. 2009). Minocycline reverses the activation of macrophages by retarding their migration to the nerve injury after chronic constriction injury and spared nerve injury (Ghanouni et al. 2012; Mika et al. 2010). In Wld^s (slow Wallerian degeneration) mice in which recruitment of macrophages to the site of injury is delayed, the development of thermal hyperalgesia is also prevented (Myers et al. 1996; Sommer and Schafers 1998). Additionally, cytokines and chemokines secreted by macrophages, such as TNF-α (tumor necrosis factor-α), interleukins IL-1β, IL-6 and MIP-1α (macrophage inflammatory protein 1-α) are potential mediators of hyperalgesia through direct receptor-mediated actions on afferent fibers or indirect actions involving further mediators (Sommer and Kress 2004; Kawasaki et al. 2008; Lee and Zhang 2012). Perineural administration of activated macrophages did not evoke mechanical allodynia (Rutkowski et al. 2000), possibly because during the recruitment process macrophages are "programmed" for subsequent functions, so their direct injection is not sufficient to mimic their normal role. **Lymphocytes T** also infiltrate more into the damaged nerves, contributing to pain development most likely by IL-17 which was associated with mechanical hypersensitivity after peripheral nerve injury (Austin et al. 2015; Day et al. 2014).

In the **dorsal root ganglia (DRG)**, neutrophils, macrophages, satellite cells and lymphocytes are active triggering an immune response. **Neutrophils** invade lumbar DRG after chronic constriction injury of the sciatic nerve, a process which parallels the peak of neuropathic pain behavior (Morin et al. 2007). However, the functional implication of their close proximity to neuronal axon and soma is still unknown. In the DRG, an important role have the **endogenous macrophages** which accounts for 2–4% of the total DRG cell population (Oldfors 1980). Depending on the type of lesion, endogenous macrophages remain scattered between neurons or enlarge their cell bodies and dispose as satellite cells around neurons. The distribution around DRG neurons could possibly help in creating a gap-junction connection with the DRG neurons. Only TNF-α was located inside the resident macrophages of the DRG after lumbar disc herniation (Ristoiu 2013). **Hematogenous macrophages** invade DRG and behave similarly to the endogenous ones, contributing to neuropathic pain by an increased secretion of TNF- β, IL-1β and IL-18 cytokines or SDF-1/CXCL1 2 (stromal cell-derived factor-1)/Chemokine (C-X-C motif) (Ristoiu 2013). Downstream, TNF-α mediates the upregulation of CXCL12 in the DRG and spinal cord following spared nerve injury, thus contributing even more to the development and maintenance of neuropathic pain (Bai et al. 2016).

Increased aggregation of DRG CD8+ **T-lymphocytes** was described after sciatic nerve chronic constriction injury (Hu et al. 2007). However, the same cells were described at the DRG level as important for the resolution of chemotherapy-induced neuropathic pain via IL-10 (Krukowski et al. 2016), thus suggesting a complex role depending on the type of neuropathic pain.

In the DRG, **satellite glial cells (SGCs)** ensheathe the somata of primary sensory neurons to form functional sensory units. After a peripheral lesion, the SGCs surrounding small and medium-sized neurons are preferentially activated in an early phase, but they shift to large diameter neurons as time goes on. Gap junction-mediated coupling between them or with the DRG neurons was

described after chemotherapy-induced neuropathic pain, experimental autoimmune encephalomyelitis and diabetic neuropathy (Warwick and Hanani 2013; Warwick et al. 2014; Hanani et al. 2014), although purinergic transmission mediated by P2x4 and P2x7 ATP receptors could also contribute to satellite cells-DRG neurons communication associated with neuropathic pain (Xie et al. 2017; Ying et al. 2017).

Central nervous system responses to peripheral injury are influenced by the infiltration of the blood-borne immune cells or by the activation of endogenous microglia and astrocytes. **Neutrophils** infiltration in the spinal cord parenchyma were suggested to contribute to the pathogenesis of painful diabetic neuropathy or of the pain associated with spinal cord injury (Yokota et al. 2016; Newton et al. 2017). Increased infiltration of CD4+ **lymphocytes T cells** and IL-17 were associated with spinal nerve ligation neuropathic pain (Sun et al. 2017), but not with the spared nerve injury neuropathic pain model, too (Gattlen et al. 2016).

Microglia, the **resident macrophages** of central nervous system play a very important pro-nociceptive role and act as initiators of neuropathic pain (Tsuda et al. 2005). After partial sciatic nerve ligation an invasion of **hematogenous macrophages** into the spinal cord was described, but they finally differentiated into microglia (Zhang et al. 2007). In the healthy CNS microglia are not dormant, but perform immune surveillance by extending, retracting their ramified processes and continuously sampling the extracellular space for possible perturbations without overall cell displacement (Nimmerjahn et al. 2005). After an injury to the peripheral nervous system microglia rapidly activate: their cell body increases in size, proximal processes become thicker, distal branches are less ramified, specific membrane ruffles develop and the cells move to the damaged site where they show increased phagocytic activity and release of pro-inflammatory mediators (Hanisch and Kettenmann 2007). Specifically, IL-15 and IL-18 were associated with microglia after CCI and SNL spinal nerve ligation (Ristoiu 2013). The transition of microglia to a state of reactive gliosis following peripheral nerve injury is induced by a range of neuronally released mediators, such as matrix metalloproteinase 9, neuregulin 1, chemokines, ATP and endogenous danger signals (also known as alarmins). An increased number of activated microglia has been associated with different neuropathic pain models (Ristoiu 2013). Figure 19.7 summarizes the time course of macrophages and microglia activation according to the neuropathic pain model.

Fluorocitrate which blocks both astrocyte and microglia inhibits neuropathic pain, while minocycline which is a specific inhibitor only for microglia blocks the development of neuropathic pain but has no effect on the already established pain, suggesting that microglia might be more important in the initial phases of neuropathic pain, while astrocytes might be more important in maintaining it (Marchand et al. 2005).

Astrocytes make up the majority of glial cells in the CNS and have critical roles in neuronal development and establishing and maintaining the blood brain barrier. In the resting state, astrocytes have thin processes with which they isolate neurons and oligodendrocytes to help maintain a stable microenvironment around them, by regulating extracellular ion concentrations of K^+, Ca^{2+} and neurotransmitters. After an injury to the peripheral nervous system, astrocytes undergo hypertrophy,

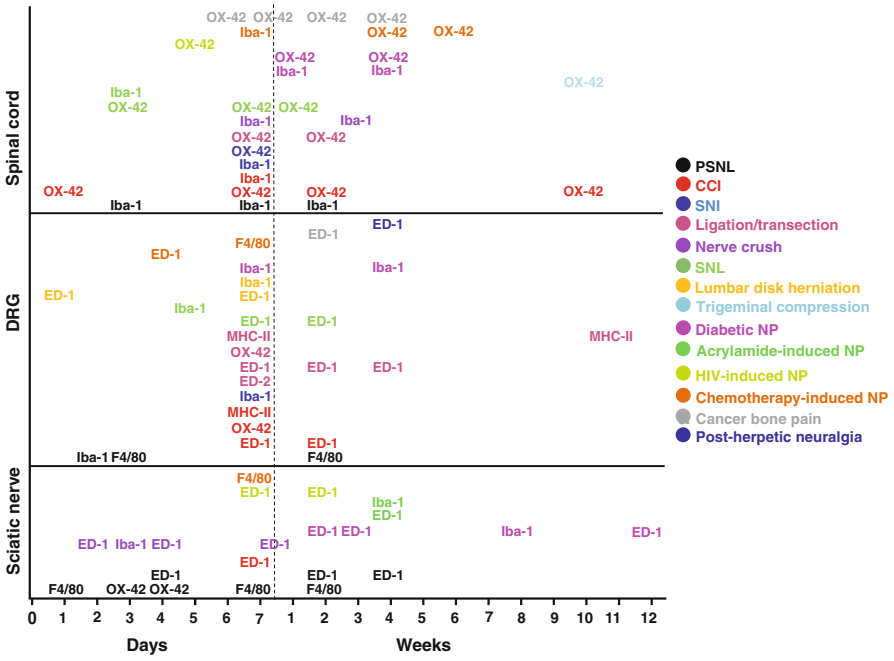

Fig. 19.7 The macrophages/microglia activation according to the pain model. Depending of the neuropathic pain model, the hematogenous and endogenous macrophages/microglia activate at different time points in sciatic nerve, dorsal root ganglia and spinal cord. The hematogenous macrophages express ED1/CD68, OX-42/Cd11b, F4/80 and MHC-II (major histocompatibility complex class II) markers, the resident macrophages express Iba-1 (ionized calcium binding adaptor molecule 1) and ED2/CD163 markers and microglia express OX-42/Cd11b and Iba-1. *PSNL* partial sciatic nerve ligation, *CCI* chronic constriction injury, *SNI* spared nerve injury, *SNL* spinal nerve ligation, *NP* neuropathy (Ristoiu 2013)

proliferate, increase expression of specific markers and release pro-inflammatory mediators like TNF-α, IL-1β, IL-6, MCP-1, prostaglandin E2 and nitric oxide (Milligan and Watkins 2009). Activation of astrocytes was described in several neuropathic pain models including chronic constriction injury of the sciatic nerve, spinal nerve ligation, lumbar radiculopathy or spinal cord injury (Ren 2010).

Like for inflammatory pain, TRPV1 and TRPA1 channels are also involved in neuropathic pain development as it was reviewed elsewhere (Basso and Altier 2017). Cytokines which are known to modulate TRP channels in inflammatory conditions, maintain the activation of these channels and facilitate the transition from acute pain to chronic pain. Some of the cytokines were specifically associated with TRP channels and neuropathic pain. **TNF-α** was shown to generate heat hyperalgesia in a mouse cancer model by enhancing the *TRPV1* expression and amplitude of capsaicin and heat-activated currents via p38/MAP (mitogen-activated protein) kinase and PKC (Constantin et al. 2008) and it is considered to be important, together with IL-6 and IL-1β, in the central sensitization of TRPV1 receptors

associated with early thermal hyperalgesia in painful diabetic neuropathy (Bishnoi et al. 2011). In addition, together with IL-1β, TNF-α was proposed to mediate the sensitization of TRPV1 receptors in a model of chronic constriction injury (Malek et al. 2015). An increased release of TNF-α by the satellite glial cells in the DRG was described in cancer chemotherapy-induced peripheral neuropathy due to paclitaxel treatment, which further down activates *TRPA1* in nociceptive DRG neurons (Wu et al. 2015).

IL-6 was specifically associated with bone cancer pain by functional upregulation of TRPV1 receptors in DRG neurons through the activation of JAK/PI3K signaling pathway (Fang et al. 2015), but there are no data about IL-6, TRPA1 activation and neuropathic pain. Chemokine ***MCP-1/CCL2*** released from neuronal synaptic vesicles in the spinal cord is a major mediator of pain after peripheral nerve injury by activating TRPV1 (Van Steenwinckel et al. 2011), similar to ***MIP-1α/CCL3*** chemokine which sensitize TRPV1 receptors and it was associated with CCI-induced neuropathic pain (Sun et al. 2016). In a murine model of chemotherapy-induced allodynia, vincristine treatment induced infiltration of circulating $CX3CR1^{+}$ monocytes into the sciatic nerve which, after activation by the chemokine **CX3CL1**, secreted reactive oxygen species that in turn activated the receptor TRPA1 in sensory neurons and evoked pain (Old et al. 2014).

19.4 Brain Networks Involved in Pain Processing

The nociceptive component of the pain system cannot explain why pain hurts. The suffering aspect of the multidimensional pain experience is generated at supraspinal levels of the neuraxis. Consider the situation when a person trades a thumbtack. Pain triggers a suite of processes: (1) location of pain, (2) evaluation of its intensity and quality, (3) a generalized discomfort, (4) a negative valence, (5) a high arousal, (6) focusing attention to the injured foot, (7) motivation to reduce pain, (8) motor plan to achieve this, (9) learning to avoid future wounds, by carefully considering where to walk (Zaki et al. 2016).

Noxious somatic and visceral stimuli activate, in a coordinated manner, several brain regions (Fig. 19.2), such as the thalamus, where the spinothalamic tract containing second order projection neurons ends, the anterior cingulate cortex (ACC), the insular cortex, the primary and secondary somatosensory cortices (S1 and S2), the prefrontal cortex, the basal ganglia, the amigdala, the nucleus accumbens and the cerebellum (Peirs and Seal 2016). All these brain areas, which are activated in functional magnetic resonance imaging (fMRI) studies, constitute the **pain matrix** (Schweinhardt and Bushnell 2010). This network of brain areas are involved in constructing the multidimensional experience of pain; the different dimensions are the sensory- discriminative aspects of the pain sensation, the affective-motivational aspects of hurting and the cognitive-evaluatory aspects which are involved in the descending control mechanism devoted at maintaining the homeostatic balance of the organism.

The pain matrix is a collection of brain regions which activates, but none in particular is uniquely devoted to pain perception. Rather, a unique coordinated activation of various regions happens in every different type of pain: acute, tonic ongoing and chronic (Tracey and Johns 2010). The involved brain areas spans sensory, discriminatory, emotional, motivational, cognitive, evaluative, motor, decision-making and brainstem modulatory circuits, which are activated in a flexible manner, producing endless varying painful experiences (Tracey 2016).

Recent studies try to advance our knowledge about pain generation mechanisms on molecular, cellular and system levels, in healthy organisms, but also in dysfunctional conditions, when the "good" pain, turns into chronic pain.

The **thalamus nuclei** as relay stations have an important role in gating and filtering nociceptive information, which is further transmitted to cortical and subcortical regions. The two modes of firing of the thalamo-cortical neurons: tonic and bursting, are thought to represent two types of nociceptive transmission to the cortex. The increase of burst firing and decrease of tonic firing is associated with reduced visceral pain sensation, indicating that a switch between the two firing modes constitutes a gating mechanism (Cheong et al. 2008; Kuner 2010).

The **anterior cingulate cortex (ACC)** is probably involved in signaling the unpleasantness associated with acute pain. Several studies support this view. Using the thermal grill illusion to stimulate healthy persons, ACC activation was detected, but only when the cold and warm stimuli where applied simultaneously, in an alternatively spatial arrangement, which produces the anomalous pain experience (Craig et al. 1996). Increased activity in the ACC was shown also in conditions of experimentally induced sadness, social rejection or exclusion, suggesting that ACC is associated also with emotional pain (Yoshino et al. 2010). The anatomical connection of ACC to the amigdala (Gabbott et al. 2005) suggests that ACC is involved in processing anxiety and fear generated by painful experiences. Supporting this idea, optogenetic activation of ACC pyramidal neurons in mice, has induced an anxiety- and depression like behavior (Barthas et al. 2015) and has lowered the mechanical pain threshold (Kang et al. 2015). It was shown that presynaptic long term potentiation (LTP) and postsynaptic LTP can occur simultaneously and additively in ACC neurons (Koga et al. 2015). These forms of synaptic plasticity can explain the relation between chronic pain and anxiety, which reinforce each other. The mechanisms of LTP induction in ACC neurons are similar to those which were discovered in the hippocampus in the context of learning and memorizing (Zhao et al. 2005). The unpleasantness of chronic pain could be encoded by postsynaptic LTP, triggered by NMDA receptors activation, and the following increased AMPA-receptor trafficking to the synaptic density. Anxiety which accompanies chronic pain, could be encoded by presynaptic LTP and triggered by kainate-receptors activation which continues with an increase of neurotransmitter (glutamate) release (Bliss et al. 2016).

Synaptic plasticity in the healthy ACC is required for the physiological processing of painful stimuli, which includes fear memory as a homeostatic factor influencing behavior. Fear memory enables the prediction of future dangers. Although acute pain is short lasting, it triggers persistent synaptic changes which

contribute to the formation of fear memory (Tovote et al. 2015). But, dysregulated or exaggerated LTP in the ACC can produce chronic pain related anxiety, which is no longer adaptive. Also, temporal precision of information coding by the ACC neurons was found to be altered in chronic pain, as reflected by an increased neuronal jitter (Li et al. 2014).

Pain influences also the **hippocampal neurogenesis** in adults. Neurogenesis of granule cell in the hippocampal dental gyrus is decreased in mice with nerve injury (Apkarian et al. 2016). Survival of newborn neurons is reduced in presence of neuropathic pain, and in stressful conditions (Romero-Grimaldi et al. 2015). This decreased neurogenesis and a reduction of hippocampal volume observed in chronic pain patients, could be related to the affective and cognitive decline emerging in chronic pain.

A decrease of **brain gray matter** was reported in patients with phantom limb pain, chronic back pain, irritable bowel syndrome and other pain forms (Detloff et al. 2014). This decrease is thought to be the consequence of pain, that means of the high frequency of the nociceptive input (Hashmi et al. 2013) and it is partially reversed when the treatment is successful.

Brain networks involved in cognitive processes influence the magnitude of the perceived pain. Fluctuations in activity of three distinct networks are involved in the degree of attention focusing on pain: (1) the salience network, which detect biologically relevant stimuli and is activated by pain. It contains the anterior insular cortex, the mid-cingulate cortex and the temporoparietal junction; (2) the default mode network (DMN) which is active in a relaxed, task free state and specifically when attention is focused away from pain. The DMN includes medial regions of the brain as the medial prefrontal cortex, the posterior cingulate cortex, the precunneus, the medial temporal lobe, the retrosplenial cortex (Raichle et al. 2001); (3) the descending pain control system, which includes the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate cortex, the periaqueductal gray (PAG). Activation and functional connectivity between these areas are correlated with the level of reported pain relief. This top-down modulation influences the signal transmission in the spinal dorsal horn, using endogenous opioids as mediators. The important role of the DLPFC exerted modulation is revealed through a transiently applied lesion to DLPFC, using transcranial magnetic stimulation (TMS), which succeed to abolish the placebo induced analgesia (Krummenacher et al. 2010). The same system is engaged when distraction occurs, reducing the perceived pain level (Eippert 2013). When attention is focused on pain, the DMN is deactivated. In contrast, when the connectivity between DMN and PAG is enhanced, pain is no more the principal object to engage attention (Seeley et al. 2007). Patients with chronic pain suffer alterations of the interplay between these three networks, paying more attention to their pain (Kucyi and Davis 2015).

The **descending modulatory pathway** has both components: an antinociceptive one which is needed and used when escape from danger is crucial, and the pronociceptive one, which activates to promote healing of the injury. When the pronociceptive component is prolonged after healing, transition to chronic pain happens (Tracey 2011).

The pain experience can be analysed in a theoretical framework, which considers perception as an inference, which uses prior information to generate expectations about the futures perceptions. The pain-related expectations will be compared with the new incoming sensory input. The sensory input can either confirm the expectation, or can infirm it. In this later case a prediction error signal is generated and a new learning rule which uses this teaching signal, will update the expectation (Wiech 2016). Non-optimal expectations updating can be either premature, or delayed. Premature updating can be risky and can absorb great amounts of attentional resources in hypervigilant patients. Delayed updating is characteristic for chronic pain sufferers that lead to their change resistant mental model of pain. This view allows integration of the cognitive processes into the perceptual process. As such, the descending control system could be seen as a component of a larger recurrent network, which transmits prediction error signals at all levels of the central nervous system.

Summarizing, the pain related information is encoded in the brain pain matrix, by specific patterns of activity which involves different brain areas, regions not devoted only to pain processing, but which have multiple other functional roles in the general economy of the organism. The temporarily active functional networks are specific to one or another physiological function. It was suggested that parts of the nociceptive pain matrix are shared by the empathic pain, which arises when someone observes somebody else in pain (Zaki et al. 2016).

Pain-like experiences can develop also in the absence of nociception, e.g. the phantom limb pain, the central poststroke pain, the empathic pain or cases when the origin of pain cannot be found. When pain persist, its affective aspects can become dominant and cause a lot of suffering. Imaging studies were done to identify endophenotypes of acute and chronic forms of pain, in order to relate the genetics of normal pain sensitivity and of different chronic pain states to useful biomarkers, which could facilitate the clinical diagnose (Tracey 2011). "*Endophenotypes are measurable components (biochemical, anatomical or cognitive characteristics) of a condition or disease that have a simpler link to genetic underpinning than the disease syndrome itself*" (Gottesman and Gould 2003). Biomarkers would be useful to clarify questions about the etiology of pain.

Irene Tracey's studies (Lee and Tracey 2013; Tracey 2011) succeeded to find some significant endophenotypes for the pain experience, which unravels physiologically important connections in the pain matrix. Thus, a genetically determined balance or imbalance between the anti- and pronociceptive components of the descending modulatory pathway, could be a realistic endophenotype. The **insular cortex** has been shown to be the most consistently activated region during pain experiences (Apkarian et al. 2005; Segerdahl et al. 2015; Wiech 2016).

The **frontal-limbic-brainstem network** is involved in regulating the amount of perceived pain. Distraction from pain, reduces the perceived pain and activates the cingulo-frontal cortex, the thalamus and the periaqueductal gray (PAG), through top-down gating mechanisms; in contrast, negative emotional experiences as fear and anxiety, increase the perceived pain. The ventrolateral prefrontal cortex is involved in regulation of these negative feelings via connections with the amygdala

and nucleus accumbens. When this regulation fails, and fear cannot be reduced via extinction learning, pain is amplified through parahippocampic mechanisms (Tracey 2011). It is interesting that the connectivity between the anterior insula and PAG anti-correlates with anxiety: a weaker connection correlates with higher anxiety and a lower threshold for pain in hypervigilant patients (Fair et al. 2007). The connectivity between insula, DMN and the right attentional network is stronger in patients with fibromyalgia which report increased spontaneous pain intensity (Napadow et al. 2010).

Volumetric changes in the prefrontal cortex (PFC) were evidenced. A decrease of the ventromedial PFC volume was found to be associated with higher levels of anxiety and depression (Pezawas et al. 2004); in contrast to fear extinction which is positively correlated with the thickness of the ventromedial PFC and its level of activation (Milad et al. 2007).

Markers in brain neurochemistry indicate some changes in patients with chronic pain. Higher levels of glutamate were found in the insula and amygdala in patients with fibromyalgia (Harris et al. 2009), and increased levels of inositol in the amygdala and thalamus of fibromyalgia subjects which accuse higher levels of pain, fatigue and depression (Valdes et al. 2010).

Biophysical markers of potentials endophenotypes were identified in the presence of EEG gamma oscillations (65–90 Hz) induced by noxious stimuli, in the primary somatosensory cortex, the region which encodes the sensory component of pain. A positive correlation between the amplitude of the gamma waves and both the intensity of noxious stimulation and pain intensity was found in humans (Gross et al. 2007). A lower gamma frequency (30-45 Hz) was detected in the electrocorticogram measured in rats with chronic inflammatory pain, over the primary somatosensory cortex (Wang et al. 2016). In the same study an increased coupling between the amplitude of gamma power and the phase of theta oscillations was recorded in the chronic pain condition. This coupling suggests the existence of a modulatory activity of the thalamus, or some other brain area, on the somatosensory cortex during the development of chronic pain.

EEG gamma activity was recorded also over the prefrontal scalp sites (32–100 Hz) of human subjects, and was used to predict successfully the subjects pain rating. The pain/gamma relation was not changed in low hypnotizable subjects, but disappeared when highly hypnotizable subjects were tested during the highs of hypnosis (Croft et al. 2002). A mindfulness training was found to bring pain-relief (Zeidan et al. 2012) and this effect was shown to be correlated with an increased post-training connection between the anterior insular cortex and the anterior midcingulate cortex. Thus, a top-down pain network dynamics modulation is possible (Su et al. 2016).

We have discussed here some pieces of the big physiological puzzle which could allow us to understand the generation of the different types of unnecessary pain and to imagine more effective therapies.

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Chapter 20
Connectomics in Patients with Temporal Lobe Epilepsy

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Keywords Structural connectivity • DTI • Functional connectivity • fMRI • Effective connectivity • Cortico-cortical evoked potentials • Single-pulse electrical stimulation • Altered connectivity • Temporal lobe epilepsy • Stereo-EEG

20.1 Why Is Brain Connectivity an Important Topic?

The human brain is ia amazingly complex structure whose functionality, including high-order cognitive functions, is determined by intricate connectivity patterns between tens of billions of neurons (Azevedo et al. 2009). The signaling between neurons is deceivingly simple, using binary-like electrical impulses, such that the multitude of brain functions, that are often performed concurrently, are the result of connectivity patterns across various spatial scales (Bullock et al. 1977; Budd and Kisvarday 2012), that implement a mixed sequential, parallel or hierarchical architecture. The brain regulates breathing and heart rate, collects and processes sensory information, and controls all the voluntary and involuntary movements and actions. While some of these functions are performed by well-defined areas of the brain (i.e. visual stimuli are processed solely by the primary visual cortex), some higher level functions (i.e. speech production, problem solving, music performance)

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can only be accomplished by various brain areas working together in a serial or, more likely, in a parallel or distributed design (Sigman and Dehaene 2008).

The study of brain connectivity refers to the interactions of various constituents of the brain, and can be defined for different time and spatial scales: (1) Microscale (connections between individual neurons and synapses), (2) Mesoscale (micro-columns and their connections), and (3) Macroscale (brain regions and fiber pathways). In humans, the micro and mesoscale structural connectivity patterns remain largely unknown due to the limitations of the currently available technology and the fact that assessing the connectivity at these scales require post-mortem microscopic analysis.

In this chapter, we will review the state of the art methods used to assess the macroscale structural, functional and effective connectivity, and discuss the altered connectivity patterns in patients with temporal lobe epilepsy (TLE).

20.2 Connectivity Studies in Epileptic Patients

Epilepsy, the second most frequent neurological disease after migraine, is characterized by transient changes in brain synchrony resulting in seizures with a wide range of clinical manifestations. In many cases, the disease can be controlled with anti-epileptic drugs (AED), significantly reducing or completely stopping the spontaneous seizures occurrence. However, in about one third of the epileptic patients the AEDs are not effective, and the surgical treatment is offered as a last resort (Kwan and Brodie 2000).

Evidence acquired over the last decades suggest that, although seizures may have one or more seizure onsets, epilepsy is a network disease (Kramer and Cash 2012; Bernhardt et al. 2013; Holmes and Tucker 2013; Kopell et al. 2014).

A presurgical evaluation step is needed for precisely identifying the seizure onset zone (SOZ), the epileptogenic network and for the functional mapping of the eloquent cortex (Kahane et al. 2003; Lüders et al. 2006) that has to be left outside the resection area in order to avoid functional deficits. During this step, patients are implanted with subdural and/or depth electrodes and intracranial EEG is continuously recorded for long periods of time (a few days to 2–3 weeks) until at least one habitual seizure spontaneously occurs. The electrodes are used not only to record from the putative seizure onset zone(s) and the cortical areas involved in the organization and propagation of the ictal activity, but also to perform electrical stimulation and functional mapping of the eloquent cortex. Therefore, the electrodes implanted over wide areas of the brain in the epileptic patients provide an exceptional opportunity to stimulate and record electrical activity directly from various structures of the brain, based on which effective connectivity patterns at mesoscale and macroscale can be calculated.

20.3 Structural Connectivity

Structural connectivity refers to the fiber pathways and the synapses between neurons that make possible short and long distance communications within the brain. While studies have shown that there is limited cortical neurogenesis after birth (Bhardwaj et al. 2006; Gould 2007; Ernst et al. 2014), there is a strong neuronal plasticity that allows connections between neurons to change, providing a basis for the evolution of individual behavior and constant cognitive learning. In this context, we refer to "learning" in a more general way, to include not only the process of conscious learning (i.e. a foreign language, traffic legislation, etc.), but also a wide range of background learning processes, like forming new memories, encoding new sensory information or developing a set of reactions to the external stimuli.

It is remarkable that, from the structural connectivity perspective, there is an insignificant variability between individual human brains (Sporns et al. 2005). This statement means that anatomically, all brains are virtually equal and the differences in human behavior and cognition are a consequence of the functional and effective connectivity patterns which form over the structural connectome. The functional and effective connectivity greatly varies across individuals, and we will discuss this variability later in this chapter.

The state of the art non-invasive methods for studying the brain's structural connectivity are based on diffusion MRI, a neuroimaging technique first introduced by Bihan and Breton (1985). This method relies on the diffusion of water molecules to create contrast on the MRI images. Under the assumption that water molecules flow along neuronal fibers, also termed white matter tracts, it is possible to extract information about the tissue architecture. To date, the diffusion spectrum imaging (DSI) is one of the most advanced methods of studying white matter tractography (Wedeen et al. 2005). Unlike the previously wide-used diffusion tensor imaging (DTI), the DSI is able to resolve crossing fibers within a voxel. However, the lack of standardization of parameters used for tractography analysis causes uncertainties in the evaluation of results, which in many studies are considered purely probabilistic (King et al. 1994; Hua et al. 2008).

An obvious advantage of the diffusion imaging methods is that they may be performed non-invasively on both healthy and diseased subjects. To date, a couple of white matter atlases have already been published (Mori and Crain 2005; Yeh and Tseng 2011) and can be used as reference for abnormal structural connectivity changes causing or caused by various neurological diseases, including epilepsy.

Epilepsy is a neurological disease characterized by the recurrence of spontaneous seizures, but the causes of epilepsy are not completely understood yet (Scharfman 2007, 2010). While some of these causes are structural lesions that are visible on MRIs (tumors, focal cortical dysplasias – FCDs type II, strokes, vascular malformations, hippocampal sclerosis, etc.) (Ettinger 1994), other causes (e.g. FCD type I) are more subtle and invisible on the MRI (Kabat and Król 2012; Arya et al. 2016; Doležalová et al. 2016; Wang et al. 2016).

In the MRI negative cases, it is more difficult to delineate the seizure onset zone and invasive recordings are often performed. However, once the seizures onset zone and the epileptogenic network are identified, it is possible to retrospectively analyze the diffusion MRIs and compare the structural connectivity of the brain areas implicated in seizure generation and propagation, against a physiological connectivity atlas like CMU-60/NTU-90 (Yeh and Tseng 2011) or a cohort of healthy control subjects.

The fractional anisotropy (FA) is a value between 0 and 1 that describes the degree of anisotropy in a process of diffusion. Its maximal value corresponds to the diffusion in one direction. A decrease of FA in TLE patients has been previously reported (Ahmadi et al. 2009; Besson et al. 2014), which is specific for axonal demyelination (Song et al. 2002) and degeneration (Harris et al. 2016).

In a population of 21 patients, it was demonstrated that the uncinate fasciculus and parahippocampal fiber tracts can be used to lateralize the epileptic seizure onset in 90% of the patients participating in the study (Ahmadi et al. 2009). Moreover, of eight pairs of major fiber tracts, six ipsilateral and four contralateral fiber tracts exhibit a FA decrease in the subset of patients with left TLE, while for the patients with right TLE only four ipsilateral fiber tracts showed lower FA when compared to controls. Indeed, Besson and colleagues confirm that left TLE induces larger alterations in the white matter tracts then the right TLE (Besson et al. 2014). Figure 20.1 (Besson et al. 2014) shows the nodes with significant connectivity decrease when compared to healthy control subjects. For left TLE, the largest alterations in struc-

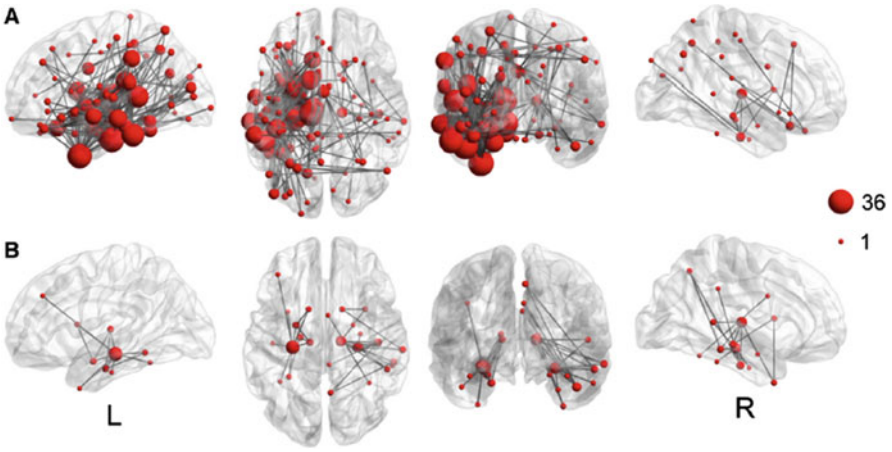

Fig. 20.1 Graphs showing diminished connectivity strength in patients with *left* (**a**) and *right* (**b**) TLE, compared to control subjects. *Spheres* represent the number of disconnections per node. The *black lines* represent diminished connectivity strength between two nodes. In *left* TLE, diminished connectivity prevailed on the left hemisphere and in particular on the left temporal neocortex. In *right* TLE, the deafferentation pattern was less pronounced and with a relative emphasis in the limbic system, bilaterally (Reproduced from Besson et al. 2014)

tural connectivity are ipsilateral, predominantly in the temporal lobe, while for the right TLE the alterations are less extended, involving bilaterally the limbic system.

While some studies proposed the use of diffusion MRI images for deriving epilepsy biomarkers of pathological tissue (Liu et al. 2016), such a biomarker is still far from being clinically validated. One of the reasons is that such studies are based on epileptic patients and healthy control subjects, where structural abnormalities are easier to be observed. There are many other neurological diseases that are associated with white matter abnormalities such as autism (Libero et al. 2016), schizophrenia (Zhuo et al. 2016), and Parkinson's disease (Arena et al. 2016), and therefore with structural connectivity changes, in the absence of epilepsy. Such evidence greatly reduces the specificity of white matter abnormalities as an epilepsy biomarker. However, in many epilepsy centers, DTI scans are performed during the presurgical evaluation and they contribute to some extent to the final decision on the seizure onset zone localization.

While useful to assess the direct connections between brain regions, DTI and DSI do not provide any information about the directionality of these connections. Moreover, these methods can not differentiate between active and inactive connections (Freund et al. 2013). However, the state of connections can be probed with functional connectivity methods, and the directionality of the connections are easily identified by effective connectivity methods.

20.4 Functional Connectivity

Functional connectivity refers to "temporal correlations between remote neurophysiological events" (Friston et al. 1993). As opposed to the structural connectivity, a functional connection between two brain regions does not necessarily require an anatomical connection between them. Instead, the two brain regions may be anatomically connected by a network hub that, depending on the method used for assessing the functional connectivity, may or may not be evidenced by the connectivity analysis.

As the brain relies on serial and parallel processing for performing a wide range of cognitive and perceptual tasks (Sigman and Dehaene 2008), the term "functional" refers to a special kind of connectivity between various brain areas, which is both dynamic and selective. For example, the episodic memory is processed by a network consisting of the medial temporal lobes, the prefrontal cortex and parts of the parietal cortex, however, during correct and incorrect memory retrieval tasks, different patterns of functional connectivity form between these regions (Watrous et al. 2013).

A large part of the literature on functional connectivity is based on functional MRI (fMRI) studies. The high incidence of fMRI studies is, to a great extent, due to the non-invasiveness of the method, which measures the hemodynamic response of neurons during task-related neural activations. Being based on MRI, the whole brain is scanned and the spatial resolution usually ranges between 1 and 5 mm, which is the MRI voxel size. The choice of the voxel size is a trade-off

between increased spatial resolution and the downside of longer scanning times and diminished contrast caused by less blood flow through the voxel. The temporal resolution is roughly 2 s, the amount of time needed for a significant change in the hemodynamic response. To be able to identify important neurophysiological events, like interictal spike discharges, and correlate their occurrence with changes in the hemodynamic response, fMRI is often combined with EEG (EEG-fMRI) (van Graan et al. 2015). Indeed, an animal study (Logothetis et al. 2001) showed that the hemodynamic response in the visual cortex of monkeys is correlated with the local field potentials recorded from the same area.

fMRI and EEG, as combined or separate methods, can be used for computing functional connectivity using both data and model-driven analysis based on correlations, cross-coherence, statistical parametric mapping, clustering analysis and many others. A vast literature has been written on the subject and more details about these analyses can be found, for example, in Salek-Haddadi et al. (2003), Li et al. (2009), and Rosa et al. (2010).

For epileptic patients undergoing invasive presurgical evaluation, the same analysis methods can be applied to intracranial EEG, with a limited spatial coverage of the brain given by the limited number of electrodes sampling the brain, but very convenient when the goal of the study is to assess the functional connectivity of well localized brain areas (Ko et al. 2013).

The human brain, facing structural changes provoked by surgical interventions or various lesions, injuries, strokes etc., attempts to restore its functionality through plasticity. This affirmation is supported by a large number of studies that report the recovery of various functions over a certain period of time (Duffau et al. 2002, 2003; Hutchinson 2011; Hart et al. 2014).

The functional connectivity in the epileptic brain is abnormal, and it is caused by one of these two situations: (1) the functional connectivity is disrupted by the seizure onset zone and the epileptogenic network which may partially overlap with other functional networks, and (2) an abnormal pattern of functional connectivity may be developed in order to restore a brain function that has been affected by the presence of epilepsy or the medical/surgical treatment. There is a subtle difference between the two cases and it refers to the brain's ability to restore its functions. In the first case, the TLE patients score low in neuropsychological tests and do not improve over time (Hermann et al. 2007; Jaimes-Bautista et al. 2015), while in the second case, the TLE patients, especially children, may improve at a variable pace (Gleissner et al. 2005, 2016; Galarza et al. 2014).

In patients with TLE and mesio-temporal lobe epilepsy (MTLE), the functional connectivity is often decreased, as shown by a wide range of methods. A magnetoencephalography study demonstrated a decreased widespread resting state functional connectivity in MTLE patients (Englot et al. 2015). Interestingly, no significant connectivity alterations were observed in the mesio-temporal structures, and no increase of connectivity was reported for either left or right MTLE patients (Fig. 20.2). Bettus and colleagues have shown in a resting-state fMRI study that the functional connectivity between the temporal pole, amygdala, anterior and posterior hippocampus, and the entorhinal cortex was decreased in 18 out of 22 MTLE

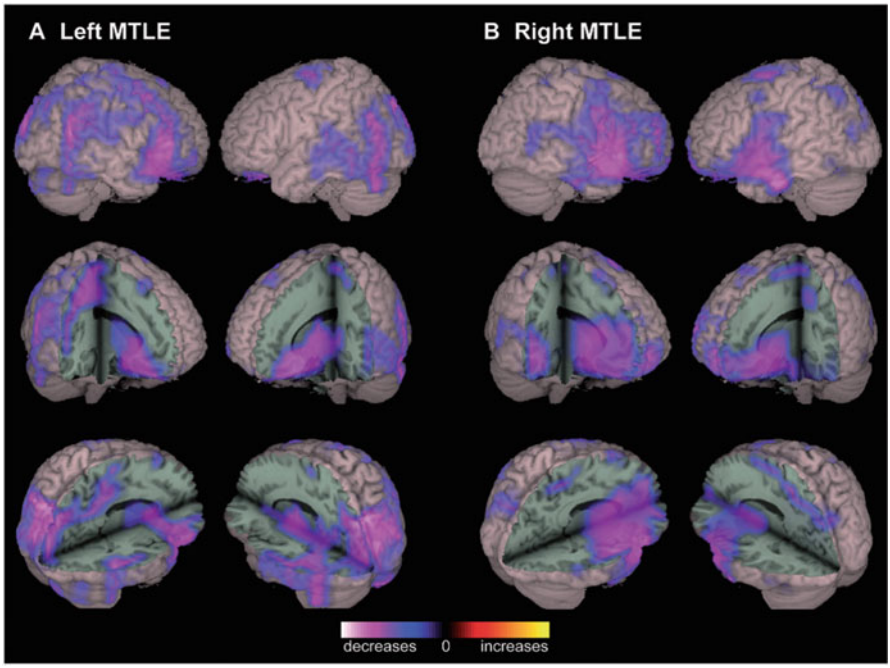

Fig. 20.2 Decreased resting-state functional connectivity in patients with MTLE. (**a**) Patients with left MTLE demonstrate decreased functional connectivity, compared to control subjects, in widespread regions including right lateral frontal, bilateral posterior temporal, bilateral parieto-occipital, and right perisylvian neocortex, as well as basal forebrain, basal ganglia, anterior thalamus, posterior orbitofrontal cortex, posterior cingulate/precuneus, and right anterior insula. (**b**) Similar decreased connectivity is observed in patients with right MTLE,particularly in the perisylvian and lateral frontal neocortex, as well as in the basal forebrain, basal ganglia, anterior thalamus, orbitofrontal cortex, and insula. No regions of increased connectivity are observed, and significant connectivity alterations are not seen in the mesial temporal structures. Connectivity maps represent t-tests ($p < 0.01$) of alpha-band imaginary coherence in patients with left ($n = 18$) or right ($n = 12$) MTLE compared to controls, overlaid on a 3D-rendered template brain (Reproduced from Englot et al. 2015)

patients, compared to healthy controls, ipsilateral to the seizure onset localization, in both left and right hemisphere (Bettus et al. 2010). However, in the same study they confirm some previous results (Bettus et al. 2009) showing that the functional connectivity of the contralateral mesio-temporal structures is increased, preferentially involving the amygdala and the hippocampus.

Similar resting-state fMRI studies have found an increased connectivity of the limbic structures, with different patterns in left and right TLE groups (Morgan et al. 2012), and even regardless of the lateralization of TLE (Haneef et al. 2014) (Fig. 20.3).

Studies of fMRI and related techniques offered some promising results for the localization the epileptic tissue (Pittau et al. 2012, 2014; Tousseyn et al. 2014;

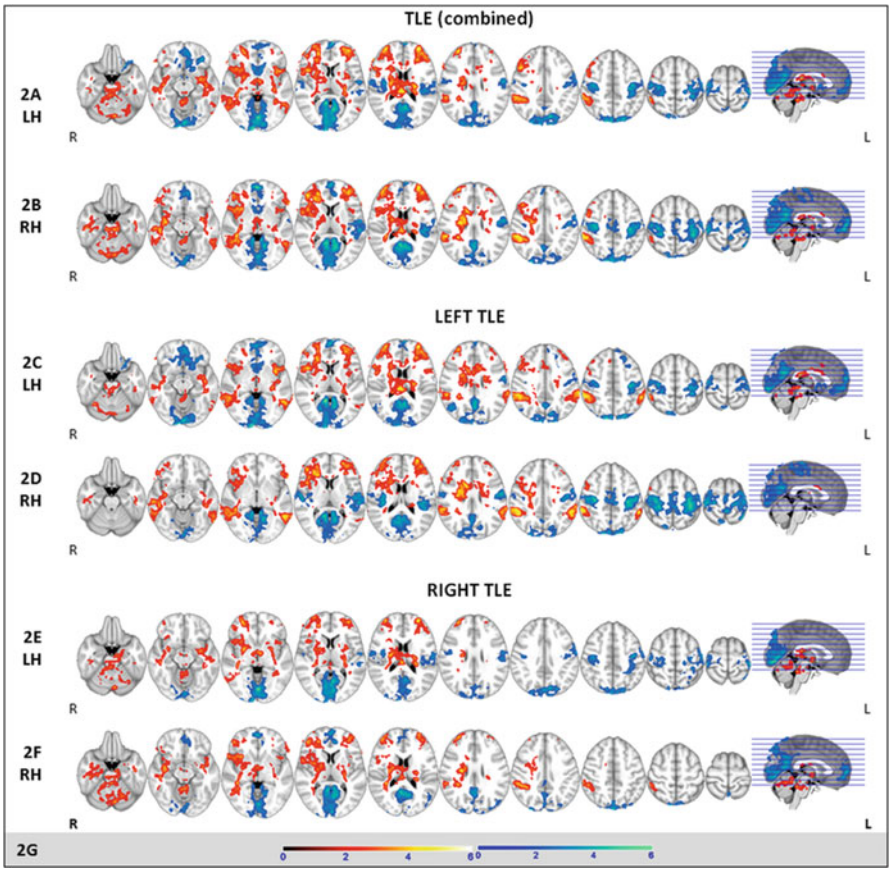

Fig. 20.3 Areas of increased (*hot colors*) and decreased (*cold colors*) connectivity compared to controls with *left* (*LH*) and *right* hippocampal (*RH*) seeds, respectively, in all cases of TLE (*A*,*B*), left TLE (*C*,*D*) and right TLE (*E*,*F*) (Reproduced from Haneef et al. 2014)

Englot et al. 2015; van Graan et al. 2015), however their clinical utility is still a matter of debate (Centeno and Carmichael 2014).

Although the fMRI results sometimes point directly towards the epileptogenic zone, they often provide complementary information whose interpretation is made in the light of several other neuroimaging methods. To the best of our knowledge, no clinical decision is made solely on the results of an fMRI.

Functional connectivity between temporal lobe structures, as measured by the synchronization likelihood (Stam and van Dijk 2002) of interictal recordings of intracranial EEG, was shown to be higher in mesio-temporal lobe epilepsy patients, compared to control patients whose epilepsies were extra-temporal (Bartolomei et al. 2013), as illustrated in Fig. 20.4. The findings have been confirmed by several studies showing increased functional connectivity within the seizure onset zone, and

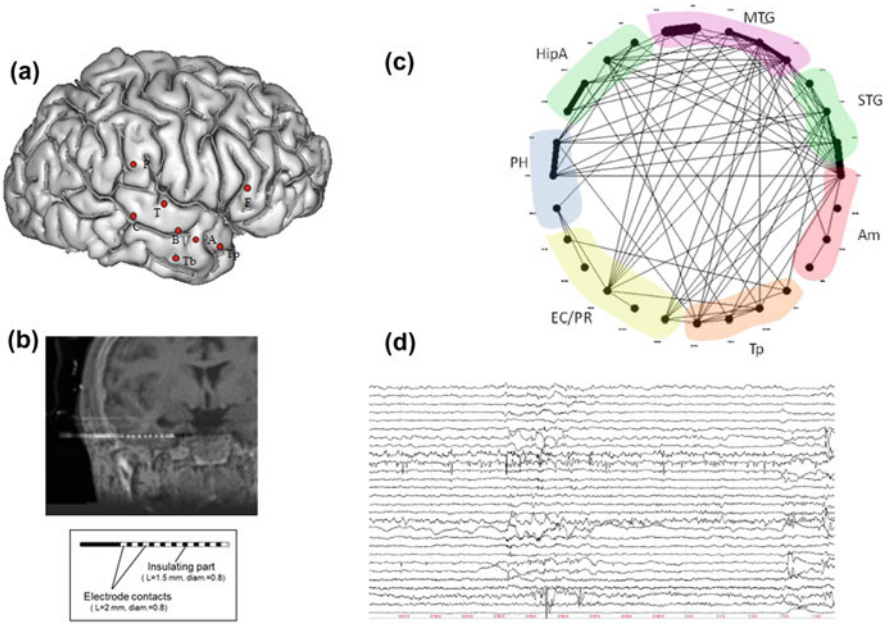

Fig. 20.4 Positioning of the SEEG electrodes in a patient with MTLE. Electrode labels: *TP* temporopolar cortex; (**a**) amygdala (mesial contacts) and the anterior part of the middle temporal gyrus (*MTG*) (lateral contacts); (**b**) anterior hippocampus (medial contacts) and mid-MTG (lateral contacts); Tb- entorhinal cortex (internal contacts) and the anterior part of the inferior temporal gyrus (lateral contacts); (**c**) posterior hippocampus (medial contacts) and the posterior part of MTG (lateral contacts); *T* – insula and the anterior part of the superior temporal gyrus (*STG*); *P* – parietal electrode. (**b**) Trajectory of the electrode labeled Tb passing through the collateral sulcus seat of the perirhinal cortex (*PR*) and reaching the entorhinal cortex (*E*). (**c**) Graph representation and synchronization pattern in a patient with MTLE. Synchronization between seven regions (28 contacts) is depicted using a thresholded graph representation. *Abbreviations*: *HipA* anterior hippocampus, *PH* parahippocampal and posterior hippocampus region, *EC/PR* entorhinal cortex and perirhinal cortex region, *Tp* temporopolar cortex, *Am* amygdala, *STG* superior temporal gyrus, *MTG* middle temporal gyrus, (**d**) Example of 20 s of interictal SEEG recordings. Channels 1–20 are from the mesial temporal structures and channels 21–28 from neocortex (Reproduced from Bartolomei et al. 2013)

reduced functional connectivity between the seizure onset zone and surrounding brain areas (Warren et al. 2010; Klimes et al. 2016).

20.5 Effective Connectivity

The effective connectivity is defined as "the influence one neural system exerts over another" (Friston et al. 1993). As neurons communicate remotely through axonal propagation of action potentials, being able to understand the direction

of the information flow and the time dynamics of these interactions is of utmost importance.

The state of the art methods for studying the effective connectivity in humans are a trade-off between the spatial extent of the brain areas that can be investigated and the level of detail at which the connectivity may be assessed (Ugurbil 2016). Many of the non-invasive methods used for mapping the functional connectivity can be used to map the effective connectivity by performing different type of analyses on the time series recorded (hemodynamic response, magnetoencephalography or EEG signals), most often based on Granger causality (Granger 1969; Bressler and Seth 2011; Seth et al. 2015), dynamic causal modelling (Friston et al. 2003; Stephan et al. 2007), directed transfer function (Franaszczuk et al. 1994) or other derived methods (Blinowska 2011; Penny 2012). While these methods allow for whole brain mapping of the effective connectivity, they are highly sensitive to a large number of artefacts and restricted to large-scale interactions between brain areas.

The epileptic patients undergoing presurgical evaluation provide a unique opportunity to study the effective connectivity at the micro- (single-unit level), meso- (microcolumns) and macro-scales. This can be achieved using microelectrodes (Fisher et al. 2010; Mottonen et al. 2015), multi-electrode arrays (Schevon et al. 2010), subdural electrodes (Conner et al. 2011; Entz et al. 2014) and depth electrodes (David et al. 2013; Donos et al. 2016a). However, electrodes are always implanted for clinical reasons, therefore they mainly target brain areas suspected of epileptogenic activity. In stereo-EEG implantations, additional electrodes are usually implanted for functional mapping of the eloquent cortex which needs to be spared during the resection, delineating the resection limits and, sometimes, for excluding an alternative hypothesis of ictal discharges being generated remotely from the suspected epileptogenic areas (Kahane et al. 2003). In the end, some of the electrodes' contacts will prove to be outside the epileptogenic zone (Kahane et al. 2006; Lüders et al. 2006), in what a large number of studies consider to be healthy brain tissue (Matsumoto et al. 2004, 2007; Conner et al. 2011; Entz et al. 2014; Keller et al. 2014a, b; Donos et al. 2016a). This classification of pathological and physiological intracranial EEG recordings, based on the epileptogenicity of the brain tissue located in the proximity of the electrode's contacts, allow for the invasive study of effective connectivity, in human subjects, and the identification of abnormal connectivity patterns in the epileptogenic network.

The epileptogenic zone (EZ) was shown to exert influence over the non-epileptic zone (NEZ) in TLE patients (Bettus et al. 2011). Bettus and colleagues used blood oxygen level dependend (BOLD) and intracranial EEG signals, separately, and obtained the above mentioned results from both methods (Fig. 20.5). However, for the functional connectivity they reported higher values in EZ when using intracranial EEG and lower values in EZ when using BOLD signal, relative to NEZ.

Effective connectivity is, by definition (Aertsen and Preissl 1991), a dynamic and condition-dependent type of connectivity. On some level, this explains the large number of studies of effective connectivity based on interictal and ictal periods, various sleep stages, on EEG recorded during cognitive tasks or during various types

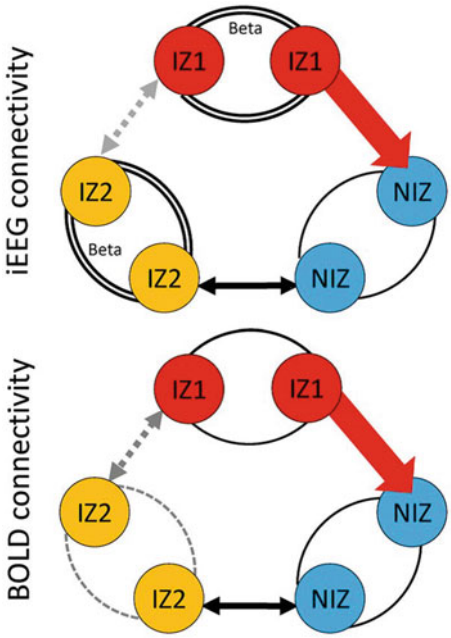

Fig. 20.5 Functional and effective connectivity graphs during interictal period. The regions of interest shown are: epileptogenic/primary irritative zone (*EZ/IZ1*); secondary irritative zone (*IZ2*); non irritative zone (*NIZ*). The curved lines represent within-zone functional connectivity. NIZ to NIZ connectivity is considered as 'normal' functional connectivity. *Double curved lines* represent significantly increased functional connectivity compared to 'normal' one, *grey* and *dotted curved lines* represent significantly decreased functional connectivity, and *grey curved lines* indicate a trend of decreased functional connectivity. *Arrows* represent inter-zone effective connectivity. Unidirectional *red arrows* correspond to a significant direction index between zones. *Bidirectional arrows* correspond to non-significant direction index between zones. *Grey and dotted double arrows* represent significantly lower functional connectivity between IZ1-IZ2 compared to connectivity between other zones (Reproduced from Bettus et al. 2011)

of brain stimulation, and the fact that, sometimes, the results do not completely overlap.

Scalp EEG studies showed increased ictal effective connectivity, as revealed by partial directed coherence (Baccalá et al. 2004) and directed transfer function (Lu et al. 2012), between EEG channels located over the EZ. Intracranially, many other studies confirmed the possibility of localizing the EZ using effective connectivity computed on ictal (Mullen et al. 2011; van Mierlo et al. 2013) or interictal EEG (Wilke et al. 2009; van Mierlo et al. 2011).

Another method of studying the effective connectivity is using direct electrical stimulation applied to a pair of intracranial contacts. Stimulation-evoked responses can be recorded by other EEG contacts located in brain areas that have a directed connection with the stimulated brain location. The responses to low frequency stimulation (<1 Hz) were initially named cortico-cortical evoked responses (CCEPs),

as they have been introduced on subdural electrodes (Matsumoto et al. 2004). In the recent years, this stimulation method has been extended to stereo-EEG electrodes but the terminology of the responses remained CCEP, even if mesial structures are involved (Enatsu et al. 2014). CCEPs were successfully used to study the language (Matsumoto et al. 2004; Conner et al. 2011; Yamao et al. 2014), motor (Matsumoto et al. 2007; Enatsu et al. 2013), limbic (Enatsu et al. 2015) and visual (Matsuzaki et al. 2013) networks, as well as more extended brain regions by performing group analysis over larger populations (David et al. 2013; Entz et al. 2014; Donos et al. 2016a). However, the reproducibility of results is sometimes an issue, partially because of the inter-patients variability of the epileptic network's extent and localization, and partially because of the slightly different stimulation protocols used by different research groups (Donos et al. 2016b).

The above enumerated studies attempted to map physiological effective connections, by excluding the contacts located in the epileptogenic cortex. For the purpose of assessing the abnormal effective connections in TLE patients, it is important to compare the physiological connections with the pathological ones. An indirect way of showing increased outbound effective connectivity is by showing that EZ is more excitable using CCEP. Indeed, the EZ associated with repetitive spiking and paroxysmal fast patterns exhibited higher excitability than brain regions in the NEZ (Enatsu et al. 2012b). Similar findings were reported by other studies (Iwasaki et al. 2010; Enatsu et al. 2012a), suggesting an increased connectivity of the EZ.

Although TLE patients are usually pooled together in group analyses, the seizures may involve different brain structures within the temporal lobe. It is therefore important to be more specific about the patterns of effective connectivity and study them at the sublobar structure level. Our group has recently published a whole-brain structural-effective connectome of the human brain (Donos et al. 2016a), where single pulse electrical stimulation (SPES) (Valentín et al. 2002) was used to assess the effective connectivity of 80 brain structures and map the connections over a diffusion spectrum imaging atlas (Yeh and Tseng 2011). Using the stimulation protocol described in detail in Donos et al. 2016a, b, we have mapped the effective connectivity of eight mesio- and inferior-temporal lobe structures from both hemispheres (amygdala – A, hippocampus – Hc, entorhinal cortex – E, temporal pole – TP, inferior temporal gyrus – ITG, medial temporal gyrus – MTG, superior temporal gyrus – STG, and the fusiform gyrus – F). In some patients, these contacts were part of the EZ, in others they were located outside EZ, allowing us to perform a differential analysis of the effective connectivity between two structures by computing an epileptogenicity modulation index (*EZMI*) based on the amplitude of the CCEPs (Fig. 20.6), defined as:

$EZMI = \frac{R^{EZ}_{A\to B} - R^{NEZ}_{A\to B}}{R^{EZ}_{A\to B} + R^{NEZ}_{A\to B}}$, where $R^{EZ}_{A\to B}$ is the connectivity between structures A and B, calculated according to the method described in Donos et al. 2016a, in the subset of patients where structure A is part of the epileptogenic network, and $R^{NEZ}_{A\to B}$ is the connectivity between the same structures when A is non-epileptogenic.

The outbound effective connectivity of a brain structure is therefore characterized by *EZMI*, the number of other brain structures it connects to, and the connection

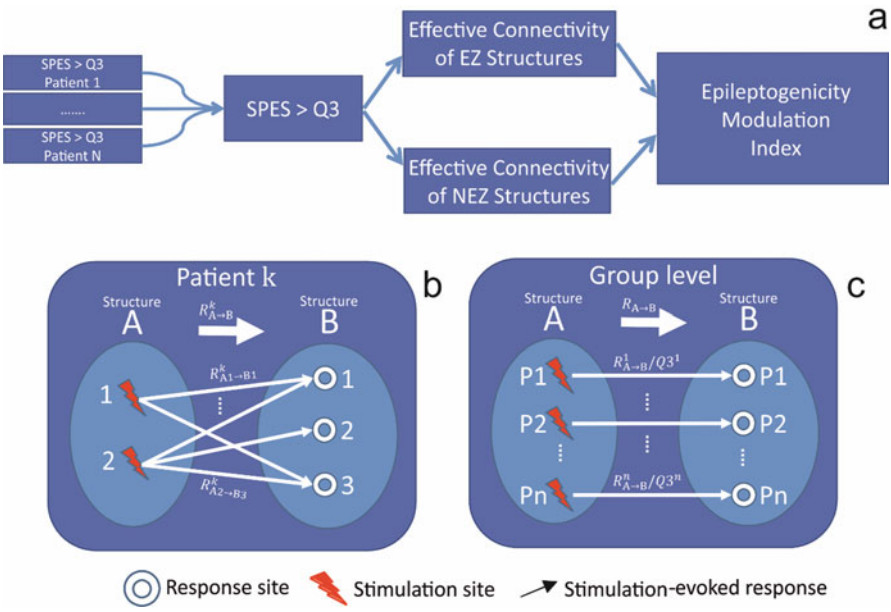

Fig. 20.6 (**a**) The workflow for calculating changes in the effective connectivity of epileptogenic structures; (**b**) a detail of the steps followed for calculating the effective connectivity $R^k_{A\rightarrow B}$ between two structures (*A, B*) implanted with multiple contacts, in a single patient. The effective connectivity is calculated separately for two subset of contacts, located in epileptogenic and non-epileptogenic areas, the differences being captured by the epileptogenicity modulation index; (**c**) details of the process of calculating the average effective connectivity in the entire patient group, by the normalization of patients' responses by normalization with the patient-specific activation threshold (Adapted from (Donos et al. 2016a))

strength with these structures, regardless of their inclusion in the EZ. Preliminary results computed on 41 patients are shown in Fig. 20.7. The amygdala, the entorhinal cortex and the temporal pole exhibit predominantly increased effective connectivity patterns (Fig. 20.7a, d, h), while the hippocampus, fusiform gyrus, superior and inferior temporal gyrus have the majority of connections with a negative modulation index, pointing towards patterns of decreased effective connectivity (Fig. 20.7b, c, e, g). Many of these connections are in agreement with a study of the effective connectivity of the limbic system (Enatsu et al. 2015), however, Enatsu and colleagues do not make a distinction between epileptogenic and healthy brain tissue, and conclude that further studies are needed to validate the connections in epileptic patients. Increased local functional connectivity in MTLE patients been previously reported (Bettus et al. 2011; Bartolomei et al. 2013), and the epileptogenic areas seem to have reduced overall connectivity with the surrounding non-epileptogenic tissue (Warren et al. 2010). Indeed, such effective connectivity patterns have also been observed in MTLE patients, for example the entorhinal (Fig. 20.7d) and the inferior temporal gyrus (Fig. 20.7g) are connected only to other temporal lobe

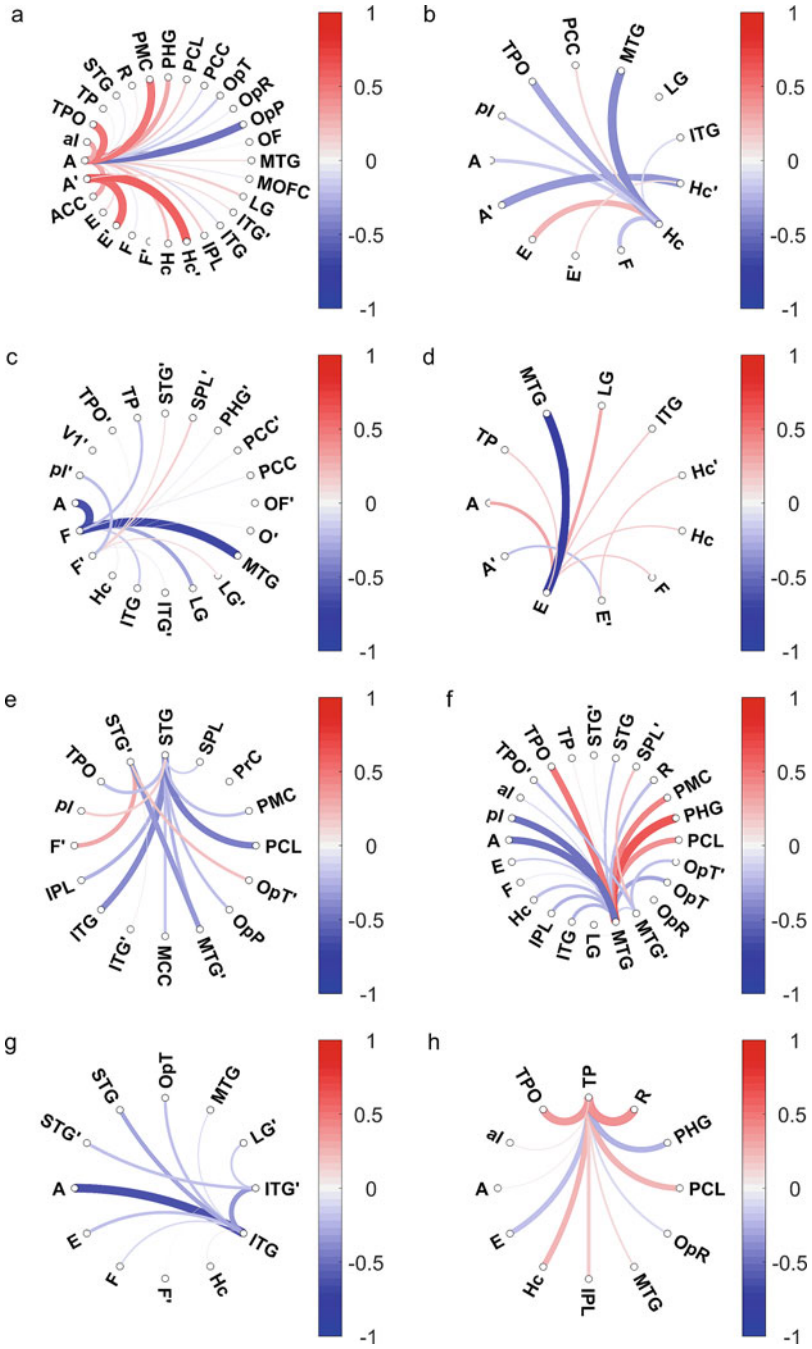

Fig. 20.7 Effective connectivity patterns of eight mesio-temporal structures: (**a**) amygdala (*A*), (**b**) hippocampus (*Hc*), (**c**) fusiform gyrus (*F*), (**d**) entorhinal cortex (*E*), (**e**) superior temporal gyrus (*STG*), (**f**) middle temporal gyrus (*MTG*), (**g**) inferior temporal gyrus (*ITG*), and (**h**) temporal pole

structures, supporting the idea of strongly interconnected EZ structures, and a significant segregation between the EZ and non-EZ.

Some properties of temporal epileptic networks are readily apparent when analyzing the 8 connectivity graphs. The first result, that deserves more detailed investigation in the future, is that the strongest physiological connections have the highest/lowest modulation index. It thus seems that epilepsy preferentially deconstructs the most important physiologic pathways. As the correlation between tract width and connection's strength is relatively week ($r2 < 0.11$, $p < 10^{-10}$) (Donos et al. 2016a) this does not seem to be caused by the preferential fiber loss in large tracts, but rather to pathological activity that potentiates the connections' strength. Second, the pattern of connectivity seems to differ in both healthy and pathologic structures between hemispheres, in line with the many studies reporting differences between right and left temporal epilepsies. Although the relatively large patient population in our study increases the chances of bilateral alterations, these were not the rule. For example, the well-known connection between the superior temporal gyrus and middle temporal gyrus surpassed our criteria for a valid effective connection only on the left hemisphere. This is possibly related to the lateralization of the dorsal auditory pathway in the speech dominant hemisphere (Zaehle et al. 2008). Even in homologous pairs the strength can vary widely across hemispheres. For example the amygdala-hippocampus connection is much stronger on the left – a finding that can explain the higher network disruption reported for LTLE (Yasuda et al. 2015), in accordance with the higher memory deficits reported by these patients. The course of the connectivity changes is generally concordant between homologous pairs, although it can occasionally take opposite values. An example would be the entorhinal – amygdala connection, the most cited propagation route for mesial temporal lobe epilepsies (Stoop and Pralong 2000). Our patient population exhibits a stronger pathological connectivity (positive *EZMI* values) on the right, the left hemisphere having an opposite modulation.

Overall, the results demonstrate a disconnection of epileptogenic structures. The Hc is generally disconnected from other structures, in agreement with the findings of Pittau et al. 2012, for instance. The middle temporal gyrus has a mixed pattern of connectivity, with the right MTG exhibiting enhanced pathological connectivity

Fig. 20.7 (continued) (*TP*). The strength of the effective connections are proportional to the width of the arcs connecting the structures, while the modulation index is color-coded. *Red* arcs represent connections that are stronger when the stimulated structure is part of EZ, while *blue* arcs represent connections that are stronger when the stimulated structure is outside EZ. Brain structures located in the left hemisphere are marked with an apostrophe. The labels used in the figure are: *MCC* Middle Cingulate Gyrus, *MOFC* Mesial Orbito-Frontal Cortex, *OF* Orbito-Frontal, *PMC* Premotor Cortex, *R* Precentral Gyrus, *A* Amygdala, *E* Entorhinal, *F* Fusiform Gyrus, *Hc* Hippocampus, *ITG* Inferior Temporal Gyrus, *MTG* Middle Temporal Gyrus, *PHG* Parahippocampal Gyrus, *STG* Superior Temporal Gyrus, *TP* Temporal Pole, *aI* Anterior Insula, *OpP* Operculum Parietalis, *OpR* Operculum Rolandis, *OpT* Operculum Temporalis, *pI* Posterior Insula, *IPL* Inferior Parietal Lobule, *PCC* Posterior Cingulate Cortex, *PCL* Paracentral Lobule, *PrC* Precuneus, *SPL* Superior Parietal Lobule, *C* Cuneus, *LG* Lingual Gyrus, *O* Lateral Occipital, *TPO* Temporo-Parieto-Occipital Junction, *V1* Primary Visual Cortex

with structures located outside the temporal lobe. Our results show that the anterior temporal structures, namely the amygdala, temporal pole and entorhinal cortex exhibit enhanced connectivity when part of the epileptogenic network, while the more posterior– hippocampus, fusiform, inferior and superior temporal gyrus are disconnected. These results support the idea of a functional reorganization of the epileptogenic temporal lobe, isolating the cognitive areas while engaging more the paleocortex in its relationship with the rest of the brain. This mixed dynamic can represent the substrate of the frequent cognitive and psychiatric comorbidities reported in these patients.

20.6 Future Directions

At present, the neuroscience community has a large number of technical and analytical methods to study the human brain connectivity, in vivo, across various spatial scales. Moreover, the network topology may be considered constant over different time scales. For example the same underlying structural connectivity is constant in ranges of hours to several years, but the functional and effective connectivity patterns that are mapped over this topology vary greatly to accommodate a wide range of higher brain functions, dynamically changing over short time periods of down to tens of milliseconds (Honey et al. 2007).

The biggest challenge of brain connectivity research is to find a way of integrating connectivity patterns not only across time and spatial scales, but also across investigation modalities. Recent studies have shown a moderate overlap of results obtained by some of the most used methods for the study of brain connectivity. Jones et al. (2014) compared connectivity results obtained from fMRI, electrical stimulation during resting state fMRI, CCEPs and diffusion MRIs, with the biggest overlap, though modest in absolute value, occurring between CCEPs and fMRI, followed by the one between CCEPs and diffusion MRI. While some of these results may be complementary and provide useful information for clinical diagnostic and treatment of TLE and MTLE, they may also be misleading (Bettus et al. 2011), in the absence of reliable models accounting for the differences between the investigation modalities.

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Chapter 21
Mind the Reward: Nutrition vs. Addiction

Cosmin Sonea, Anca-Liliana Opris, Manuel F. Casanova, Ioan Opris, and Marian Vladimir Constantinescu

Abstract Nutrition and reward are two important functions of the brain. To understand their underpinnings we look into the neural processing underlying the mechanisms of reward and nutrition at the interface with cognition. The common denominator of nutrition and reward functions is "food" intake that represents the energy source for all vital functions of an organism. In this chapter, we briefly discuss these two neural systems involving the sensory encoding of taste, the digestive system for nutrition, the reward mechanisms for food and drug addiction, together with its implications on cognition, as well as the neural substrate of human obesity and addiction. Finally, we touch on the idea that some nutrients and rewards require attention in order to prevent obesity and addiction.

Keywords Mind • Reward • Nutrition • Gut • Digestive system • Food-brain connection • Addiction • Drug • Obesity • Yale Food Addiction Scale

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21.1 Introduction

Our sensory systems generate internal representations of the outside world, including its physical (vision, sound, touch and temperature) and chemical (taste and olfaction) senses (Kaas 1989). Nutrition and reward are two key functions involved with food taste and intake. Food intake-provides energy for all vital functions of the organism (Morton et al. 2014). Under normal conditions, both the amount of energy (in calories) used to perform a certain activity and the food intake are balanced by a homeostatic system that keeps the stability of body fat content over time. However, this homeostatic system can be overridden by the activation of 'emergency response circuits' (Morton et al. 2014) that mediate feeding responses to emergent or stressful stimuli. Inhibition of these circuits is, therefore, permissive for normal energy homeostasis to occur, and their chronic activation can cause profound changes in body fat mass, that may have life-threatening consequences (Morton et al. 2014, Gearhardt et al. 2011).

Investigations of the relationship between nutrition (reward) system and cognitive functions clearly provide valuable clues to our understanding of the mind (Opris et al. 2009; Smith and St. John 1999; Smith et al. 2000; Volkow et al. 2008b). Here, we briefly discuss the crucial operation of the reward and nutrition systems, including the sensory encoding of taste by taste buds, the digestive system, the reward mechanism with its implications on cognition, as well as, the overlapping neural circuits in human obesity and addiction (Volkow et al. 2014).

21.2 The Digestive System

Our mind uses energy for neuronal processing and for this purpose nutrition is vital (Morton et al. 2014). Here, we examine the food-brain connection from the anatomical and functional perspectives, by looking into the substrates of the digestive system, the sensory function of taste, the blood-brain-barrier, and the neuronal processing in the guts, the brainstem and the cortex (Erickson et al. 1980, Erickson 2000).

21.2.1 Anatomical Substrate of the Digestive System

The anatomical organization of the digestive system plays a vital role in food-intake and the reward mechanisms.

The Digestive System The digestive system (Fig. 21.1) is a morphological and functional assembly of organs that digest and absorb ingested foods, as well as, the elimination of unavoidable residues (Rolls 2016). A digestive system turns food into energy and basic nutrients (Gershon and Erde 1981). The gastrointestinal tract

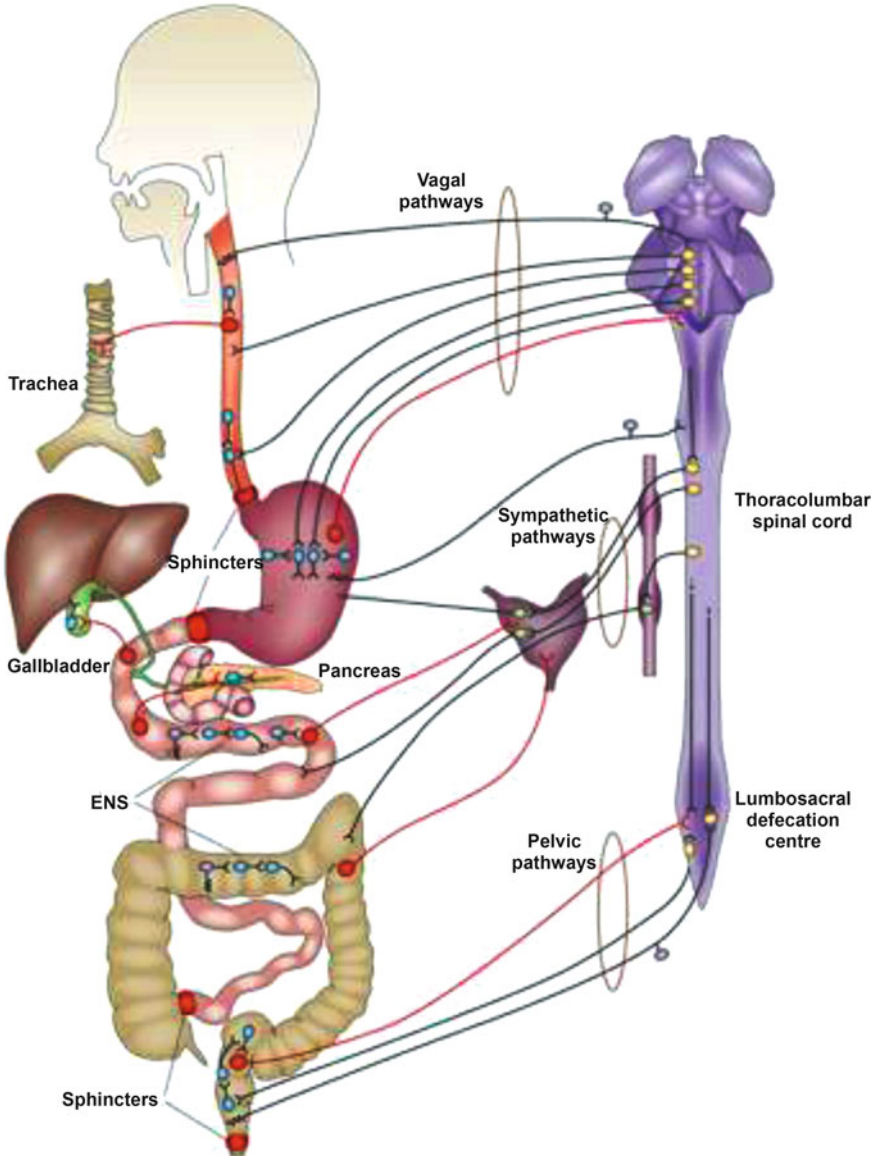

Fig. 21.1 The gastrointestinal tract with its innervation. On the *left side* is displayed the gastrointestinal tract and on the *right side* its corresponding neural connections between gastrointestinal organs, The digestive system contains full reflex circuits of the ENS (motor neurons and interneurons in *blue*, sensory neurons in purple). Pathways from the gastrointestinal tract project outwards, via intestinofugal neurons (*red*), to the CNS (neurons in *yellow*), sympathetic ganglia, gallbladder and pancreas. Neurons in sympathetic prevertebral ganglia (*green*) receive both CNS and ENS inputs. Sensory information goes both to the ENS, via intrinsic primary afferent (sensory) neurons (*purple*) and to the CNS via extrinsic primary afferent neurons (also *purple*) that follow spinal and vagal afferent routes. Pathways from the CNS reach the ENS and gastrointestinal effector tissues through vagal, sympathetic and pelvic pathways. Abbreviations: *CNS* central nervous system, *ENS* enteric nervous system (With permission from Furness 2012)

is a long and muscular tube that functions as a food processor for the animal body. By digestive tract is understood the digestive system formed by a series of organs: buccal cavity, pharynx, esophagus, stomach, small intestine, and large intestine. Adjacent organs of the digestive system are teeth, tongue, salivary glands, liver, bile and pancreas.

The *oral cavity* is the initial, cranial segment of the digestive tract in mammals. The *tongue*, *teeth* and *salivary glands* are located inside the mouth. The oral cavity has the role of eating the food and feeling it with saliva, as well as, swallowing. The teeth (n = 32) are implanted in the dental alveoli. The main component of the teeth is the dentine covered with an enamel layer. The teeth have blood vessels and nerves under the dentin in a soft region known as the pulp. Dentition in adults is composed of: incisors, canines, molars and premolars. Teeth have a role in mastication.

The *tongue* is a muscular structure with a role in catching, mastication and swallowing of food, and it intervenes in appreciating the taste of food through taste sensitivity. The tongue ensures the mixing and pushing of food to the teeth, and the masticatory muscles perform the mandible movements. The masticatory movements are achieved by activating a sequence of unconditional lifting and lowering of the mandible.

Salivary glands are disseminated or clustered exocrine glands, that secret saliva and play a role in buccal digestion (Gershon 1998).

The *pharynx* is a short tube that represents the intersection of the airway with the digestive tract. Above the larynx is a cartilage called epiglottis, which closes swallowing. It has the role of leading foods from the mouth to the stomach. It is made of striated fibers.

The *esophagus* is a muscular tube that traverses the chest cavity. It is located behind the trachea. The esophagus consists of several layers or tunics. From the inside out, these layers are: the mucous tunic (contains mucus secreting glands), the submucosa tunic (forming folds), the tunic (including longitudinal and circular fibers) and the outer or adventitial tunic (which is the protective layer). The esophagus innervation is ensured by the vagus nerve and the esophageal nerve plexus.

The *stomach* is a cavitary organ located between the esophagus and the duodenum. It is a food storage space where it will mix with the gastric juice and undergo a chemical and mechanical transformation to complete digestion. The stomach wall consists of four layers - mucosal, submucosal, muscular and serous. The stomach also secretes hydrochloric acid and digestive enzymes that continue digestion of foods that have started in the mouth.

The *small intestine* is made up of: the duodenum (fixed part) that is connected to the bile and the pancreas. The small intestine has many folds and a mucosa lined with microvilli. In the small intestine, walls are smooth, longitudinal and circular muscle fibers that perform segmentation and peristaltic movements. Among the villi in the thickness of the intestinal mucosa are the intestinal glands, which secrete the intestinal juice. The chemical digestion of proteins, carbohydrates, and lipids is completed with the glycolitics, proteolytics, and lipolytics enzymes present in it.

The *liver* is the most voluminous dark red digestive gland. It weighs, in general, between 1.5 and 2 kg. It stores many vitamins, such as vitamin A, B12 and a number of essential trace elements. The secretion product, called bile, is temporarily stored in a bladder reservoir. The bladder does not contain ferments, but plays an important role in the digestion of nutrients.

The *pancreas* is a mixed gland with exocrine secretion (pancreatic juice containing trypsin, lipase and amylase used in the decomposition of nutrients in food) and endocrine secretion (secreting the hormone called insulin).

The *large intestine* is the segment of the digestive tract between the ileocecal (or ileococcal) and the anal canal. It includes: cheek, colon and rectum. It is characterized by the absence of intestinal villi, by the presence of long glands, and by its abundance of caliciform cells. In the large intestine there are symbiont bacteria that help in the formation of faeces, water absorption and synthesis of vitamins B and K.

The digestive system has 6 important functions: ingestion, secretion, mixing and movement, digestion, absorption and excretion (Johnstone et al. 2014). The coordination of these functions has implicated cortical modules (layers and minicolumns), subcortical nuclei (basal ganglia and thalamic nodes), and brainstem structures (midbrain, pons and medulla) are the components of the brain architecture. These structures use sensory inputs, like taste and smell (Rolls 2005, 2016).

21.2.2 The Taste

Taste is a sensory function that has the role of "evaluating the nutritious content of food and preventing the ingestion of toxic substances" (Chandrashekar et al. 2006, Huang et al. 2006; Nelson et al. 2001). The emerging understanding of taste is based on five basic sensations: sweet, sour, bitter, salty and umami. Sweet taste allows the "identification of energy-rich nutrients", umami permits the "recognition of amino acids", salt taste ensures the "proper dietary electrolyte balance", and sour and bitter "warn against the intake of potentially noxious and/or poisonous chemicals" (Chandrashekar et al. 2006). Moreover, taste in humans includes the "pleasure and enjoyment of a meal" (Chandrashekar et al. 2006).

The anatomical "substrates" of taste detection involve the taste-receptor cells (TRCs; Fig. 21.2a). TRCs are assembled into "taste buds", which are "distributed across different papillae of the tongue and palate epithelia" (Chandrashekar et al. 2006). Taste buds are made up, depending on the species, from 50 to 150 taste receptor cells distributed in various forms: circumvallate, foliate and fungiform. Circumvallate taste buds are distributed on the back of the tongue. Foliate papillae are clustered into two groups positioned at either side of the tongue. Fungiform papillae are found on the two anterior thirds of the tongue. Moreover, the perception of taste in humans is extended by olfactory, visual and somatosensory inputs (Zampini and Spence 2012).

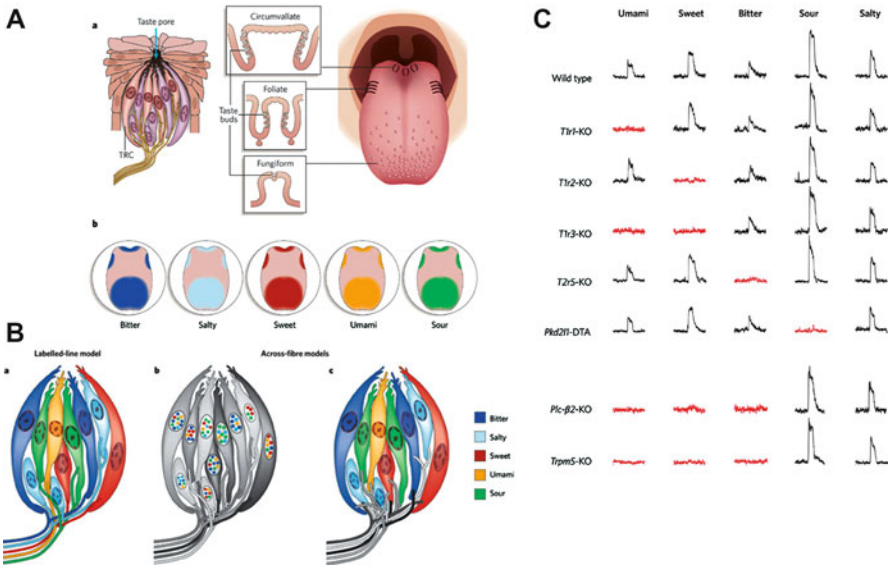

Fig. 21.2 The taste. (**a**). Taste-receptor cells, buds and papillae. a, Taste buds (*left*) are composed of 50–150 TRCs (depending on the species), distributed across different papillae. Circumvallate papillae are found at the very back of the tongue and contain hundreds (mice) to thousands (human) of taste buds. Foliate papillae are present at the posterior lateral edge of the tongue and contain a dozen to hundreds of taste buds. Papillae contain one or a few taste buds and are found in the anterior two-thirds of the tongue. TRCs project microvillae to the apical surface of the taste bud, where they form the 'taste pore'; this is the site of interaction with tastants. b, Recent molecular and functional data have revealed that, contrary to popular belief, there is no tongue 'map': responsiveness to the five basic modalities - bitter, sour, sweet, salty, and umami - is present in all areas of the tongue (With permission from Jayaram Chandrashekar, Mark A. Hoon, Nicholas J. P. Ryba & Charles S. Zuker, The receptors and cells for mammalian taste. Nature, 444: 288–294). (**b**). Encoding of taste qualities at the periphery. There are two opposing views of how taste qualities are encoded in the periphery. a, In the labeled-line model, receptor cells are tuned to respond to single taste modalities - sweet, bitter, sour, salty or umami - and are innervated by individually tuned nerve fibres. In this case, each taste quality is specified by the activity of non-overlapping cells and fibres. b, c, Two contrasting models of what is known as the 'across-fibre pattern'. This states that either individual TRCs are tuned to multiple taste qualities (indicated by various tones of grey and multicoloured stippled nuclei), and consequently the same afferent fibre carries information for more than one taste modality (b), or that TRCs are still tuned to single taste qualities but the same afferent fibre carries information for more than one taste modality (c). In these two models, the specification of any one taste quality is embedded in a complex pattern of activity across various lines. Recent molecular and functional studies in mice have demonstrated that different TRCs define the different taste modalities, and that activation of a single type of TRC is sufficient to encode taste quality, strongly supporting the labelled-line model (Chandrashekar et al. 2006). (**c**). Sweet, umami, bitter and sour are mediated by specific receptors and cells. The traces show recordings of tastant-induced activity in nerves innervating the tongue in wild-type and various gene-knockout (KO) mice or cell ablation studies (Pkd2l1-DTA). T1R1 + 3 functions as the umami receptor, T1R2 + 3 is the sweet receptor, T2Rs are bitter receptors (T2R5 is a high-affinity cycloheximide receptor), PKD2L1 is a candidate sour receptor, and PLC-β2 is the effector and TRPM5 the transduction channel of sweet, umami and bitter pathways. Note the extraordinarily specific taste deficits (red traces) in each genetically altered mouse line. Pkd2l1-DTA refers to animals expressing diphtheria toxin in PKD2L1 cells. (With permission from Chandrasekar et al. 2006)

In a simplistic view, each of the five basic taste sensations (bitter, sour, sweet, salty and umami) are recognized by various cells (encoding these peripheral signals) that express unique receptors (Fig. 21.2b) tuned to detect each basic taste (Chandrashekar et al. 2006; Smith and St. John 1999). The traces in Fig. 21.2c show recordings of taste-induced activity in nerves of the tongue in wild-type and various gene-knockout mice.

21.2.3 The Food-Brain Connection

Taste Circuit Neurophysiological studies of brainstem, thalamic or cortical taste neurons are providing important insight into the basic properties of the central taste circuitry (Katz et al. 2001, Di Lorenzo 2000). Deciphering how information flows from the tongue to sensory integration centers in the brain, ultimately dictate feeding behavior. The taste cortex, localized in the anterior insula, encodes "separate and combined representations" of the taste, temperature, and "texture of food in the mouth" independently of hunger. Thus, taste is encoded independently of "reward value" and "pleasantness". In terms of circuitry, within one synapse inside the orbitofrontal cortex, these sensory inputs are "combined" by associative learning with olfactory and visual inputs for some neurons. These cells encode "food reward value", because they respond to "food only" and "correlate linearly" with "subjective pleasantness" (Chandrashekar et al. 2006; Erickson 2000; Everitt and Wolf 2002). Cognitive factors, including selective attention to affective value modulate the representation of the reward value of taste, olfactory, and flavor stimuli in the orbitofrontal cortex and a region to which it projects, the anterior cingulate cortex. These food reward representations are important in the control of appetite and food intake (Gearhardt et al. 2011). Individual differences in reward representations may contribute to obesity, and there are age-related differences in these reward representations. Implications of how reward systems in the brain operate for understanding, preventing, and treating obesity are described (Stice et al. 2008).

(i) ***Prefrontal cortical connections to reward structures***: Distinct domains (dorso-lateral, medial, orbitofrontal, anterior cingulate) of the prefrontal cortex in primates have a set of connections with the dopaminergic neurons in the ventral tegmental area (VTA) suggesting that they have different roles in cognition (Opris et al. 2013), memory (Goldman-Rakic 1996), emotion (Rolls 2000) and the control of behavior (Fig. 21.3).

(ii) **The gut**. Michael Gershon claims that the gut/enteric system interacts with the central nervous system during the production of neurotransmitters like serotonin in the digestive tract suggesting that the gut system behaves like a second brain (Gershon 1998). Recent studies show that direct stimulation of the gastrointestinal tract with nutrients induces release of the catecholamine neurotransmitter dopamine (De Araujo et al. 2012). Changes in dopamine efflux produced by direct stimulation of the gastrointestinal tract were found to reflect the caloric load of the nutrients, suggesting

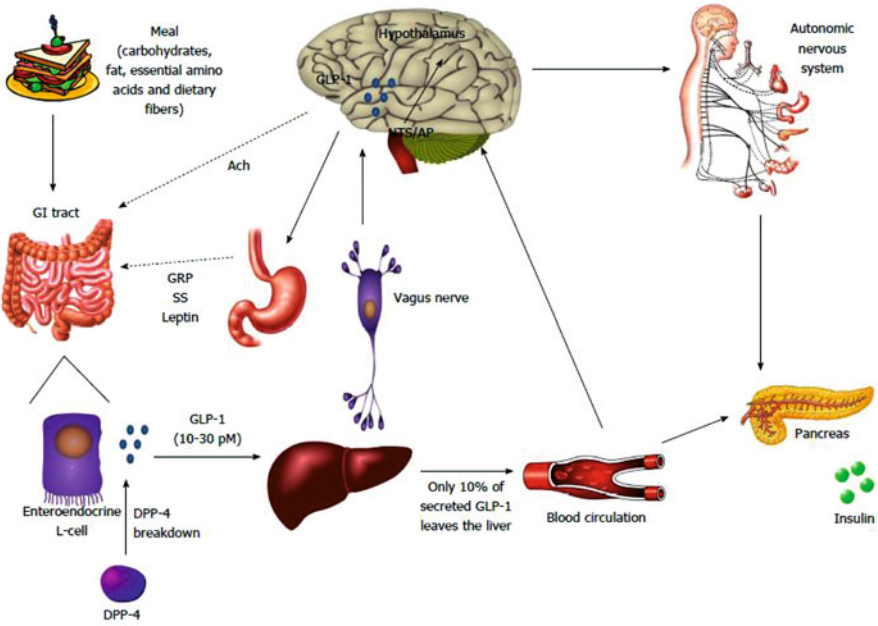

Fig. 21.3 The food brain connection. The gut-brain axis for the actions of glucagon-like peptide-1. After a meal ingestion, gastrointestinal (GI) tract is rapidly stimulated and glucagon-like peptide-1 (GLP-1) is secreted in the gut lumen by enteroendocrine L-cells. Besides the direct interaction of nutrients with L-cells, neural (acetylcholine) and endocrine (gastrin-releasing peptide, somatostatin, and leptin) mechanisms are also involved in the control of GLP-1 secretion after food intake. Bioactive GLP-1 diffuses into the capillaries, immediately beginning to be degraded by dipeptidyl peptidase-4, so that more than 50% of the hormone is inactivated before reaching the portal circulation. In the liver, a further large amount is truncated, thus only 10% of the secreted GLP-1 leaves the liver and enters the systemic circulation and may reach the pancreas, the brain and other tissues via the endocrine pathway. However, the passage of GLP-1 through the hepatoportal vein activates vagal afferents nerves that initiate a neural signal towards the brain. In the central nervous system, the metabolic information is received by the solitary tract nucleus and the AP in the brainstem, which synthesize and project the GLP-1 to the hypothalamus. The GLP-1 receptor signaling is involved in the central control of energy homeostasis and food intake, and several autonomous functions, such as glucose-dependent stimulation of insulin secretion and inhibition of glucagon secretion in the pancreas, cardiovascular effects, regulation of gastric emptying and of endogenous glucose production in liver and glucose uptake and storage in muscle and adipose tissue. *GRP* Gastrin releasing peptide, *Ach* Acetylcholine, *SS* Somatostatin, *DPP-4* Dipeptidyl peptidase-4, *AP* Area postrema. Emanuel Monteiro Candeias, Inês Carolina Sebastião, Susana Maria Cardoso, Sónia Catarina Correia, Cristina Isabel Carvalho, Ana Isabel Plácido, Maria Sancha Santos, Catarina Resende Oliveira, Paula Isabel Moreira, Ana Isabel Duarte Gut-brain connection: The neuroprotective effects of the anti-diabetic drug liraglutide. World J. Diabetes 2015 June 25; 6 (6): 807–827. (With permission from Candeias et al. 2015)

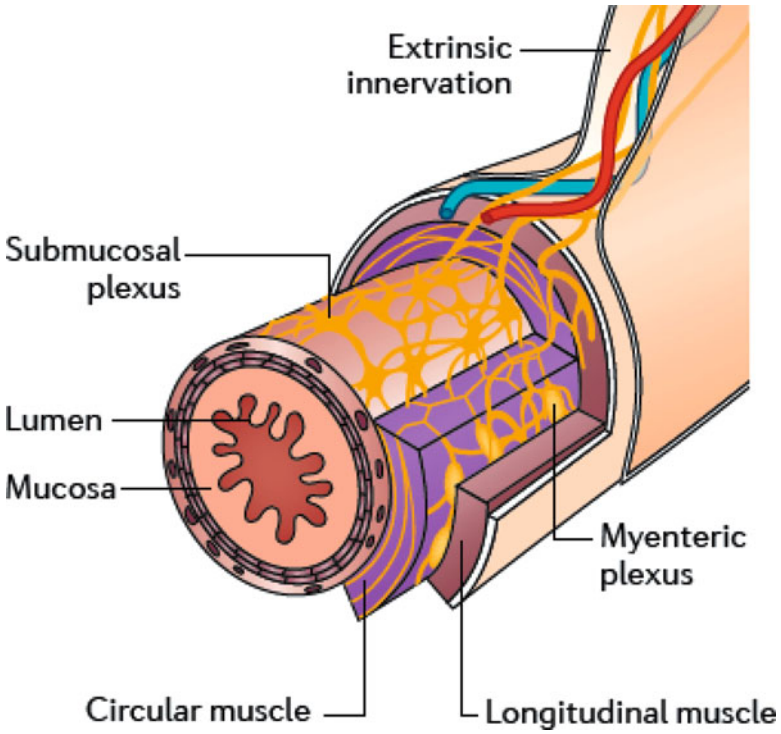

Fig. 21.4 The schematic of the small intestine illustrating the organization of the enteric nervous system (ENS) in its location within the intestinal wall. The myenteric plexus is located between the longitudinal and circular layers of smooth muscle whereas the smaller submucosal plexus is located in the dense connective tissue of the submucosa, just underneath the mucosa. Note that no nerve fibres actually enter the enteric lumen or its epithelial lining. The extrinsic innervation reaches the bowel through the mesentery along with the vasculature (With permission from Rao and Gershon, 2016)

that dopamine signaling may function as a central caloric sensor that mediates adjustments in intake according to the caloric density of a meal (De Araujo et al. 2012). In fact, inhibiting dopamine receptor signaling disrupts flavor-nutrient associations and impairs the regulatory capacity to maintain constant caloric intake during intra-gastric feeding (De Araujo et al. 2012, Fig. 21.4).

(iii) **The brainstem** plays an important role in nutrition, because its structures are the first to receive signals from the body related to energy status and the gut (Lundy 2008; Khlaifia et al. 2017). The brainstem controls the flow of signals between the brain and the entire body. It also controls basic body functions such as swallowing, breathing, heart rate, blood pressure, arousal (awake and sleep; Takakura et al. 2013; Abbott et al. 2013). Neurons get all their nutrients via the aerobic metabolism of glucose (Pellerin 2010). Since this metabolic process requires large quantities of oxygen, the nervous

system requires a high blood flow (around 50 cc/100 grams of tissue/minute). Neurons will begin to malfunction at lower levels (below 15 cc/100 grams of tissue/minute), resulting in death quite rapidly.

(iv) **The blood brain barrier** (BBB) plays a key role in the selective transport of substances into the brain (Chen and Liu 2012 and Vidu et al. 2014). Smaller molecules are more likely to cross the barrier. Nutrients cross the barrier to the brain via a facilitated diffusion process that couples nutrient's movement with the movement of an ion down its concentration gradient (Banks 2008, 2012).

21.3 The Reward System

The reward system may be looked at from anatomical and functional perspectives (Kalivas and Nakamura 1999; Haber and Knutson 2010). Ingested substances (food, drink, drug) activate a reward system in the ventral tegmental area (Schultz 2000), amygdala (Everitt et al. 1999), nucleus accumbens (O'Donnell and Grace 1996)), dorsal striatum (Delgado et al. 2003) and the limbic part of prefrontal cortex (Pears et al. 2003; Rolls 2000; Tremblay and Schultz 1999).

In Fig. 21.5 we show a schematic representation of limbic cortical–ventral striatopallidal circuitry underlying reward. The circuit shows a bottom-up flow of sensory information to prefrontal cortical areas, and top-down prefrontal-neostriatal projections carrying behavior-related signals. The prefrontal cortex (orbitofrontal and anterior cingulate) projections interact in the NAc in a way that is modulated by mesolimbic DA and that, in turn, can modulate the release of DA (O'Donnell and Grace 1996; Floresco et al. 2001). Such prefrontal mechanisms may influence cocaine seeking through their convergent projections to the NAc, perhaps competing for access to response strategies subserved by different cortical–striato-pallido-thalamo-cortical reentrant loops (McFarland and Haber 2002) (Fig. 21.5). Prefrontal executive control involvement distinguishes between actions (orbitofrontal and anterior cingulate) and habits (dorsolateral prefrontal cortex). One feature of conditioned reward/drug seeking is that Pavlovian associations between discrete stimuli or contexts and the effects of cocaine determine the behavioral response. Conditioned reinforcement depends critically on the basolateral nuclei of amygdala (BLA; Cador et al. 1989; Burns et al. 1993) and its interactions with the NAc (Everitt et al. 1999).

21.3.1 Anatomical Substrate of the Reward System

The reward system is organized hierarchically at cortical (orbital frontal cortex and anterior cingulate cortex), subcortical (nucleus accumbens) and midbrain (ventral tegmental area, VTA; pars compacta of substantia nigra, SNc) levels. The reward circuitry may be labelled based on its substrate: food, drink, and pleasure/hedonic (Wise 2002).

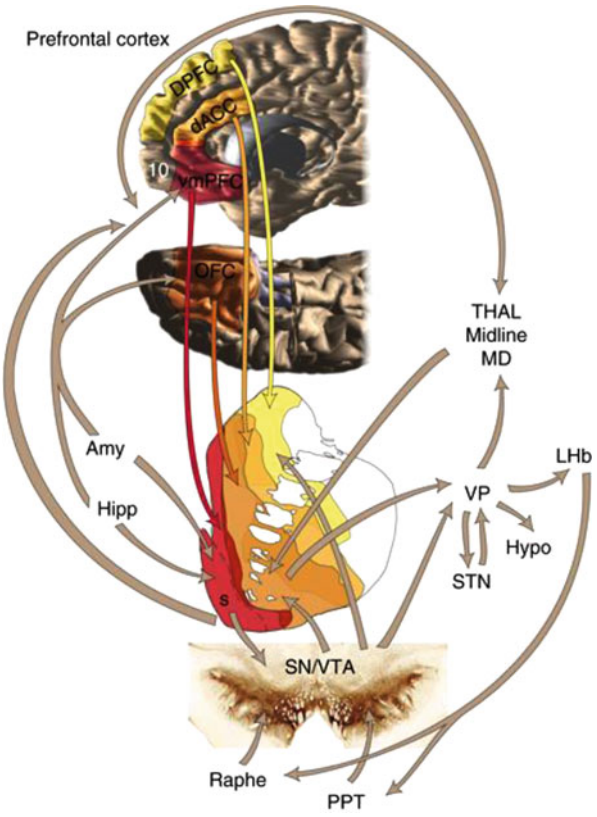

Fig. 21.5 Reward System. Schematic illustrating key structures and pathways of the reward circuit. *Red arrow* input from the vmPFC, *dark orange arrow* input from the OFC, *light orange arrow* input from the dACC, *yellow arrow* input form the dPFC, *brown arrows* other main connections of the reward circuit. *Amy* amygdala, *dACC* dorsal anterior cingulate cortex, *dPFC* dorsal prefrontal cortex, *Hipp* hippocampus, *LHb* lateral habenula, *hypo* hypothalamus, *OFC* orbital frontal cortex, *PPT* pedunculopontine nucleus, *S* shell, *SNc* substantia nigra, pars compacta, *STN* subthalamic nucleus., *Thal* thalamus, *VP* ventral pallidum, *VTA* ventral tegmental area, *vmPFC* ventral medial prefrontal cortex. (With permission from Haber and Knutson 2010)

21.3.2 Functional Substrate of the Reward System

From the functional perspective, the reward system interacts with the taste system (sensory level), the digestive (enteric) system with a key role in nutrition, the motivation for action (motor system), the cognitive system (learning and memory), and the emotional (hedonic, pleasure) limbic system (cortical and subcortical level) with dopaminergic neuromodulation (Rolls 2016; Richard et al. 2013). Nutrition and reward systems are intertwined (Richard et al. 2013; Volkow et al. 2011).

21.3.3 The Reward Based Decision Making

A key variable of decision making is the gain, or the potential outcome associated with different choice options (Opris and Bruce 2005). This is the case of consumers that examine the positive and negative attributes of a product prior to a decision to purchase. People also use knowledge from previous/past experience to decide

which restaurant has the best food for diner. However, the saliency of reward is an incentive variable for decision making (Bush et al. 2002), and mostly in addictions (Opris et al. 2009). Other decision variables are the prediction error in reinforcement learning, which represents the deviation between expected and actual outcomes, or the decision threshold in sequential sampling models, which determines the amount of information needed to be collected before a decision is made (Opris and Bruce 2005). Thus, further experimental insight is needed to develop integrative approaches that explain reward-based decision making on different phenomenological levels (Bush et al. 2002).

21.4 Addiction to Food vs Drug

Addiction is characterized by inability to consistently abstain, impairment in behavioral control, compulsivity (persistent behavior, inappropriate to the situation, leading to negative consequences) diminished recognition of significant problems with one's behaviors and interpersonal relationships, a dysfunctional emotional response (Volkow et al. 2002; Volkow et al. 2011; Volkow and Wise 2005).

In terms of brain circuitry, there is reduced baseline activity of several regions of frontal cortex, as inferred from brain imaging studies in substance abuse and eating disorders, brain changes in prefrontal cortex (Opris et al. 2012), problems with working memory, attention and behavioral inhibition, impulsivity (acting on sudden urges), compulsivity (driven by irresistible inner forces), difficulties of frame shifting difficulties (stubborn thinkers), and reward saliency (short versus long term).

21.4.1 Obesity

Obesity and drug addiction (Fig. 21.6) may be both regarded as disorders in which the saliency of reward (food or drugs, respectively) becomes "abnormally enhanced" relative to others (Volkow et al. 2011). This view is supported by the fact that both food and drugs have "powerful reinforcing effects" mediated, in part, by dopamine increases in the limbic circuit (ventral tegmental area, VTA, nucleus accumbens and pars compacta of substantia nigra) that, under certain circumstances could overwhelm the brain's homeostatic control mechanisms (Volkow et al. 2011). Such parallels suggest shared circuits and vulnerabilities between addiction and obesity (Volkow et al. 2011). Indeed, imaging studies have shown that, both obese and drug-addicted individuals suffer from impairments in dopaminergic pathways that regulate neuronal systems associated with conditioning (memory/learning), impulse control (behavioral inhibition), and interoceptive awareness (Kuehn et al. 2016). The reward values of both food and substances of abuse are associated with increased level of extracellular dopamine in the nucleus accumbens (Wang et al.

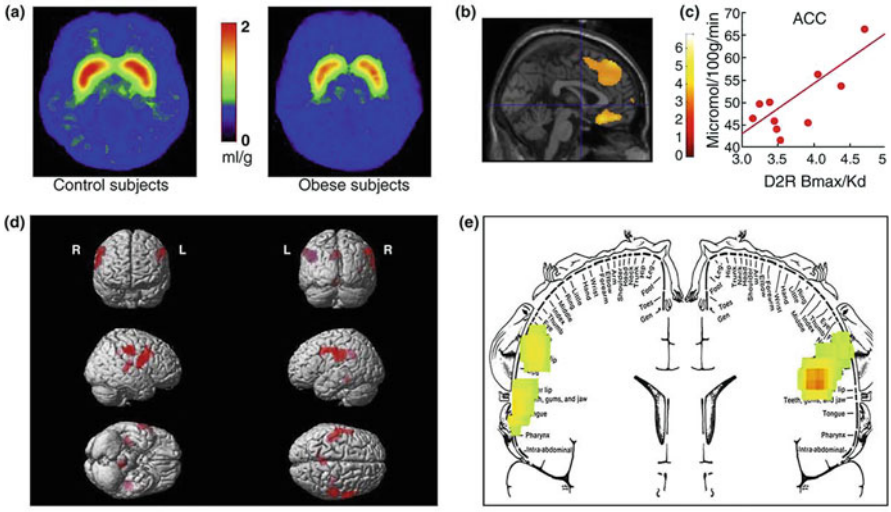

Fig. 21.6 Food Addiction in Obesity. Hyperphagia could result from a drive to compensate for a weakened reward circuit (processed through dopamine regulated corticostriatal circuits) combined with a heightened sensitivity to palatability (hedonic properties of food processed in part through the somatosensory cortex). (**a**) Averaged images for DA D2 receptor (D2R) availability in controls (n = 10) and in morbidly obese subjects (n = 10). (**b**) Results from SPM identifying the areas in the brain where D2R was associated with glucose metabolism, these included the medial OFC, ACC and the dorsolateral PFC (region not shown). (**c**) Regression slope between striatal D2R and metabolic activity in ACC in obese subjects. (**d**) Three-dimensionally rendered SPM images showing the areas with higher metabolism in obese than in lean subjects ($P < 0.003$, uncorrected). (**e**) Color coded SPM results displayed in a coronal plane with a superimposed diagram of the somatosensory homunculus. The results (z value) are presented using the rainbow scale where *red* > *yellow* > *green*. When compared with lean subjects, obese subjects had higher baseline metabolism in the somatosensory areas where the mouth, lips and tongue are represented and which are involved with processing food palatability. Modified, with permission, from (Volkow et al. 2008a) (**a**–**c**) and (Wang et al. 2002) (**d**, **e**) TO Modified, with permission, from (Volkow et al. 2011) (**a**–**e**)

2001). Moreover, PET imaging studies have shown reduced levels of dopamine receptors in mesolimbic reward circuit, observed in both patients with obesity and drug dependence (Volkow and Wise 2005).

Drugs addicts share many characteristics with compulsive overeaters such as: seeking "reward" from substance, hedonic food, highly palatable food, and processed food with added sugars/salt/fat (von Ranson et al. 2011).

21.4.2 The Yale Food Addiction Scale (YFAS)

YFAS is the first procedure "designed specifically to assess signs of addictive-like eating behavior" (Gearhardt et al. 2009). YFAS has two scoring options: i) a "symptom count" ranging from 0 to 7 that reflects the "number of addiction-like criteria endorsed", and ii) a dichotomous "diagnosis" that indicates whether a "threshold of three or more symptoms" plus clinically "significant impairment" or distress has been met. YFAS has received "psychometric support" in a non-clinical population (Gearhardt et al. 2009; Pedram et al. 2013), "binge eating" population (Gearhardt et al. 2012), obese "bariatric" surgery patients (Clark and Saules 2013; Meule et al. 2012), and a diverse clinical sample (Davis et al. 2011).

The second version (YFAS 2.0) was published in the Psychology of Addictive Behaviors (Gearhardt et al. 2016). YFAS 2.0 was developed to maintain consistency with the current diagnostic understanding of addiction and to improve the psychometric properties of the original YFAS. Both versions of the YFAS are similarly associated with elevated body mass index, binge eating, and weight cycling. However, exceeding the food addiction threshold was more strongly associated with obesity for the YFAS 2.0 than the original YFAS. Thus, the YFAS 2.0 appears to by a psychometrically sound measure that reflects the current diagnostic understanding of addiction to further investigate the potential role of an addictive process in problematic eating behavior.

21.4.3 Drug Addiction

Opris and colleagues compared neuronal firing recorded simultaneously in PFC layers 2/3 and 5/6 under cocaine vs control and correct vs. error trials (Opris et al. 2012). Consistent with previous reports (Opris et al. 2012), cognitive workload (number of images in the match phase and duration of delay) in the delayed-match-to-sample (DMS) task (see Fig. 21.7a) was manipulated by increasing visual complexity and/or duration of delay on each trial (Hampson et al. 2011, Deadwyler 2010). PET imaging of [18F] fluorodeoxyglucose uptake in the brains of monkeys performing the same DMS task has demonstrated differential processing by separate brain areas, depending on cognitive workload (Robbins and Arnsten 2009; Deadwyler et al. 2007). Both neuronal and metabolic activity in these prefrontal areas has been shown to be altered by cocaine, which impaired performance on high cognitive workload trials (Opris et al. 2012). Figure 21.7b, c shows results "consistent" with previous findings and "tracks" the change in performance in the same session on a trial-wise basis with cocaine injection midway through the session. As the number of trials "progressed", the even distribution of error vs. correct trials (Fig. 21.7d) in the "control" half of the session, changed after cocaine administration (Trial 61) to "more cumulative errors", relative to fewer correct trials, in the "cocaine" half of the same session. Figure 21.7d shows the "effects of cocaine" on task performance

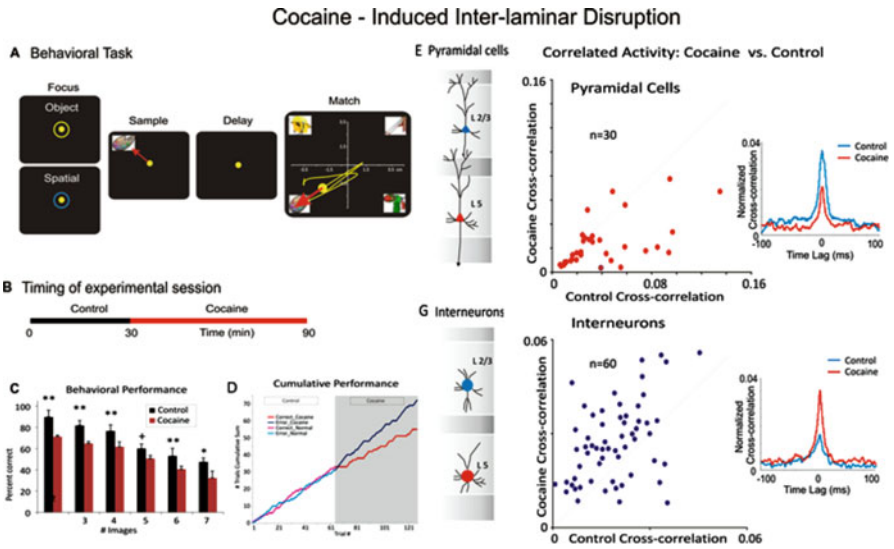

Fig. 21.7 Prefrontal cortical microcircuit of drug addiction. Disrupted cross-laminar cortical processing in prefrontal cortex. (**a**). Behavioral paradigm using the DMS task. (**b**). DMS session timeline shown for combined Control (saline) and Drug (cocaine) administration phases of the same trial. (**c**). Mean percent correct performance on Cocaine vs. Control trials. (**d**). Single session example of the change in cumulative distribution of correct and error trials during control (saline) vs. cocaine segments of the session. (**e**). Pyramidal cells. (**g**). Interneurons. (**f**, **h**). Scatter plots of normalized cross-correlation coefficients from inter-laminar/interneuron cell pairs and in the neural firing in the two subsets of data. Overlay CCHs show synchronized firing for pyramidal cell pairs (**i**) and interneurons (**j**). Taken from (Opris et al. 2015b, b, c). (With permission from Opris et al. 2012)

in the second half of the session with respect to "cognitive load" (Hampson et al. 2011) indicated by the decrease in the mean percent correct responses when the number of distracters increases, during target selection. Figure 21.7d shows the effects of cocaine on task performance in the second half of the session with respect to cognitive load (Hampson et al. 2011) indicated by the decrease in the mean percent correct responses as a function of the increase in the number of distracters (Images 2–7) in the Match phase during target selection. In association with this decrement in DMS performance midsession injection of cocaine produce a significant decrease in inter-laminar cross-correlations compared with correlations of the same cell pairs (n = 30) in the Control half of the session. The scatter plot of normalized cross-correlation coefficients in Fig. 21.7e, f shows that those cell pairs with lower correlation coefficients in the cocaine post-injection half of the session exhibited less change (diagonal line) following cocaine injection than cell pairs with higher coefficients in the Control half of the session. Thus, the higher the inter-laminar correlation under normal conditions, the more likely cocaine reduced that correlation in the same cell pair in the second half of the DMS session. Interestingly, the increase in correlated firing post cocaine injection vs. control for GABA-ergic

interneurons is shown in Fig. 21.7g, h. This is illustrated in Fig. 21.7g and h as a cocaine-induced increased synchronized laminar firing, which under normal (nondrug) conditions exhibited lower levels of firing synchrony (Opris et al. 2015a, d). This drug-induced reduction in synchronized firing for pyramidal cells (Fig. 21.7e, f) and increase in synchrony for interneurons (Fig. 21.7g, h), might reflect a symmetry breaking induced by cocaine,

These findings are in close agreement with prior studies showing marked influences of acute administered cocaine in altering task-related neural firing (Hampson et al. 2011; Opris et al. 2009; Anderson et al. 2008; Stuber et al. 2005; Volkow et al. 2005; Bradberry 2000) and support the notion that dopaminergic modulation of pFC neuron firing may be responsible for regulating columnar processing in a manner that controls decision-making and target selection in cognitive tasks (Graybiel 2008; Opris et al. 2015a, b, c, d; Volkow et al. 2005; Rao et al. 1999; Mountcastle 1997; Opris and Casanova 2014; Opris et al. 2011; Opris 2013).

Finally, this demonstration of performance-related minicolumnar processing could provide insight into the basis for other types of cognitive impairments involving decision-making and executive function in humans as a result of disease, injuries, or other disorders (Volkow et al. 2005; Opris et al. 2012).

21.5 Implications of Nutrition for Cognition and Disease

Insufficient intake of selected vitamins, or certain metabolic disorders, may affect cognitive processes by disrupting the nutrient-dependent processes within the body that are associated with the management of energy in neurons, which can subsequently affect synaptic plasticity, or the ability to encode new memories.

Alzheimer's Dementia The Alzheimer's disease is identified by the presence of amyloid plaques and neurofibrillary tangles in the hippocampus (Wang et al. 2015). Some of its symptoms are the forgetting of words and names, delusions and hallucinations. Moderate or mild malnutrition can cause an increased risk for Alzheimer's disease (Yildiz et al. 2015). Dementia is a common form of age-related cognitive decline. Dementia interferes with normal functioning operations, as well as a significant amount of memory loss. One kind of dementia is vascular dementia (Imfeld et al. 2013), which has risk factor for strokes that are related to nutrition such as diabetes and obesity. Increased blood pressure can raise the risk for dementia.

Aging and Memory Disorders Foods that are rich in Omega-3 fatty acids have been shown to decrease the risk of getting Alzheimer's disease (Hjorth et al. 2013). Omega-3 fatty acids, primarily Docosahexanoic acid (DHA), which is the most prevalent omega-3 fatty acid found in neurons, have been studied extensively for use in the possible prevention and therapy of Alzheimer's disease (Thomas et al. 2015). Some studies (cross-sectional) suggest that reduced intake or low brain levels of DHA are associated with earlier development of cognitive deficits or development of dementia, including Alzheimer's disease. A diet that is rich in antioxidants will also

help get rid of free radicals in your body, which could be a cause for Alzheimer's disease (McGeer and McGeer 2013). The buildup of beta amyloid plaques, a marker highly associated with Alzheimer's disease, generates cell damaging free radicals. Therefore, the role of antioxidants as protectants against Alzheimer's disease has become a hot topic of study. Simple dietary modification, towards fewer highly processed carbohydrates and relatively more fats and cholesterol, is likely a protective measure against Alzheimer's disease.

21.6 Conclusion

The knowledge of the neuro-circuitry for food intake, addiction, and overlap with neurocognition was evaluated. Whereas pathways of food addiction were well demonstrated in animal studies, the challenges arise when translating animal addiction models to humans. Research on brain reward systems and food intake suggests that the study of the food–brain connection has the potential to develop a meaningful definition of food addiction. Moreover, some nutrients and rewards require attention in order to prevent obesity and addiction.

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Part IV
Computational Approaches and Neurointerfaces

Chapter 22
Grid Cells-From Data Acquisition to Hardware Implementation: A Model for Connectome-Oriented Neuroscience

Diana Deca

Abstract One of the main challenges in modern neuroscience is to extract causal information from the brain in a way that it can be reproduced in a different substrate, such as a computer or a robot. While some major advancements have been made in neuroscience towards that goal, ranging from the discovery of the action potential, to cortical columns, to grid cells and their crystalline structure, there is no single model at the moment on how to best acquire and model and implement such data.

While the correlation between light or sound stimuli with spiking activity is by now rather well established, the causal connection between higher-level stimuli, such as a complex environments, learning, memory, or decision making and neuronal spiking activity is not entirely clear. One exception to this vagueness is the discovery of grid cells.

Keywords Grid cells • Connectome • Whole brain emulation • Mathematical objects • Hardware implementation • Causal neuroscience

22.1 Grid Cells

Grid cells are place-modulated neurons whose multiple firing locations describe a periodic triangular array covering an open space. They play an essential role in the brain's navigational system, acting as a coordinate system. Interestingly, the crystalline structure of the grid cells firing fields is not a result of sensory experience, but does change in response to environmental cues.

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One of the most striking features of grid cells is their symmetrical arrangement. On average, grid spacing increases from one module to the next by a factor of 1.42, or the square root of 2. This enables the inner ring of the grid hexagon to double from one module to the next.[1]

22.2 Finding Patterns in Nature: From Plato to Grid Cells

While the discovery of grid cells in the brain led many neurobiologists to wonder how such quasiperfect patterns can appear in nature, it is worth investigating the history of pattern discovery in different natural phenomena, as well as some of the most common models of how they might emerge. We will briefly go through the theory initially formed by Plato and others in Ancient Greece which suggests that instead of asking how patterns can occur in nature, we should rather be asking how life or nature can appear within these patterns, which form the inherent structure of the universe, and according to the Greeks, even have a higher ontological standing than their natural and imperfect instantiations (for example, a natural hexagon is less "real" than the perfect hexagon that we make use of in mathematics).

This discovery has raised a lot of attention from the philosophical fields, as it refers to the question of whether there are patterns in nature. In biology and in particular in neuroscience, perfect patterns have rarely been observed.

22.2.1 Plato's Mathematical Objects and Grid Cells

One of the first philosophers to refer to these patterns and their existence in nature is Plato. Plato argued for the existence of universals, which consisted of ideal forms (or eidos εἶδος) that physical objects were imperfect copies of. Interestingly, he suggested that the basic structure of the universe evolved from simple geometric shapes to more complex ones. These shapes, now known as platonic solids are the cube, tetrahedron, octahedron, dodecahedron and the icosahedron (to which we can add the common cube, in order to get all 5 possible polyhedra, in which every face is the same, and every face is a regular polygon) (Fig. 22.1).

By stretching and modifying the different parts of these 5 polyhedra, we can obtain most of the forms that we see in nature.

The deeper meaning of this is related to Plato's concept of mathematical objects, which have a higher level of existence than natural objects. This idea was later used by philosopher Frege to argue against the psychologist notion that mathematical objects exist only in our heads which, to Frege, was the same as claiming that mathematical objects do not exist. Indeed, the discovery of grid cells functions as

[1] Moser et al. (2013).

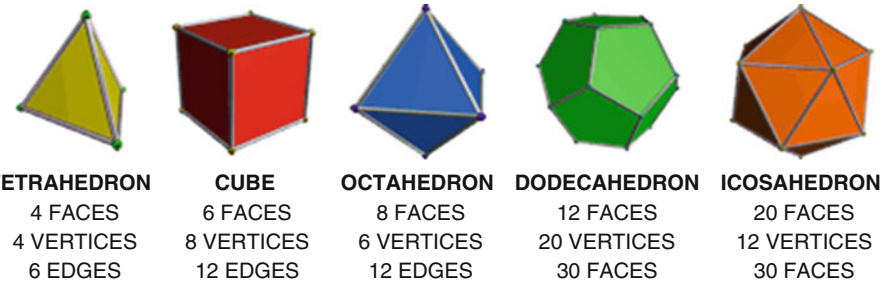

Fig. 22.1 The 5 known perfect polyhedra (Adapted from Maths resources (Euler et al. 2015))

a proof that mathematical objects, or patterns, do exist in nature and in the way the brain perceives the world. It also shows that mathematics is not merely in the mind, since patterns can be observed experimentally in the brain. As philosopher Frege[2] later pointed out that, if mathematical objects were only in our minds, then we would not be able to calculate anything new. If we all died, the statement "4 is greater than 2" would suddenly become false, which is not the case. So, if mathematics and all fields that come out of it can be used to make true statements about the world via deduction without the use of human experience, then grid cell patterns can be explained in a similar manner and can map space largely independently of human experience, as was shown experimentally. More simply put, Plato's legacy would suggest, consistently with the discovery of grid cells that the world does have an inherent structure and that our brains and minds have proven to be somewhat well equipped for exploring and understanding that structure.

This also means that the brain itself, in all its complexity, also has an inherent structure which we can understand and reconstruct.[3]

In this discussion, as other philosophers have pointed out, it is important not to confuse the idea or the concept of a mathematical object, like the concept of a grid map in our case, with the instantiation of it, such as a grid map observed experimentally when analyzing the spiking patterns of a single cell. The border between the concept and its instantiation becomes more blurry when the instantiation (ie. the actual grid map) does not change in response to sensory stimuli. The grid maps in grid cells do not cease to exist when we stop recording them, nor do they begin to exist when we record them for the first time.

[2]Frege and Austin 1953.

[3]Balaguer, Mark, "Platonism in Metaphysics", *The Stanford Encyclopedia of Philosophy* (Spring 2016 Edition), Edward N. Zalta (ed.)

22.2.2 Alan Turing's Theory of Hexagonal Patterns and Grid Cells

Although Alan Turing has been famous mostly for his work in computer science, I will now focus on his 1952 paper called "The Chemical basis of Morphogenesis", where he describes how non-uniformity can arise out of a uniform state..[4] According to Turing, a system of chemical substances, called a morphogens, can develop a pattern as a result of an instability of a homogenous equilibrium, which is in turn triggered by random disturbances. These random disturbances are in fact a competition between reagents termed activators and inhibitors. The balance and arrangement between excitatory and inhibitory inputs in the formation of grid cell firing patterns will be explained in more detail towards the end of this chapter, especially in the attractor network model of grid cells. If the inhibitors diffuse faster than activators, then spatial patterns can emerge where the activation concentration will be high, surrounded by areas of high inhibitor concentration. If we were to have an image of this, then probably the most likely pattern is either a stripe or grids with many, roughly circular regions of high activator concentrations. Turing proposed in his paper that such a mechanism could be responsible for some types of morphogenesis or pattern formation in biology.

Based on Alan Turing's reaction-diffusion model of pattern formation, we can see that the patterns generated in this way are very similar to the ones created "naturally". A number of simulators of this model are available online for generating such patterns and comparing them with the ones seen in biology (Fig. 22.2).[5,6]

Since this chapter is concerned with finding patterns in the brain, two examples of such structures in the brain are grid cells in the MEC and cells in cortical columns in the visual, auditory, barrel, and other cortices (with clustering becoming more apparent in higher mammals). More brain areas are likely to have this columnar structure in the human cortices, with a higher concentration of nearby excitatory inputs bordered by a similar number of inhibitory inputs. This theory is also consistent with the Hebbian fire-together-wire-together theory as well as its Stentian complement.[7] The stripes described by Turing are more similar to the ocular dominance columns observed in the visual cortex.[8]

[4] Turing (1952).

[5] TexRD

[6] Kondo and Miura (2010).

[7] Fyfe 2005.

[8] Hubel and Wiesel. 2005.

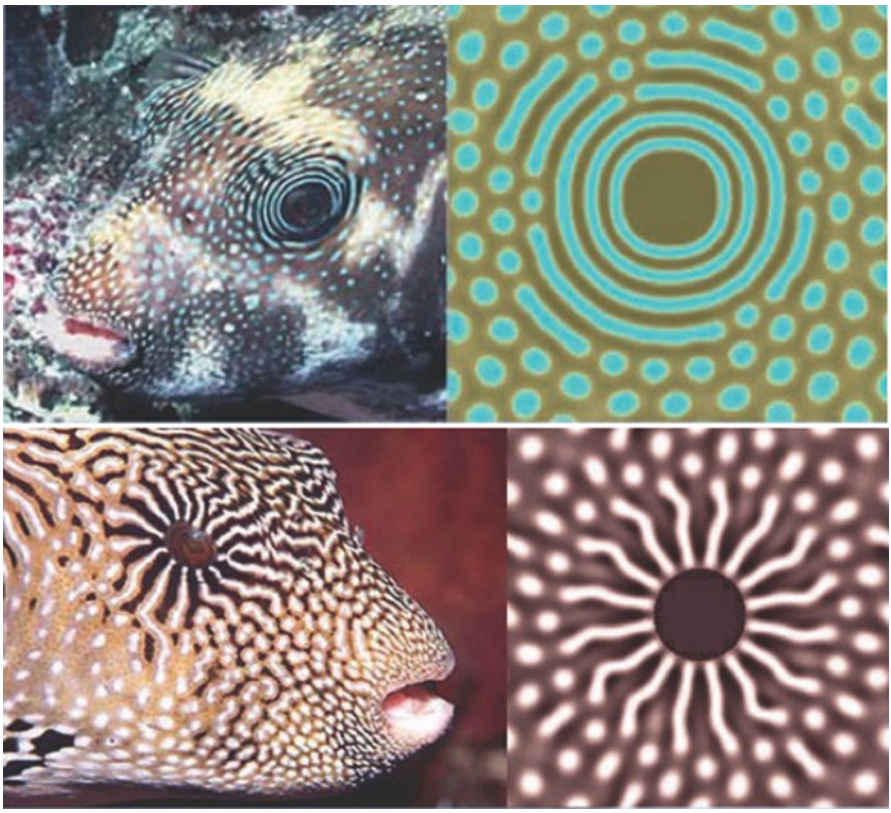

Fig. 22.2 Photographs of zebrafish markings, and the corresponding Turing pattern simulations on the *right* (Adapted from Kondo and Nakamasu, PNAS, 2009)

22.2.3 Grid-Like Arrangement of Conceptual Knowledge in Humans

In a recent paper, Constantinescu et al.[9] hypothesize that concepts are organized in the human brain into a cognitive map, allowing conceptual connections to be made in a similar manner to how grid cells are formed as a result of inputs from different kinds of cells. This hypothesis is based on the observations made in human fMRI studies showing hexagonal symmetry between the blobs observed in the brain during grid-cell-related activity. Also, humans navigating conceptual knowledge showed a similar hexagonal signal in a number of brain areas. This grid-like signal was also found to be consistent across sessions acquired more than 1 week apart. The authors suggest that the human brain can navigate through concepts in the same

[9]Constantinescu et al. (2016).

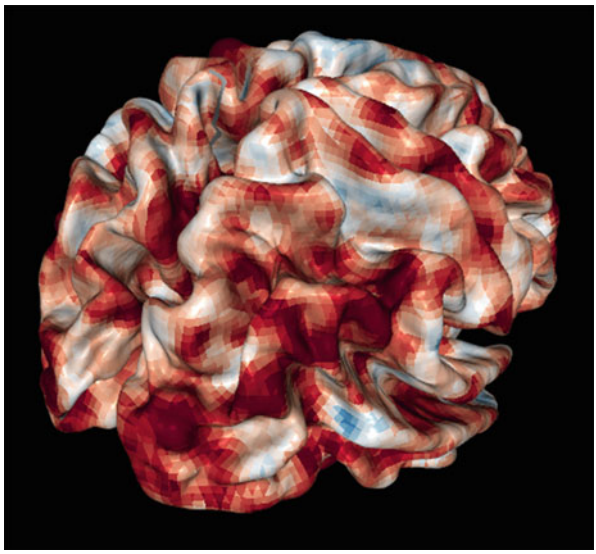

Fig. 22.3 Identified hexagonally symmetric signals across the whole brain (Adapted from Constantinescu et al. (2016))

way it navigates through two-dimensional space. The rest of this chapter will aim at exploring this possibility as well as the evidence for this hypothesis (Fig. 22.3).

Human grid cells have been observed in intraoperative recordings[10] and are likely to be the source of the hexagonal patterns observed during fMRI recordings during virtual navigation.[11,12,13] These signals could be observed in the MEC, but also in other areas, such as the medial parietal and the lateral temporal cortices. The authors suggest that a grid-like activity pattern in the brain areas commonly involved in the brain's resting state activity, which have also been associated in the past with manipulation of conceptual knowledge such as imagination, memory, scene construction and valuation, raising the possibility of a common principle for forming and navigating through abstract concepts similar to the principle of grid cell functioning. Another line of evidence for this hypothesis comes from the finding that human hippocampal cells appear to code for individual concepts in humans.[14] The authors used fMRI to test if humans use a hexagonally symmetric code when navigating through abstract conceptual representations. The task used is similar to the one where the subjects navigate physical space, except that these dimensions were organized in abstract space. The 28 subjects had to learn that bird stimuli were associated with different Christmas symbols. The correlations between the two types of stimuli were not random, but varied according to the length of the neck and

[10] Jacobs et al. (2013).

[11] Doeller et al. (2010).

[12] Kunz et al. (2015).

[13] Horner et al. (2016)

[14] Quiroga et al. (2005).

that of the legs. Thus, each stimulus could be described within a two dimensional conceptual bird space, based on the bird's neck-leg ratio. The participants underwent behavioral training before the imaging sessions, until they reached an accuracy level of 72.8% in predicting outcomes. Despite randomizing the stimuli with regards to orientation, hexagonally symmetric signals across the whole brain could be observed. The authors focused on the brain areas where these hexagonal BOLD signals were strongest. The brain areas overlapped anatomically with the navigation-related network and the default-mode network. They focus particularly on brain areas where grid cells have been recorded in humans during spatial tasks, namely the mPFC (medial prefrontal cortex/cingulate) and the entorhinal cortex. Interestingly, they found that subjects with stronger hexagonal modulation had a better performance in memory and conceptual knowledge tasks. The experimenters also tested for hexagonal consistency between separate sessions acquired at half an hour apart and the between-session consistency was dependent on the behavioral performance and the strength of the hexagonal arrangement of the BOLD signal. As for consistency between sessions more than 1 week apart, the strongest consistency was observed in the vmPFC. Hexagonal consistency was also observed between the entorhinal cortex (the main brain area for grid cells) and the vmPFC, suggesting this hexagonal consistency might in fact be modulated by grid cells.

Some models of grid cell mapping of space suggest that spatial representations emerge from a "continuous attractor network", which permits small variations of a spontaneously generated representation based on one's trajectory.[15] Given a network with recurrent connectivity and global inhibition, initially random patterns will spontaneously give rise to an organized "bump" of activity of cells with similar activity patterns. These activity patterns are likely to change based on direction and speed. In the case of single grid cells, which exhibit "theta phase precession", it is currently thought that there is a somatic intrinsic oscillator at theta frequency with several dendritic oscillators, which reflect the velocity. When these patterns are integrated within a single grid cell, a grid map is obtained. Models of grid cell functioning will be explored in more detail in future sections.

Based on the existing models of grid map formation, which are constantly being updated or corroborated by new experimental data, biologically inspired distributed algorithms for use in technical autonomous navigation systems are currently being developed within the GRIDMAP[16] project. Some of the objectives of this transdisciplinary project include implementation of grid pattern formation in a mobile robot and testing whether the robotic system can use these biologically-inspired algorithms in order to map novel environments, as well as exploring ways of optimizing this process.

The aim of this chapter is exploring the role of the crystalline structure of grid cells in the greater context of the Connectome seen as an ongoing biologically-

[15]Tsodyks and Sejnowski (1995).

[16]"Grid Cells: From the Brain to Technical Implementation (GRIDMAP)." *GRIDMAP*. Web. 19 Sept. 2016.

inspired emulation of brain functions, providing deeper insight into how the experimental data on grid cell function and integration can be modeled and emulated in a mobile robot and finally providing a model for how experimental data from the brain can be obtained in order to provide a causal model of brain functions and help implement these functions in other substrates in a feedback loop where experiments, models and robotic implementations can help inform and update each other with the aim of generating a consistent connectome where physical principles that govern brain functioning can be causally understood and emulated in a different substrate.

22.3 Grid Cells as Proof That Causal Information Can Be Extracted from Patterns Observed in Brain Activity

The spiking pattern of grid cells and its regularity allows for easy extraction of a general principle, which then can be applied outside the brain, such as in the case of robot navigation. By means of reverse engineering, it is then possible to see if the information extracted from brain data is in fact causal and not a mere statistical correlation. If robots using the same mapping principle as grid maps become more efficient in navigation (eg. show signs of learning after multiple trials, avoid obstacles, remember objects and other cues etc.)., then this will serve as strong evidence that the information on grid cell functioning extracted from the brain is indeed causal.

Once a benchmark test is implemented for autonomous robotic navigation using grid pattern formation in a simple environment, further testing can be done in order to include multiple variables, such as detecting the presence of objects, visual, and tactile cues, odors, head direction, speed dependence and eventually memory formation and the accumulation of conceptual knowledge.

Moreover, it will be possible to further test the attractor network model of grid cell functioning using a robotic implementation and checking whether this mechanism does indeed help with forming more grid maps in novel environments. One could imagine a hardware implementation of a neural network mimicking the hippocampus, entorhinal cortex and its associated brain areas where electricity would pass through each neuron or node, where one could test whether local excitatory inputs bounded by inhibitory ones would create spiking patterns similar to those of grid cells (Fig. 22.4).

Grid cells do not have to be the only example of causal information being extracted from the brain. The attractor network can also explain the formation of cortical columns, which are common in the barrel cortex of mice and predominate in the cortex in higher mammals. A cortical column, sometimes referred to as a cortical module, is a group of neurons in the cortex with very similar receptive fields and spiking patterns. This in turn affects their function, leading to them encoding similar features. Although it is not yet entirely clear why neurons form into columns, a number of mathematical models suggest that this may be the most efficient way

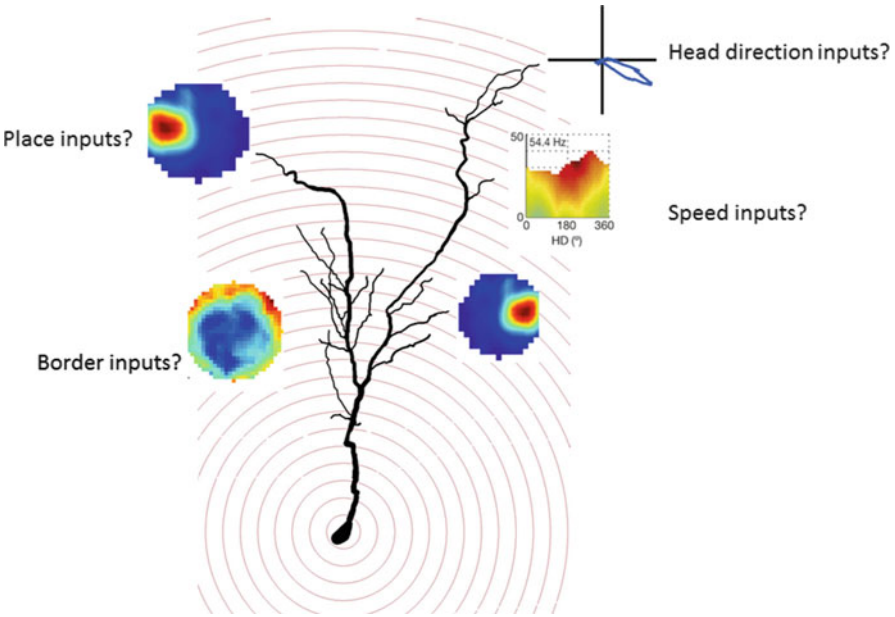

Fig. 22.4 Potential types of inputs that single grid cells may be receiving and integrating. These include different place cell inputs, border cell inputs, head direction inputs and speed inputs. Other inputs may include vestibular, visual, auditory and olfactory inputs

for neurons to store information, given a certain balance between excitatory and inhibitory inputs. There is also evidence that the column effect is also gradual. For example, while in the mouse brain many cortical areas have a salt-and-pepper or heterogeneous organization, more and more studies have shown evidence for clustering of neurons with similar properties, even in the case of grid cells in the mouse entorhinal cortex.

22.4 Grid-Like Structure of the Human Brain

Interestingly, a recent human fMRI imaging study revealed an amazingly clear 3D grid structure of the entire human brain. Wedeen et al.[17] explain that the grid structure they observed through the human brain is continuous and consistent at all scales and across humans and other primates. The fMRI scanner called Connectom can visualize the network of fibers, at a resolution ten times higher than that of a conventional fMRI scanner. While conventional scanners use the blood-oxygen level dependent signal, which after image processing results in

[17] Wedeen et al. (2012).

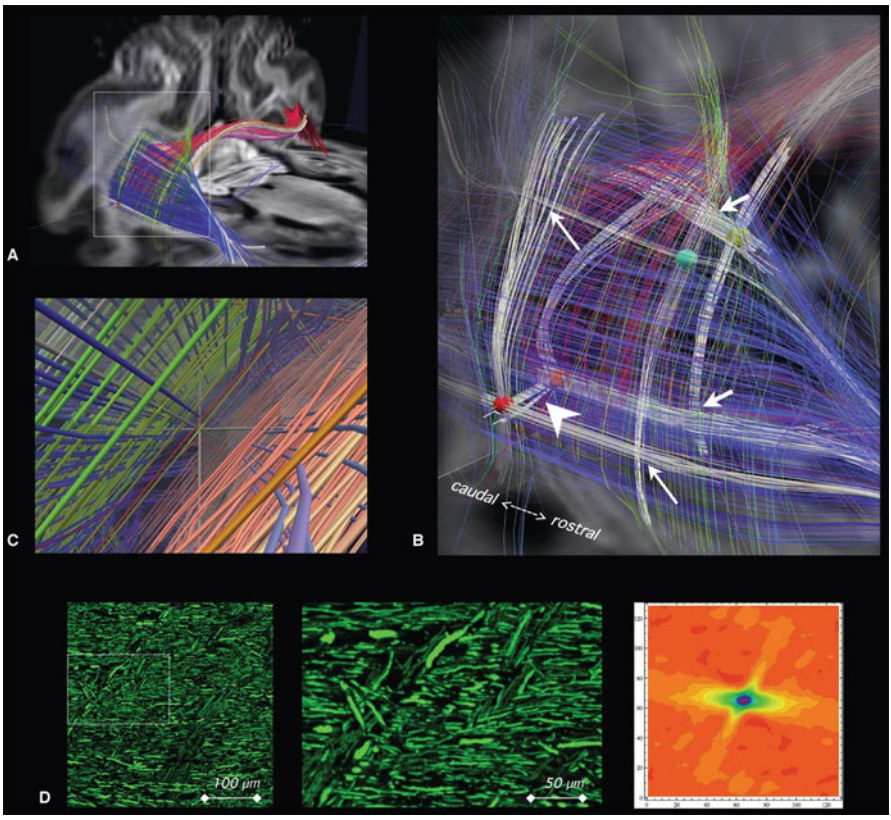

Fig. 22.5 Grid-like structure of cerebral pathways in the sagittal striatum of the rhesus monkey brain (Adapted from Wedeen et al. (2012): 1628–634. Print.). (**a**)–(**c**) show fMRI reconstructions with path neighbourhood analysis, while D shows confocal reconstructions of a sagittal slice together with tits 2D autocorrelation map)

the "blobs" indicating locations where more oxygen was delivered, this hyper-resolution MRI scanner was designed to resolve single fibers with the aim of producing whole-brain functional maps in human subjects non-invasively. The Connectom scanner's increased spatial resolution comes from a larger magnetic field which is given by stronger magnetic copper coils. In diffusion imaging, the scanner detects the movement of water inside the fibers in order to reveal their locations. Diffusion spectrum imaging (DSI) allowed for visualizing the different orientations of multiple fibers that cross in a single location (Fig. 22.5).

During early development, the brain's connections form along perpendicular pathways, running horizontally, vertically, and transversely. This initial grid-like structure, the authors suggest, guides further connectivity like the markers on a highway. If the fibers can only turn in 4 directions, this may enforce a more efficient connectivity map.

The current study was performed on postmortem brains of monkeys as well as living humans. The same grid-like structure was observed in rhesus, marmoset, galago, and owl monkeys, and, of course, in humans.

The grid structure of cortical pathways was also present in the amygdala and hippocampus.

22.5 Modelling Grid Cell Activity

As mentioned previously, one of the most attractive features of grid cells are their context-independence and providing a metric for space regardless of changes in inputs. Grid cells, border and head-direction cells are considered to form the basis of a metric representation of space.[18] Border cells tend to keep their border-related firing in different environments,[19] while in the hippocampus, different cells code for different things in different environments.[20] Thus, it makes sense to look at computational models of grid cell activity since there seems to be a common mapping principle regardless of the environmental conditions.

All models of grid cells formation have been made based on initial biological knowledge of grid cell functioning and have also helped in better understanding the data acquired over the years. Thus, they are not only useful for creating simulations or hardware implementations, but also for understanding the parameters and physical limitations of the biological processes involved in grid cell formation.

Some of the features that a grid cell model should account for are, firstly, the generation of the grid-like spiking pattern and secondly, the persistence of spatial periodicity in different environments, visual clues, speeds, and directions. These models are typically divided into two classes: oscillatory interference models, which use interference patterns generated by different oscillations of membrane potentials (Giocomo et al. 2011a, b).[21] These frequencies are generated, in these models, by running speed and direction in order to generate a spatial firing pattern.[22] The second class includes the attractor network models, which are based on a certain pattern of excitatory and inhibitory inputs which dynamically generate the grid patterns. Speed and direction are important factors in both classes of grid cell models, but the integration mechanisms are different in the two classes. Attractor network models use fixed positions as attractor states, with recurrent connectivity as the main mechanism behind the grid patterns (Fig. 22.6).

[18] Moser et al. (2008).

[19] Solstad et al. (2008).

[20] Paillard 1991

[21] Lisa M. Giocomo, May-Britt Moser, Edvard I. Moser. "*Computational Models of Grid Cells" Neuron – 08/2011*

[22] O'keefe and Burgess (2005).

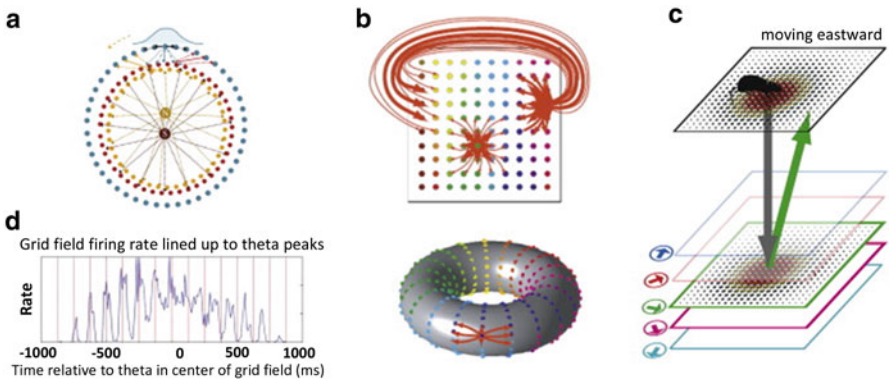

Fig. 22.6 One- and two-dimensional continuous attractor (Models adapted from McNaughton et al. 2006 (B.L. McNaughton, F.P. Battaglia, O. Jensen, E.I. Moser, M.B. Moser. Path integration and the neural basis of the 'cognitive map' Nat. Rev. Neurosci., 7 (2006), pp. 663–678). (**a**), (**b**) Show a one-dimensional and two-dimensional version of an attractor network,respectively. (**c**) Shows the movement of the bump in such a model and (**d**) shows a spiking model)

A network can have a number of attractors,[23,24] with each one being activated by a certain combination of inputs. If the inputs are continuous, then a continuous attractor is formed. The Mexican hat connectivity model is based on the idea that cells receive recurrent excitatory inputs from clustered neurons with similar features, with inhibitory inputs located further away from the cluster, resulting in a bump of focused activity. The excitatory activity bump of the Mexican hat would move in the direction of the animal and according to the speed of movement.

One of the earliest attractor models used an activity pattern which imprinted a grid map onto each neuron in the medial entorhinal cortex of rats based on its movements.[25] Based on the clustered activity concept, multiple bumps of activity would emerge in this way. However, in this model, each cell was assigned a single head direction preference. When combining the speed inputs and the head direction tuning as well as the inhibitory inputs, the model enforced a single moving direction. The model had its limitations, such as the network activity being reset for different portions of the environment. So, the grid pattern started to deteriorate when using more realistic time periods. Also, in this initial model, neurons at the border of the cluster were firing excessively. If recurrent connections between border neurons are assumed in this model, then this problem can be more easily avoided. The McNaughton model includes layers of speed and direction-selective cells receiving

[23] Amit et al. (1985).

[24] Amit et al. (1987).

[25] Fuhs (2006).

inputs from grid cells.[26,27] Moreover, grid spacing increases in a stepwise manner along the MEC dorsoventral axis.[28] Attractor models are all based on the assumption that grid cells with similar spatial phase follow the hebbian rule. This has not been proven by experimental data yet.

The second class of grid cell models is the one based on oscillatory interference which use the changes in membrane-potential change frequencies in order to make a statement about the direction and speed in a periodic pattern. The model has also been extended to single grid cells, where the baseline oscillator is the soma which interacts with several dendritic oscillators. The spiking frequency of the latter was thought to be determined by the animal's velocity.[29,30] If the modulation direction would differ in multiples of 60°, then a triangular pattern would form. This prediction is both interesting and more difficult to test, since the main focus is for now on cell populations. One line of experimental evidence supporting this model is the finding that loss of global theta rhythm leads to loss of firing periodicity of grid cells.[31,32] However, in vitro slice recordings show a high level of noise within the membrane-potential oscillations, as well as varying frequencies.[33] It cannot be ruled out at this point that synchrony is achieved in awake animals during exploration of actual environments. In short, the main idea behind oscillatory interference is that when enough dendritic inputs and the somatic oscillations are in phase, then the threshold is crossed and a spike is generated. The pattern of oscillatory interference created in this way will resemble that of a grid across an open space. The time window for somatic grid cell coincidence detection vary from short to long also dorsoventrally in the MEC (Garden et al. 2008).[34] These properties depend on the morphological features of the neurons, in particular of the distribution of two ion channels.

One interesting question that is relevant for robotic implementations of a grid cell-based navigational system is the extent of space that can be efficiently mapped by these grids. Data suggests that a modulo code can represent up to 2000 m of

[26]B.L. McNaughton, F.P. Battaglia, O. Jensen, E.I. Moser, M.B. Moser. Path integration and the neural basis of the 'cognitive map' Nat. Rev. Neurosci., 7 (2006), pp. 663–678

[27]Navratilova, Zaneta, Lisa M. Giocomo, Jean-Marc Fellous, Michael E. Hasselmo, and Bruce L. Mcnaughton. "Phase Precession and Variable Spatial Scaling in a Periodic Attractor Map Model of Medial Entorhinal Grid Cells with Realistic After-spike Dynamics."*Hippocampus* 22.4 (2011): 772–89. Print.

[28]Barry et al. (2007).

[29]Burgess et al. (2007).

[30]Giocomo et al. (2007).

[31]Brandon et al. (2011).

[32]Koenig et al. (2011).

[33]Dudman and Nolan (2009).

[34]Tuning of Synaptic Integration in the Medial Entorhinal Cortex to the Organization of Grid Cell Firing Fields – Derek Garden, Paul Dodson, Cian O'donnell, Melanie White, Matthew Nolan Neuron – 12/2008

space with a resolution of 6 cm for each linear dimension.[35] It is therefore interesting to explore the feasibility of such mapping in both more experiments as well as in robotic implementations of grid cell models. Another similarly interesting question is whether these large-scale grid maps are mapped by grid cells through a single representation, or whether the large-scale representation is only a combination of smaller maps.[36] Therefore, new grid cell models will have to account for these data.

A better understanding of the mechanisms of space mapping will provide constraints for future models of information processing in general. For example, the oscillatory interference may well apply to any type of functional integration in cells, for example in direction-selective cells and their integration of direction- and orientation-selective inputs, tone-responsive cells and the integration of inputs that code for different frequencies, as well as the integration of whisker-dependent inputs in cells in a given barrel. Keeping in mind that the morphologies of these cells may differ a lot, thus affecting their integration properties, it is very likely that a single unifying principle of integration can be formulated, while keeping morphology as a variable. The case of grid cell integration is particularly interesting, as grid cells integrate a number of lower-level inputs, such as visual input, vestibular input, as well as direction and speed-dependent inputs, in order to generate a high-level output, namely a metric for space. This is likely to be the case for other higher-level functions, such as planning, decision making, memory etc., as high level functions are known to be dependent on information from primary sensory areas.

22.6 Hardware Implementation of Existing Grid Cells and Other Cell Types

This section will focus on describing a hardware implementation of some of the models made based on existing data and knowledge on grid cells and their functioning. The current hardware model is called ratSLAM[37] and it serves as a model of place, grid, and border cell interactions implemented in a SpiNNaker spiking neural hardware, made using the Nengo package for neural engineering and hosted onto a mobile robot. The model implemented in the hardware uses Spatial Envelope Synthesis (SES), which produces grid, place, and border cells by interfering velocity tuned neural oscillators, so they do rely to a large extent on the oscillatory interference models. The place, grid, and border cells in the models perceive theta oscillations at around 8–12 hz from “theta cells”. This oscillation frequency increases when the agents velocity is matched to the preferred velocity of a given theta cell. This mechanism allows for the oscillation frequency to follow the velocity of the rat (or robot), while the phase, that is relative to the oscillator, tracks

[35] Fiete et al. (2008).

[36] Derdikman et al. (2009).

[37] Galluppi et al. (2012).

the distance covered by the robot. The authors also showed that by combining the outputs of the theta cells at particular phases in their oscillations, they can explain measured data in the rat hippocampus. The cells created in this way implemented in the robotic hardware can perform Simultaneous Localization and Mapping (SLAM). Within the hardware, the space mapping cells designed as spiking networks using a material called SpiNNaker. The software used, called Nengo, is commonly used for simulating large-scale neural networks. In Nengo, one starts by defining the neuronal types to be simulated and then forms connections between these groups and defines the type of neural computations to be made. Therefore, one could also use Nengo to model other types of neuronal computations for a given hardware, for example direction-selective cells for movement detection, frequency-tuned cells for sound localization and perhaps even attempt to model higher-level function such as memory formation or decision making, keeping in mind that since these systems are not well documented yet with sufficient experimental data, the number of assumptions in this case with be larger than in the case of grid cells for example. In the case of navigation, theta cells are implemented as ring oscillators which are tuned to specific speeds and directions. This model is then implemented in the 4-chip SpiNNaker hardware, equipped with a 1Gb SDRAM and 18 ARM968 cores in an asynchronous network-on-chip. This is then linked to another 6 neighbour chips. This board is the connected to the robot actuators via 6 asynchronous links. In this way, the robot is then seen by the board as another SpiNNaker chip and the signals sent by the board are translated by the rgbit via a micro-controller.

In this version of SpiNNaker, the place cells were designed to represent a simplified environment and to code for landmarks of "home" and "cheese". Grid cells were implemented into the hardware in order to provide the robot with updated displacement information, thus forming a stable spatial map. The resulting robot was therefore able to locate the two landmarks.

A similar model of grid- and place cell-based robotic navigation was done, called BatSlam,[38] using the same RatSlam model, this time mimicking the bat's sonar system-based navigation system.

Another more recent study also used RatSlam.[39] They also implemented this algorithm into a mobile robot, which was equipped with RGB – D sensor. The images acquired by the sensor are used as an input for scene recognition, creating a sort of "cognitive map". The resulting robot then has to reach a target destination. Its planner creates a local path to reach this target. Another map that records detected obstacles is created towards the target destination. Some of the limitations of this model include the slow (0.2 m/s) due to high computational cost of updating all systems as well as the short distance traveled, making the success rate in locating the target inversely proportional to the distance, mainly due to the low recall rate, also a cause of the high computational cost.

[38] Steckel and Peremans (2013).

[39] Tian et al. (2013).

In a more recent paper, the same group created what they call a more human-like navigational system.[40] In this model, a multilayered asymmetrical local navigational module is created which limits incoming information by only computing local sensory information in order to guide movement. The authors therefore excluded the costmap and the local path from the model in order to increase computational speed. A grid-based direction planner, also called a global planner, is used in this new model in order to extract instructions on directionality, which create the navigation patterns. The cognitive map is then built in the same way with the RatSLAM algorithm. The mapping and navigation results are improved compared to those reported in their previous paper, largely due to the increased recall rate.

22.7 Connectome-Aimed Causal Neuroscience: From Theory to Data Acquisition to Hardware Implementation

As mentioned before, the aim of this paper is to follow the discovery of grid cells and related neurons that help form the brain's navigational systems, as well as more recent findings and looking at how they informed computational models and how these models helped in the understanding of grid cells and in designing future experiments. From this perspective neuroscientific data acquisition and modelling worked in a feedback loop, helping inform on improving each other. It is very important to keep in mind that both in data acquisition in neuroscience as well as in modelling certain assumptions have to be made and that these assumptions are always falsifiable. For example, the RatSLAM-based model which had a relatively poor performance in both speed and memorizing previous positions was considered to be unrealistic given the experimental observations made in rats and their speed in movement and space mapping. Therefore, a more realistic model could be made. Similarly, models on oscillatory interference and the Mexican hat model are also falsifiable especially by imaging data looking at grid cell function both at the single cell level of input integration as well as at the level of neuronal populations. For example, if it turns out that grid cells do not show clear clustering of similarly tuned grid cells, then the models which assume the existence of activity bumps will have to account for that. Similarly, if studies on single grid cells, either via electrophysiology or imaging will show no signs of oscillatory interference in grid cells, but rather mostly backgpropagation, then this will shift the paradigm towards the Mexican hat models. Nevertheless, these models are important for helping neuroscientists create experimental setups where the questions posed by the models can be tested.

Not only do grid cell data and computational models help inform and update each other, but there is also a third level of reverse engineering in this case, namely the hardware implementation of grid cell models into robotic navigational systems.

[40] Shim et al. (2014).

This third level is important because the behavior of the robots can immediately be tested in a navigation task similarly to experimental animals. Since this third level is closer to engineering than neuroscience, it is quite binary in terms of its assessment: the robots either navigate the environment in a realistic fashion, or they do not (either they are slow, loose balance, fail to remember landmarks or fail to efficiently map space in a grid-like manner). Once the robots obtained in this way become realistic enough, either more modules can be included in order to mimic the increasing complexity of the navigational system of the human brain, such as vestibular, visual (as in the latest version of the RatSLAM), auditory (sonar-like as in the case of BatSLAM) or mnemonic inputs. If the aim of these robots is not necessarily a better understanding of the biological navigational system but rather a biologically-based robot that has superior navigational abilities (for example, should there be enough computational power, both a vision-based and a sonar-based system could be used for feedback) could be built. Last but not least, successful feedback at all three levels of understanding (experimental, mathematical, and robotic) brings scientists closer to understanding a universal principle for navigation in a substrate-independent manner.

An ever-increasing understanding of these physical principles which are considered to underlie "the mind" is bound to be incremental and can always be improved at all levels. A causal understanding of neuroscientific principles and their testing implies an incremental effort to make causal connections within neuroscience, rather than just correlations between behavior and neural data.

Most importantly, neuroscientific discoveries such as these do not only tell us something about the neural correlates of subjective perception or navigation in particular, but given the context-independent nature of grid cells specifically, these insights impact on our understanding of the nature of reality in general. By looking at how real space is mapped and how this informs active navigation, for example, we can look at the correlation between environmental features and how an agent acts within it. By including more modules, like vision, olfaction, and sound, our understanding of the relation between space and our brains becomes clearer. Going back to Immanuel Kant, it may be that grid cells together with border, place, and speed cells are able to generate "synthetic a priori" judgements about a given space. It will be interesting to further explore this possibility in robotic versions of this and see whether the robots are able to form a grid map of a virtual environment or of a previously unexplored environment. Going back even further to Aristotle's mathematical objects, it may be that these grids are in fact in the physical world and the brain is only starting to understand them and use them in its favor for navigational purposes.

The aim of this chapter is also to argue that this model for data extraction and embedding it into a larger connectome project can be applied to many other modalities. For example, the case of direction selective cells for motion detection (A synthetic vision system using directionally selective motion detectors to recognize collision, Shigang YUE↓ and F. Claire Rind), or sound localization from frequency tuned cells (Mobile Robot Broadband Sound Localisation Using a Biologically Inspired Spiking Neural Network, Jindong Liu, Harry Erwin and Stefan Wermter).

Memory formation, storage, and retrieval in the hippocampus can be similarly tested, starting with the clearest neuroscientific data in simple memory tasks, to its software implementation and then further testing with similar stimuli as in the case of mice or rats.

From the perspective described above, of reverse engineering a given brain function, in this case navigation, from experimental data to computational models to a hardware implementation working in a feedback loop and constantly updating each other, the connectome becomes feasible as an ever-expanding attempt to identify the physical principles behind brain functioning.

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Chapter 23
Multipotentiality of the Brain to Be Revisited Repeatedly

Yoshio Sakurai, Tomoya Ohnuki, Ryo Shiroshita, Yukitoshi Sakaguchi, Kazuki Shiotani, and Chi Jung Lee

Abstract The brain is a unified entity that cannot realize any functions in its isolated regions. It is also so dynamic that the functions of its regions and neurons are not necessarily fixed. Historically, this natural notion has been confirmed repeatedly by several experimental findings and theoretical considerations including those by Sherrington, Lashley, Hebb, Olds, and John. However, this notion, which typically can be called "multipotentiality" of the brain proposed by E. R. John, has been repeatedly ignored. Most studies in modern neuroscience are searching for fixed and peculiar regions responsible for individual, even any higher, functions and trying to detect treasured single neurons. This article emphasizes again the multipotentiality and raises promising strategies to investigate such unique features of the brain. First, we introduce the historical background and revisit the pioneering studies and consider the impacts of their views on our understanding of brain structures and functions. The second section emphasizes that the brain-machine interfaces has been presenting the multipotentiality of the brain's regions and neurons. The third section considers the clinical relevance of the multipotentiality, particularly in relation to neurorehabilitation and the recovery of function after brain damage. Finally, we introduce recent neuroimaging findings indicating the multipotentiality and suggest an adequate experimental strategy to investigate the brain functions based on the view of multipotentiality, in which the assumption of cell-assembly coding is necessarily involved.

Keywords Multipotentiality • Plasticity • Functional map • Brain-machine interface • Neurorehabilitation • Cell assembly

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23.1 Introduction

Unlike a man-made machine, the brain is a unique and enigmatic organ not completely elucidated yet. Although the brain can be classified to many small regions, each with their individual functions and structures, it also works as a unified organ, and individual constituent regions cannot realize any functions in isolation. In addition, the brain exhibits dynamism to such an extent that the functions of its regions are not necessarily fixed. This view of the brain has been repeatedly confirmed by many researchers within experiments and theoretical considerations. However, such view has been often ignored, although almost all neuroscientists more or less understand it. Very many researchers have been focusing on regional separation and searching for specific regions responsible for individual, even any higher, functions and trying to detect the treasured and task-related individual neurons. This article once again emphasizes that the brain is not a mosaic of functionally independent regions and neurons and supports the multipotentiality theory, to which cell-assembly theory is related, and suggest that we should revisit it repeatedly in the present and future researches. This article additionally raises the issues of adequate experimental studies, brain-machine interfaces (BMIs), and real plasticity for clinical treatments in relation to the multipotentiality of the brain.

23.2 History of Instable Functional Maps and Mulipotentiality of the Brain

Controlling body movements is a primary function of the brain, and the primary motor cortex (M1) is regarded as containing clearly established functional maps, in which individual regions and neurons fulfill specific roles to activate specific muscles of the body. However, even during the early twentieth century, repeated electrical stimulation to identical points in M1 did not necessarily generate identical muscle movements, and the generated muscle movements varied among the animals and from day to day (Brown and Sherrington 1912; Lashley 1923). These pioneering studies conducted approximately 100 years ago suggested that region–muscle or neuron–muscle connections in M1 are not fixed and often changed by time and experience. Recently, Fetz and his colleagues have reported such dynamic and learning-dependent connections between M1 neurons and muscles (see Fetz 2007 for review). Moreover, they have demonstrated that motor-unrelated neurons in the monkey M1 have the ability to control limb muscles with FES (Functional Electronic Stimulation) (Moritz et al. 2008). The implications by these studies are that functional maps can undergo change readily, even in M1 which has been considered to contain many well-defined borders separating the maps.

When we examine the brain in its entirety instead of specific regions, the functional maps become more flexible and the notion of well-defined borders becomes meaningless. Within the memory function, a typical example of higher functions,

the region–memory or neuron–memory correspondence varies and shows flexibility. The pioneering study by K. Lashley in 1920s found that the memory engram of mazes was consolidated not in any specific regions but in widely distributed regions covering almost all neocortices. Lashley stated "Somehow, equivalent traces are established throughout the functional area . . . within a functional area the cells throughout the area acquire the capacity to react in certain definite patterns . . . " (Lashley 1950, p. 502). Though this "equipotentiality theory" (Lashley 1921) might be too radical and the varying parts of the brain are not completely homogeneous in ability of memory retention, the notion that cells throughout the regions are able to acquire capacity and ability to react in certain definite patterns was the pioneering work emphasizing broad plasticity of the brain.

E. R. John has emphasized such broad plasticity and suggested that any neuron and region may contribute to mediating a diversity of functions and that many neurons and regions contribute to every function (John 1980). He called this assumption "multipotentiality theory". The theory does not imply that different neurons and regions are functionally equivalent or that different functions are equally dependent on diverse neurons and regions. John (1972) actually reported that the patterns of evoked electrical potentials in many different regions distributed in the brain started changing simultaneously when the animal was acquiring the discriminative avoidance task, though the shapes of patterns and the points in time when the shapes changed differed among the regions. He suggested that the brain employs plastic and statistical processing in distributed areas rather than switchboard-like processing in specific areas. J. Olds, another pioneering researcher, demonstrated learning-related multipotentiality in the brain (Olds 1975). He showed that multiple neurons in many regions started changing their firing rates almost simultaneously, although the regions showed somewhat different firing latencies when the animal was acquiring the discriminative reward-approaching task (e.g., Olds et al. 1972). Both the studies by John and Olds surely indicate that many neurons distributed across many regions have a capacity to change their activity during learning, which is a typical operation to induce plasticity in the brains. Y. Sakurai confirmed that the multipotentiality notion was valid when learning was accomplished. He examined multineuronal activities in several brain regions of the rat when performing a working memory task (Sakurai 1990a, b). The results showed that all regions demonstrated all types of task-related neurons during performance of the task (Fig. 23.1). The implications are that all regions have the ability to be involved in the memory process and each region has the ability to contribute to the different functions. The proportions of involvement were somewhat different among the regions, suggesting that the results support the notion not of equipotentiality but of multipotentiality of the brain.

The multipotentiality theory suggests that any region may contribute to mediating a diversity of functions. However, there have been several disputes to allocate a specific and only function to a region. An example of such disputes is spatial/nonspatial controversy about the hippocampal function. Although it is historically well-established that the hippocampus is involved in processing of spatial information, several studies have reported hippocampal contribution to both

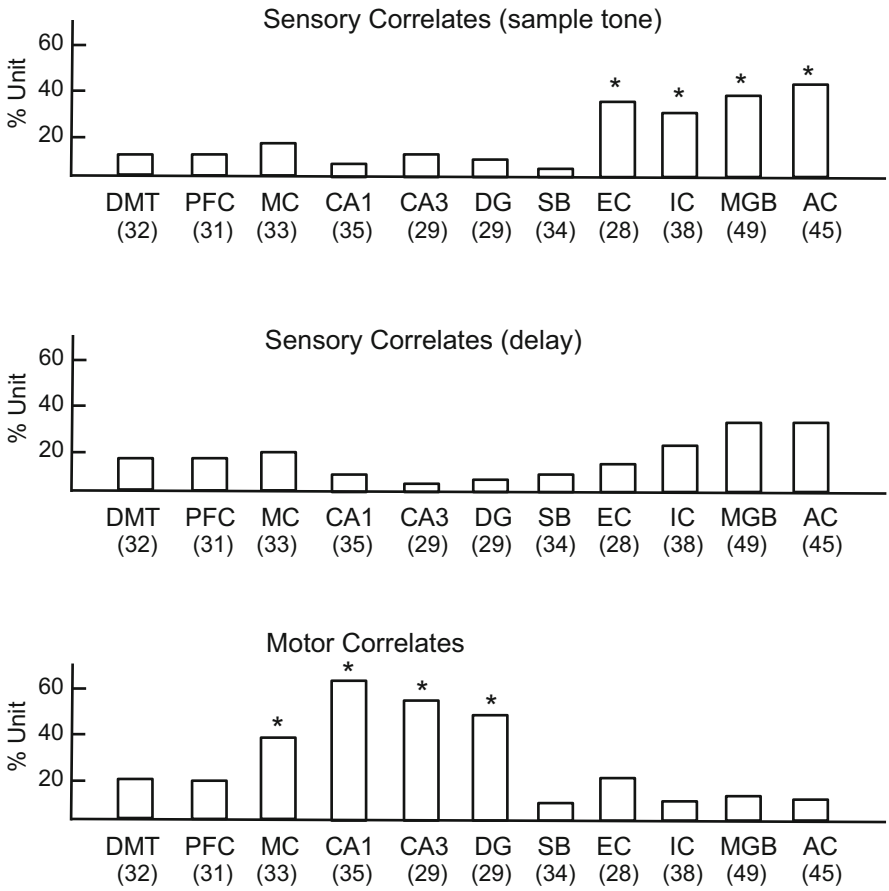

Fig. 23.1 Proportions of task-related neurons during an auditory working memory task in rats in a previous study (Sakurai, 1990a, b). *Upper panel* Proportions of neurons with sensory correlates, i.e., differential activation between the discriminative tones, during presentation of the sample tones to be retained during the delay periods. *Middle panel* Proportions of neurons with sensory correlates during the delay periods. *Lower panel* Proportions of neurons with motor correlates, i.e., differential activation between go and no-go responses, immediate prior to the responses. The asterisk (*) signifies a statistically significant difference ($p < 0.05$) among the regions. DMT, dorsomedial thalamus; *PFC* prefrontal cortex, *MC* motor cortex, *CA1* hippocampal CA1 subfield, *CA3* hippocampal CA3 subfield, *DG* dentate gyrus, *SB* subicular complex, *EC* entorhinal cortex, *IC* inferior colliculus, *MGB* medial geniculate body, *AC* auditory cortex. Numbers in parentheses are the total neurons recorded in each region (Reconstructed from Sakurai 1990b)

spatial and nonspatial functions (e.g., Hampson et al. 1999). D. S. Olton stated "Is the hippocampus a spatial or a mnemonic processor? The answer is clearly yes. Comparison of these two approaches might proceed best if the question was changed, perhaps to: 'How does the hippocampus process both spatial and nonspatial, mnemonic information?'" (Olton et al. 1989).

The above brief history demonstrates that the brain is not a precision machine but rather a plastic and integrated organ characterized by many distributed regions, each of which shows multipotentiality for multiple functions. However, the main stream of modern neuroscience has been attempting to clarify unique functions of individual regions and neurons as well as to classify the regions into even more detailed and smaller components. According to this dominant but outdated paradigm, classification of each region's and neuron's unique functions, if any, is regarded as "clarification of the brain".

23.3 Multipotentiality and Brain-Machine Interfaces

Approximately 15 years ago, an innovative research method, termed "brain-machine interface (BMI)," was introduced to neuroscience (Chapin et al. 1999). This method has once again moved the focus to multipotentiality of the brain (Lebedev and Nicolelis 2006; Nicolelis and Lebedev 2009; Moran 2010; Lebedev and Nicolelis 2011; Nicolelis 2012; Lebedev 2014). In some BMI studies (Wessberg et al. 2000; Carmena et al. 2003), the neurons not only in the precentral (motor) cortical areas but also in the postcentral (parietal) had ability to predict motor movements and the neurons whose activities were used as signals representing information of motor movements were randomly distributed in the motor cortex. Even the neurons which were randomly selected from the non-motor area and were unrelated to motor movement in nature actually attributed to the accuracy of movement prediction when the number of the neurons used for the BMIs were increased (Wessberg et al. 2000; Carmena et al. 2003). These clearly indicates that the information on motor movements and forces is widely distributed in cortical neurons.

These conclusions from the BMI studies are explicitly challenging the classical view of functional localization based on the assumption of rigid functional maps and have suggested that the functional boundaries are not strictly definite but rather obscure and dynamic. Some BMIs do not necessarily require the selection of functionally specific motor neurons (e.g., Moritz et al. 2008) or, as described above, a specific motor area to improve their performance in brain control of devices. Therefore, BMI research is surely contradictory of the view of extremely rigid and subdivided functional maps and clearly supports the theory of multipotentiality of the brain, suggesting that any neuron and region can mediate diverse functions and that many neurons and regions can contribute to many functions, although different neurons and regions do not always have complete equivalence of functions or different functions are not always equally dependent on diverse neurons and regions. It is advantageous within the use of a BMI as a neuroprosthetic system to have the potential to utilize any neuron and any brain region unrelated to the target functions replaced by the BMI.

Some studies have reported that the use of BMIs clearly induced changes in the plasticity of neuronal activities and functions (e.g., Zacksenhouse et al. 2007; Ganguly et al. 2011). Moreover, BMIs can induce the changes in neuronal activity

in the regions not used for device control (Koralek et al. 2012, 2013). Therefore, BMIs can be actively applied to research on the extent to which the brain can change and to determine how the brain can be changed more efficiently. The implications of the former are that BMI studies are able to classify the actual plasticity of the brain. A recent paper (Oweiss and Badreldin 2015) reviews the development process of BMIs and emphasizes the relationships between BMIs and neuroplasticity. The latter suggests that the development of BMIs will lead to the development of better methods of neurorehabilitation to induce changes in neuronal activities and connections facilitating functional compensation (Dobkin 2007; Fetz 2007; Jackson and Fetz 2011; Miller and Weber 2011). Actually, another recent paper (Gulati et al. 2015) reported that learning with BMI operation enhanced neuronal activity in the regions near the structure damaged by stroke in the rat, which had shown disability of motor movements due to the brain damage. These findings and theories can contribute to clinical treatments for patients with impaired brain function and are certainly related to multipotentiality of the brain regions.

23.4 Multipotentiality and Neurorehabilitation

The basic paradigm for BMIs is identical with that for neuronal operant conditioning (neural biofeedback) (Fetz 2007). As it has been pointed out (Dobkin 2007; Fetz 2007; Sakurai et al. 2014; Sakurai and Song 2016), neuronal operant conditioning is a core mechanism of BMI control and can elucidate the potential of neuronal plasticity. Such elucidation necessarily contributes to progress of neurorehabilitation methods (Raskin 2011). In order to allow applicability of neuronal operant conditioning to clinical use, it should be shown that the conditioning does not require selection of functionally specific neurons or regions. In patients with motor deficits, for example, it would be impossible to enhance inherent motor neurons for compensation of motor deficits as very many inherent motor neurons are already lost. Therefore, it should be necessary for neuronal operant conditioning to have the potential to enhance any neuron and hopefully any brain region unrelated to the target functions to be compensated (Sakurai et al. 2014). This is again related to the theory of multipotentiality of the brain.

We actually reported in our previous study (Sakurai and Takahashi 2013) that the neurons showing rapid enhancement in firing rates and synchrony during the neuronal operant conditioning originally manifested no behavior-related activity responsible for motor responses and had been randomly selected from the hippocampus. This result indicates that neurons not initially involved in adaptive behavioral performance can be enhanced by the conditioning and can be subsequently utilized to compensate for loss of motor functions responsible for adaptive behavior. Moritz et al. (2008) had previously indicated such a notion from their findings that the monkeys could learn to use task-unrelated neurons to control an external device when they were enhanced by operant control training. An issue to be addressed is whether any neuron and region can be available for the conditioning

to enhance the higher functions in the sensory and higher brain regions, such as motor functions. Addressing this issue involves testing the validity of the view of multipotentiality of the brain.

Clinical treatment taking into account multipotentiality should be seriously considered, and the classical view of the brain as a complex but rigid organ does patients with brain damage a disservice. The modern imaging technique of functional magnetic resonance imaging (fMRI) has demonstrated broad plastic changes in the brain after injuries and neural defects and has suggested the possibility of functional recovery by adequate treatment to induce the plasticity (Ungerleider et al. 2003; Rocca and Filippi 2006). A recent study employs a novel method of BMI based on real-time fMRI (rtfMRI) and has succeeded self-regulation of the functional connectivity between different brain areas and of distributed brain networks (Ruiz et al. 2014). They emphasize the significance of their methodology to achieve self-regulation of brain functions and applicability of it for potential alleviation of neuropsychiatric disorders. Clinical research within the field of neurorehabilitation has also indicated that some well-devised treatments, such as selected behavioral manipulation, multimodal stimulation, and repetitive transmagnetic stimulation (rTMS) could induce experience-dependent plasticity in the nervous system and broad reorganization of cortical functional maps (Pekna et al. 2012). Chapman and Mudar (2014) and Chapman et al. (2015) introduces growing evidence suggesting training-induced enhancement of cognitive brain performance by engaging efficient communication across the widespread neural networks, e.g., the Default Mode Network (DMN) and the Central Executive Network (CEN), in normal and clinical populations. In addition, recent experimental studies using animals are revealing cellular and trans-regional mechanisms underlying temporal plasticity and functional recovery (Murata et al. 2015); these studies support the notion of multipotentiality theory, which will contribute to further development of clinical treatments and progress within experimental research.

23.5 Conclusion

It has been reported that the human brain can reorganize the sensory deprivations by cross-modal neuroplasticity in visual-related cortices (Bedny et al. 2011). In blind individuals, visual processing regions can be activated by auditory and tactile stimuli. Recently Ortiz-Terán et al. (2016) investigated functional reorganization in regional and distributed neural-systems in late-onset blind (LB) and congenitally blind (CB) cohorts. They revealed the critical role of recipient multi-sensory integration areas in network reorganization and cross-modal plasticity in blind individuals and suggest that cross-modal neuroplasticity and adaptive sensory-motor functions may potentially occur through reorganization in multimodal integration regions.

Regarding attentional processing, the view of multipotentiality is becoming prominent. Although many studies have showed that the various particular brain

areas are related to the process of attention, Rosenberg et al. (2016) recently revealed that the extent of attentional abilities depend on the functional connectivity in whole brain, not only in specific regions in human. They conducted the sustained attention task and analyzed functional connections between 268 distinct brain regions using fMRI. The result showed that a specific brain connection was not always needed for the task and whole brain network is more important for higher attention. Their findings contribute to understanding how the whole brain networks comprehensively work for higher brain functions.

Those recent findings and the historical studies introduced in this article confirm that the brain demonstrates multipotentiality of its regions and neurons in particular in learning and higher functions including cognition and attention. This means that finding a peculiar functional localization and a peculiar function of a single neuron can not contribute to clarifying how the brain is functioning. This is consistent to the suggestion by a recent review article (Hampshire and Sharp 2015), which states "a more holistic approach that considers how common network mechanisms support diverse cognitive processes to fully understand the neural basis of behavioral control."

The view of multipotentiality and the holistic approach on it inevitably requires an adequate experimental strategy of recording multiple neurons from multiple regions during multiple tasks (Fig. 23.2) rather than the recording single neurons from a single region during a single task. Such a strategy should be the standard and used in present and future recording experiments. It could uncover unique features of the brain to be distinguished from precision machines, and concurrently, unique features of information coding in the brain, such as coding by closing loops in microcircuits in prefrontal cortex and hippocampus (Opris et al. 2012, 2013, 2015b).

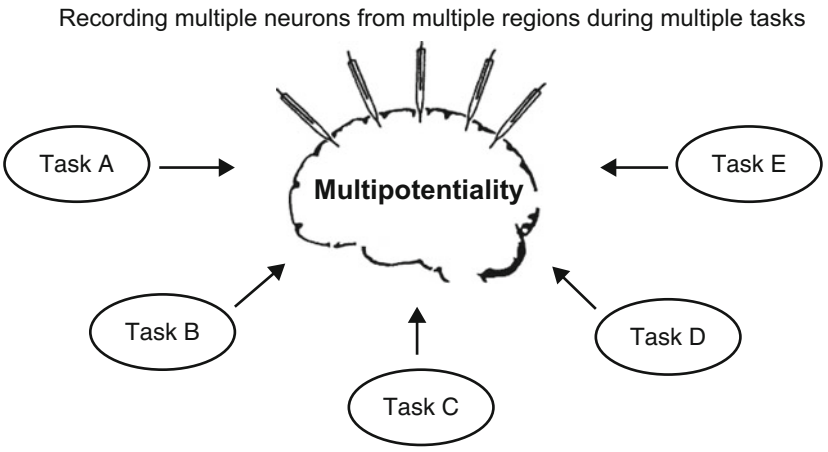

Fig. 23.2 The standard strategy to be used in recording experiments based on the view of multipotentiality of the brain (Reconstructed from Sakurai 1999)

Clarification of coding in the microcircuits can contribute to implementation of BMIs (Opris et al. 2015a).

The strategy is also particularly related to research of coding by cell assemblies (Hebb 1949). As many researchers have defined (Eichenbaum 1993; Sakurai 1996, 1999; Harris 2005; Sakurai and Takahashi 2008; Buzsaki 2010; Wallace and Kerr 2010; Sakurai et al. 2013), the cell assembly is a group of functionally connected neurons and represents neuronal information in the working brain. Figure 23.2 is essentially identical with that to detect cell assemblies (Sakurai 1999). In addition, the cell-assembly coding is related to development of BMIs (Nicolelis 2003; Nicolelis and Lebedev 2009). The theory of multipotentiality, therefore, is strongly combined with the assumption of cell-assembly coding (Sakurai 2014) and should be further verified by present and future neuroscience research, including BMI and neurorehabilitation studies.

Figure 23.3 briefly illustrates the concept of multipotentiality based on the descriptions in this article. The brain functional map dynamically changes especially in learning and higher functions (top in Fig. 23.3). BMI and neural operant conditioning often cause the change of functional map to control external devices

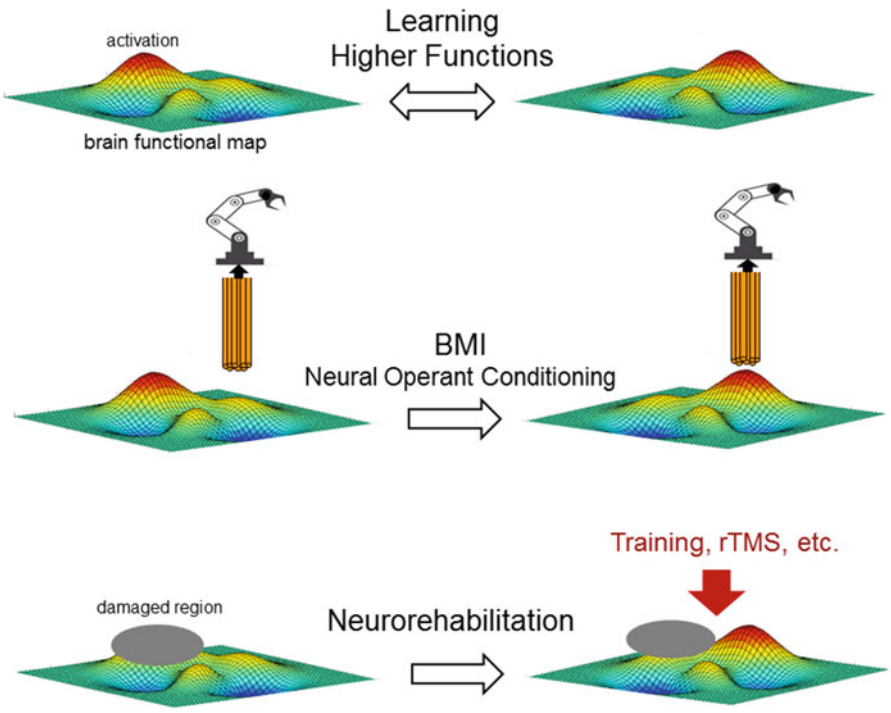

Fig. 23.3 Brief illustration of the concept of multipotentiality in relation to learning and higher functions, BMI and neural operant conditioning, and neurorehabilitation (Some parts of the figure are reconstructed from Microsoft Clip Arts)

efficiently (middle in Fig. 23.3). Training for recovery and the recent techniques, e.g., rTMS, in neurorehabilitation often facilitate the change of functional map to compensate the damaged brain region (bottom in Fig. 23.3). Thought the illustration is too simple to suggest detailed mechanisms underlying the dynamic changes of functional maps, we should at least recognize that the brain functional localization is not absolute and can be easily modified by the normal actions and the recently developing techniques.

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Chapter 24
Characterization of Complex Brain Functions with Sparse Nonlinear Dynamical Modeling

Dong Song and Theodore W. Berger

Abstract Building computational models to explain and mimic complex brain functions is one of the most challenging goals in science and engineering. In this article, we describe a specific form of input-output model of brain functions termed sparse generalized Laguerre-Volterra model. In this approach, input and output signals are spike trains a brain region receives from and sends out to other brain regions. Brain function is defined as its input-output transformational properties that can be represented by a multi-input, multi-output nonlinear dynamical model. Using regularized estimation and basis functions, sparse form of the model can be derived to reduce model complexity and better capture the sparse connectivities in the brain. This approach has been successfully applied to the human hippocampus. The resulting hippocampal CA3-CA1 model accurately predicts the CA1 (output) spike trains based on the ongoing CA3 (input) spike trains and provides a computational basis for developing hippocampal memory prostheses.

Keywords Brain • Hippocampus • Spike • Nonlinear dynamical model • Sparsity • Regularized estimation • Volterra kernel

24.1 Modeling Brain Function as Input-Output Transformation

The brain is probably the most complex and powerful information processing system in the universe. It performs highly sophisticated cognitive functions such as perception, reasoning, language, learning, and memory that still cannot be achieved or even approximated by artificial systems. Building computational models to explain and further mimic brain functions has long been one of the most challenging goals in science and engineering.

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A major obstacle in modeling the brain is dealing with its high degree of complexity. Indeed, even a single functional brain region typically achieves its functions with formidably complicated neural circuits that typically consist of millions of neurons, billions of synapses and axon fibers. At individual neuron level, information processing involves numerous molecular, sub-cellular and cellular processes and mechanisms (Johnston and Wu 1995). In brief, when a spike arrives at the presynaptic terminal of a neuron, it opens voltage-dependent calcium channels and causes calcium influx that triggers presynaptic transmitter (e.g., glutamate) release. Neural transmitters diffuse across the synaptic cleft to open (i.e., change the conductances of) post-synaptic ligand-gated receptor channels such as the AMAP and NMDA receptors, and result in post-synaptic currents. Post-synaptic currents are filtered and integrated in dendrites and the cell body to generate the post-synaptic potential. This process is jointly determined by the neuron's morphology, passive (i.e., resistive and capacitive) properties of the membrane, and active (i.e., voltage-dependent) membrane conductances such as sodium channels, potassium channels, calcium channels, and chloride channels, that each have multiple sub-types with distinct electrical and chemical properties. When the post-synaptic potential is depolarized to a certain degree, a brief electrical pulse, i.e., spike, is generated by the interplay between fast sodium channels and delayed rectifier potassium channels and propagate along the axon fiber to the presynaptic terminals of other neurons. The exact spike timing and pattern is also influenced by other membrane ionic channels such as transient potassium channels, calcium-gated potassium channels, and after-hyperpolarization potassium channels. The post-synaptic potential further influences the conductance of voltage-dependent receptor channels such as the NMDA receptors, as well as the resulting post-synaptic currents, which in turn change the post-synaptic voltage. Due to the complex properties of ionic channels and this constant voltage-conductance-current interaction, it is extremely difficult, if not impossible, to decompose the overall emergent signal processing properties of a neuron into the functions of a set of electrically-segregated subcomponents.

There are two commonly used approaches to model the brain (Song et al. 2009a). One approach is internal and mechanistic. It is driven by the goal to explain brain functions as the multi-scale interactions of the underlying biological processes and mechanisms (Hines and Carnevale 1997). In this approach, membrane ionic channels are represented with Hodgkin-Huxley models; ionic receptor channels are described by kinetic models; neuron morphology is reconstructed as electrically connected compartments based on the geometric shape of the neuron. A neuron is modeled as its equivalent electrical circuit that integrates the models of membrane and receptor channels. Since all internal processes and mechanisms are explicitly modeled, this so-called compartmental neuron model often contains hundreds of compartments each includes tens of Hodgkin-Huxley models and thus becomes highly complex. Finally, the model of a brain region is constructed with a large number of single neuron models interconnected topographically based a connectivity matrix derived from anatomical data. Due to the complexity of compartmental neuron models and the large number of neuron models included, simulating brain functions with such a mechanistic approach is extraordinarily complicated and time consuming, and often requires sophisticated software and hardware systems.

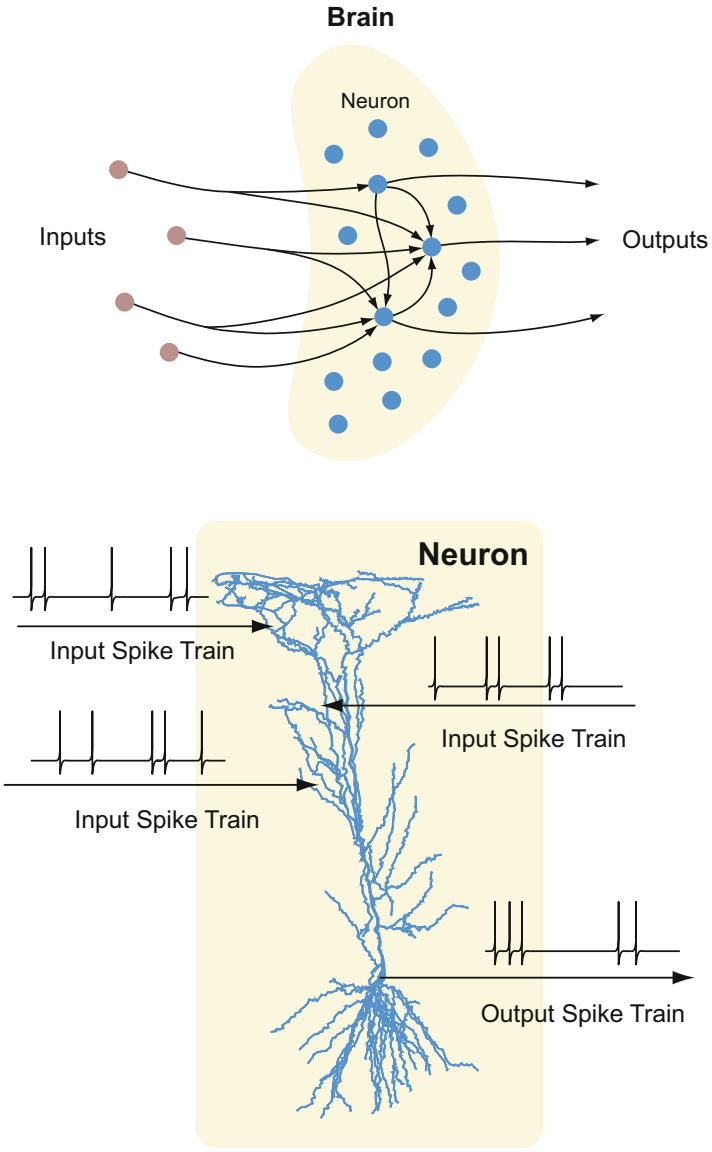

Fig. 24.1 Modeling brain functions as the transformations from input spike trains to output spike trains

An alternative approach, by contrast, seeks to model the brain with respects to its input-output properties, as opposed to its internal mechanisms. In this input-output modeling approach, brain functions are described as transformations from the input signals to the output signals (Fig. 24.1). Since the complex interactions between internal mechanisms are implicitly included in the model as their joint effects

on the resulting input-output relation, an input-output model of the brain usually takes simpler mathematical form with much less computational expense. Due to its computational efficiency and functional relevance, this input-output modeling approach has become a powerful tool for studying brain functions, and found many applications in computational neuroscience and neural engineering (Berger et al. 2005, 2011, 2012; Schwartz 2004; Hampson et al. 2012a; b).

In this article, we describe a specific form of input-output model of brain functions termed sparse generalized Laguerre-Volterra model. In this model, the input and output signals are the spike trains a brain region receives from and sends out to other brain regions. The functions of a brain region is defined as its input-output transformational properties. The goals of this model are to (1) quantitatively and accurately describe the transformation from the input spike trains to the output spike trains of a brain region, and (2) provide identifiable and irredundant model variables that can be related to important biological processes and mechanisms to facilitate model interpretation.

24.2 A Nonlinear Dynamical Model of Spiking Neuron

A brain regions receives spike trains from other brain region(s) as its inputs and sends spike trains to other brain region(s) as its outputs. A model of this brain region thus takes the form of a multi-input, multi-output (MIMO) model that consists of a series of multi-input, single-output (MISO) models representing the output neurons (Fig. 24.2).

The MISO spiking neuron model has a physiologically plausible structure that contains the following five components (Song et al. 2007; Song and Berger 2009): The first component is a MISO feedforward block K transforming the multiple discrete input spike trains x to a continuous hidden variable u that can be interpreted as the somatic synaptic potential. It includes the effects of presynaptic short-term synaptic plasticity, AMPA and NMDA receptor channels, dendritic and somatic integration determined by the morphology and membrane channels. This component has the most complexity in the whole structure. The second component is a noise term ε capturing the level of uncertainty in the system and rendering the whole spiking neuron model stochastic. This noise term includes both the intrinsic neuronal noise and the uncertainty in the membrane potential caused by unobserved inputs (i.e., inputs not included in the MIMO model). The third component is an adder that sums the synaptic potential, the noise, and the feedback potential to form the membrane potential w of the neuron. The fourth component is a threshold function θ. When the membrane potential w crosses θ, an action potential is generated in the output y. The threshold reflects the joint effect of fast sodium channels and delayed rectifier potassium channels in spike generation. The fifth component is a feedback block h transforming the output spike into the post-synaptic spike-triggered after-potential a. This transformation includes the effects of both the intrinsic membrane properties of the neuron (e.g., inactivation

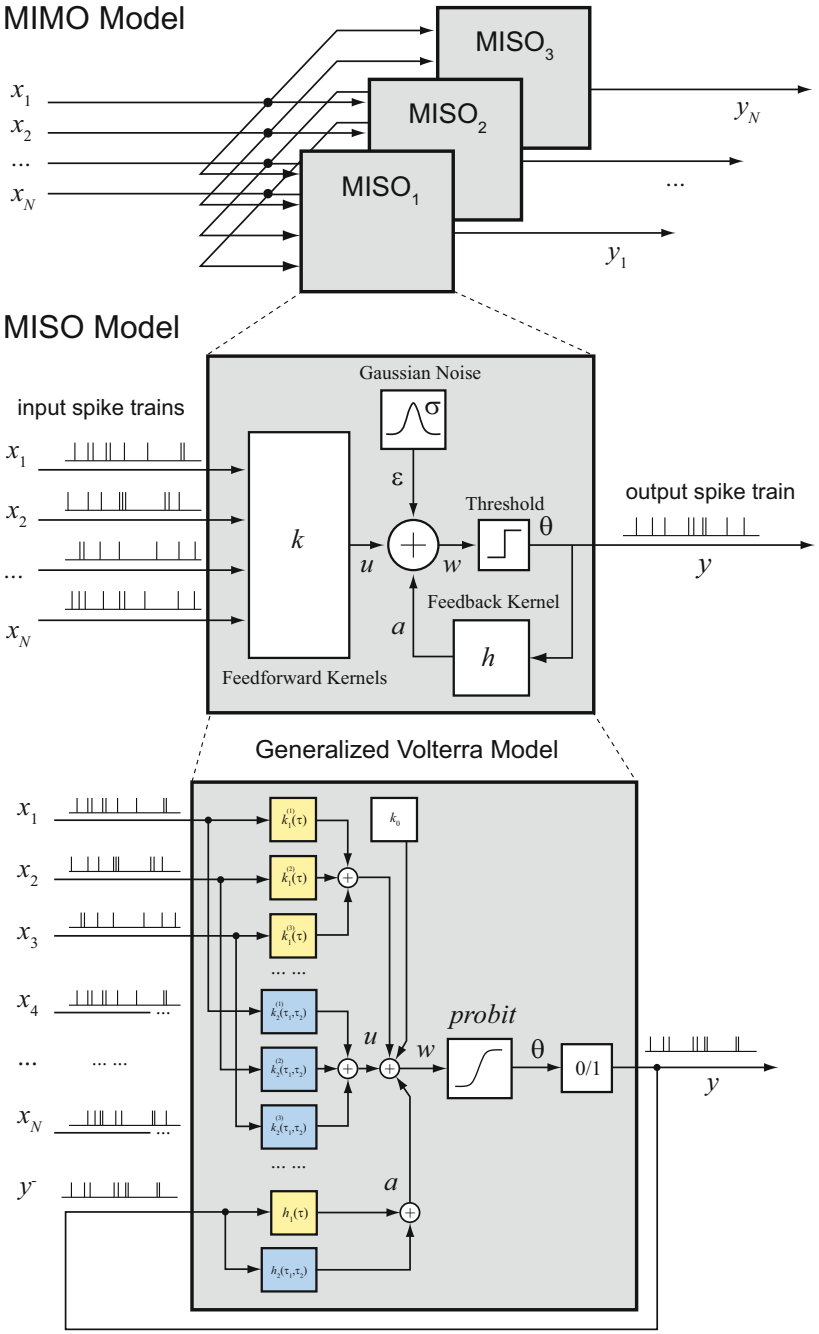

Fig. 24.2 A MIMO nonlinear dynamical model consists of a series of multiple-input, single-output (MISO) generalized Volterra models of spiking neurons

of delayed rectifier potassium channels and hyperpolarization caused by after-hyperpolarization potassium channels) and the external feedbacks from inhibitory interneurons (e.g., $GABA_a$ and $GABA_b$ mediated hyperpolarization). Functionally, this component forms the refractory period of spike generation and also influences the output spiking patterns.

Mathematically the model can be expressed in the following form where K and h are modeled as second-order Volterra series:

$$w = u(k, x) + a(h, y) + \varepsilon(\sigma) \tag{24.1}$$

$$y = \begin{cases} 0 \text{ when } w < \theta \\ 1 \text{ when } w \geq \theta \end{cases} \tag{24.2}$$

$$u(t) = k_0 + \sum_{n=1}^{N}\sum_{\tau=0}^{M} k_1^{(n)}(\tau)\, x_n(t-\tau) + \sum_{n=1}^{N}\sum_{\tau_1=0}^{M}\sum_{\tau_2=0}^{M} k_2^{(n)}(\tau_1, \tau_2)\, x_n(t-\tau_1)\, x_n(t-\tau_2) \tag{24.3}$$

$$a(t) = \sum_{\tau=1}^{M} h_1(\tau)\, y(t-\tau) + \sum_{\tau_1=1}^{M}\sum_{\tau_2=1}^{M} h_2(\tau_1, \tau_2)\, y(t-\tau_1)\, y(t-\tau_2) \tag{24.4}$$

Variables x and y are input and output spike trains. k and h are the feedforward and feedback Volterra kernels, respectively. Zeroth-order kernel k_0 is the resting membrane potential that determines the input-independent baseline firing rate of the neuron. First-order feedforward kernels $k_1^{(n)}$ describe the linear relation between the nth input x_n and u, as functions of the time intervals τ between the past time and the present time. Second-order feedforward kernels $k_2^{(n)}$ describe the nonlinear interaction between pairs of spikes in the nth input x_n as they jointly affect u, in addition to their individual first-order effects. First-order feedback kernel h_1 and second-order feedback kernel h_2 can be interpreted similarly by treating preceding y as an extra input. N and M are the number of inputs and the system memory length, respectively. Noise term ε is assumed to be Gaussian with a standard deviation σ.

The equations above constitute a nonlinear dynamical model of spike train input-output transformations. The system nonlinearity comes from the static threshold nonlinear function, and more importantly, the double convolutions (i.e., multiplications) in the Volterra series. Higher-order terms can also be included to capture higher order nonlinearities. The system dynamical property is captured by the convolutions between kernel functions and input/output spikes, where the current output $y(t)$, as well as hidden variables $u(t)$, $a(t)$ and $w(t)$, are affected not only by the current input $x(t)$ but also past input $x(t\text{-}\tau)$ and output $y(t\text{-}\tau)$ within the system memory window.

A nice feature of the Volterra series is that it expresses the system nonlinear dynamics in a linear form. In Eqs. 24.3 (or 24.4), the nonlinear operation is the multiplication of x (or y). Since xx (or yy) can be pre-calculated and treated as known

variables, the nonlinear relation between x (or y) and u (or a) is essentially the linear relation between $[x, xx]$ (or $[y, yy]$) and u (or a). In addition, the collective effect of the pre-threshold Gaussian distributed noise ε and the threshold function θ is equivalent to a Gaussian cumulative distribution function, which is the *probit* link function in a generalized linear model. The whole MISO spiking neuron model thus can be considered a specific form of generalized linear model that consists of a cascade of a Volterra model and a generalized linear model, and for this reason is termed a generalized Volterra model (GVM) (Fig. 24.2) (Song et al. 2009b). At this stage, modeling the brain function becomes a multivariate nonlinear dynamical regression problem.

24.3 Reducing Model Complexity with Basis Functions

One main difficulty in estimating a Volterra model is due to its large number of coefficients (i.e., k and h). To reduce the model complexity, both feedforward and feedback Volterra kernels can be expanded with basis functions b such as the Laguerre basis (Fig. 24.3) (Marmarelis 1993; Song et al. 2013):

$$u(t) = c_0 + \sum_{n=1}^{N}\sum_{j=1}^{J} c_1^{(n)}(j) v_j^{(n)}(t) + \sum_{n=1}^{N}\sum_{j_1=1}^{J}\sum_{j_2=1}^{j_1} c_2^{(n)}(j_1, j_2)\, v_{j_1}^{(n)}(t) v_{j_2}^{(n)}(t) \tag{24.5}$$

$$a(t) = \sum_{j=1}^{J} c_1^{h}(j) v_j^{h}(t) + \sum_{j_1=1}^{J}\sum_{j_2=1}^{j_1} c_2^{h}(j_1, j_2)\, v_{j_1}^{h}(t) v_{j_2}^{h}(t) \tag{24.6}$$

$$v_j^{(n)}(t) = \sum_{\tau=0}^{M} b_j(\tau)\, x_n(t-\tau) \tag{24.7}$$

$$v_j^{h}(t) = \sum_{\tau=1}^{M} b_j(\tau)\, y(t-\tau) \tag{24.8}$$

In the equations above, x and y are convolved with basis functions b to form v. Volterra series are expressed with v and the sought coefficients become c_0, $c_1^{(n)}$, $c_2^{(n)}$, c_1^{h}, and c_2^{h} for k_0, $k_1^{(n)}$, $k_2^{(n)}$, h_1, and h_2, respectively c_0 is equal to k_0. J is the number of basis functions. The Laguerre basis is group of orthonormal basis functions with exponentially decaying shapes. It can effectively fit a variety of temporal processes with a small number of basis functions when the decaying rate is appropriately chosen. After basis function expansion, the number of model coefficients is no longer dependent on the sampling rate. MISO spiking neuron model becomes a generalized Laguerre-Volterra model (GLVM) and the modeling goal is to estimation the Laguerre-Volterra model coefficients c.

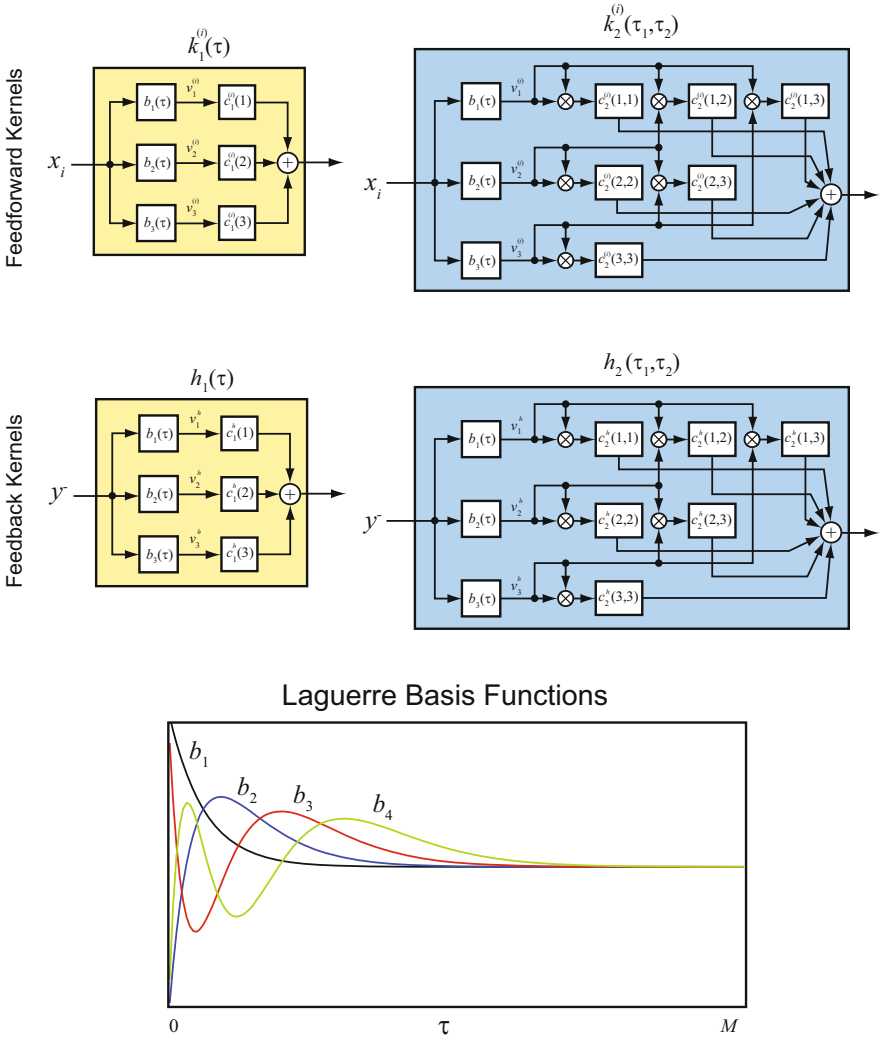

Fig. 24.3 Generalized Laguerre-Volterra model is formed by expanding feedforward and feedback kernels with Laguerre basis function

24.4 Reducing Model Complexity with Regularized Estimation

The generalized Laguerre-Volterra model described above assumes an all-to-all input-output connection. However, neuronal networks are typically sparsely connected. Given a neuron in a network, it receives inputs from only a subset of its possible input neurons. MIMO Model complexity can be greatly reduced if each

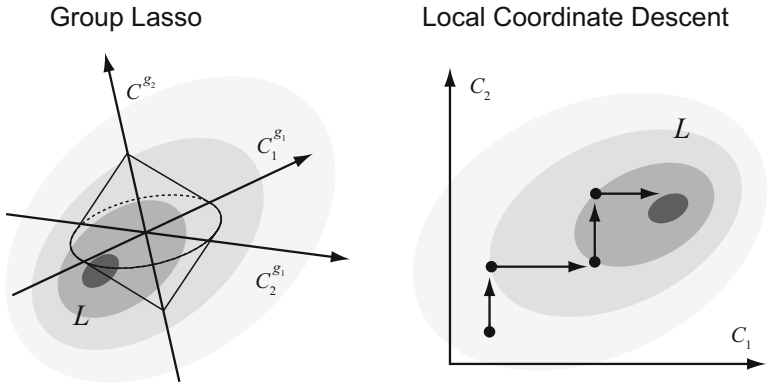

Fig. 24.4 Estimate sparse generalized Laguerre-Volterra models using group lasso model selection and local coordinate descent methods

MISO model takes a sparse form. In addition, since a sparse model utilizes fewer model coefficients, it can effectively avoid overfitting and yield better out-of-sample prediction (Song et al. 2013).

24.4.1 Estimating Sparse Model with Group Lasso

Sparse model representation can be achieved with a group lasso estimation method. Group lasso can be considered a combination of L-1 norm regularization (i.e., lasso) and L-2 norm regularization (i.e., ridge regression) (Yuan and Lin 2006; Tibshirani 1996). It does variable selection at the group level and variable shrinkage within groups (Fig. 24.4). The reason group lasso is chosen to estimate sparse GLVM is that the Laguerre basis are global basis with basis functions expanding the whole memory range, the coefficients thus should be estimated collectively to fit the unknown function. This is different from using a local basis such as the B-spline basis (de Boor 1972), where the basis functions expand only a local range, so the coefficients can be estimated independently, and a group bridge estimation method is more appropriate (Huang et al. 2009).

Specifically in a GLVM, model coefficients are grouped with respect to each input and each model order. With first-order and second-order terms, there are a total of $2N+2$ groups for N inputs and one output. With group lasso, the coefficients are selected and estimated simultaneously at the group level by minimizing a target function S consisting of the negative log-likelihood $-l$ and a grouped penalty term involving the summation of $L2$-norm of each group (Fig. 24.4).

$$S(c) = -l(c) + \lambda \left(\sum_{n=1}^{N} \left\| c_1^{(n)}(j) \right\|_2^1 + \sum_{n=1}^{N} \left\| c_2^{(n)}(j_1, j_2) \right\|_2^1 + \left\| c_1^h(j) \right\|_2^1 + \left\| c_2^h(j_1, j_2) \right\|_2^1 \right) \tag{24.9}$$

$$l(c) = \sum_{t=1}^{T} [y(t) \log\ p(t) + (1 - y(t)) \log(1 - p(t))] \tag{24.10}$$

$$p(c) = \Phi(u(t) + a(t)) \tag{24.11}$$

Φ is the Gaussian (normal) cumulative distribution function that calculates the probability p of the membrane potential w being higher than the threshold θ. It is essentially a sigmoidal function that transforms the summation of post-synaptic potential u and after-potential a into a value between 0 and 1. It reflects the joint effect of the pre-threshold Gaussian noise and the threshold function. T is the data length. The sparsity parameter λ controls the level of sparsity. A larger λ leads to sparser (fewer non-zero coefficients) estimation of the model and vice versa.

24.4.2 Implementing Group Lasso with Local Coordinate Descent

Group lasso defines the target function S that leads to group sparse models. Minimization of S can be implemented with a local coordinate descent (LCD) method (Breheny and Huang 2009; Robinson et al. 2015), in which the model coefficients are updated one by one along fixed descent directions with line search (Fig. 24.4). The main advantage of this method is that the computational cost increases only linearly with the number of coefficients. Therefore, LCD can be used to reliably and efficiently solve very large-scale models, i.e., high-order models or models with a large number of inputs.

In LCD, optimization of model coefficients c is performed by iterating between (a) making a quadratic approximation of the log-likelihood l at the current estimated linear predictor at each step, and (b) individually updating the estimate of each coefficient. The local quadratic approximation of l requires the calculation of second derivative vector w of l with respect to the current estimate of the linear predictor, composed of elements.

$$w(t) = \frac{\partial^2 l(t)}{\partial \Phi^{-1}\left(\tilde{\theta}(t)\right)^2} \tag{24.12}$$

which depends on the chosen link function. The calculation of $w(t)$ for the *probit* link function is given in a previous paper (Song et al. 2013). In LCD, w is recalculated

after updating all individual coefficient estimates. The model residual value $\tilde{r}$ is used to accelerate estimation and updated after each coefficient estimate.

For simplicity, in the following we express each group of coefficients $c_1^{(n)}(j)$, $c_2^{(n)}(j_1, j_2)$, $c_1^h(j)$, and $c_2^h(j_1, j_2)$ as a vector c_q with individual elements ${}^c\text{qp}$ where $q = 1, 2, \ldots 2N+2$ and $p = 1, 2, \ldots, P_q$. P_q is the total number of coefficients in group q. It is apparent that P_q is equal to J and $J(J+1)/2$ in first-order and second-order groups, respectively. Similarly, all corresponding convolution vectors $v_j^{(n)}(t)$ and $v_j^h(t)$, and their element-wise products, $v_{j_1}^{(n)}(t)v_{j_2}^{(n)}(t)$ and $v_{j_1}^h(t)v_{j_2}^h(t)$, are expressed as ${}^v\text{qp}$; the collection of all vectors within a group is expressed as matrix ${}^V q$, which are all combined to form V. The concatenation of c_0 and all ${}^c\text{qp}$ is denoted as c.

The algorithm for estimating $\tilde{c}$ is described below:

1. Start with a set of the initial values of $\tilde{c}$
2. Calculate w with Eq. 24.10
3. $\tilde{r} = y - \Phi(V\tilde{c})$
4. $\tilde{c}_0 \leftarrow v_0^T W\tilde{r}/v_0^T W v_0 + \tilde{c}_0$
5. $\tilde{r} \leftarrow \tilde{r} - \left(\tilde{c}_0 - \tilde{c}_0^*\right) v_0$
6. For each group $\tilde{c}_q$
   (a) If $\frac{1}{T}\left\|V_q^T\tilde{r} + V_q^T V_q c_q\right\| < \sqrt{P_q}\lambda_i$
      (i) $\tilde{r} \leftarrow \tilde{r} + \tilde{c}_{qp} V_q$
      (ii) Set $\tilde{c}_q = 0$
   (b) Otherwise, for each $\tilde{c}_{qp}$
      (i) $\tilde{c}_{qp} \leftarrow \frac{\frac{1}{T}v_{qp}^T W\tilde{r} + \frac{1}{T}v_{qp}^T W v_{qp}\tilde{c}_{qp}}{\frac{1}{T}v_{qp}^T W v_{qp} + \lambda_i\sqrt{P_q}/\left(\left\|\tilde{c}_q\right\| + \delta\right)}$
      (ii) $\tilde{r} \leftarrow \tilde{r} - \left(\tilde{c}_{qp} - \tilde{c}_{qp}^*\right) v_{qp}$
7. Repeat (2) through (6) until convergence

In the above algorithm, * denotes the estimate from the previous iteration; W is a diagonal matrix with elements w; δ is a small value added to prevent division by zero. In addition, each column of V must be standardized before estimation.

As stated above, the relative importance of the likelihood and the penalty term is controlled by the sparsity parameter λ (Eq. 24.9). λ can be optimized with the Bayesian information criterion (BIC) or the multi-fold cross-validation (CV) procedure.

24.4.3 Model Validation and Prediction

Model goodness-of-fit can be evaluated with a Kolmogorov-Smirnov (KS) test based on the time-rescaling theorem. In this article, we use normalized KS-score,

i.e., the ratio between the maximal distance between the KS plot and diagonal to the distance between the 95% confidence bound and the diagonal, as the final measure. If the normalized KS score is below 1, the KS plot is within the bounds and the model is considered accurate.

To predict y, u is calculated with inputs x and the estimated feedforward kernels. This forms the deterministic part of pre-threshold potential w. A Gaussian random sequence with the estimated standard deviation is then generated and added to u to render w stochastic. At each time t, if w crosses threshold θ, a spike is generated, i.e., $y(t)$ is set to one, and a feedback process a is triggered and added to the future values of w. This is equivalent to transforming $u + a$ into the firing probability θ and then generate 1 and 0 with a Bernoulli random process. The calculation then move on to time $t + 1$ with updated w until it reaches the end of the data length.

In summary, with group lasso and LCD methods, MIMO GLVMs are estimated in a sparse form with fewer model coefficients. MIMO model complexity is further reduced. The resulting sparse GLVM (sGLVM) yields a highly parsimonious representation of the brain input-output function (Song et al. 2009c, 2013).

24.5 Simulation Studies

The effectiveness of the sGLVM framework is first tested with simulated systems (Fig. 24.5). A spiking neuron model is designed to have 64 possible input neurons, each of which generates an independent Poisson random spike train with mean firing rate of 5 Hz. The majority of these input neurons does not connect to the output, with 16 out of 64 inputs have non-sparse first-order effects and 8 out of 64 inputs have non-sparse second-order effects. All non-zero first-order effects and second-order effects are identical, i.e., k_1 and k_2 have the same shapes. Using 3 Laguerre basis functions, there are a total of 577 coefficients to estimate (3 per k_1, 6 per k_2 for each input), where 106 out of 577 coefficients are non-sparse. A total of 800 seconds is simulated with a 2 ms bin size. The simulated input and output spike trains are used to estimate the sGLVM of this MISO system. Non-sparse maximum likelihood estimation (MLE), where target function $l(c)$ is maximized, is also performed for comparison.

The estimation results are shown in Fig. 24.5. First-order kernels k_1 are 1-D vectors quantifying the first-order causal relationships between each input and the output as functions of the time intervals. Second-order kernels k_2 are 2-D matrices describing the second-order joint effects of pairs of input spikes on the output in addition to their individual first-order effects. The left column shows the true kernels for the 64 inputs, with top and bottom subplots showing k_1 and k_2, respectively. The middle column shows the MLE results. It is evident that MLE cannot reveal the sparse connectivity between the inputs and the output. In addition, it yields inaccurate estimation to both zero-valued and non-zero-valued kernels due to serious overfitting. By contrast, results show that the sGLVM can correctly recover the system sparsity and accurately estimate the kernels.

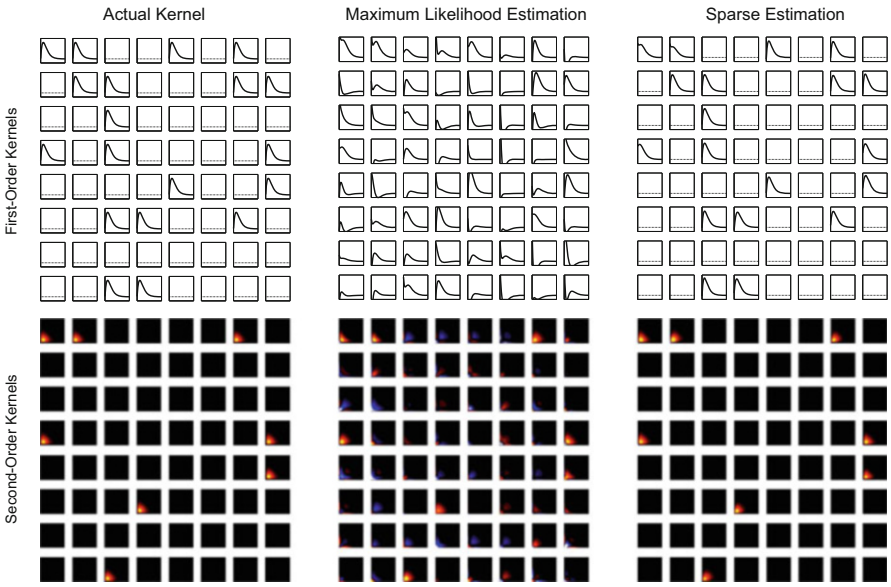

Fig. 24.5 Sparse estimation is tested with a 64-input system with sparsely distributed first-order and second-order feedforward kernels (k_1 and k_2)

24.6 Applications on Hippocampal Memory Prostheses

Finally, we apply the sGLVM to study the human hippocampus. The goal is to build a MIMO model that can accurately predict the output spike trains based on the input spike train. Such a model is required for developing hippocampal prostheses that can be used to bypass a damaged hippocampal region and thus restore memory functions lost in diseases or injuries (Berger et al. 2005; Song et al. 2014).

Hippocampal CA3 and CA1 spike trains are recorded from epileptic patients performing a memory-dependent, delayed nonmatch-to-sample (DNMS) task as the model inputs and outputs, respectively (Song et al. 2015). Previous anatomical and physiological studies have shown that the hippocampal CA3 region provides the majority of the inputs to the hippocampal CA1 region. Depending on the specific surgery procedure, electrode placement, and condition of each patient, various numbers of neurons are recorded. In this article, we present one set of results from a patient with unilateral recordings from anterior and posterior hippocampus (Song et al. 2016).

We have recorded 48 CA3 neurons and 49 CA1 neurons from this patient. The estimated MIMO model thus contains 49 48-input, single-output models. Figure 24.6 shows the first-order and second-order Volterra kernels (feedforward and feedback) of one representative MISO model. MIMO models are formed by concatenating all MISO models. Model goodness-of-fits are evaluated with the out-of-sample normalized KS-scores of each MISO model. In this patient, out of 49

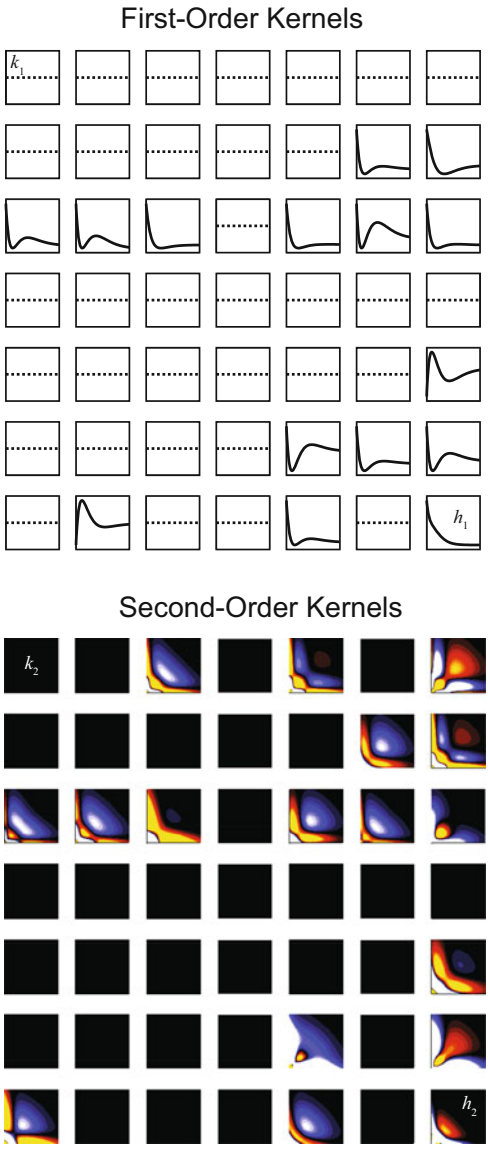

Fig. 24.6 First-order and second-order feedforward kernels (k_1 and k_2) and feedback kernels (last subplot in each figure; h_1 and h_2) of one sparse MISO model of human hippocampus

MISO models, 22 (44.9%) sparse and 7 (14.3%) non-sparse MISO models show a KS plot within the 95% confidence bounds. Sparse models significantly out-perform their corresponding non-sparse models in 44 (89.8%) outputs.

CA1 spatio-temporal patterns are predicted from the CA3 spatio-temporal patterns using the estimated sparse MIMO CA3-CA1 models (Fig. 24.7). Two 100 s long segments containing multiple DMS trials are shown. Neurons are ordered descendingly with respectively their mean firing rates. It is evident that this sparse

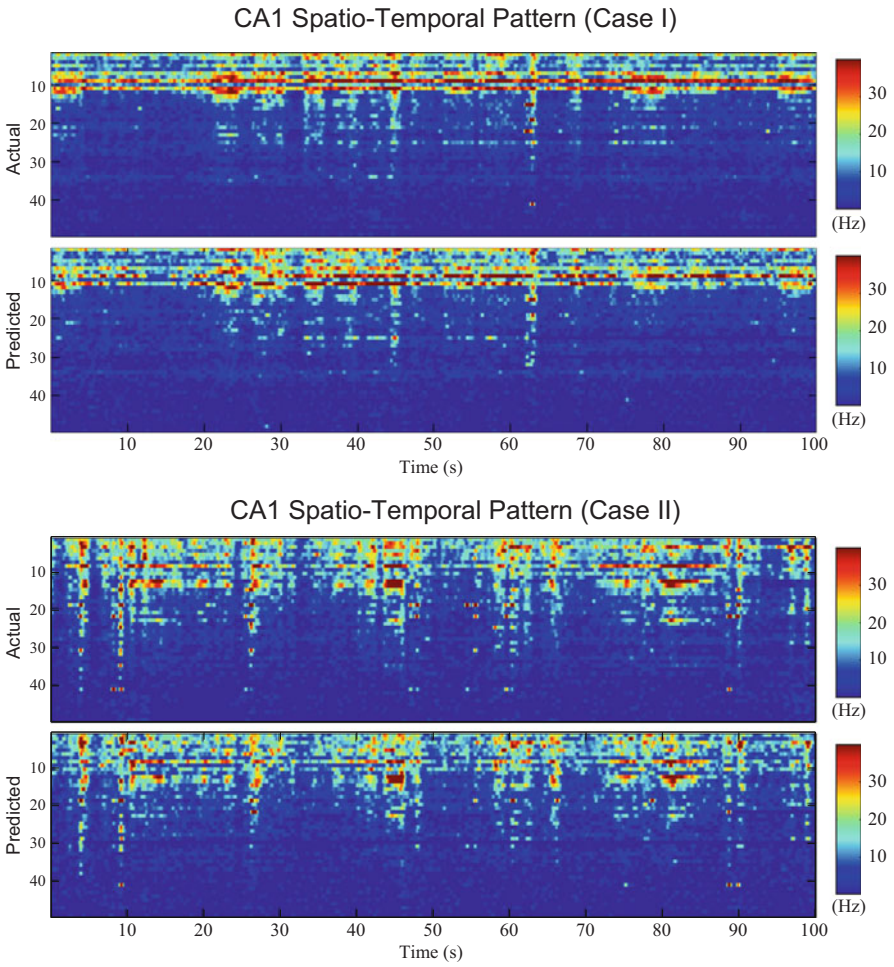

Fig. 24.7 Predicting CA1 spatio-temporal patterns from CA3 spatio-temporal patterns with the sparse MIMO model

MIMO model highly accurately predicts the CA1 spatio-temporal patterns on a single-trial basis. The prediction captures both the global trend and fine details of the CA1 patterns.

24.7 Discussions

In this article, we formulate a nonlinear dynamical modeling approach for modeling the brain functions. In this approach, brain functions are represented as the input-

output transformational property of the brain region, which can be described with a MIMO nonlinear dynamical model. Since the biological mechanisms are implicitly included in the model as their effects on the system nonlinear dynamics, as opposed to explicitly built in the model, this input-output modeling approach represents brain functions in a more parsimonious and mathematically tractable form, compared with the detailed mechanistic modeling approach. To reduce model complexity and better capture the sparse connectivity in the brain, regularized estimation is applied to yield sparse form of the model. The resulting sGLVM has been successfully applied to the modeling of the hippocampus and provides a computational basis for building hippocampal memory prostheses.

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Chapter 25
Controlling Attention with Neurofeedback

Mehdi Ordikhani-Seyedlar and Mikhail A. Lebedev

Abstract We are witnessing a rapid development of neurofeedback (NF) based applications that give human subjects a capacity to monitor and modify their own brain activity. Practical goals of NF systems include treatment of neurological disorders, and even augmentation of normal brain function. Attention deficits are a class of disorders to which NF-based therapy is applicable. Here we review the challenges of NF implementations for the control and treatment of visual attention. These implementations generate close-loop feedback using electroencephalographic (EEG) and other recording methods that sample brain signals related to different aspects of attention. Despite the progress achieved in the studies of neural mechanisms of attention, extraction of information representing attention from brain activity is still a difficult problem because of the presence of other overlapping neural signals. Therefore, it is important that attentional NF systems employ behavioral tasks and computational algorithms that dissociate signals of interest from the interfering signals. Notwithstanding recent advancements in this field, fundamental challenges still exist for the development of efficient clinical applications.

Keywords Visual attention • Electroencephalography (EEG) • Brain-Machine Interface • Neurofeedback (NF) • Feature extraction • ADHD • Event-related potentials (ERPs) • Neural oscillations • Steady-state visual evoked potential (SSVEP)

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25.1 Introduction

The visual system of the brain transforms complex visual scenes into robust representation which can be utilized by the other brain systems (motor, sensory, sensorimotor and cognitive) and consciously perceived. This transformation deals with a large amount of input information, and it is critical for the brain to select the behaviorally relevant information content (Sprague et al. 2015). Attention is the ability to block unwanted information and enhance the processing of relevant information. This key cognitive function often dysfunctions in neurological disorders. Patients with attention deficits cannot concentrate continuously on one task, and they easily get distracted by the surrounding stimuli. One of the most common attentional disorders is attention-deficit/hyperactivity disorder (ADHD), which is characterized by hyperactivity, impulsivity and inattentiveness. The symptoms arise in childhood and can be extend to adulthood. Studies have shown that 15–40% of the adults diagnosed with ADHD still carry the symptoms (Biederman et al. 2000; Faraone et al. 2006). ADHD can significantly impair academic, occupational and social performance (Fleming and McMahon 2012). According to a meta-regression analysis of 102 studies, worldwide prevalence of ADHD is about 5% (Millichap 2008; Polanczyk and Rohde 2007; Skounti et al. 2007). Typical treatment strategies have been mostly focused on medications such as psychostimulants. However, the side effects associated with these pharmacological agents often make these substances unsuitable for long-term usage (Conners et al. 2001; Greenhill et al. 2001). Children may develop anxiety symptoms following treatment by psychostimulants for 6 months and longer (Vance et al. 1999). There is also a considerable risk of misuse or abuse of psychostimulants (Kollins 2008; Steiner et al. 2014a). Psychological therapy is an alternative treatment that reduces ADHD symptoms in approximately 30% of cases (Zarin et al. 1998). Overall, currently available therapies for ADHD are only partially effective and new solutions are needed.

Here we review a novel treatment strategy for patients with attention disorders. This strategy is based on neurofeedback (NF) approach (Arns et al. 2009; Lim et al. 2010, 2012). NF is an artificial sensory loop that makes brain signals available to the user. In NF applications, external devices serve as intermediaries, such as computers that process and display NF, and neurally controlled robotic limbs (Lebedev 2014; Lebedev and Nicolelis 2006; Nicolelis and Lebedev 2009; Wolpaw et al. 2000; Donoghue et al. 2004; Schwarz et al. 2014). A related term for such systems is *brain-machine interface* (BMI). BMI researches emphasize the ability of neural control of external devices, whereas NF researchers emphasize the feedback component. This difference is minor because practically all BMIs include some type of NF, and the majority of NF systems include a neurally controlled device. Both BMIs and NF systems decode neural signals and translate them into the representations that users can easily understand (Fig. 25.1). The decoding consists of recognition of neuronal patterns and attributing them to certain brain functions or states. After the state is detected, the system generates appropriate NF for the

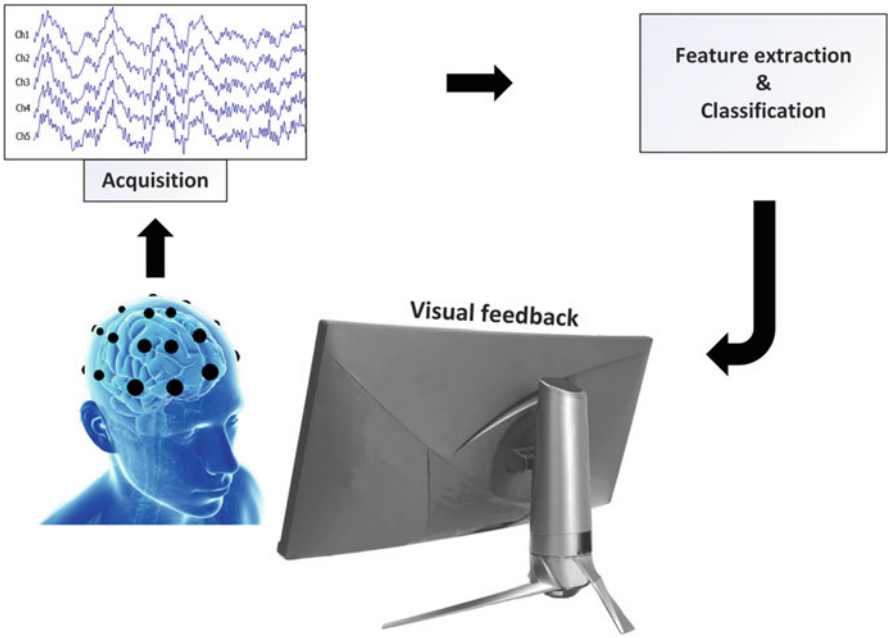

Fig. 25.1 Schematics of a neurofeedback system. Signals are acquired using a recording system (in this case, EEG recordings). In the signals processing step, appropriate features of the signals are extracted and classified, so that an indicator of neural activity can be delivered through a visual feedback to the subject. Using such a neurofeedback, the subject can monitor his/her performance in real-time (Figure adopted from Kaulitzki 2014; https://www.back2gaming.com/wp-content/uploads/2016/04/ROG-Swift-PG348Q-Back-2.png)

subject. If an unhealthy state is decoded, a patient would attempt to correct his/her own brain activity to achieve functional improvement. This therapeutic approach is called NF therapy. The most common NF therapy for humans is based on electroencephalography (EEG; Fig. 25.2), a non-invasive, portable and easy to use method (Bamdadian et al. 2014; De Vos et al. 2014; Kashihara 2014; Kus et al. 2013; Tonin et al. 2013; Yang et al. 2014). The other methods include electrocorticography (ECoG; Fig. 25.2) (Freeman et al. 2003; Leuthardt et al. 2009; Leuthardt et al. 2004; Schalk 2010), magnetoencephalography (MEG; Fig. 25.3) (Ahn et al. 2013; Bianchi et al. 2010; Mellinger et al. 2007), functional magnetic resonance imaging (fMRI; Fig. 25.3) (de Charms et al. 2005; Logothetis 2003; Ruiz et al. 2013; Sato et al. 2013), near infrared spectroscopy (NIRS) (Coyle et al. 2004; Khan et al. 2014; Power et al. 2012; Sitaram et al. 2007; Waldert et al. 2012), and multi-electrode intracranial implants (Carmena et al. 2003; Ifft et al. 2013; Lebedev et al. 2005, 2011; Nicolelis et al. 2003; Nicolelis and Ribeiro 2002; Peikon et al. 2009; Zacksenhouse et al. 2007).

NF therapy has been already applied to a variety of neurological disorders, including disorders of attention (Gevensleben et al. 2014; Hillard et al. 2013;

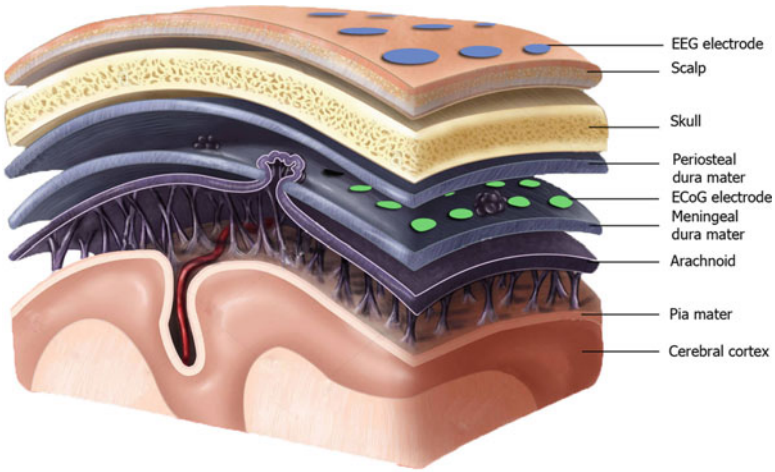

Fig. 25.2 Different recording methods. The electrical activity of the brain can be recorded invasively using ECoG (in *green*) or non-invasively using EEG (in *blue*). ECoG has higher spatial resolution than EEG since it samples neural activity closer to the brain. Notwithstanding the advantages of ECoG, non-invasive nature of EEG makes it convenient for clinical use (Figure adopted from http://c8.alamy.com/comp/G1560N/an-illustration-of-the-membranes-that-enclose-the-brain-and-spinal-G1560N.jpg)

Fig. 25.3 fMRI and MEG recordings. In these recording techniques, electrodes are located at a distance from the head. In addition to its high spatial resolution, fMRI makes it possible to acquire signals from subcortical regions. Conventional fMRI machines suffer from very poor temporal resolution, a property which makes this method less suitable for real-time experiments. MEG, on the other hand, is a sophisticated device that obtains relatively high spatial and temporal resolutions. Major drawbacks of fMRI and MEG as components of NF system are lack of portability, high price of facilities and restrictions imposed on the subjects while recording (Figure adopted from http://image.shutterstock.com/z/stock-vector-human-brain-medical-schematic-simplified-illustration-on-white-74522395.jpg)

Lofthouse et al. 2012a; Steiner et al. 2014b; Zandi Mehran et al. 2014). Therapies for ADHD usually employ visual displays (Arns et al. 2014). As to the recording methods, some have already proved effective for attention control and for treatment of ADHDs, such as EEG, NIRS and ECoG; whereas others such as MEG and fMRI require further research (Ahn et al. 2013; Bruhl 2015; Okazaki et al. 2015; Sokunbi et al. 2014; Stoeckel et al. 2014; Sulzer et al. 2013). Implementing an attention-based NF is quite challenging due to extremely complex neural representation of attention (Ming et al. 2009; Rossini et al. 2012). Fundamental understanding of neurophysiological manifestations of attention is essential for extracting appropriate signals and dissociating them from the interfering neural activities (Sanei and Chambers 2008). Notwithstanding these difficulties, clinical NF systems for attention control have been already developed for subjects suffering from ADHD (Christiansen et al. 2014; Heinrich et al. 2014; Holtmann et al. 2014a, b; Micoulaud-Franchi et al. 2014; Steiner et al. 2014c).

25.2 Decoding of Visual Attention from Neural Signals

25.2.1 Neural Mechanisms of Visual Attention

While our sensory receptors constantly detect and deliver to the brain overwhelming amounts of information, the brain ends up using only a tiny amount of this information simply because its processing power is limited. Reduction of the incoming sensory information is performed by the brain mechanism known as selective attention. High-level cortical areas, particularly the areas of the frontal cortex, play a key role in selective attention by requesting the types of information the brain needs and guiding its processing. Attentional functions suffer when these areas are damaged. For example, damage to prefrontal cortex (PFC) causes loss of attentional control (Ferrier 1886). Neurophysiological and functional neuroimaging studies by Posner's group (Fan et al. 2005; Petersen and Posner 2012; Posner and Rothbart 2007) have provided a wealth of information on the mechanisms of attentional control and cortical circuitry involved. These studies have shown that attention is controlled by a network of interconnected areas that are also closely linked to oculomotor control. The key players of this attentional/oculomotor network are the frontal eye field (FEF), parietal cortical areas and subcortical structures, particularly superior colliculus. The selective attention network works together with yet another, overlapping network of areas that sustains the focus of attention, called *sustained attention*. Sustained attention maintains the focus of attention on the selected stimulus. It is composed of the parietal cortex, right frontal cortex and locus coeruleus (Corbetta et al. 2008). Volumetric analysis in ADHD subjects showed that they have smaller frontal cortex compared to healthy subjects (He et al. 2015). Such neuronatomical findings explain the deficits in both selective

and sustained attention (Avisar and Shalev 2011; Gomes et al. 2012; Pritchard et al. 2008; Wang et al. 2013).

Attention-based NF systems strive to control both selective and sustained attention, as they typically require both selecting a visual target and focusing on it (i.e., aspects of selective attention) and mental endurance training (i.e. sustained attention). The NF of systems also deal with endogenous and exogenous drives for attention. Indeed, attention can be driven either by the external stimulus (exogenous attention) or the internal intention by the observer (endogenous attention). *Exogenous attention* is the response to low-level features of a sensory input (Egeth and Yantis 1997; Wolfe and Horowitz 2004). Low-level properties include such features as stimulus intensity, color and contrast. Depending on the behavioral content, these features can trigger different responses, some of them completely involuntary, such as looking at an unexpected light flash. In *endogenous attention*, attentional focus is voluntarily selected by the subject, often before any sensory stimulus occurs (Desimone and Duncan 1995; Posner et al. 1980). Endogenous attention is important because it allows to search for and anticipate particular types of information. Posner designed a behavioral paradigm to dissociate the characteristics of endogenous and exogenous attention. In this paradigm, two stimuli are shown on the screen to the left and the right from a central fixation point. Participants are asked to fixate their gaze at the central point while attending to the right or left stimulus. Importantly, the subjects attend covertly, i.e. without looking at the attended locations. In Posner's experiments, participants were instructed to press a button when a target (a digit or letter) appeared at the left or right location (Posner 1980). To instruct where to attend, a cue was presented at the center of the screen. This cue preceded stimulus onset, and corresponded to the upcoming stimulus location in 80% of the trials. In the remaining 20% of trials, the target location did not match with the cue and appeared at the unattended location. This study showed that the reaction time was faster when the target was presented at the attended locations. The longer reaction time for the stimulus appearing at the unattended location was explained by a conflict between the endogenous and exogenous attention. Busse et al. (2008) investigated neurophysiological mechanisms underlying these two types of attention. They recorded from single neurons in the middle temporal area of macaque monkeys, while manipulating monkeys' endogenous and/or exogenous attention. The task was a double-cueing paradigm where the first cue instructed the monkey to attend endogenously while awaiting a second cue. The second cue was unpredictable, and therefore engaged exogenous attention. It signaled to either shift or maintain the current focus of attention. This study showed that endogenous attention was associated with an increased neuronal activity. However, this neuronal activity was transiently interrupted for approximately 70 ms when attention was exogenously attracted to the second stimulus. After this short interruption, the neuronal activity was restored to the previous level when endogenous attention was reengaged. These findings suggest that the interruption of endogenous attention by exogenous attention is a complex process which involves endogenous and exogenous components, as well as an interaction between them.

Both endogenous and exogenous attention can be maintained with and without eye movements (i.e., overtly or covertly, respectively). In his premotor theory of attention Rizzolatti et al. (1987) suggested that essentially the same neural circuits in the parietal and frontal regions are responsible for both covert and overt attention. For overt shifts of attention, eye movements are prepared and executed, whereas for covert attention they are prepared but not executed. The premotor theory of attention found support in the results of imaging studies that showed an overlap between the parietal and frontal regions activated during covert and overt attentional tasks (de Haan et al. 2008). Additionally, neurons in the intermediate layer of superior colliculus which has been long known to be involved in saccades, are also engaged in covert attentional shifts (Ignashchenkova et al. 2004). Golla et al. (2005) reported a clinical case of impaired overt attention in a cerebellar disorder, and suggested that the cerebellum plays a role in spatial attention.

Lebedev and Wise (2001) studied neural representation of attention in conjunction with the representation of other behavioral variables, such as spatial memory, target of movement and gaze angle, which often coincide with the orientation of attention but still can be controlled independently. In one study, the neuronal activity in monkey's dorsal premotor cortex (PMd) that reflected the orientation of selective spatial attention was compared with neuronal activities that represented motor preparation such as saccades and gaze angle. The monkeys' attention was attracted by a robot whose movements instructed when a reaching movement could be started. The target of movement varied. It was either the location of the feeder mounted on the robot or a location of a different feeder. Results from this study showed that approximately 20% of PMd neurons responded to the orientation of selective spatial attention, which could be disengaged from the other spatial variables. These attention-tuned PMd neurons may contribute to gaze-independent (covert) attention in behaviors that involve stimulus-response incompatibility. In another study Lebedev et al. (2004), tested whether the main function of prefrontal cortex (PF) was the maintenance of working memory, as strongly claimed by many authors. To investigate alternative possibilities, neuronal activity was recorded from PF while monkeys performed an oculomotor task that required remembering one location but attending to a different location. The highest response from a large subpopulation of PF neurons was found to reflect attention rather than working memory. This indicated that PF has a major contribution to selective spatial attention. Human studies have consistently demonstrated impairments of frontal cortex in ADHD (Dirlikov et al. 2015; Praamstra et al. 2005). Dirlikov et al. (2015) examined cortical morphology in 93 children with ADHD using brain imaging technique. They found that the cortical surface in PF and premotor cortex of these children was reduced. Several neuroimaging studies suggested that visual attention is controlled by a network of cortical areas interconnected with the FEF. Gray matter of this network is substantially affected in ADHD, including gray matter of the dorsal and ventral prefrontal cortices, dorsal anterior cingulate area and inferior parietal cortex (Szuromi et al. 2011; Valera et al. 2007). Jonkman et al. (2004) suggested that the frontal lobe performs early selective filtering. Indeed, a recent study of resting-state

EEG by Keune et al. (2015) suggested that frontal cortex abnormalities are a reliable marker for ADHD.

Neural oscillations are often used as markers of attention. Oscillations originate from synchronous activity of neuronal populations of different sizes, from local to very large. They can be detected in local field potentials (LFPs; Fig. 25.4) recorded with invasive electrodes for local population of neurons, or EEGs recorded noninvasively from the scalp for much larger neuronal population (Kahana 2006). Oscillations (Fig. 25.5) are conventionally classified into five frequency bands: δ (1–4 Hz), θ (4–8 Hz), α (8-12 Hz), β (12–30 Hz) and γ (30–80 Hz). Attentional effects have been reported for each of these frequency bands. For instance, anticipation of a certain stimulus by attending to a specific spatial location is associated with α-band attenuation (Rohenkohl and Nobre 2011). These rhythms are also involved in gating of information flow between brain regions (Fu et al. 2001; ter Huurne et al. 2013). To investigate the relationship between brain oscillations and ADHD, ter Huurne et al. (2013) used a motion coherence detection task where subjects were instructed to direct attention to either the left or right visual field. The attended stimulus was a random dot kinematogram, a field of chaotically moving dots. Subjects were instructed to respond after the dot pattern started to move coherently in the horizontal but not vertical dimension in the attended hemifield. Dot movements in the unattended hemifield had to be ignored. In healthy subjects, lateralized and sustained α oscillations were detected in the visual cortex during the period when the subjects prepared to respond. In patients with ADHD, oscillations started but they were not sustained and often stopped before the stimulus onset. Furthermore, lateralization of α oscillation was highly correlated with the degree of spatial attention in the healthy group, but not in the ADHD group (ter Huurne et al. 2013). In NF training experiments, children with ADHD learned to increase α-power following 18 training sessions (Escolano et al. 2014). Overall, these studies suggest that brain oscillations can be used to monitor neural regulation of attention and improve it using neurofeedback therapy.

25.2.2 Attention-Based NFs

In a typical NF setting, a visual task such as a video game is employed to engage subjects' attention. While the subjects play the game, their attention-related brain signals are extracted from using an appropriate neural recording method, processed by mathematical algorithms, and fed back to the subjects using a computer display. Successful performance is acknowledged. NF-therapy of this type was first introduced by Elbert et al. (1980). This study demonstrated self-regulation of slow cortical potentials using a continuous visual feedback. The majority of researchers agree that such NF-training can trigger brain plasticity and, after it continues for several training sessions, eventually improve attention in patients with deficits (Rossini et al. 2012; Dobkin 2007).

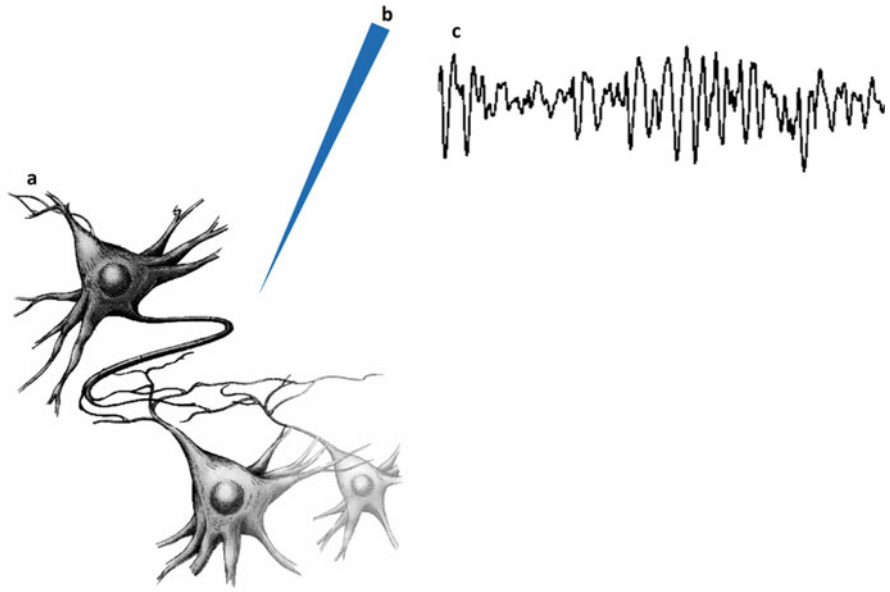

Fig. 25.4 LFP recordings. LFPs recording have the highest SNR of all recording methods mentioned in this chapter. The recording microelectrodes (**b**) are located in the cortical layer in immediate proximity to neurons (**a**). The signals sampled by the LFP microelectrodes represent a sum of potentials from neurons distributed in a 50–350 μm wide area (Figure adopted from http://es.slideshare.net/xiocorod/transmisindelimpulsonervioso-sinapsis0pdf)

NF systems can be implemented with both invasive and non-invasive recording methods. Invasive methods utilize electrodes that penetrate the brain (e.g. LFPs and single-unit recordings) or are placed on the surface of the brain (e.g. ECoG). These systems require an invasive surgery to implant the electrodes, and thus bears conventional risks associated with open surgery. Non-invasive NFs, on the other hand, do not require any surgery and can be easily and safely implemented. Non-invasive sensors are placed on the scalp (e.g. EEG and fNIRS), or in some implementations make no contact with the head (e.g. MEG and fMRI). Additionally, *hybrid* or *multimodal* NFs employ combinations of different recording methods. Fazli et al. (2012) developed a multimodal NF system consisting of the combination of NIRS and EEG that improved the signal classification accuracy in 90% of participants. Furthermore, such multimodal NFs showed higher sensitivity and specificity and were more resistant to environmental noise.

While NF research on attention-based NF systems is progressing, different studies convey varying levels of optimism regarding this approach. Several studies claimed success of NF training (Gevensleben et al. 2009; Leins et al. 2007; Steiner et al. 2011; Wangler et al. 2011), whereas others questioned these findings. For example, Arns et al. (2009) analyzed literature on NF therapy for ADHD and optimistically concluded that this treatment was “efficient and specific”. Lofthouse

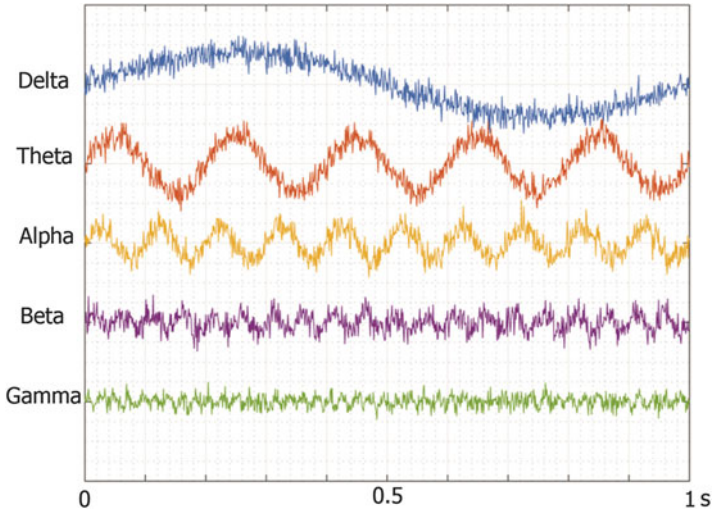

Fig. 25.5 Most common EEG oscillations. Lower frequencies such as delta (1–4 Hz) and theta (4–8 Hz) waves are increased in inattentive states. The role of alpha (8–12 Hz) waves are controversial across different studies. Beta (12–30 Hz) and gamma (30–80 Hz) oscillations are indicative of a high attention state

et al. (2012b) called this method of therapy "probably efficacious" based on their analysis of the research conducted from 1994 to 2010, where the majority of studies utilized θ/β ratio (see below). However, Vollebregt et al. (2014a) came to a different conclusion in their systematic review of frequency-band based NFs for ADHD (Ordikhani-Seyedlar et al. 2016). According to them, there was no substantial effect of treatment on any neurocognitive variable affected by ADHD. These diverse opinions highlight the need for further research on EEG features that would better represent characteristics of attention. Below we discuss the main approaches in this field and the ways they could be improved.

25.3 EEG Features for Attention-Based NFs

Feature extraction is a critical part of NF design (Shahid and Prasad 2011). During this processing stage, specific characteristics are extracted from brain recordings, which are then decoded and converted into NF. Depending on the recording method, different features can be used. For example, single-unit spikes are usually converted into neuronal firing rates, whereas EEGs are converted into the spectral power or parameters of event related potentials (ERPs). The selection of features depends on the way the user communicates with the NF system. In the NF design called endogenous NF, subjects self-generate neural patterns (Nicolas-Alonso and Gomez-Gil 2012). Alternatively, in the NF design called exogenous NF, neural responses are

evoked by an external stimulus, and subjects modulate these responses, usually by focusing attention on the relevant stimuli.

25.3.1 Neural Oscillations

The frequency-domain analysis of EEG recordings over different scalp locations is commonly used to extract features for endogenous NFs (Ossadtchi et al. 2017). Here, time-dependent changes in the EEG spectra for different electrodes are detected using EEG time-frequency (TF) analysis. For example, TF analysis can detect the variations of brain oscillations resulting from transient synchronization of neuronal activities over a millisecond time scale (Sanei and Chambers 2008). Using this method, we are able to measure EEG changes associated with attention, such as synchronization of specific EEG bands when subjects attend to a particular object. Attention-related synchronization of neural activity can be detected using a variety of recording methods, including single-unit recordings from brain neurons. For example, activity of V4 neurons were recorded while monkeys attended to behaviorally relevant stimuli and ignored distractors (Fries et al. 2001). These neurons increased their gamma-band synchrony while decreasing low-frequency (<17 Hz) synchrony when the monkeys attended. Rougeul-Buser and Buser (1997) recorded ECoGs in freely moving cats and observed that the frequency band in the range of 10–14 Hz increased in sensorimotor cortex. This type of oscillations, called μ-rhythm or "expectancy rhythm", increased when an animal actively attended to a place where a mouse (target stimulus) was expected to appear. The μ-rhythm epochs were often followed by a brief 20 Hz (β-range) ECoG burst. Thorpe et al. (2012) reported topographical details of these ECoG patterns. Attention was accompanied by μ-rhythm enhancement over parietal regions, whereas β-band activity enhanced in frontal motor areas. Such oscillatory patterns correspond to increased functional connectivity between the areas that process relevant information while suppressing unwanted cross-talk caused by irrelevant stimuli (Daitch et al. 2013).

High-frequency oscillations (>30 Hz) correspond to increased attention level (Kaiser and Lutzenberger 2005; Koelewijn et al. 2013; Musch et al. 2014). This has been shown, for example, using microelectrode recordings in freely behaving monkeys (Fries et al. 2001). Attention-related oscillations can generate higher frequency than the typical γ frequency (30–80 Hz) (Crone et al. 2006). Ray et al. (2008) presented human subjects with a sequence of tactile and auditory stimuli separated by pseudo-random time intervals. The tactile stimuli were delivered using a "tactile cylinder", which the subjects gripped with their hands. The auditory stimuli were delivered through a headset. The subjects were instructed to attend to one of the two modalities (auditory or tactile) and respond to the attended stimulus with a button press (Ray et al. 2008). The attended stimuli enhanced high γ activity (80–150 Hz) in the cortical areas that processed the corresponding modality: attention to auditory stimuli activated auditory cortex whereas attention to somatosensory stimuli activated somatosensory cortex. Additionally, these high-gamma oscillations

occurred in PFC irrespective of the attended modality. This result is consistent with PFC being involved in the global attentional system (Dirlikov et al. 2015; Keune et al. 2015) regardless of the sensory input modality. Yet another study reported that attention in humans was associated with ultra-high frequency oscillations of approximately 350 Hz that occurred in frontal and centro-parietal regions in response to somatosensory stimuli (Ozaki et al. 2006). Several hypotheses have been proposed to explain the role of ultra-high-frequency oscillations in attention. One hypothesis states that low-amplitude, ultra-high frequency activity is a background neural noise that enhances neural processing (Benzi et al. 1982). For example, adding a small amount of noise to a neural circuit increases the synchrony between its elements (Ward et al. 2006). Such stochastic resonance can improve stimulus detection because ultra-high-frequency noise lowers detection threshold (Benzi et al. 1982). The stochastic resonance driven by γ waves can play a role in high cognitive functions (Ward et al. 2006). A similar resonance can be produced by injecting noise to the brain using electrical stimulation (Medina et al. 2012).

A number of NF systems for controlling attention have been developed based on the interplay between different EEG spectral bands. A recent study showed that healthy subjects can quickly learn to self-modulate their γ-oscillation in superior parietal cortex by alternating between the attentive and rest states (Grosse-Wentrup and Scholkopf 2014). This NF system correctly decoded brain states in about 70% of cases. Several of studies on attention-based NFs employed the ratio of power in specific spectral bands as the signal feature to be classified. This ratio was calculated as $\beta/(\alpha + \theta)$ in many reports (Nagendra et al. 2015). The higher the ratio, the higher is the level of attention. Other studies used θ/β ratio (Heinrich et al. 2014; Clarke et al. 2013; Dupuy et al. 2013; Vollebregt et al. 2014b) that decreased with enhanced attention. These ratios assume that θ and α rhythms are higher in inattentive state whereas β rhythm is stronger when a person pays attention. For example, spectral EEG composition prior to stimulus presentation is indicative of the level of visual attention (Busch et al. 2009). Several additional characteristics of EEG oscillatory rhythms can be used to assess the level of attention. Instantaneous phase of EEG oscillations is one such characteristic (Busch et al. 2009). In the experiments of Busch et al. (2009), subjects were instructed to detect a brief (6 ms) light flash presented either at an attended or unattended location. Hit and miss rates were found to be affected by the phase of EEG oscillations at the time of stimulus presentation. Additionally, stimuli preceded by strong α activity were less likely to be detected by the subjects, an observation consistent with the previous literature (Babiloni et al. 2006; Ergenoglu et al. 2004; Hanslmayr et al. 2007; Thut et al. 2006). In the next study on the relationship between EEG phase and detection of attended and unattended stimuli, Busch and VanRullen (2010) explored the relationship between the EEG pattern prior to the stimulus and the EEG response to the stimulus. These EEG responses were higher when EEG was at a certain phase just prior to the stimulus onset, and the responses were low for the opposite EEG phase (Busch and VanRullen 2010). The periodicity of EEG was 100–150 ms in these experiments. These findings agree with several other reports (Busch and VanRullen 2010; Lakatos et al. 2008; Makeig et al. 2002).

25.3.2 ERPs

Event-related potentials (ERPs) represent a summed response of large neuronal populations to a stimulus. An ERP consists of multiple voltage swings that occur on a millisecond time scale. Specific ERP components have been linked to different neural origins (Cohen 2013), including the neural origins associated with attention (Gherri and Eimer 2011; Matheson et al. 2014; Wu et al. 2009; Jones et al. 2013; Zheng et al. 2014). Depending upon which modality (e.g. visual, auditory, etc.) is engaged, ERPs are generated in the corresponding primary sensory areas (Harter et al. 1984). Selection of the appropriate ERP components and related scalp locations is essential to achieve an efficient ERP-based NF. Farwell and Donchin developed an ERP-based experiment in 1988 (Farwell and Donchin 1988). They placed a single electrode over the Pz (central-parietal) site and instructed subjects to look at a 6×6 matrix of alphanumeric characters and attend to a specific target character within the matrix while rows and columns periodically flashed. Attended stimuli evoked stronger ERPs and thus could be identified. Averaging over 30 trials was required to improve the signal-to-noise ratio and assure accurate decoding.

For better design of ERP-based NFs, it is important to take into consideration the detailed sequence of ERP components. The first component is the C1-wave generated in the primary visual cortex (Steven 2014) and detected typically 40–60 ms after the stimulus, mostly by the posterior midline electrodes in the EEG. C1 peak occurs at 80–100 ms post-stimulus. The polarity of C1 changes depending on the location of the stimulus in the visual field, i.e. whether the response comes from the upper or lower part of calcarine sulcus. The polarity change is a unique characteristic of C1-wave that was used in many studies as a marker for V1 sources. However, more recent neuroimaging studies have challenged the view that the sources originate exclusively in V1. Ales et al. (2010) used fMRI retinotopic mapping to identify the location of different visual cortical regions such as V1, V2 and V3 overlaid on a high-resolution structural MRI. This technique allowed them to acquire a 3D representation of the upper and lower visual field projection in V1 and adjacent areas, V2 and V3. Contrary to previous studies, they found that sources in V1 do not fully correspond to the sign reversal of the voltage deflection. Furthermore, polarity changes for the upper and lower field stimuli were also observed in V2 and V3 areas. This suggested that the polarity inversion criterion was not a reliable method for source localization. Yet another study by Kelly et al. (2013) claimed that C1-wave is not initiated from V1. It was also reported that attention dose not influence the C1 component (Fu et al. 2010; Martinez et al. 1999). According to Martinez et al. (1999), although primary visual cortex is involved in attention, it does not serve as the locus of initial attentional gain control for sensory inputs. Kelly et al. (2008) disagreed with this and proposed that attentional selection does occur at the early visual processing stage. In that study, target brightness and location were adjusted for each participant in order to reduce inter-subjective variability in C1. After this adjustment, it became clear that C1 was enhanced

due to spatial attention, which indicated that the gating occurred before the visual information arrived in V1.

The second component is the P1-wave that starts 60–90 ms after the stimulus and peaks at 100–130 ms. It contains early and late portions generated from middle occipital gyrus and fusiform gyrus, respectively (Di Russo et al. 2002). P1 is sensitive to the direction of spatial attention (Hillyard and Anllo-Vento 1998). Luck and Hillyard (1995) studied attentional modulation of P1 using a stimulus display that consisted of 14 gray items and 2 colored items. Subjects were instructed to report presence or absence of specific colored-item (feature detection condition) or the shape of a specific colored item (conjunction discrimination condition). Just after the onset of the search array, a task-irrelevant stimulus appeared either at the location of relevant or irrelevant item. The ERPs for irrelevant stimulus was larger for the relevant location compared to irrelevant location. In such ERPs, P1-wave was present only in the discrimination condition and not in the feature detection condition. This indicated that conjunction discrimination recruited additional attentional resources. Mangun et al. (2001) employed a paradigm, where subjects were instructed to pay attention to one direction and ignore the other. They found that the P1 magnitude was larger for the attended compared to unattended location. The study of Mangun et al. (2001) also showed that P1 response was generated not only by the contralateral hemisphere but also by the ipsilateral one. This observation was difficult to explain in terms of redistribution of attentional resources between the hemispheres. Klimesch (2011) suggested that these results were due to P1 inhibition at two different levels. In the task-irrelevant pathways (e.g. ipsilateral hemisphere) inhibition blocked information processing, whereas in the task-relevant pathways it increased the SNR by enabling precisely timed activity in neurons with strong responses while suppressing the neurons with weak responses.

N1-wave contains an early component generated 140 ms after the stimulus in the frontal and two late components generated in parietal and lateral occipital cortices (onsets of 150–200 ms respectively) (Ceballos and Hernandez 2015; Clark and Hillyard 1996; Luck 2005). Visual spatial attention affects the magnitude of N1-potential (Hillyard et al. 1998). One specific characteristic of N1-wave is its insensitivity to simple physical features of the stimuli such as light intensity and contrast. This was demonstrated in the experiment where a 6×6 matrix alphanumeric matrix (similar to Farwell and Donchin's paradigm) could be either high-contrast or low-contrast (Shishkin et al. 2009). Although the visual stimuli varied in contrasts, N1 characteristics remained the same in both high- and low-contrast tasks. Two features of N1 are interesting: first, N1 is robust regardless of the paradigm design, which makes it suitable to compare different studies; second, there is no need to make detection paradigm excessively demanding as N1 is strong enough even for clearly visible stimuli. Therefore, N1-based paradigms are comfortable for ADHD subjects. This is a critical issue for ADHD subjects as they often experience fatigue or visual discomfort (Cao et al. 2014; Kooij and Bijlenga 2014). It has been shown that about two-third of children with ADHD suffer from visual problems, such as light irritability (Kooij and Bijlenga 2014).

Visual discomfort is an important factor, especially when NF is intended to be used on a daily basis for training and rehabilitation purposes (Sakurada et al. 2015).

The characteristics of N1 change over consecutive training sessions makes *this component* a potential marker for evaluating the progression of neurofeedback therapy. N1-wave is also useful for comparison across groups of subjects. For instance, in an experiment of (Latham et al. 2013) checkerboard stimuli appeared for a short time (92 ms) either in the left or right hemifield on a gray background. Subjects were instructed to respond by pressing a button as soon as the stimulus appeared. There were two groups of participants: professional video-game players and non-professional players. It was found that N1 latency was substantially shorter in expert players compared to inexperienced ones.

Following N1-wave, P2-wave occurs mostly for the anterior and central locations. The magnitude of P2 is higher when the stimulus occurs relatively infrequently (*oddball*). From this point of view, the anterior P2 is similar to P3-wave (see below) with the difference that P2 represents simple features (e.g. color) of the stimulus, whereas P3 is responsive to more complex features (e.g. combination of color and shape). P2-waves over the posterior electrodes are often harder to distinguish from the other overlapping components such as N1, N2 and P3 (Steven 2014). It has been reported that the magnitude of P2-wave substantially varies in ADHD individuals compared to the healthy subjects (Banaschewski et al. 2003, 2008; Broyd et al. 2005). Studies have shown that P2 not only has larger amplitude, but also different topographical distribution in ADHD compared to healthy individuals (Banaschewski et al. 2003; Broyd et al. 2005; Ortega et al. 2013; Barry et al. 2009). The P2 component is associated with automatic processing and inhibition of irrelevant information (Barry et al. 2003).

P3 component (also called P300 since it peaks at 300–500 ms post-stimulus) consists of two sub-components: P3a and P3b. P3a is detected over the fronto-central scalp region. About 60–80 ms later, P3b can be detected for all sensory modalities. An important characteristic of P3a component is that this sub-component decreases when a stimulus repeats more than five to ten times in a row (Friedman et al. 2001; Lynn 1966; Sokolov 1969). The amplitude of P3b in parietal regions varies between 5 and 15 μV (Soltani and Knight 2000). It is especially prominent following the occurrence of an oddball stimulus among a sequence of frequently repeating background stimuli. P3b, in many publications, is simply referred to P3 or P300. P3 was proposed as a marker for ADHD (Szuromi et al. 2011; Doyle et al. 2005). Patients with ADHD have significantly lower P3 amplitude during attention tasks compared to healthy subjects (Szuromi et al. 2011). It was suggested that P3 magnitude reflects the degree of attention, whereas, the latency of P3 corresponds to the speed of stimulus processing (Polich 2007). Yet, P3 is not a unique indicator of attention deficiency since it is also altered in other conditions, such as externalizing psychopathology, substance use, conduct disorder and antisocial behavior (Bertoletti et al. 2014; Burwell et al. 2014).

An ERP-based system was first developed in the 1980s by Farwell and Donchin (1988). This implementation had a relatively low bit-rate or information transfer rate (ITR). Bit-rate in an indicator of the amount of information that can be

communicated between the brain and the computer per unit time (van der Waal et al. 2012). In Farwell and Donchin's NF, this rate was approximately 12 bits min^{-1}. Zhang et al. developed a visual P300-speller which was able to communicate at the ITR of 20 bits min^{-1}. The performance is substantially higher for visual-ERP based system compared to auditory (1.54 bit min^{-1}) and tactile (7.8 bit min^{-1}) modalities (van der Waal et al. 2012; Furdea et al. 2009). Panicker et al. (2011) observed that combining ERP with other NF protocols such as steady-state visual evoked potential (SSVEP) increases ITR to 19.05 bits min^{-1}.

The SNR of ERP-based systems could be efficiently enhanced by collecting several responses and calculating their average value. This operation cancels out noise whereas the stimulus-locked responses persist. The more responses are recorded, the higher is the SNR. However, collecting too many responses slows down the operations. Accordingly, a trade-off between the accuracy and speed of the system should be considered. ERPs bear another major limitation because ERP amplitudes and latencies vary across-trials. The amplitude of P3 is positively correlated with the inter-trial intervals. To keep P3 amplitude reasonably high (10–20 μV) inter-trial interval should be around 8 s (Polich and Bondurant 1997). This long interval limits real-time performance. Furthermore, intervals between oddball stimuli typically occur at random times, which introduces ERP-amplitude variability.

25.3.3 SSVEP

SSVEP is another widely used protocol (Lesenfants et al. 2014; Palomares et al. 2012; Reuter et al. 2015; Wu and Su 2014; Zhang et al. 2010). Visual evoked potential (VEP) is triggered by a visual stimulus such as a flickering of a checker board at a specific frequency (Punsawad and Wongsawat 2012). Presentation of repetitive light flashes, or flickers, triggers VEPs entrained to the stimulus frequency. These entrained responses can be detected in the EEG of the visual and parietal cortical areas. SSVEP-based systems achieve high SNR over a few seconds of stimulation (Dmochowski et al. 2015). SSVEP-based systems can be easily implemented using graphical interfaces such as video games (Lim et al. 2010, 2012; Leins et al. 2007; Bakhshayesh et al. 2011). In a typical SSVEP-based paradigm, multiple objects flicker at various frequencies while the subject attends to one of them.

SSVEPs have been used in communication devices for people with severe paralysis (Muller-Putz and Pfurtscheller 2008). SSVEP-based systems are accurate and resistant to artifacts. For example, Bin et al. (2009) decoded SSVEPs with a 95.3% accuracy and the ITR of 58 $\pm$ 9.6 bits min^{-1}. This is a considerably higher ITR compared to other systems, such as those based on ERPs. Muller and Hillyard (2000) designed a paradigm that combined SSVEPs and ERPs. They found a positive correlation between the amplitudes of SSVEP and N1 and N2 component of ERP. SSVEP paradigms usually utilize the flickering frequency greater than 6 Hz.

In a recent study, flickering frequency of up to 100 Hz was tested (Dreyer and Herrmann 2015). One of the unique advantages of using high-frequency SSVEPs is that subjects do not perceive the flicker and feel more comfortable. The flicker is barely perceived for stimulus frequencies above 40 Hz (Lin et al. 2012). Sakurada et al. (2015) demonstrated that in addition to the visual comfort, classification accuracy is higher when SSVEP frequency exceeds 50–60 Hz. Training time of ADHD is also shorter for such high frequencies (Kooij and Bijlenga 2014).

SSVEPs can be detected not only in conscious state, but also in anesthetized subjects. Several experiments detected the flicker frequencies from the occipital electrodes when SSVEP technique was employed in fully or partially anesthetized animals whose eyes were kept open in front of a flickering display (Harnois et al. 1984; Xu et al. 2013).

The harmonics of the SSVEP frequencies in some cases work better for decoding than the spectral peak at the main frequency (Muller-Putz and Pfurtscheller 2008; Allison et al. 2010; Ordikhani-Seyedlar et al. 2014). Muller-Putz et al. (2005) reported particularly good results when they used three harmonic peaks. Kim et al. (2011) and others (Garcia et al. 2013; Zhang et al. 2015) also reported that visual spatial attention modulates the second but not the first harmonic of the flicker frequency.

25.4 Prospects for NF in Research of Attention

In our opinion, the most important future challenges for attention-based NF applications include:

1. Reducing noise: Noises originates not only from mechanical and electrical artifacts, but also from irrelevant brain activities. The latter type of noise is more difficult to deal with because it cannot be handled simply by improving recording methods. To address the issue of irrelevant brain activities, better understanding of brain processing is needed. Such an understanding should be a foundation for selecting appropriate neural features representing characteristics of attention. Additionally, we need a better understanding of neural processing in patients with disorders of attention. It is important that appropriate neural features are used in therapeutic NF systems. Incorrectly selected features may lead to unwanted functional changes instead of the desired improvement of attention. For example, using EEG α-band to regulate attention has certain caveats. In tasks where a distracting stimulus should be ignored irrelevant information is suppressed by increasing the α-rhythm. However, in some other tasks where there is no specific distractor, α-band may increase due to inattentiveness and drowsiness. Therefore, α-band based NF may enhance drowsiness instead of enhancing attention.
2. Development of reliable criteria to quantify effects of NF training: The effectiveness of NF therapy is usually assessed by comparing neural patterns recorded before and after the training. However, enhancement in EEG features does not

guarantee functional improvement. For example, increase in β-band power is a popular indicator of increased attention. However, this frequency band may be enhanced because of other functional changes unrelated to attention per se. Zhang et al. (2008) found that β-power increases when macaque monkeys suppress their movements. Therefore, outcomes of NF therapy should be assessed using a combination of indicators, including neural features, behavioral measures and psychological characteristics.

3. Inter- and intra-individual variabilities: Sources of variability include non-stationarity of EEG signals (Vidaurre et al. 2011) as well as the behavioral non-stationarities (Iturrate and Montesano 2013), including the ones related to reward schedule (Opris et al. 2011). NF algorithms should account for these types of variability during a continuous session of NF therapy.
4. Developing user-friendly systems: current NF systems usually require the presence of an expert to conduct training sessions, from attaching EEG electrodes to operating computer equipment. User-friendly and highly automated NF systems are needed for patients to be able to conduct training sessions alone.

25.5 Conclusions

NF offers exciting opportunities for rehabilitation of patients with neural disabilities, including new therapies for attention disorders, such as ADHD. Several studies of NF for attentional enhancement have already shown promising results. Yet, many challenges remain. The main challenge is to combine the expertise from neuroscience and neurology with the advances in technologies and computational algorithms of NF and BMI systems. We foresee that the merger of these multidisciplinary contributions will eventually lead to effective therapies for attentional dysfunctions.

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Chapter 26
Towards a Visual Story Network Using Multiple Views for Object Recognition at Different Levels of Spatiotemporal Context

Marius Leordeanu and Rahul Sukthankar

Abstract We present a general computational multi-class visual recognition model, which we term the Visual Story Network (VSN). Our proposed model aims to generalize and integrate ideas from different successful hierarchical automated recognition approaches, relating models from computer vision and brain science, such as today's successful deep neural networks and more classical ideas for visual learning and recognition from neuroscience, such as the well-known Adaptive Resonance Theory. Our recursive graph-based model has the advantage of enabling rich interactions between classes and features from different levels of interpretation and abstraction. The Visual Story Network offers multiple views of a visual concept: the basic, bottom-up view, is based on the objects's current local appearance. The higher level view is based on the larger spatiotemporal context, such as the role played by that concept in the overall story. This story includes the spatial relations and interactions to other objects, as well as events and global information from the scene. The structure of the VSN can be efficiently constructed by step by step updates, during which new features or complex classifiers are added one by one. Given a certain VSN structure, its weights could also be fully learned or fine-tuned, end-to-end, by efficient methods such as backpropagation with stochastic gradient descent. VSN is, in its general form, a graph of nonlinear classifiers or feature nodes that are automatically selected from a large pool and combined to form new nodes. Then, each newly learned node becomes a potential new usable feature. Our feature pool can contain both manually designed features or more complex classifiers pre-learned from previous steps, each copied many times at different scales and locations. In this manner we can learn and grow both a deep, complex graph of classifiers and a rich pool of features at different levels of abstraction and interpretation. At every stage the VSN cand be fully trained, end-to-end, either in a

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supervised way or in a novel naturally self-supervised way, which we will discuss in detail. Our proposed graph of classifiers becomes a multi-class system with a recursive structure, suitable for deep detection and recognition of several classes simultaneously.

Keywords Object recognition • Visual learning • Classifier graph • Computer vision • Visual story • Video analysis • Deep detection • Layers of perception • Spatiotemporal context • Co-occurrences

26.1 Scientific Context

Visual object recognition is based on relative, hierarchical and recursive cognitive processes, from the recognition of object parts, attributes, whole objects, interactions between them and their contextual relationship to other objects and the scene. It is no surprise that some of the most competitive architectures in object category recognition today have a deep hierarchical structure (He et al. 2015; Hinton 2010; Hinton et al. 2006; Krizhevsky et al. 2012). There are many successful hierarchical approaches, including the face detector of Viola and Jones (Viola and Jones 2004) based on classifier cascades, the object detector of Felzenszwalb et al. with a Part-Based Model and Latent SVM's (Felzenszwalb et al. 2010a), Conditional Random Fields (Quattoni et al. 2007), classification trees, random forests, probabilistic Bayesian networks and directed acyclic graphs (DAGs) (Jensen and Nielsen 2007), hierarchical hidden Markov models (HHMMs) (Fine et al. 1998) and methods based on feature matching with second-order or hierarchical spatial constraints (Conte et al. 2004; Lazebnik et al. 2006; Leordeanu et al. 2007). Even the popular nearest neighbor approach to matching SIFT features (Lowe 2004), using RANSAC with geometric verification could be modeled with a hierarchical structure: finding correspondences between individual features would take place at a first stage of processing, while the rigid transformation computation and verification could be implemented with linear transformations at higher levels of processing. One proposal for performing such hierarchical geometric reasoning in a neural architecture is the work by Hinton et al. (Hinton et al. 2011) on *capsules*.

Hierarchical classifiers are currently enjoying a great practical success due to the development of efficient methods for deep learning in neural networks. Considered by many to be a real scientific breakthrough in artificial intelligence, Deep Learning has already been broadly adopted by industry in a variety of applications including object recognition in images (He et al. 2015; Hernandez 2013; Rosenberg 2013; Wang 2013) and speech recognition (Hinton et al. 2012a). Systems based on Deep Learning have won major machine learning and computer vision competitions, such as Netflix, Kaggle and ImageNet challenges (see (Bengio et al. 2013) for a review). The recent success of deep classification systems and the long-term scientific interest in their research and development strongly motivate our work on formulating a general deep detection and recognition network with the potential to overcome many of the limitations of current hierarchical models.

26.1.1 Overview of Our Approach

We propose a general recognition and learning strategy based on a graph structure of classifiers, which we term the Visual Story Network. Our model is based our previous Classifier Graph (Leordeanu and Sukthankar 2014) for images. While following the same principles of the Classifier Graph, the Visual Story Network addresses in more depth the problem of visual understanding over both time and space and, thus, considers the larger spatiotemporal context when reasoning about objects, their interactions, events and their role in the overall story in which they take part. As presented in a later section, the VSN also proposes a novel way to perform self-training in an unsupervised manner, by taking advantage of the natural statistics of objects, scenes and the flow of events in videos.

We first present our general Classifier Graph in the context of image recognition, then present the full Visual Story Network for both images and videos. We relate our models to approaches from two different but related fields, both fundamentally based on algorithms and computation: computer vision, which is based on engineering ideas and computer experiments, and neuroscience, that is more biologically inspired.

26.2 The Classifier Graph

The nodes of the classifier graph are individual classifiers, which could be of any type (e.g., anonymous intermediate classes, object parts, attributes, objects, categories, materials or scenes). Each classifier operates over its dedicated region, at a given location and scale relative to the image or bounding box. It functions as a detector with a certain search area over which it computes and returns its maximum response—this area could be relatively small and local or large (e.g., equal to the entire image). The classifiers at nodes in the graph influence each other through a directed set of edges, such that the output of one (the parent) could be input to any other (the child).

The node classifiers can be viewed in the role of excitatory or inhibitory input features, providing favorable or non-favorable *context* to their children. Different from most approaches, we make no conceptual distinction between low-level features, intermediate anonymous classes, parts, objects, properties or context—these are all simply classifiers and can freely influence each other through directed links, between any two levels of abstraction. They are free to form collectively a *contextual environment* for each other. This flexible graph structure and the classifiers at nodes are learned from scratch over several training epochs, through an efficient supervised or self-supervised learning scenario (see Sect. 7) combined with a natural, unsupervised clustering and organization of the training data (Sect. 5). In a manner that is loosely reminiscent of cascade correlation (Fahlman and Lebiere 1990), each node adds a single new layer to the graph, using a nonlinear classifier

(which could be simple such as a logistic classifier or a more complex one, such as a deep convolutional neural network) with inputs that are automatically selected from the existing pool of features (Sect. 5). The pool of features is first initialized with manually designed descriptors that operate over raw or mid-level input (pixels, gradients, edges, color, texture, soft-segmentation etc.), randomly sampled over many scales and locations with different instantiating parameters. Each new classifier learned (new node in the graph) is defined for a specific location and scale, with a certain search area (to allow a specific location flexibility w.r.t. the window center of reference). Once learned it becomes a potential new feature: copies of it at many different scales, locations and with different search areas are added to the pool of potential features.

In this manner, we simultaneously grow both an arbitrarily complex and recursive directed graph of classifiers and a pool of features, which represent classifiers (previously learned graphs) at different geometric scales, levels of abstraction and localization uncertainty.

26.3 Intuition

The graph nodes in our classifier graph are similar to the ones in a neural net: each one represents a non-linear unit. These units could be simple, like a single neuron, or more complex, like an entire net. One other important difference from neural networks is our ability to connect classes from any levels of abstraction, using both top-down as well as bottom-up links; note that the meaning of *top* and *bottom* in our hierarchy is conceptual rather than physical. We will explain this in detail. The edges are directed, from an input node (this is the parent node that plays the role of an input or contextual feature) to the classifier node (or the child). Our motivation is that parts, objects and scenes influence each others' confidence of recognition, so one particular class *detector* could take as input the outputs of other classes' detectors. In principle, any *recognizer* at any level could function as *context* or *input feature* for the recognition of any other class at any other level.

Predictions at higher levels of abstraction (*I am in a room so...*) could function as *context* for the prediction at lower levels (... *I expect to see a chair*). The probabilistic influence could also go the other way around: *Since I see a chair then I could expect to be in a room*. In the latter example, the *chair* becomes context for the *room*. The same two-way relationships can happen at lower levels, between a part (e.g., a wheel) and the whole (e.g., the car). In a classifier graph, directed edges can be formed between any two abstraction levels in either direction: *Being in a car service shop means I can expect to see car wheels* or the other way around with a weaker but still positive influence: *I see a car wheel, so I might be in a car service shop*. In our framework, parts and objects are equal citizens: what distinguishes a part from another distinct object or the scene is only its dedicated region (the pixels in the image corresponding to the *wheel* of a car are a subset of those that correspond to the *car*; in fact, they are both *car* and *wheel* pixels at the same

time), whereas *the mechanic*, for example, is a different object only because it does not share pixels with *the car*. Also, parts play for objects a role that is similar to the one played by objects for the scene. Nevertheless, conceptually, all four: the part (*the wheel*), the objects (*the car* and *the mechanic*) and the scene (*car service shop*) are just different classes, recognized by their own dedicated classifiers, each composed of a nonlinear unit (e.g. logistic, tanh, ReLu) (with its different input connections), a relative scale, location with respect to the coordinate system of the image or bounding box, and different search area (location uncertainty over which a maximum response is computed). Thus, our proposed system treats parts, objects, anonymous intermediate classes, materials and scenes in the same universal way: as classifier nodes in a free graph-like structure.

26.3.1 One Class: Multiple Classifiers

Our proposal is somewhat unusual in that a single concept is represented using multiple classifiers, some of which may be learned early—typically focusing on lowlevel pixel/feature inputs—while others are learned late; the latter having many parents that are themselves concept classifiers that aim to represent the traditional notion of parts, scene or context. We detail this point and its consequences below.

It is clear that there is one directed edge from the part (*chair*) to the whole (*room*) and a different one from the whole (*room*) to the part (*chair*). As parts influence the existence probability of the whole, the presence of the whole indicates the likely presence of the part. At the same time, it seems to lead to a *chicken and egg* problem of mutual dependencies (or cycles in a graph), which, in probabilistic inference, is typically handled using iterative procedures. Here, we first seek a feed-forward approach, which suggests an intriguing hypothesis—the co-existence of several classifiers for the same class, which act at different levels of understanding, with different triggering contextual, input features. While we do not exclude the possibility of having cycles, for now we limit the classifier graph to a feed-forward structure. The existence of a class at different levels of abstraction, as part of larger and more complex contexts, will also be addressed in the spatiotemporal Visual Story Network (Chap. 7).

Having several classifiers for the same visual concept offers several unexpected potential benefits. One is that each classifier has its own possibly independent way of making mistakes, thus by combining several classifiers the ensemble is more powerful with smaller variance. Our research on object recognition with pairwise interactions (Leordeanu et al. 2007) as well as our more recent work on feature selection and learning with minimal supervision (Leordeanu et al. 2016) prove, once more, this fact: groups of classifiers, even when they are weak by themselves, can be very strong in combination. Another benefit is that of robustness to missing features. When one classifier for the concept lacks sufficient support, another classifier for the same class employing a different set of features could still be sufficiently sure of its response. Consider an example where a certain object, such as a *chair*, is represented

using two classifiers: (1) a classifier based primarily upon HoG features and (2) a stronger classifier that relies on a global scene recognizer (which in turn takes input from a variety of object classifiers, including the first chair classifier in addition to a weaker version of a scene based on classifying Gist (Oliva and Torralba 2001) features). Clearly, the two chair classifiers will have different failure modes and be robust to different conditions.

Here is another example to better understand how the same visual context could be interpreted at different levels of abstraction by different classifiers: let us imagine how a poorer low-res independent (without input context from the outside) *person* detector could be used to increase the confidence that we are *at the beach*. That reasoning, combined with similar weak classifiers for *water*, *sand* and *boats* will then be used to become confident that *we are indeed at the beach*. Once we *see* the beach, we will use that information to trigger more powerful classifiers (that use outside context and relationships to other classes) for better recognizing all of the above: *person, water, sand, boat and... beach*, again. Thus, employing multiple classifiers for the same concept enables us not only to simulate any iterative inference procedure, but also move up the level of understanding, recognition and confidence. This type of structure can be expressed very naturally in the classifier graph. The idea also establishes an interesting connection to recent approaches for high-level vision tasks using hierarchical inference with auto-context (Tu and Bai 2010). Interestingly enough, our framework suggests the possibility of having different levels of depth for the same visual concept. Classifiers with shallow levels, such as the first person classifier, could function in easier situations and act as a filter of easy negatives, whereas the last person classifier, which considers contextual interactions to other objects and the scene could be useful in more difficult scenarios. By effectively combining multiple pathways, at different levels of depth, we could build a stronger overall classifiers. This is reminiscent of the residual connections from the recently proposed successful ResNet architecture (He et al. 2015).

Another advantage of multiple classifiers per class is that we could better handle the large intra-class variability present in real-world images: people in images could appear in different sizes, shapes and resolutions, under different poses, at different locations, in various scenes, while establishing a wide range of interactions with other people or objects. By having many classifiers for the same category, *people*, we could test all these cases simultaneously. Then, the outputs from the ensemble of *person* classifiers could be aggregated for a final answer using a variety of known methods (e.g., taking the max, weighted average or using some voting strategy).

Here we should also mention the issue of localization. Our classifier graph predicts the existence of the category over a certain search area, or region of presence w.r.t. a center reference location, over which a max output is returned (e.g., the classifier for "Is there a person somewhere in the right half of the scene?" would be different from a classifier for "Is there a person in this precise location of the scene w.r.t. the image center?"). Taking the maximum output over a search window/region is directly related to max pooling in convolutional networks (Krizhevsky et al. 2012) and maxout units from (Goodfellow et al. 2013).

Therefore, relative to this central location (of the image, or bounding box of attention), we could have multiple classifiers for the same class but at different locations, scales and with different regions of presence. We believe this idea of sharing the core of a classifier makes sense—let us consider the following examples: in the case of a face classifier the right eye is different from the left eye, yet they are both *eye* classifiers; for a car, the front wheels are different from the back wheels, yet they are both "wheels"; the person right in front of me needs a different classifier, with different properties, than a distant person that I barely see with my peripheral vision, yet they are both "persons"—I could talk to the one in front of me, but not with the distant one. Sometimes the presence of a certain object anywhere in the scene is all we need to know, its specific location being unimportant, while in other case the specific location is crucial: for example, during a soccer game, the location of the goalkeeper is crucial during a penalty, but not so important when the ball is in the other half of the field—the two cases are distinct and could be recognized by distinct classifiers with different levels of location and pose refinement, as well as technical knowledge. We could also think of the core classifier, responds to the question "what", while its combination with the specific location or area of presence, is more related to the question "where". Traditionally, the questions "what" and "where" are seen as being processed along two separate complementary pathways in research studying the function of the human brain (Grossberg 2015). In our basic classifier graph model they are strongly intertwined, such that each node has attached to it both a "what" classifier as well as an expected location, or area of presence. In our full Visual Story Network we will discuss more situations where they could be treated in a separate, but complementary way. Also note that in current powerful object detector models, based on neural networks, the "what" and "where" pathways share a common base of features and subsequent processing is split across two independent subnets, one for localization and the other for classification. What we suggest in our VSN is that the two pathways could later be combined to reach a certain level of agreement, or resonance as proposed in Grossberg's Adaptive Resonance Theory (Carpenter and Grossberg 1987; Grossberg 1976; Grossberg 2000). Also note that the existence of multiple pathways for processing the same type of visual inputs and concepts is in agreement with the classical work of Lashley in the 1950s (Lashley 1950), who concluded that memory and learning is distributed across the brain and there is not a confined single local part of the brain representing an engram that performs processing related to a specific memory. Visual concepts are thus connected to many parts of the brain and it is very likely that they involve several classifiers for the same abstract concept, where each classifier could be learned from different events and moments in time, connected in a complex way to visual and non-visual context.

Thus, the classifier graph avoids shoehorning the multiple facets for a concept into a single classifier. And while we believe that later classifiers are likely to contain refined versions of classifiers learned in earlier layers, this condition is not imposed—it emerges naturally from the data when merited.

26.3.2 One Graph: Multiple Classes

Classification at lower levels of abstraction (*I see a pillow*) could help with classification at the higher levels (*It is likely to be on a bed, chair or in a closet*) and form part-whole relationships. Classes at similar levels could influence each other and establish "interactions" (*If I see a hand moving in a certain familiar rhythm then I am expecting to see it touch a pen or a keyboard*). These ideas also suggest a multi-class system in which recognition of one class is achieved through recognition of many others—a task that superficially appears to be a binary classification problem (e.g., "is there a face in this image?") can actually be a multi-class one under the hood. We strongly believe that since classes are so interconnected in the real world, they should also be interconnected and jointly learned within the same recognition system.

In the real world, related classes are likely to be found together in a given scene and interact with each other in rich ways through both space and time. Thus, they create a story that helps both for recognition and in the semantic understanding of the scene. It is a fact known since the times of the ancient Greeks, and also confirmed by recent psychological research, that humans are much better at learning, understanding and remembering concepts that are related in a coherent story (Connelly and Clandinin 1990; Pahl and Rowsell 2010; Schank and Abelson 1995). Some engineered, artificial computer vision systems (Farhadi et al. 2010) also take advantage of the special kinds of relationships between objects and their role in the overall story in order to give a higher level interpretation of an image. Objects are not only represented through appearance ("how they look"), but also functionally ("what they do") and how they relate to other objects in both space and time. We believe that vision addresses levels of understanding that go beyond physical surfaces. Grossberg argues in his ART, FACADE and ARTSCAN models that "all consciously visible percepts are surface percepts" (Chang et al. 2014; Grossberg 2015). While we agree that it is hard to image something visible that does not have a surface, we further argue that some of these visible surfaces, when looking at a specific object, might come from memory and could be related to stories in which the present object category has been involved. For example, the photo of Neil Armstrong's footprint on the moon, evokes much more than the few shades of grey seen in poor resolution—we "see" beyond the pixels present in the image. Especially in cases of occlusions or very poor resolution, the surfaces are more in the mind than in the actual image. This fact is related to another interesting phenomenon, that of illusory contours—boundaries that are clearly perceived even though they are not explicitly visible in the image (there is no measurable edge signal at the pixel level). It is only through the higher level interpretation of the mind that these boundaries start existing at the conscious level of qualia. In our recent work on boundary detection we also argue that these boundaries that are consciously seen are separating regions that could be defined semantically, at different levels of interpretation, not just at the low pixels level of image signal (Leordeanu et al. 2014).

Stories that describe interactions between objects and how they relate to each other, both spatially and temporally, at low as well as higher levels of abstraction, are fundamental representations for intelligent understanding. Physical objects as well as more abstract concepts could be understood by means of actual stories communicated verbally or experienced in real life. Thus, the activations of classifiers within the classifier graph can be viewed as efforts towards explaining a complex visual scene in the form of a story.

To summarize, our multi-class system is based on the following main ideas:

- **Co-occurrence and interactions, object-to-object relationships**: certain categories usually co-exist (co-occur). The presence of one is strong evidence for the presence of the other. Each could be context for the other. If two classes tend to co-occur and interact, then the output of a classifier for one of them should be useful as an input feature for the classifier of the other.
- **Relativity of classes, co-existence, opposition and part-whole relationships:** classes sometimes exist only through their relationship to other classes. Contrast and similarity is fundamental to "seeing" different classes. *White* is seen in opposition to *black*, *blue* (sky) to *yellow* (sun) and *cold* is felt in opposition to *warm*. A flower is a flower in similarity to other flowers, but in opposition to leaves, grass or branches, and as part of trees or gardens. To see a car we need to see at least some parts of it: the car and its parts co-exist simultaneously, sharing the exact same 3D space. While the parts trigger the *subjective, perceptual existence* of the car, the car is in fact a different, separate entity than its parts, recognized by at least one dedicated classifier. In human vision, the separate existence of the car from its parts, which form it, is also suggested by some patients suffering from visual agnosia (Farah 2004; McCarthy and Warrington 1986; Warrington and James 1988), who, do not seem to have a problem with seeing, but with understanding the meaning of what they see, or with seeing objects as *wholes*, which actually results in a limited capacity to see. This brings up the question: Isn't the case that our apparently single, unified conscious visual perception is in fact a simultaneous multi-level process with many different subjective realities being perceived at the same time? Objects are also learned and understood through stories, which give them meanings, their perception being triggered by some behavior in a specific context. There is a story behind every perceived thing, and the story often triggers the "seeing", the very existence of that thing in our subjective reality.
- **Re-use of prior knowledge:** once we have learned classifiers for many categories, it would be a waste not to use them to learn new classes. Such classifiers could include both manually designed features as well as other feature detectors and anonymous classes discovered from previous learning tasks (e.g., using autoencoders (Hinton et al. 2006; Rifai et al. 2011)). Learning everything from scratch every time we deal with a new classification problem is not efficient. This is also in agreement with the recent "fine-tuning" procedure in deep learning, which consists of re-learning only a few top layers in a deep architecture with pre-learned weights, in cases when the new training data is limited compared to the data that has been used for learning the full net so far.

To better appreciate the interconnectedness of classification, consider the following two examples.

Example 26.1 Imagine that we are in the countryside and we see a horse running through the grass. Although we may say that we see the horse *clearly*, in reality the horse is quite far and on the basis of shape alone, we may not be confident as to the object's identity. However, the combination of several factors, such as its color, the way it moves (both in terms of its articulation/gait and its motion against the background) and its size (possibly inferred from the nearby trees), all combine to convince us that *this thing* is a horse. In other words, our "seeing" of the horse depends a lot on "seeing" as well as "knowing" many other things — all of which can be considered as inputs to our subconscious recognition of this animal.

Example 26.2 Consider the superficially straightforward binary classification task of recognizing a white horse against a dark background. How is this considered a "multi-class" problem in the classifier graph?

First, we note that even in the absence of external context, a horse is recognized as such through the complex interplay of various properties: its overall shape, the shapes and relative configurations of its body parts (head, four legs) and the presence of distinctive features such as a mane and tail. Some of the body parts (e.g., eyes) could be object classifiers that are shared with broadly related animal species; others may be distinct to horses (e.g., mane) or even to this particular horse (hide pattern). Since all of these classifiers are treated identically in the classifier graph, it is the activation patterns of all the classifiers that enables us to recognize the horse—and just as in traditional multi-class problems, the *lack* of positive firing from classifiers (e.g., wings, wheels, clothes) provides crucial information.

26.3.3 Simultaneous Perceptual Layers of Recognition

We have discussed the possibility of co-existence, within the structure of the classifier graph, of several classifiers per category, as part of a deep multi-category recognition system. The graph is able to recognize simultaneously many different classes and sub-classes, at different levels of abstractions, and use them as context for each other. Classes are defined w.r.t. each other, with multiple classifiers for a given class, each capturing a different individual learning experience, from various training epochs, at different stages of abstraction. The representation of a given class starts with simpler, context-independent classifiers and evolves by the addition of more complex classifiers that establish interactions to other classifiers for objects and the scene, to eventually form spatiotemporal stories; see Sect. 7 for a discussion on learning spatiotemporal categories from video.

In this section we want to pay a closer attention to the issue of simultaneous category recognition at different interpretation levels. Let us consider the woman's face in Fig. 26.1 and try to play a brief mind experiment. Imagine looking at point on the pupil of the left eye of the woman's face. What type of pixel is it? Is it a

Fig. 26.1 Drawing of a woman's face. Each pixel of the drawing simultaneously belongs to many categories. For example, a pixel *on the pupil*, also supports *an eye, a face, and a person*. Each category is *seen* by different classifiers, some specialized for the same class. Underneath the holistic visual experience of *seeing a woman's face*, many classifiers at many levels of abstraction are simultaneously combined together to form a contextual environment for each others' recognition

pupil pixel, an eye pixel, a face pixel or a woman's pixel? We should soon realize that the pixel belongs to all these categories at the same time, and many more. It simultaneously sits on a pupil, an eye, a face, and a person. Since the face image is made of pixels, all of them have to play different roles at the same time, for a *full human-like understanding* of the image. Also note that the pixel in question could be classified by many eye classifiers simultaneously, starting from a low-res, generic eye, to a more refined classifier that takes in consideration more fine features of the eye. At the very top level we could have classifiers that consider the fine geometrical alignments to other parts of the face and be sensitive to symmetry, harmony and a general sense of beauty.

Also note that all these classifiers should be in agreement for a resonant, convergent and unified view of the face. Thus, if the pixel is seen as pupil pixel, it is also seen as an eye pixel. Moreover, the top-down and bottom-up views should agree the pixel should be seen as a pixel sitting on a pupil, both from the bottom up view of the pupil that is based on the local pupil's appearance but also from the top-down view of the eye which considers the pupil within the larger, higher level view of the whole eye. The two views are resonant, they agree. This is directly related to the idea of resonance in Grossberg's Adaptive Resonance Theory, where for something to be consciously seen there needs to be an agreement, or resonance, between the features generated by the bottom-up view and the once produced by the top-down view (Grossberg 2015). Grossberg suggests that "all conscious states are resonant"—in other words, when seeing happens at the conscious level, then all these views, top-down and bottom-up, are in harmony.

26.3.4 Learning the Classifier Graph

As discussed before, the output at any node in the graph could, in combination with other outputs constitute evidence for the presence of another class. We will use the existing classifiers at nodes in the graph as potential features, along the initial pool of visual input features, for learning new nodes. The idea of re-using the previously learned classifiers as potential new input features is also related to work on learning annotations from large datasets of weakly tagged videos (Aradhye et al. 2009), where Aradhye et al. learned annotations in stages, with each stage retaining only the most confident annotations. Employing classifier scores from previous stages as features in the current stage enabled the system to more accurately learn annotations through this form of composition, even in the presence of label noise.

We could model the classifiers at nodes with linear models, such as logistic regression, or linear Support Vector Machines (SVM). We could also use, as nodes, more complex classifiers. The graph is learned node by node: for every graph update we automatically select the relevant features (which could be previously learned nodes), using boosting and fit a logistic linear classifier (or linear SVM). Once the features are selected, learning is easy. At this level, learning constitutes a way of constructing the architecture of the graph. Once the graph is constructed, of course that we could use end-to-end training for adapting all the weights, or we could take a strategy closer to fine-tuning, where we adapt only a few selected layers of weights. Note that all we need to require for end-to-end training to be possible is to have nonlinear differentiable functions at the nodes. If we use neural computational models then full training is possible. The learning of structure is different from the current deep neural nets that have a fixed structure. Our classifier graph comes as an extension, giving the possibility of adapting and growing the structure when needed. In case of real-time video, for example, when training data is potentially unlimited, we need to consider growing the graph and, thus increasing its capacity to learn.

There are two difficult aspects with growing the classifier graph: (1) how to sample and organize the training set in order to learn multi-class models and increasingly more sophisticated classifiers for each concept, an approach that is related to an idea known as curriculum learning in the machine learning literature (Bengio et al. 2009), and (2) how to choose the relevant features from the pool of initial features and previously learned classifiers. We employ unsupervised clustering and boosting strategies in order to handle these issues, as discussed below.

26.4 Computational Formulation

The important elements in creating and growing the classifier graph are: (1) the first features considered (the initial feature pool) when we start learning the graph; (2) the inference method used for classification, given a certain classifier graph; (3) learning the graph: how to choose the positive and negative training examples for each epoch, how to select the relevant features from the pool and how to learn a new node.

26.4.1 Initial Feature Types

The initial features are the *atomic* classifiers that are not explained by previously trained input nodes. They represent the first level in our hierarchical (directed graphical) structure, most of them being rooted in the raw input from sensors. Among the first input features, we also consider previously trained classifiers, feature detectors and auto-encoders on various, potentially related classes. In order to comprehensively capture different visual aspects of objects, we need to look at various sources of information, such as shape, color, texture, occlusion regions and boundaries, foreground/background segmentation cues. Each dimension captures a different view of the data: the list of potential features should be comprehensive, redundant and discriminative. Current work on deep nets spends significant computation on learning features (sometimes referred to as basis functions or explanatory factors (Bengio et al. 2013)), directly from pixels. The motivation behind learning directly from raw input is that hand-crafted features are not optimal. One advantage of current neural networks systems comes from their ability to learn specialized features at the cost of expensive computation and very large quantities of training data. Interesting examples of learned features, besides the common-looking edges, corners or Gabor-like filters, include neural units that encode spatial transformations (Memisevic and Hinton 2010). Such learned features are harder to guess or design manually (Fig. 26.3).

Different from the common trend of exclusively learning from data, we argue for a more hybrid approach. Nodes in a classifier graph may employ both engineered and learned features. As long as the engineered features have a differentiable functional form, they could be adapted for any task and integrated into a fully trainable system from end to end. More importantly, once learned, features should be saved and re-used in future classification tasks, instead of having to learn them from scratch for each task. Classifier graphs can thus leverage learned feature detectors, such as auto-encoders (Hinton et al. 2006; Rifai et al. 2011), from previous classification tasks, designed features, such as SIFT (Lowe 2004), Shape-Context (Belongie et al. 2000) and HoG (Dalal and Triggs 2005), which have proved themselves in a wide range of computer vision problems and applications, as well as learning completely new features. Utilizing engineered features may reduce the depth in deep, hierarchical learning, reduce both training time and training data size, reuse prior knowledge and improve generalization. Bootstrapping early nodes in the classifier graph with a simple HoG descriptor combined with a linear classifier may eliminate the need to learn an equivalent relatively large three-layer network that operates directly on pixels without precluding the opportunity of learning features during later stages. Thus, classifier graphs reject the false dichotomy between employing traditional engineered features or learning features from scratch in a deep architecture. Also note that in our graph, nodes could represent entire deep networks so the main advantage of our model is its ability to create, from previously learned nets and systems, larger and more sophisticated once in an automatic way.

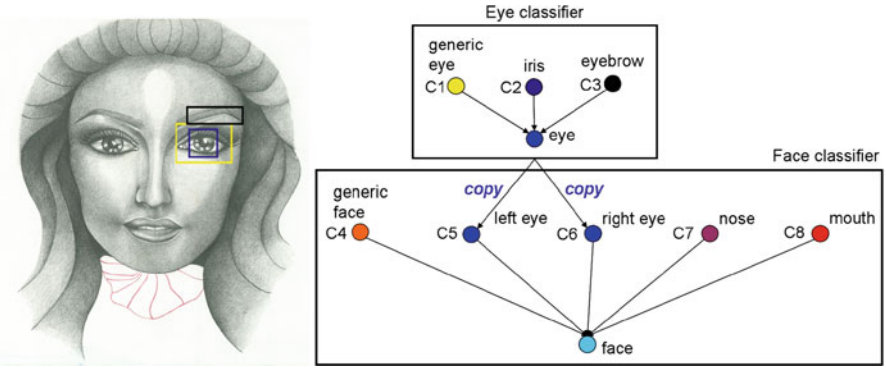

Fig. 26.2 Schematic description of a recursive, hierarchical face classifier. The initial node classifiers use the initial features types (e.g., HoG descriptors) and linear logistic regression. Once new classifiers (nodes) are learned, many random copies of them at different locations, scales and with different search areas (*region of presence*) are added to the pool of potential features. In this manner, input features could achieve recursively any level of abstraction. With each learning iteration a set of potentially more powerful and specific features are picked automatically using boosting and a one-layer classifier is learned. The process is repeated in this manner leading to a recursive structure, which could potentially handle any number of classes with links both bottom-up and top-down between different levels of interpretation and abstraction. The explicit labels used in this example (eye, nose, mouth, face) are given for clarity of presentation. In reality, intermediate classes or sub-classes (e.g., facelets) could be discovered and learned automatically. In this example: an eye classifier is first learned. Copies of it are added to the pool, at different locations, scales and with different search areas (regions of presence). When a face classifier is learned, the eye classifier with a given location, scale and search area, could be picked automatically and added to the graph, together with its own parent nodes (generic eye, iris and eyebrow) and their relative location and search area relative to their child, the *whole eye* classifier

In our system (see Fig. 26.2), we could consider, for example, among others, some of the most successful visual features in recognition today: SIFT (Lowe 2004) (individual object matching), Haar wavelets-like features (Viola and Jones 2004) (face detection), HoG (Dalal and Triggs 2005) (pedestrian detection and general object category recognition) and the similarity transformation neural units learned in (Hinton et al. 2006). We also propose local histograms over several cells of color hue values (good for natural categories), similar local histograms of Gabor filter responses (to encode texture and material properties), and foreground/background segmentation cues (to capture the object's silhouette).

We extend the idea of selecting from a large pool of Haar-like features computed at many different scales and locations (w.r.t. a reference box) (Viola and Jones 2004) and include in our feature pool many other classifiers and feature types, at different relative scales and locations. We augment each classifier with a *region of presence* or search area, similar to max pooling in convolutional nets: the output returned by the feature detector is its maximum response over the search area. We maintain a large pool of such features that is grown together with the graph. Once learned, each new unit node is copied many times with randomly varied scale,

location and search area and added to the feature pool for later use. This pool is effectively our overall graph, as it contains many copies of all the subgraphs learned on the way, in a recursive manner together with their edges. Intriguingly, the generation of copies with randomly varied location, scale and region of presence parameters relates to the *reproduction and mutation phases* in genetic programming (Koza et al. 1999), a relatively distant subfield of artificial intelligence, where the space of computer programs is explored using Darwinian-inspired operators, such as *reproduction*, *mutation* and *cross-over*, that manipulate blocks of code. In our case, *cross-over* would correspond to combining sub-graphs of two separate classifier nodes—even though we did not discuss the case of creating new features by random recombination, we do not exclude this interesting possibility for enlarging our pool of features. Moreover, many genetic programming approaches represent programs as graph-structures, which reveals another similarity to our approach in which classifiers are represented by graphs and sub-graphs.

The classifiers' copies are only pointers to the original classifiers, plus the transformation parameters (location, scale and search area). We refer to the copies as *feature-nodes*, while the original learned node is termed the *concept-node*, and contains the actual classifier, input links and their weights. The classifier graph structure is deeply recursive: each concept-node is a class detector on its own, which calls, through its input parent nodes their own concept-nodes. The recursive calls continue until the first-stage classifiers are reached.

26.4.2 Classification by Deep Detection

Each feature-node i has an associated classifier C_i (a pointer to the concept-node C_i), a center location p_i relative to its child node, a dedicated region (scale) S_i (such as a rectangle of a certain size, for a box classifier), and a search area $A_i(p_i)$ (or region of presence) relative to its center location p_i. As in classical max pooling, the classifier C_i is applied at every position inside $A_i(p_i)$ and the maximum output is returned. A concept-node is a new node learned, with no relative scale (its scale is the whole bounding box given), and no search area (its output is considered in the middle of the bounding-box). Concept-nodes are always child nodes and all child nodes are effectively concept-nodes (see Fig. 26.5). After they are created, they are copied (as feature-nodes) and added to the feature pool for later selection to become parent nodes. When the node (a feature-node from the pool) has a relatively strong geometric relationship with its child (e.g. the right eye relative to the face's center), its area $A_i(p_i)$ of search will be small. At the other end of the spectrum, when the node i represents a completely different, location independent object that might be anywhere in the scene, $A_i(p_i)$ might cover the entire image (e.g., *Is there a mechanic somewhere inside the car service shop?*). The maximum classifier output, found at each node i, is then passed to its children (the nodes that need it as input). This results in a recursive algorithm for deep detection and classification (see Algorithm 26.1).

We start from a given child node N_{child} by calling the $DeepDetection(N_{child})$ routine. In turn, node N_{child} applies the detection procedure at each of its parents nodes. Then, they recursively call the same local detection function at every location inside their search area, also for all their parents and return the maximum output. Their parents will do the same, until the first ancestor classifier nodes are reached (the ones rooted only in the initial features). To avoid redundant processing on overlapping max pooling areas, an efficient implementation of the recursion should take advantage of dynamic programming, caching and memoization by moving bottom up in the hierarchy and saving the intermediate results for each search area along the way. First, for a given child node, we can immediately find the union of all locations, scales and search areas for all initial features and concept-nodes that will be called during the recursive call. Starting from the bottom-up, with the initial features first, each classifier will be called after the concept-nodes of its parents have returned an output for all locations and scales. We can guarantee a single call per location and scale for a given concept-node. The algorithm is also adaptable to parallel implementations, as independent classifiers, for which all parents have finished, can be applied simultaneously.

Algorithm 26.1 Deep Detection: $out = DeepDetection(N_i)$

Goal: detect object from the level of node N_i.
Input: current node $N_i = \{C_i, p_i, S_i, A_i\}$.
$P \leftarrow$ parents of node N_i.
for all locations $p \in A_i(p_i)$ **do**
  if P is empty **then**
    $\mathbf{x} \leftarrow$ feature vector at p for classifier C_i.
  end if
  if P is not empty **then**
    for all parent nodes $N_j \in P$ **do**
      Set location of N_j relative to child: $p_j \leftarrow p_j(p)$.
      Set response at p_j: $\mathbf{x}(j) = DeepDetection(N_j)$.
    end for
  end if
  Set node response at p: $r(p) = C_i(\mathbf{x})$.
end for
Max pooling over area $A_i(p_i)$: $out = max_{p \in A_i(p_i)} r(p)$.
return *out*

Searching for the maximum output over a certain area is similar to a scanning window strategy for detecting a single best *seen* object in that particular region. As mentioned above, the search area is found relative to each of the node's children (in the DAG): when a node has several children, its absolute location will be different for each of them. The recursive max pooling approach results in a hierarchical, deep detection system, also related to the deep quasi-dense matching strategy in the recent work on large displacement optical flow (Weinzaepfel et al. 2013). The hierarchical classification approach follows a part-based model, which could be arbitrarily deep

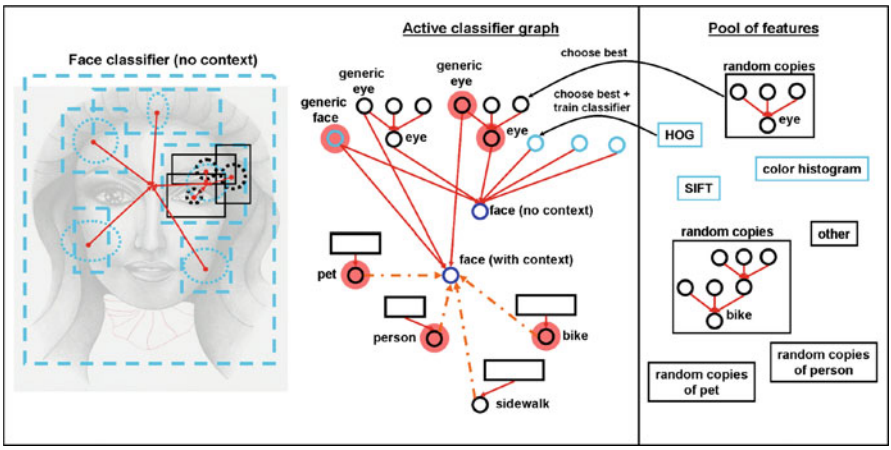

Fig. 26.3 *Left*: face with a superimposed context-independent part-based classifier. A separate classifier for the left eye is chosen as an input feature for the next level face classifier. *Middle*: an active classifier graph with different hierarchical levels. *Red solid arrows* indicate bottom-up relationships, while *orange dashed-dotted arrows* show top-down or lateral relationships. Classifiers in *black* are subgraphs selected as input features from the pool of features (*right column*). *Light blue circles* indicate classifiers learned on initial basic feature types (e.g., HoG, SIFT, other existing feature detectors). Semi-transparent *red circles* indicate local search areas of individual classifiers. Each area is relative to the child node. *Right column*: pool of candidate input features that can contain both basic visual features as well as simple or complex learned classifiers and their full classifier subgraphs

and complex when combined with the large pool of features and classifiers. It is also suitable for detection with contextual information, and, as mentioned before, it is meant to handle several classifiers for the same class (see Fig. 26.3).

26.5 Learning the Graph and the Pool of Features

For learning the graph there are two non-trivial aspects: feature selection and choosing the appropriate training examples for each training epoch. For feature selection we propose two possible schemes. The first, recently published (Leordeanu et al. 2016), learns classifiers as averages of subsets of features and thus it implicitly performs feature selection. It is able to learn from very limited training data, while have a strong generalization power. We will not present it here in detail and refer the reader to (Leordeanu et al. 2016). Our second proposed scheme, which we will present in more detail here, is weakly related to (Viola and Jones 2004), that combines the supervised Adaboost re-weighting of samples with natural, unsupervised clustering. During each epoch we use a certain organization of the

positive training data into several, potentially overlapping, clusters. The negative training samples, which could contain any class different from the positive label, are not clustered. Then, at each iteration, after testing the newly added feature detector, we apply standard Adaboost re-weighting of the training samples. The next detector selected from the feature pool is the one with best performance on separating the cluster with maximum sum of sample weights from the negative class. In this manner, we take advantage of Adaboost supervised weighting to minimize the overall ensemble exponential loss on all training samples, but we use the natural unsupervised clustering of the positively labeled data to select diverse feature detectors specialized for different views of the positive training set. Interestingly enough, we have observed such a fruitful collaboration between unsupervised clustering of the data and supervised or semi-supervised training on two seemingly unrelated problems, that of graph matching (Leordeanu and Hebert 2008) and learning for graph matching (Leordeanu et al. 2009). One important aspect here is the method(s) chosen for clustering and the distance function used by the clustering algorithm.

Clustering the Training Data Samples

Clustering of the training data could take advantage of both *natural clustering* in the data (for example, using k-means on different types of initial features and image descriptors, e.g., HoG) or/and spatial and temporal coherence (by collecting training samples from video sequences). Note that clusters need not be disjoint, as we choose different features and parameters for clustering, we could end up having many clusters with overlapping elements. Since the clusters need not be disjoint, we propose to perform several rounds of clustering using different algorithms (Kaufman and Rousseeuw 2009) (e.g., hierarchical clustering, K-means clustering), different descriptors of the data samples (e.g., descriptors computed at different sub-windows of the training samples, using different types of information, such as gradients, color, word counts, subspace and frequency analysis, just to name a few) and different distance functions, which could range from simple Euclidean distance in feature space, to more sophisticated distances computed from feature matching, such as the pyramid match kernel (Grauman and Darrell 2005), spatial pyramid kernel (Lazebnik et al. 2006) or matching with geometric constraints (Leordeanu and Hebert 2005; Lowe 2004). We could keep as final clusters the ones with high quality, estimated with both internal measures, such as the Dunn index (which finds dense, well separated clusters) and external ones, such as cluster *purity*. If negative samples are also considered for clustering, cluster *purity*, in our case, would measure the percentage of positive samples in a cluster with a positive majority.

We also expect that the spatial and temporal coherence and natural geometric and appearance transformations, which naturally take place in video sequences, will constitute a rich source of training data and a solid basis for clustering. Moreover, the user provided keywords on most freely available videos on the internet, represent weak labels that could be effectively used for grouping together videos with common labels. Such a strategy had been successfully applied to automated video annotation on the very large video corpora from YouTube (Aradhye et al. 2009). We

will come back to discuss the possibility of learning from video and representing spatiotemporal concepts in Sect. 7.

Our approach has several advantages:

1. At each iteration, we push the next classifier to be as different as possible from the rest of the ensemble by choosing the farthest positive cluster (in the expected error sense). This maintains classifier diversity even in our case, when new features/classifiers are not weak. It is known that Adaboost typically does not handle well ensembles of strong classifiers, due to lack of classifier diversity—strong classifiers are too good by themselves and the different soft weighting of each sample does not help much (Li et al. 2008).
2. By training over natural dense clusters we consider only representative samples and avoid over-fitting the mislabeled or noisy data points.

The overview of how we select and train new feature detectors is presented in Algorithm 26.2 (Figs. 26.4 and 26.6):

First, we divide our overall training time into several epochs. During each epoch we apply Algorithm 26.2. Each epoch learns from a different training set, based on a particular clustering of the training samples (e.g., during each epoch we could use a specific subset of the clusters). Regarding the training sets of each epoch, we have several possibilities: (1) for each epoch we use a different subset of the positive clusters, thus obtaining a different *view* of the same class, or (2) after each epoch, we could change the label of the positive class, when in the multi-class setting.

Algorithm 26.2 Learning with Clusterboost

F: current pool of features/classifiers
Set the observation weights $w_i = \frac{1}{N}, i = 1, 2, \ldots, N$.
Initialize clusters of positive samples $C_j, j = 1, 2, \ldots, N_C$.
for all k = 1,2, ...,K **do**
1) find C^* of positive samples, with maximum sum of weights $C^* = \text{argmax}_C \sum_{i \in C} w_i$.
2) find best classifier F_k (x) using a feature from F, that separates C^* from negative data, with current weights.
3) Let err_k be weighted error of $F_k(x)$, according to $w_i's$, on all training samples.
4) set $\alpha_k = \log \frac{1-\text{err}_k}{\text{err}_k}$.
5) Set $w_i \leftarrow w_i \exp[\alpha_k I(y_i \neq F_k(x_i))]$ for all $i = 1,..., N$.
end for
Learn a linear logistic classifier H for the current node
using the K outputs of F_k as input features.
Update feature pool F with many modified copies of H.
End of training epoch. Return H and updated F.

During each epoch we limit the number of nodes to be selected with Clusterboost at K; we stop early, even if classification on training set is not perfect. That will keep the graph sparse, avoid overfitting and add a novel node to the pool of features relatively soon. Note that sparse networks tend to generalize better (Bengio et al. 2013), an idea on which the recent successful Dropout training is partly based (Hinton et al. 2012b).

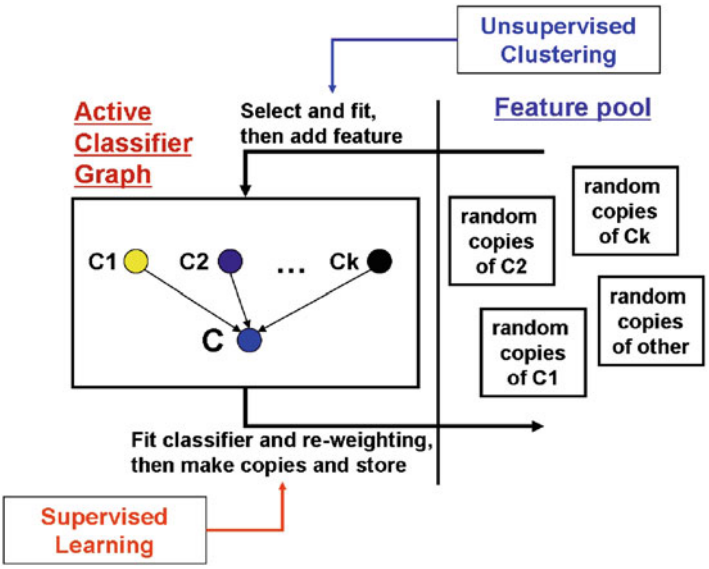

Fig. 26.4 Clusterboost: we select optimal input feature-nodes from a large pool, guided by a classification error measure that combines unsupervised clustering with supervised weighting of the training samples. Features are selected and added sequentially. The final classifier weights are recomputed simultaneously with supervised learning. Many random copies of the classifier (the concept-node), at different relative locations, scales and with different max pooling areas are added to the feature pool, followed by improved re-clustering using evolved distance functions that consider the new features added. In this manner, Clusterboost can be repeated, epoch by epoch, and a large, complex classifier graph can be learned

After selecting K nodes we re-learn a logistic regression classifier, one per epoch, to better fit the weights simultaneously (unlike Adaboost), and obtain a probabilistic output (last part of Algorithm 26.3). After each epoch the node classifier is copied, together with a pointer to its subgraph, at randomly varying locations p, scales S, and max pooling search areas A (regions of presence), all w.r.t. the reference bounding box. These many modified copies are added to the pool of features, so that at a later epoch we could use them as new input features. In this manner we can have arbitrarily complex classifiers as input feature candidates, which could lead to features of any level of abstraction and interpretation. Once a feature is selected, its subgraph (which is part of the feature) is automatically added to the graph. The subgraph addition is not expensive, as only pointers to the subgraph will be used in the copy of the feature. Also, before adding a new feature from the pool we first check to see whether it is already in the graph. If a very similar version is already there, we re-use the existing node, thus connecting nodes across many levels of abstraction. The overview of our overall classifier graph learning scheme is presented in Algorithm 26.3.

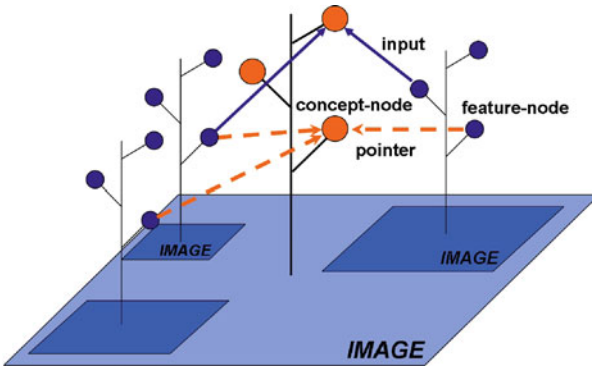

Fig. 26.5 Each new node learned is a child node, or a concept node (in *orange* here): it operates over the entire image (*bounding box*), thus it has no search area, its location is the image center and its relative scale is 1. After it is learned it is copied many times at various locations, scales and with different search areas and added to the pool of features, as potential future parent node (here in *dark blue*)—these are the feature nodes as they link through pointers to the original classifier that they represent. A careful inspection of the figure reveals the recursive nature of classification in our graph: each parent node operates at a certain scale, or bounding box (here in *dark blue*), which is effectively its input image—it calls its classifier through a pointer and passes to it its image. From the child's point of view the image is "the whole image" and, in turn, the child (*orange circle* here) calls its parents, which again, call their orange classifier (through the pointer), and so on. The process repeats itself until orange circles with no parents are reached—the ones which function directly over the image input through the initial feature types. We speculate that transitions from children to parents and change in focus of attention from feature nodes to concept nodes (through pointers) may be consistent with how saccades operate in the human visual system. The featurenodes are activated through the peripheral vision and memory system, while the orange concept nodes are activated through the attentional system

Algorithm 26.3 Classifier Graph Learning

Initialize the feature pool F_0.
Time starts: $t \leftarrow 0$.
repeat
1) A new learning epoch starts (Algorithm 26.3).
2) Select node: train a new classifier node H by Clusterboost with current pool of features F_t.
3) Update graph: add H and its subgraph G_H to G.
4) Make random copies: generate new features F_{new} of the form $\{H, p_t, S_t, A_t\}$ by sampling from (p, S, A).
5) Update feature pool $F_{t+1} \leftarrow F_t \cup F_{new}$.
6) Select a new training set.
7) $t \leftarrow t + 1$. Go back to step 1.

until Stopping criterion is met.
return Graph G and feature pool F.

Evolving distance functions:

The unsupervised clustering of the training samples strongly depends on the feature descriptors that play an important role in defining the distance or similarity functions between training examples. So far we have considered only the initial,

manually designed feature types for building the descriptors used for clustering. As we learn new and more powerful features we could expect to improve our ability to perform unsupervised learning before starting a new supervised training epoch (Fig. 26.4). We propose to study ways to use the classifiers learned along the way in order to better organize the training data between training epochs. The outputs of the current classifiers could be used to form updated descriptors of the training images. More precisely, each image i could have a descriptor vector $\mathbf{d}_i$, such that $\mathbf{d}_i(k)$ could be the output of classifier k run on the image i. Thus, each new classifier in the feature pool adds a new element to the descriptor of each image. The similarity between any two images will be a function of these descriptors and evolve from one training epoch to the next. Consequently the unsupervised clustering will also change. This approach could provide a natural inter-play between supervised and unsupervised learning, both co-evolving through many stages of training. One possible similarity function could consider the ratio of the number of co-occurring positive outputs (size of the intersection: $\mathbf{d}_i \wedge \mathbf{d}_j$) to the total number of positive outputs (size of union: $\mathbf{d}_i \vee \mathbf{d}_j$).

26.5.1 Human in the Loop

The organization of the training samples could be also performed manually. We sketch here a high-level, general strategy for possible manual organization of the training data. Classes and sequences initially given should be simpler: learning basic shapes, centered, size-normalized, with fewer colors and less cluttered backgrounds. Then, more complex scenarios should follow: deformations, illumination changes, more difficult classes, but still relatively simple. If possible, we should focus on categories that are sub-parts of the final classes we want to learn, with a very consistent and related context. Once we have the graph and the feature pool initialized with detectors for basic categories and a relatively deep structure, the sequences of more difficult and higher-level classes should come in. We could first think of a specific, more limited world, and gradually expand it. For generating different views, besides the unsupervised clustering approach, one based on spatial and temporal coherence could also be useful (e.g., images for one view could be from frames of the same video sequence).

While cropped images are ideal for learning bottom-up relationships, top-down relationships that go from the level of the scene, or nearby objects, to the level of object/category of interest need information from surrounding regions, which do not contain the object. Thus, if such contextual top-down or lateral relationships are desired, the training images should contain both the object of interest inside its given ground truth bounding box/region (e.g., the eye) as well as surrounding related areas and objects (e.g., the face, the neck, human body, other people, the whole scene etc.). The information given for each training image could be of similar format as in the PASCAL Challenge (Everingham et al. 2010), with the ground truth bounding boxes for all objects and categories present in the image.

26.6 Implementation Details

How large is the classifier graph, how many nodes can we expect it to have? How many edges? What is the computational cost to perform inference once we have the graph constructed? In order to provide approximate answers, we first need to clarify other technical details, such as: how many copies of a concept-node do we need to make? Isn't this number prohibitively large, given that we want to randomly sample locations, scales and search areas? What does it mean to make a copy? Given that each node is an arbitrarily complex graph, can we afford to copy it many times?

Let us start with Figs. 26.5 and 26.7 and try to estimate how many copies of a node (subgraph) should we expect to make in order to cover sufficiently dense the scale, location and search area parameters' space. We do not expect the potential locations p of objects in an image to require very dense sampling. For example, human peripheral vision has a very low resolution, so we do not expect us to be able to perfectly localize an object in the image at the periphery without bringing the object into focus and performing extra fine-tuned localization and geometric fitting, which could interpolate between discrete locations, scales, and local changes in poses and viewpoint. We consider that about 100 locations would be a good rough estimate of a sufficient number of locations.

For each location and scale we estimate, on average, about 100 different search areas. Of course that the actual number of locations, scales and search areas should also depend on the actual category and could be increased or reduced after some initial training. Buildings, for example, are large objects in most images, they are expected to be found over a limited range of scales and locations. Birds on the other

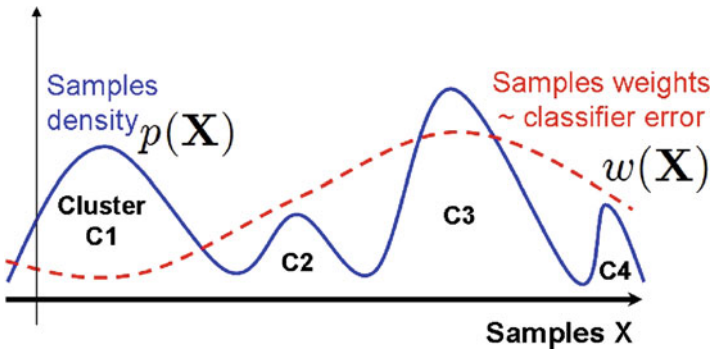

Fig. 26.6 *Blue plot*: natural density of the data points in some feature space. This natural generative probability is *discovered* by unsupervised clustering. The clusters are expected to be correlated with the classification error, as points from the same cluster are similar to each other and are expected to receive similar labels from the classification algorithm. Since supervised learning should take in consideration the natural clustering of the data, we propose a modified, more robust version of Adaboost, which trains its weak classifiers on individual clusters. These clusters are prioritized based on sample weights, which are correlated with the exponential loss for Adaboost

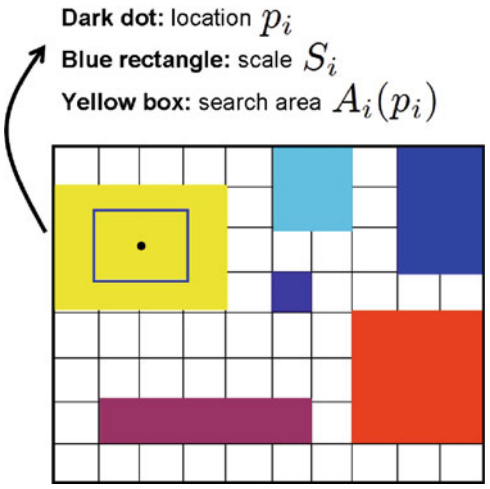

Fig. 26.7 Sampling over locations, scales and search areas cover the space uniformly. *Colored rectangles* represent possible search areas for a given feature (feature-node) in the pool of features. We argue that the granularity of sampling does not need to be very dense and that local refinements, geometric transformations and fitting could fill the gaps in the continuum if needed

hand are usually small and could *a priori* be anywhere in the image. It would be safe to consider about 5 different scales on average, so that we end up with a rough estimate of maximum 5×10^4 copies (feature-nodes) per classifier type.

As mentioned before, we do not need to store an actual copy of the original child node and its subgraph (which could be as large as the whole graph), but only a pointer to it: each of the 5×10^4 copies (or feature-nodes) would need only a few bytes (up to kilobytes) of information to encode the pointer to the classifier type (the concept-node), the location, scale and search area (indexed in a finite set of possible search areas). If we allow about 10^4 possible visual concepts and an average of 10 different views (classifiers) per concept, we end up with 10^5 different visual classifier types (also referred to as child nodes, or concept-nodes), for a total of about 5×10^9 (five billion) feature-nodes (feature detectors) in the pool of features. For the 10^5 classifier types (known as child nodes or concept-nodes), we have to store maximum K input nodes (as edges/pointers) and the weights on their incoming edges. Our initial estimate of the storage required by the whole system would range between hundreds of gigabytes to a few terabytes of data.

26.7 The Visual Story Network in the Spatiotemporal Domain

After presenting our basic Classifier Graph model and different ways of learning and computing with it, we are now ready to discuss the Visual Story Network addresses vision in both space and time. We want to take in consideration both how objects relate in static images as well as how they interact in dynamic environments. In order to understand the meaning, at a visual level, of a certain object category, we need both local information, such as appearance and shape, as well as the higher

level understanding of the role played by that object class in the bigger picture of the video. This concept immediately relates to another task, that of translating videos into language. How can visual understanding help in forming linguistic descriptions of the world, and how, in turn, can language help in disambiguating visual interpretations? We fundamentally want to understand what objects are, from the level of their appearance, shape and viewpoint to the level of their interactions to other objects and the scene, and the final role they play over a certain period of time, within the larger story.

26.7.1 Relation to the Classifier Graph for Images

The visual story network is an extension of the classifier graph, proposed in the previous sections for image recognition. It extends the classifier graph in the realm of video sequences, for learning and recognition of spatiotemporal concepts, such as human actions and activities, human-object interactions, and generally, events that involve objects that act and interact over time. Our classifier graph could be immediately extended to spatiotemporal classes, if we see it as an *Always On* intelligent vision system, which learns not only appearance-based classifiers with geometric relationships, but also events that take place over time. The motivation and intuition discussed in the introductory sections apply in spatiotemporal domain as well. Scenes, objects and parts could be statistically related not only through spatial relationships, but also through temporal ones. A category could appear (or take place, if it is an event) within a certain time period relative to another one, during an event of a certain type. The time period, which relates the parent category to the child, is the time domain equivalent of the search area, or region of presence, discussed in the spatial realm of images. Most ideas presented in the previous sections on images, such as multiple classes for a single category, the overall multi-class recognition system, learning and classification, immediately transfer in the spatiotemporal domain. The main ideas behind the classifier graph, as also described in the introduction, are not limited to a single moment in time.

Let us look at the following example. Imagine the category: *eating a selfprepared omelette*. This is a special case of *eating an omelette*, it might be one of the many classifiers dedicated to the concept of *eating an omelette*, which could take advantage of temporal context from the immediate past, when the person who eats, had been involved in *preparing the omelette*—an event that could have its own dedicated classifier and specialized features. The relationships between the two classifiers, related to eating and preparing, are temporally ordered: preparing the food must happen before eating it. For preparing the food, certain events should happen in a specific order: gathering the necessary ingredients (e.g., eggs, salt, milk, oil) should be followed by cracking the eggs into a bowl, beating them, adding a little bit of salt and pepper, then cooking on a pan. Certain events and objects appear in a certain temporal order and at certain relative spatial positions, while others are less rigidly linked in space and time. For example, while frying should

definitely take place after cracking the eggs, adding salt could, in principle, happen at any time. Exact relative time differences and spatial dependencies might not be needed for classification, in the same way the region of presence discussed before could vary from very large to a single point. Some events or objects are temporally related only by a weak co-occurrence (e.g., salt may be added at any time during cooking a certain meal), while others are strictly ordered in time at precise relative temporal locations (e.g., boiled eggs are ready after three minutes of boiling). Many people make their omelettes in different ways: some use butter for frying, others use oil; some add vegetables or meats, others prefer only salt. The styles of cooking, and the manner in which the cook performs the act of cooking will differ from person to person. Many different classifiers might be learned for the same task of preparing an omelette, depending on the individual experience and cultural context.

The classifier graph is a recursive network of classifiers that form a deep graph structure. This visual system could be always on, reminding of the classical recurrent neural networks models (Williams and Zipser 1989). Some nodes could be triggered by previous events and maintained on for a short period of time, while others could pay attention to present input. Once a spatiotemporal volume is presented to a working classifier graph, memory and attention could function together in order to perform spatiotemporal scans and recursive recognition, by adding a third, temporal dimension to the system presented before. A related model, the hierarchical temporal memory system (George and Hawkins 2005), also considers temporal windows of classifier co-occurrence for establishing relationships between discovering and recognizing spatiotemporal patterns.

26.7.2 Three Principles of the Visual Story Network

The main principles of the Visual Story Network are based on the general idea that visual understanding is based on the dualism and also contrast between an object and its context where, by context, we mean either the spatial scene and the overall understanding of the current image, as well as the longer spatiotemporal story which relates past scenes and events with the current state of world and the object of interest. The main role of the context is to find a consensus between the foreground object and the larger story (that includes past events and interactions with other objects). The object distinguishes itself from its context, providing contrast to its background. Being different from the background is a common and important property of foreground "things". This difference shows that the foreground brings something new, which could provide a complementary and dual pathway for visual understanding. There is one way to understand what things are based on how they look, or the foreground appearance, and another by understanding their role in the story, that is based on the exterior events and objects from the background. Thus, the object and its context become complements for each other and represent, in fact, equivalent alternatives for visual understanding. Below, we split this main principle

in two, one related to context as "scene of the image" and the other related to context as the larger "story", or spatiotemporal volume of exterior objects, features and past events.

The Object-Scene Dualism The inter-dependence between an object and its scene is the first task that should be considered, when reasoning about context. How could information from the global scene, that is, the background, improve visual recognition of an individual object. Our idea differs from most current approaches as it is based on the two complementary views of an object, which, we believe, should be jointly considered: (1) an object is seen and recognized based on its own, intrinsic features such as appearance and shape and (2) the same object should be interpreted from the perspective of the overall scene. The overall larger area around the object will also tell what this object is. Imagine the case of a car wheel: the car tells that at a specific location should be a wheel and that we could safely imagine a wheel as being there. Then, the wheel-only classifier usually confirms (or not) this hypothesis, but only when it has sufficient information. In many cases, it does not, due to blur, bad lighting conditions or insufficient image resolution. In those cases the scene provides a safety belt and a plausible answer in order to give a coherent view of the overall image.

Each Object Plays a Role in the Visual Story Once we obtain image content at the semantic level of objects and spatial relations between them, we could safely move towards the video domain and also track their changes, in order to eventually create a visual story. The novelty introduced by the temporal dimension is *change* and such changes are usually manifested through the appearance or disappearance of objects in the scene, as well as changes in their relations. Relations usually change first, it is through them that we first notice differences in the world: objects move around each other, interact, pass by one another, while remaining mainly stable. Note that objects could be understood at higher semantic levels and so could be their relationships. Any change, at any level should be regarded as an event that can potentially be part of a story, of an intelligent interpretation of the video content. We present in a later section implementation aspects of these ideas and also give some examples from our current research, for now we stay a little longer at the intuitive level. The intuitive insights could bring us closer to finding a coherent computational formulation of stories in the context of video understanding. We should note that changes in the time dimension could happen at any level of abstraction and could be considered over larger periods of time, not just from frame to frame. Each extra level of abstraction usually brings more invariance in interpretation, so changes at higher levels will be less frequent but more meaningful it is those that we should pay more attention to, in order to extract higher level knowledge from events happening in video. For example, we can detect that a certain street intersection went from being busy to not busy, or that a certain person went from buying from the store to walking back home. These types of changes are inferred over a certain, relatively long period of time and should be considered at the level of semantic categories, not of image derivatives or optical flow. While most current work on video understanding uses lower level motion features often based on optical flow, such as Motion Boundary

Histograms (Dalal et al. 2006), we argue that we should rather look at changes at higher level of abstractions and take, for example, derivatives in the higher level feature space. The idea relates to our previous work on action recognition (Zanfir et al. 2013), where we introduced a Moving Pose descriptor that considered both locations of joints as well as the first and second order derivatives of those joints. The joint locations were the result of a sophisticated algorithm, so in that case also, the derivatives were not computed over the noisy sensor data.

We also expect that the higher we move in the level of visual understanding the connections between classifier nodes (e.g. neurons in a CNN) should get sparser and the role of feature selection will increase. At the lower levels of processing we need dense connections to be able to capture all details of appearance of generally compact and rigid objects. In turn, at higher levels of actions and activities, objects are free to move around each other so the possibilities in the scene increase exponentially versus the single, centred-object case. At this level special attention should be given to feature selection. Let us take the example discussed earlier of a person preparing an omelette. In order to visually recognize that fact, only a few key elements have to be considered, while most of the noises and irrelevant facts and objects in the scene should be discarded. Once the few key elements are selected, often their temporal ordering is not important and can easily be discarded for best recognition: the exact moment when salt is added and the exact moment when the person is opening the fridge to get the eggs are probably irrelevant, as long as they take place within a certain relatively large interval. This feature selection mechanism fits perfectly into our general Classifier Graph model.

What Is Predicted from Context Should Match What Is Seen Locally Once we realize that context and local reasoning should match and find agreements we also realize that this principle could constitute the basis for learning in a self-supervised, or naturally unsupervised manner. It is clear that context, which includes the whole scene and the past story could be used to create predictive models of the world, and learn ways in which objects behave and interact. These models should include learning physical models of motion and interactions, as well as higher level and more subtle relations between categories. The role of the predictive model is to expect "the next thing". The closer this "next thing" is to what is actually observed at the next moment in time, the better. Self-supervised training is thus possible by encouraging an agreement between what is seen now based on local temporal and spatial information, and what is expected now using past information, or information from the outside, larger scene. We will discuss potential ways of implementing this idea in the next section.

26.7.3 Creating the Visual Story Network

We propose a general framework for the Visual Story Network, which is a single, unified model for image and video understanding, presented schematically in Fig. 26.8. It captures the story of objects, scenes and their interactions and changes

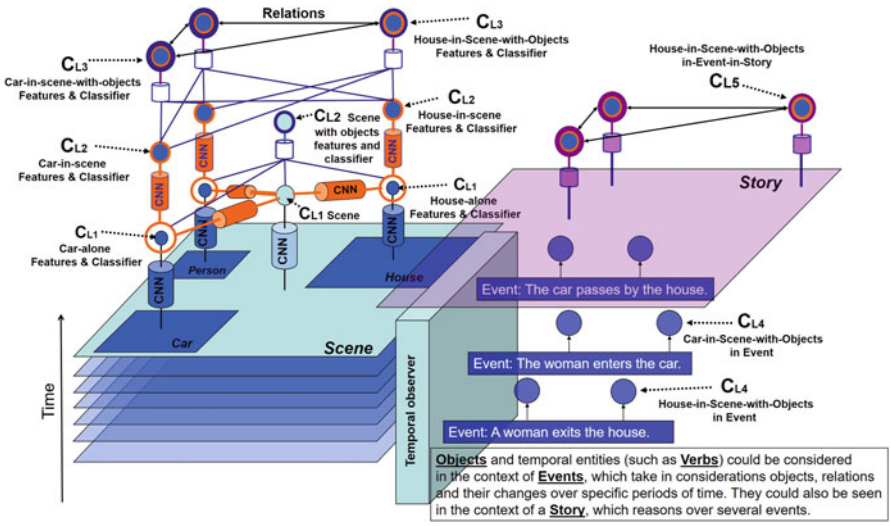

Fig. 26.8 The Visual Story Network: in our VSN prototype we adopt Convolutional Neural Networks (CNN) classifiers and features for processing information from lower to higher levels and viceversa

over time. We begin from learning objects, their relations and interactions, and move towards the higher level semantic concept of a story. At every level we apply the principles of object-context dualism and that of self-learning from it, with minimal supervision. Next we address the different parts of the VSN.

Objects and Their Scene Our first level of visual interpretation (L1) CL1 features and classifiers are learned for individual object categories, such as cars, houses and people in Fig. 26.1. The technology used could be based on current CNN architectures or on other, better models that might appear in the meantime. Regardless of the actual classifiers used, the task at level 1 is to learn a particular object class solely on information coming from its occupied area (possibly including a relatively thin surrounding border). A similar approach will be applied to the whole scene, usually represented by the entire image. Some higher level scene features will be computed for a first level of scene recognition (see CL1 Scene features and classifier). These general scene features (which will be the same for all objects present in the scene) will be combined through different object class-dependent CNN models with object CL1 features and classifiers for a scene-and-object connection. This will merge both bottom-up (dark blue) information as well as top-down from the scene-to-object information (light blue then orange)—the cylinders denote feature transformers and classifiers, which in principle could be of any type; our first choice now are CNNs, similar to those learned for image recognition (e.g. (He et al. 2015; Krizhevsky et al. 2012; Simonyan and Zisserman 2014)). We put into a single model several CNNs, one processing information from the object and the other from the scene with respect to the object. The two are then joined through an upper level network

that reaches level L2, where a CL2 classifier makes decisions based on information from both object and scene. The specialized CNN from the scene to the object will also contain a regression model that learns to predict the object bounding box. This would helpful in order to speed up object detection at test time and predict object location directly. Our model is different from present literature in the way the scene and the objects are put together into a unified model with both bottom-up and top-down connections. It is also unique in the way a single scene is supporting through a common base (the light blue) many types of objects. This common base produces features that will be used, at upper levels, by all the orange networks that link to different objects. Also note that our VSN could be trained using back propagation. As presented in the figure, this can be viewed as a large deep neural network with a specific structure.

Objects Providing Context to Each Other Once we have considered global scene information for recognizing objects we could expect to have an increased recognition accuracy. However, since the scene is taken in consideration as a whole, and most probably only at a relatively small resolution, it is possible to have missed important details in the scene that could constitute evidence for a given target class. For example, the global characteristics of a scene along with the low resolution information from the local target object window could have made us believe that we are looking at a person. However, upon closer inspection of the image, we could realize that what we initially thought to be tall buildings, and which influenced our first impression of seeing a person, were in fact tall rocks and the pixels that we initially thought to belong to a person were in fact a small tree. In that case we needed to see other objects in detail in order to boost our confidence that we are indeed seeing rocks, trees and rivers, not buildings, people and roads. This, there are contextual relationships at Level 2 that could improve recognition at an even higher Level 3, when objects are all seen clearly and can now be analyzed carefully in relation to one another. These relationships between objects at Level 3 could also be modelled by neural networks. We also believe that at this level, when we establish relations between objects, things are more discrete and independent than at the lower levels, where the classical dense neural nets are almost continuously moving from pixels, to subparts, to parts and eventually to objects. Objects are generally solid: when one object pixel moves another nearby one moves along. Their compact nature makes neural nets with dense connections ideal and probably also facilitates learning based on gradient descent. However, when objects are free to move around and are more independent of each other (than are the parts of a single rigid object), the number of possibilities and combinations is exponentially increasing. In that case, a very sparse model learned with feature selection, from immense sea of possibilities is more appropriate that gradient descent learning over many millions or even billions of connections.

At that level of objects and their interactions we should already have access to strong semantic features that should help in learning new concepts fast without the strict need to re-learn everything, from millions of examples, from the lowest level of pixels. Thus, the ability to select a group of relevant features from a large pool

and quickly combine them into a simple classifier could be crucial for fast learning from limited data. At this point we can define the visual content of an image as a collection of both low and high level features. As we mentioned before, we expect that the most relevant information that should be passed into the temporal domain comes from the higher level features. Such features could also be smoothed over time for a more robust estimation then their changes (which could be estimated with simple first or second order derivatives) would also be more accurate and stable.

Objects as Parts of Events In a static image we usually see different objects and observe relations among them, which could be at different levels of abstractions. Relations can be purely geometrical (e.g pairwise relative positions), topological (e.g. an object is to the right side of another, touches another, or contains another) or at a higher categorical level (e.g. a person looks at another person, a tennis player is waiting for the other to serve). However, most connections between objects in the real world also involve movement. Even if we could guess interactions from a single image, most relations are fundamentally based on movement. Movement and change is a key element in how objects relate to one another and, interestingly enough, it is also the key element that separates them into distinct entities. Interactions and events are described by changes at higher levels of image interpretation. When two objects interact, there is usually a change at some level of abstraction, and some of those changes could be important for understanding events, actions and activities. Finding these very few relevant changes is also a subject of feature selection. For example, when a woman gets in the car, something changes at the recognition level. When a car passes another car, something changes in the structure of the scene, also to be observed at the high level of recognition. When a man walks into a store and buys something, something again changes, in the recognition of people, objects and their relation to each other. Thus, we should define events over certain periods of time, as collections of image features computed for the corresponding frames as well as their transformations, with a special attention to changes in the values of the high level features. Then, the detected events and their features become temporal local context for objects as they are transferred from the image domain to video.

From Events to Stories Visual stories could be interpreted as events and relations between them. The relations could usually be represented in the form of certain relative temporal topology (e.g. he entered the house immediately after she left). More complex ones could also take in consideration semantic relationships between events. The level of interpretation probably does not have an upper bound, especially when expressed in sophisticated natural language, or simply conceived with human thoughts. However, given the limitation of computer vision systems today in understanding video, we believe we should address problems gradually, moving from a level of objects, simpler actions and activities, towards more sophisticated linguistic video descriptions. Like events, stories would also constitute contextual regions of space and time for objects. They will provide the environment in which the actors (objects) will play their roles.

Once we have a good idea about what happens in a video at the level of the story and how different objects interact with each other, we can use the high level

understanding of the story to go back and correct the object detection in images. For example, if we know that we are looking at a man speaking on the phone, after seeing him in the phone booth, with specific body poses and gestures, we could increase our chances of correctly detecting the phone in his hand in certain frames where we would not be able to do so based on the information from the frame alone. In the context of the story, the phone becomes the object on which the man standing in a certain way, is speaking in the phone booth, over a certain period of time. This short story will often provide sufficient contextual information to help detect and recognize the actual phone in frames. We will study ways to interpret contextual information in video at the level of the story for better classifying the objects in images. The inputs of features from the level of the story back to the objects constitute the fifth level in our VSN prototype. At this level the cycle is completed, with links going from bottom-to-top and top-to-bottom in the image, into a continuous interplay between objects and the scene, as well as between objects, scenes and stories at the video level. Once we are able to understand objects through their roles in the story, we would be better prepared to go even further and cross the border into the land of vision to natural language translation.

Dual Local-Global Self-Training Now that we have explained how we could construct and use the Visual Story Network, probably the most important missing piece is how to learn the weights and its structure in a less supervised fashion. We have discussed several possibilities of learning in the sections about the classifier graph. We have also alluded to a possible way to perform self-training when stating the third principle of the VSN. We believe that full self-training will be possible in a combination with minimal supervision. We also believe that the third principle, which tries to enforce agreement between local and global reasoning might hold the key to natural self-supervised training. During testing it is clear how to used the object contra context dualism for testing. It is intuitive to expect that context offers an alternative way of looking at objects and that the complementary views could help each other. This fact is confirmed by tests with automated image recognition systems using context (Collins et al. 2005; Desai et al. 2011; Felzenszwalb et al. 2010b; Hoiem et al. 2008; Leordeanu et al. 2016; Oliva and Torralba 2007; Rabinovich et al. 2007; Torralba 2003; Yao et al. 2012) as well as well-known theories in neuroscience (Fazl et al. 2009; Grossberg 2013; Sigala and Logothetis 2002). Learning could be understood as a way of putting in agreement the power of prediction by deep and high level contextual reasoning with fast feed forward recognition. The object vs. context dualism principle could be applied for self-learning at all levels in the VSN, starting from the image level and going all the way to the level of a story. Naturally self-supervised learning will be based on the following main ideas:

Recognition Based on Local Appearance Will Be First Completely Supervised for a Limited Number of Classes Human supervision will be used to train fast feedforward networks for recognition at the local level. At every level in the hierachy there will be a local, or bottom-up level and a global, contextual top-down one, and

at every level we will seek agreement between the two views. The bottom-up level will be fully supervised for a few, canonic classes and cases.

The Local Classifier Will Be Then Used to Train a Contextual Classifier, with Missing Local Information A deeper and more powerful pathway for top-down processing will be trained, using the local fast feed-forward net as a teacher. Both pathways will have an internal state of the world, represented by a layer of internal features. The goal of training the larger, deeper contextual classifier will be to learn to match, or predict the internal state of the local classifier. The global network will not be given information about the world at the local appearance level (in the case of images) or local temporal level (the present time). The global reasoning net will only access, in the case of temporal events, or stories, information from the past. Its job will be to predict the present and the local interpretation of the simpler net that will have access to such local and present information. In this manner, the global network, which will include backwards connections and cycles, will be forced to infer models of the world, including simple rules for motion and physical laws, as well as higher level and more subtle interpretations at the level of stories.

Once Trained the Global, Top-Down Net Will Be Used as an Oracle for the Local, Bottom-Up Net Once the top-down net learns to predict the local one, we expect it to have a reasonably good model of the world, relative to its level of functioning. As mentioned before, we will have such dual stream top-down and bottom-up pathways at different levels in the VSN: object-scene level, object-event level and object-story level. The more intelligent global nets will be used as teachers in order to refine the capabilities of the fast feed forward nets that were initially trained on simpler cases.

Resonance, Confidence and Local-Global Disagreements The ideal case, after learning, is when both pathways are in agreement and resonance takes place. In that case learning is not needed, as the two independent pathways are happily in harmony: the local net sees what the global net is able to predict based only on past or outside context. For example: the local net sees a car moving in a certain way, while the global one also predicts looking at a car that should be at a certain location moving in a certain way, based on past local and global information. While the global network is not interested so much in appearance, it is more interested in high level category interpretation. That is why the global net tries to predict higher level semantic interpretations. We also expect that the global network should be reliable when it is confident about its reasoning. Using a certain threshold for such confidence (reminding of the vigilance parameter from ART (Grossberg 2013)) we could then use the global net as a teacher for the local one, when there is a disagreement between the two and the global net is confident. For example, let us say that based on what happens at the level of story and events we could realize that a person is talking on the phone, even though the phone looks different than all other phones we have previously seen. We will use this global reasoning in order to teach the local net, based only on local appearance, that we are looking at a phone.

Thus, the local net will learn from the global one. In cases when the global net is not sure of its output and it is in disagreement with the local one, which is confident, we could perform training the other way around. We would also remember that things could be out of context, even though when they are out of context at one level, there is usually an explanation at a different level. For example, if a person is seen using a *shoe* as a *phone*, the explanation at the higher level could be that the person is making a joke—a fact that could be learned later on by the global net. When the VSN is not able to learn the supervised concepts its structure is grown using the algorithms presented in the earlier sections, on feature selection from the pool. The structure will be changed only one of the nets is not able to learn to match the other or perform supervised learning in a sufficiently acceptable way. Disagreements between the two pathways and low confidences could be a sign that more human supervision is needed and that is when such supervision should be called for. We should never take the human out of the loop, no matter how smart a system is, there are always cases when the human will be needed, to better serve human's needs, goals and principles.

26.8 Concluding Remarks

We have presented a way to construct a Visual Story Network, starting from an initial model, the Classifier Graph, for recognition and learning in images. We then moved to the domain of space and time and presented the principles and the structure of the Visual Story Network. We described in sufficient detail how this model works and how it could be learned both in a supervised way combined with a naturally selfsupervised fashion. We make several contributions. We generalize the hierarchical structure of most successful methods today, by allowing directed edges between classes at every level in the abstraction hierarchy, effectively transforming the structure into a directed graph of classifiers. This permits a relatively simple and natural way to include contextual information, which has proved to be a strong cue for visual recognition (Chen et al. 2012; Felzenszwalb et al. 2010a; Song et al. 2011; Tu and Bai 2010). The ability to reuse resources that could be potentially useful, by maintaining a large pool of many modified copies of old classifiers as potential input features to new classifiers. This could lead to good generalization. The graph, through various learning epochs, could end up learning from many different datasets, thus collecting a varied pool of powerful features. They form a library of classes, contexts and subparts, which are relevant to each other and to the given classification task. We could also envision a way to *forget*: remove from the pool less useful features that do not get picked. The structure of our model is learned by novel feature selection algorithms. The change of structure of the VSN is triggered when agreements between the local and the global net is not achieved or when the supervised learning task becomes too difficult. Learning and adapting the weights from end to end is also possible as long as the nodes (e.g. single neurons) have differentiable activation functions.We offer the possibility of growing

with simple and efficient rules an arbitrarily complex, multi-classification system. Our approach is general, uniform and recursive (the same procedure is applied for any classification task, at each iteration), also in sync with findings that reveal the surprising uniformity of neural learning and development rules in neuroscience (Edelman and Mountcastle 1978; Koralek et al. 2012). One of the more important contributions of our work is the proposed dual, local-global selfsupervised training, combined with minimal supervision. In our model, the global subnet functions as an oracle that is supposed to guess or predict, based on outside, contextual information or on past events, the state of the world at the present time. While the local network is feed forward and should quickly recognize what is happening now, the global one, using more sophisticated predictive models, varying from motion and physical based to more subtle object interactions (e.g. events and stories), is supposed to resonate with the local one, for a full, convergent and unified visual understanding. In cases when such agreement does not happen, the global net, when sufficiently confident, is used as a teacher for the local one. Supervised learning takes place only rarely, when the global network is not confident and there is large disagreement between the two global and local pathways. We believe the the dual way of seeing objects in relation to their context can explain both how vision takes place, as a full, unified experience at several levels of interpretation, and also how learning in a natural, unsupervised environment could take place—as a way of approaching and fulfilling the dual local-global view of objects.

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Part V
Beyond the Mind's Barriers

Chapter 27
Pharmacological Interventions and the Neurobiological Basis of Mental Disorders

Jonathan Y. Tsou

Keywords Psychiatry • Pharmacology • Neurobiology • Neuroscience • Biological basis of mental disorders • Dopamine hypothesis of schizophrenia • Serotonin hypothesis of depression • Interventionist accounts of causation

27.1 Introduction

In psychiatry, pharmacological research has played a crucial role in the formulation, revision, and refinement of neurobiological theories of psychopathology. Besides being utilized as potential treatments for various mental disorders, pharmacological drugs play an important epistemic role as experimental instruments that help scientists uncover the neurobiological underpinnings of mental disorders (Tsou 2012). Interventions with psychiatric patients using pharmacological drugs provide researchers with information about the neurobiological causes of mental disorders that cannot be obtained in other ways. This important source of evidence for the biological causes of mental disorders is often overlooked in philosophical analyses of psychiatry, especially in skeptical analyses that debase the biological aspects of psychopathology (e.g., Szasz 1960; Scheff 1963; Laing 1967). In discussing pharmacological interventions as a form of evidence for the physical basis of mental disorders, this paper aims to clarify the nature, reliability, and limitations of this evidence. In addition, it illustrates the central role that pharmacological findings in applied clinical contexts play in the acquisition of neurobiological knowledge in research contexts.

The main argument advanced in this paper is that pharmacological interventions with clinical populations of psychiatric patients allow scientists to draw causal inferences about the neurobiological basis of mental disorders. While the knowledge acquired in this process is not infallible or immune to revision, pharmacological

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interventions are indispensable in the articulation of scientific knowledge about the neurobiological causes of mental disorders. I advance this argument with reference to the development of neurobiological theories of schizophrenia and depression in the second half of the twentieth century. My analysis of these historical cases emphasizes the indispensable role that pharmacological interventions played in the articulation of the dopamine hypothesis of schizophrenia and the serotonin hypothesis of depression. I subsequently discuss three specific epistemic functions that pharmacological drugs serve in contributing to knowledge about the neurobiological basis of mental disorders: (1) facilitating the generation and formulation of etiological neurobiological hypotheses, (2) aiding in the testing and confirmation of neurobiological theories, and (3) permitting the refinement, elaboration, and revision of existing neurobiological theories. In the history of neurobiological theories of schizophrenia and depression, pharmacological drugs functioned as experimental instruments that realized each of these functions.

My analysis of pharmacological interventions in psychopathology research draws on philosophical accounts of science that emphasize the importance of manipulability and intervention in experimental contexts (Cartwright 1983, ch. 5; Hacking 1983; Ackermann 1985; Franklin 1986, 1996, 2010; Giere 1988, ch. 5; Woodward 2003, 2008). These philosophical analyses suggest that intervening with and manipulating theoretical (i.e., unobservable) entities in systematic ways provides philosophical reasons for believing in their existence (cf. Morrison 1990). While philosophers such as Ian Hacking (1983) maintain that experimentation *with* theoretical entities (e.g., manipulating electrons in electron guns) provides evidence for their real existence, my analysis takes the more liberal stance that experimentation *on* entities and measuring their properties can sometimes provide reasons for believing in their existence (Franklin 1996, 2010). In the case of mental disorders, my analysis suggests that there is defeasible evidence for believing that a mental disorder is a real theoretical entity (as opposed to a social construction) when it can be manipulated in systematic and predictable ways by pharmacological drugs. What pharmacological interventions ultimately reveal is the stable biological causal structure of these disorders and the specific neurobiological mechanisms that underwrite them.

27.2 Antipsychotic Drugs and Schizophrenia

Knowledge about the neurobiological causes of schizophrenia is known largely through various pharmacological interventions with antipsychotic drugs. The first antipsychotic drug (chlorpromazine) was discovered by accident in the early 1950s, which was followed by the development of other antipsychotic drugs in the 1960s and 1970s. Pharmacologists' attempt to remove the unwanted extrapyramidal side-effects associated with these first generation antipsychotic drugs led to the creation of second-generation, atypical antipsychotic drugs in the 1990s. All of these developments in pharmacology were important steps in the formulation of

the dopamine theory of schizophrenia and led to a greater understanding of the neurobiological basis of schizophrenia.

In the early 1950s, a French military surgeon, Henri Laborit, was experimenting with various drugs that could potentially treat *surgical shock*, which is an acute and sometimes fatal state that occurred during surgery (McKim 2007, pp. 287–288). Laborit hypothesized that surgical shock is caused by the excessive release of neurotransmitters, such as epinephrine, acetylcholine, and histamine; and he experimented with drugs that were known to block the release of these substances, including various antihistamines. In 1951, Laborit was able to successfully treat surgical shock with an antihistamine called RP-4560 (chlorpromazine), and he reported that he was able to put surgical patients into an 'artificial hibernation,' wherein patients would not lose consciousness, but become sleepy and disinterested with their surroundings (Laborit and Huguenard 1951). Laborit speculated about potential therapeutic applications of chlorpromazine in psychiatry and suggested to some psychiatric colleagues that the drug might be useful for treating agitated mental patients (Ban 2007, p. 496; Healy 2002, pp. 81–82).

The most important clinical trials with chlorpromazine were conducted by two Parisan psychiatrists, Jean Delay and Pierre Deniker, who learned of Laborit's trials and began using chlorpromazine to treat psychiatric patients (López-Muñoz et al. 2005, p. 118). In 1952, Delay and Deniker reported that while chlorpromazine was not successful in treating depression, it had dramatic therapeutic effects on patients in states of agitation, mania, mental confusion, and acute psychosis (López-Muñoz et al. 2005, p. 120). The researchers also reported the drug's capacity to slow motor activity, cause affective indifference, and neutralize emotions as a 'neuroleptic syndrome' (Delay and Deniker 1952).

In November 1952, chlorpromazine was made available for prescription in France under the tradename *Largactil*, which made the drug widely available to clinicians and psychiatrists around the world (Shen 1999, pp. 408–409). In 1954, Heinz Lehmann, a German born Canadian psychiatrist, suggested that chlorpromazine worked by selectively inhibiting 'affective drive' (Lehmann 1954; Lehmann and Hanrahan 1954), and his research was highly influential in promoting the use of chlorpromazine in North American psychiatry. By the end of 1955, successful treatment of schizophrenic patients with chlorpromazine were reported in numerous countries in the world, including Switzerland, the United Kingdom, Germany, Hungary, Canada, Peru, the United States, Australia, and the Soviet Union (Ban 2007, p. 296). In 1957, the American Public Health Association jointly awarded the prestigious Lasker Prize for Medicine to Laborit, Deniker, and Lehmann for discovering the antipsychotic properties of chlorpromazine (Ban 1994; Healy 2002, pp. 125–128).

The success in treating schizophrenic patients with chlorpromazine in the 1950s stimulated the search for other antipsychotic drugs, and a number of other drugs with similar antipsychotic effects (e.g., thioridazine, fluphenazine, haloperidol) were developed in the 1960s and 1970s (Healy 2004, pp. 96–7). A common problem with these first-generation ("typical") antipsychotic drugs was the presence of unwanted motor side-effects or *extrapyramidal symptoms* (EPS) that resemble the symptoms

of Parkinson's disease; EPS include symptoms such as muscular rigidity (dystonia), abnormal motion of voluntary and involuntary muscles (dyskinesia), inability to initiate movement (akinesia), inability to remain still (akasthesia), and tremors (Kring et al. 2007, p. 375). In a 1961 report, the prevalence of EPS among patients treated with antipsychotic drugs was estimated to be 38.9% (Ayd 1961), and many pharmacologists at the time believed that there was an absolute inverse relationship between the clinical efficacy of an antipsychotic drug and EPS, with stronger antipsychotic effect being associated with more EPS (Shen 1999, p. 409). This belief was refuted with the development of second-generation ("atypical") antipsychotic drugs.

While the first atypical antipsychotic drug was first synthesized in 1958, these drugs were not significantly utilized in clinical settings until the 1990s because of concerns regarding their safety. The first atypical antipsychotic drug that was developed was clozapine. This drug was developed by a research team directed by Hanns Hippius in Switzerland, who—in the early 1960s—were attempting to refute the common pharmacological belief that EPS and strength of antipsychotic effect were causally linked (Hippius 1996). Several clinical trials indicated that clozapine had a strong antipsychotic effect with minimal EPS (Bente et al. 1966; Gross and Langner 1966; Angst et al. 1971), which demonstrated that the clinical efficacy of antipsychotic drugs could be decoupled from their unwanted side-effects. Clozapine was introduced in clinical settings in a number of European countries in the late-1960s; however, it was withdrawn from the market in many countries by the mid-1970s due to concerns that agranulocytosis (i.e., a life-threatening lowering of white blood cells) was caused by clozapine treatment (Healy 2002, pp. 238–244). In the following decade, fears about the safety of clozapine allayed, and it became understood that agranulocytosis would appear for a small percentage of patients, but fatalities could be avoided through close blood monitoring (Hippius 1989, p. S4). In the United States, the introduction of clozapine was facilitated by a landmark study that demonstrated the effectiveness of clozapine (compared to chlorpromazine) on treatment-resistant schizophrenic patients (Kane et al. 1988). After clozapine was introduced in the US, a number of other atypical antipsychotic drugs (e.g., risperidone, olanzapine, aripiprazole) were quickly developed in the 1990s and 2000s (Janowsky 2004, pp. 80–81); all antipsychotic drugs currently under development are of the atypical type.

In addition to being employed as tools for treating schizophrenic patients, antipsychotic drugs—and pharmacological drugs more generally—function as experimental instruments for identifying the neurobiological causes of schizophrenia. In particular, pharmacological interventions with schizophrenic patients have played a central epistemic role in the formulation, revision, and refinement of the dopamine hypothesis of schizophrenia, which has been the dominant neurobiological theory of schizophrenia since the 1970s (Kring et al. 2007, pp. 363–365; Carlson 2008, pp. 460–466). In its original formulation, the dopamine hypothesis suggested that the symptoms of schizophrenia are caused by excessive activity of the neurotransmitter dopamine. Since the early 1980s, the symptoms of schizophrenia have been distinguished into 'positive symptoms' and

'negative symptoms' (Strauss et al. 1974; Wing 1978; Crow 1980a, b; Andreasen and Olsen 1982):

1. Positive symptoms (psychological excesses): delusions, hallucinations, and disordered thought.
2. Negative symptoms (psychological deficits): flattened emotions, poverty of speech, lack of motivation, and social withdrawal.

As discussed below, a more refined formulation of the dopamine hypothesis maintains that the positive (psychotic) symptoms of schizophrenia are caused by excessive dopamine activity. Evidence for this qualified dopamine hypothesis is supported by various pharmacological interventions. All antipsychotic drugs—typical and atypical—that can successfully treat the positive symptoms of schizophrenia are dopamine antagonists that decrease the activity of dopamine. A key discovery in the 1970s that further implicated the role of dopamine was the finding that the clinical efficacy of typical antipsychotics (e.g., chlorpromazine, haloperidol) is directly related to their affinity for dopamine receptors (Seeman et al. 1975). Indirect evidence for the dopamine hypothesis was provided by the fact that typical antipsychotic drugs cause EPS similar to the symptoms of Parkinson's disease, and Parkinson's is known to be caused, in part, by low levels of dopamine (Kring et al. 2007, p. 363). Another important piece of evidence was the finding in the early 1970s that stimulant drugs (e.g., amphetamine, cocaine) with opposite pharmacological effects as antipsychotics (i.e., dopamine agonists), when taken in sufficiently large doses, induce an 'amphetamine psychosis' that is indistinguishable from the positive symptoms of schizophrenia; and this state can be treated with antipsychotic drugs (Ellinwood 1967; Ellinwood et al. 1973).

In the early 1990s, a further elaboration of the dopamine hypothesis was articulated in a landmark paper (Davis et al. 1991), which expanded the scope of the original dopamine hypothesis by theorizing about different dopamine systems and receptors (Healy 2002, chs. 5–6). This revised dopamine hypothesis suggests that excessive dopamine activity in the mesolimbic pathway is responsible for the positive symptoms of schizophrenia, while deficient dopamine activity in the mesocortical pathway is responsible for the negative symptoms. The mesolimbic dopamine pathway (which is involved in motivation and reinforcement) is a neural pathway that originates in the ventral tegmental area and projects to the hypothalamus, amygdala, hippocampus, and nucleus accumbens (Kring et al. 2007, p. 364; McKim 2007, pp. 289–290). The original hypothesis that schizophrenia is caused by excessive dopamine activity was refined to the narrower hypothesis that the positive symptoms are caused by excessive dopamine activity in the mesolimbic pathway. This excessive activity is theorized to be caused by hyperstimulation of D_2 dopamine receptors (the main dopamine receptor in this pathway) given that antipsychotic drugs exert their therapeutic effect by blocking D_2 receptors (Abi-Dargham 2004). The revised dopamine hypothesis also suggests that deficient dopamine activity in the mesocortical pathway—and in particular, the prefrontal cortex—results in the hypostimulation of D_1 receptors (the main dopamine receptor subtype in this area), which is responsible for the negative symptoms and cognitive

impairments associated with schizophrenia (Abi-Dargham 2004). The mesocortical dopamine pathway originates in the ventral tegmental area and projects to the prefrontal cortex (Kring et al. 2007, p. 364). The hypothesis that negative symptoms are caused by deficient dopamine activity in the mesocortical pathway is supported by the facts that cognitive impairment is associated with dysfunction in the prefrontal cortex (the terminal region of the mesocortical pathway) and dopamine depletion in the prefrontal cortext (using dopamine antagonists) in animals induces cognitive impairment (Sawaguchi and Goldman-Rakic 1994). Moreover, deficits in dopamine activity in the mesocortical pathway are causally related to excessive dopamine activity in the mesolimbic pathway. The prefrontal cortex projects to limbic areas innervated by dopamine such that deficient dopamine activity in the prefrontal cortex fails to exert inhibitory control over dopamine neurons in the limbic area, resulting in excessive dopamine activity in the mesolimbic system (Kring et al. 2007, pp. 364–365; Carlson 2008, pp. 468–469). Hence, the original dopamine hypothesis posited in the 1970s was expanded from the hypothesis that schizophrenia is caused by excessive dopamine activity to the theory that schizophrenia is caused by a dysregulation of dopamine, with deficiency of dopamine activity in the prefrontal cortex resulting in an excess of dopamine activity in the mesolimbic pathway. While dysregulation of dopamine cannot tell the complete story about schizophrenia (Kendler and Schaffner 2011), abnormalities in the dopamine system are undoubtedly an important causal factor in schizophrenia.

27.3 Antidepressant Drugs and Depression

Like schizophrenia, knowledge about the neurobiological basis of depression is largely known through various pharmacological interventions with antidepressant drugs. The antidepressant properties of the first two classes of antidepressant drugs (i.e., monoamine oxidase inhibitors and tricyclic antidepressants) were discovered by accident in the 1950s. The attempt to develop safer antidepressants with fewer side-effects led to the self-conscious design of second-generation antidepressants (i.e., selective serotonin reuptake inhibitors), which were introduced to the market in the 1980s. All of these pharmacological developments in antidepressant drugs contributed to the formulation of the serotonin theory of depression and our current understanding of the neurobiological basis of depression.

The first successful antidepressant drug was iproniazid, and its antidepressant properties were discovered by accident while it was being experimented on as a potential treatment for tuberculosis (Hirschfeld 2000). In 1952, during clinical trials of iproniazid for tuberculosis patients in the United States, it was discovered that this drug significantly elevated the mood of patients; subsequent trials established that this antidepressant effect was independent of its ability to treat tuberculosis (McKim 2007, pp. 301–302). In 1957, at a meeting of the American Psychiatric Association in Syracuse, New York, data on the effectiveness of iproniazid to treat depression was presented. A year after this meeting, over 400,000 patients affected

by depression had been treated with the drug, despite the fact that iproniazid was being marketed as an antitubercular agent (López-Muñoz and Alamo 2009, pp. 1566–1567). Iproniazid turned out to be the first of the monoamine oxidase inhibitor (MAOI) antidepressants, and research into other MAOIs (e.g., isocarboxazid, phenelzine, tranylcypromine) to treat depression soon followed (López-Muñoz et al. 2007, p. 557). While MAOIs were widely used in the 1960s, enthusiasm for them waned by the 1970s because of concerns about MAOIs causing liver damage and potentially dangerous interactions with other drugs and foods. Newer MAOIs have been developed that are more specific in their actions, reversible, and less likely to interact with foods (McKim 2007, p. 301).

Another class of antidepressant drugs that were developed in the 1950s were tricyclic antidepressant (TCA) drugs, which were discovered by accident during trials to test antipsychotic drugs (Healy 1997, ch. 2). In the mid-1950s, the (typical) antipsychotic drug impramine was being tested on schizophrenic patients in Switzerland; while this drug was not effective at treating psychosis, it was found to elevate the mood of depressed patients (McKim 2007, p. 301). Subsequent trials by Roland Kuhn, who was Medical Director at the Psychiatric Clinic of Thurgau Canton, indicated that imipramine could improve the mood of depressed patients (López-Muñoz and Alamo 2009, pp. 1569–1571). By 1958, the antidepressant effects of imipramine were confirmed and it was placed on the market in Europe. In North America, the use of imipramine to treat depression was initiated by Heinz Lehmann, who conducted a study on impipramine on depressed patients that allowed the drug to be marketed in the United States (Lehmann et al. 1958). A landmark study published in 1965 (Klerman and Cole 1965) demonstrated that imipramine was superior to placebo in the treatment of depression. Following the clinical success of imipramine, a number of other TCAs (e.g., desipramine, protryptyline, clomipramine) were developed in the 1960s (Fangmann et al. 2008). The unwanted side-effects of TCAs, due to their cardiotoxicity and anticholinergic properties, spurned the search for other antidepressants.

Unlike the fortuitous discovery of the antidepressant properties of MAOIs and TCAs, selective serotonin reuptake inhibitor (SSRI) antidepressants were developed following a procedure of directed design (Wong et al. 2005). MAOIs and TCAs provided crucial information regarding what kinds of pharmacological actions were causing antidepressant effects, which allowed pharmacologists to design drugs that would have effects at a specific locus of action (López-Muñoz and Alamo 2009, pp. 1576–1578). In the 1970s, the American pharmaceutical company Eli Lilly synthesized the SSRI, fluoxetine. A pioneering paper by David Wong's research group at Lilly described the actions of fluoexetine on reuptake systems and discussed the potential of this drug for understanding serotonin function and for treating depression (Wong et al. 1974). In 1980, Lilly committed to studying fluoexetine and enlisted the psychiatrist John Feighner to conduct clinical trials on the drug. These studies suggested that fluoexetine was as effective as TCAs, but with far fewer adverse side-effects, which led Feighner to write of the "new generation of antidepressants" (Feighner 1983). In 1987, the FDA approved of the clinical use of fluoexetine, which was marketed under the tradename *Prozac*; by 1990, fluoexetine

was the most widely prescribed drug by North American psychiatrists (López-Muñoz and Alamo 2009, p. 1578). Following the clinical success of fluoexetine, other SSRIs (e.g., citalopram, sertraline, paroxetine) were quickly placed on the market (López-Muñoz and Alamo 2009, p. 1578).

As in the case of antipsychotic drugs and schizophrenia, pharmacological interventions with antidepressant drugs have been crucial experimental tools in uncovering the neurobiological basis of depression (Tsou 2013). In particular, pharmacological research played a central role in the discovery, articulation, and revision of the monoamine hypothesis of depression. The first articulation of the monoamine hypothesis in the 1960s suggested that depression is caused by deficient activity of monoamine neurotransmitters: norepinephrine (NE), serotonin (5-HT), and dopamine (DA). The monoamine hypothesis was formulated largely based on the fact that MAOIs and TCAs that can relieve the signs of depression are monoamine agonists that increase the activity of monoamine neurotransmitters. Furthermore, monoamine antagonist drugs with opposite pharmacological effects of the first-generation antidepressants (e.g., reserpine) can induce depressive symptoms in non-depressed individuals (Sachar and Baron 1979).

By the end of the 1960s, the monoamine hypothesis became revised to the serotonin hypothesis of depression. The serotonin hypothesis suggests that depression is caused by deficient activity of serotonin in the serotonin pathway that begins in the Raphé nuclei and projects through the medial forebrain bundle to the forebrain (Coppen 1967; McKim 2007, p. 304). This hypothesis gained support among researchers after studies demonstrated the powerful inhibition of serotonin reuptake in imipramine and other TCAs, which functions to increase serotonin activity (López-Muñoz and Alamo 2009, p. 1577). The serotonin hypothesis was also supported by the fact that SSRIs, which also increase the activity of serotonin, are effective at alleviating depression among a broad range of patients, although their relative efficacy among patients with severe depression is controversial (Hirschfeld 2000).

Besides pharmacological research, the serotonin hypothesis of depression is also supported a number of other independent findings. Lower production of and release of serotonin in the brain is correlated with decreased Cerebrospinal Fluid (CSF) levels of 5-hydroxindoleacectic acid (5-HIAA), which is the main metabolite of serotonin; studies have shown significantly lower CSF levels of 5-IAA among individuals who have attempted suicide, and lower levels of 5-HIAA are correlated with a higher number of suicide attempts (Åsberg et al. 1976; Roy et al. 1989; Träskmann et al. 1981). Post-mortem studies have identified increased numbers of postsynaptic serotonin receptors (e.g., 5-HT_{1A} and 5-HT_{2A} receptors), in the prefrontal cortex of suicide victims, possibly due to a compensatory response to reduced serotonin activity (Mann 1998, p. 26). Moreover, tryptophan depletion studies have demonstrated that lowering levels of tryptophan (the main precursor to serotonin), which lowers serotonin levels in individuals, causes temporary depressive symptoms among individuals with a history of depression, but not for individuals without a history of depression (Benkelfat et al. 1994; Johnson et al. 2009, pp. 203–204; Moore et al. 2000). This suggests that the diminished serotonin activity implicated

in depression is due to insensitive postsynaptic serotonin receptors. The theory that diminished serotonin activity is due to insensitive serotonin receptors rather than lower absolute levels of serotonin is supported by the pharmacological finding that antidepressants increase levels of neurotransmitters immediately, however, it takes about 2 weeks (when neurotransmitter levels have returned to their baseline levels) before patients experience relief from antidepressant treatment; it is also supported by metabolic studies that indicate that some individuals with depression do not show evidence of abnormal absolute neurotransmitter levels (Kring et al. 2007, pp. 238–240). While the serotonin hypothesis is inevitably an oversimplification, diminished activity in the serotonin system is likely to be involved in depression.

27.4 Pharmacological Drugs are Experimental Instruments in Biological Psychiatry

In the history of twentieth century psychiatry, the development of effective pharmacological treatments for disorders such as schizophrenia and depression played an important role in demonstrating the physical basis of mental disorders and moving psychiatry away from the psychoanalytic and dualist assumptions that dominated American psychiatry until the 1960s. Psychoanalysis enjoyed a period of prestige within American psychiatry from the post-war period until its eventual decline in the 1960s and 1970s (Grob 1991; Hale 1995). The "psychopharmacological revolution" of the 1950s (Baumeister and Hawkins 2005; Bhatara et al. 2005), which featured the pioneering use of pharmacological drugs to treat schizophrenia and depression, was a major contributing factor in the demise of psychoanalysis. Within psychoanalytically-oriented psychiatry, mental disorders such as schizophrenia and depression were conceived of as the externalization of subconscious and traumatic personality conflicts, and it was thought that genuine treatment required patients to discover the roots of their internal conflicts (López-Muñoz and Alamo 2009). From this perspective, the development of pharmacological drugs to treat mental disorders was regarded with skepticism by psychoanalysts since it was thought that these drugs would merely mask the symptoms of these disorders and these drugs could not address the underlying mental conflicts that genuine treatment required. The success of pharmacological treatments for mental disorders contributed to the debunking of these psychoanalytic and dualist assumptions and, eventually, to the replacement of psychoanalytically-oriented psychiatry with biological psychiatry.

In addition to their contribution to demonstrating the physical basis for some mental disorders, pharmacological drugs played a crucial epistemic role in as experimental instruments that allowed researchers to formulate the first biological, etiological theories about mental disorders. Pharmacological drugs facilitated the formulation of neurobiological hypotheses by allowing researchers to draw inferences about the neurobiological causes of mental disorders based on how clinical populations of patients responded to particular drug interventions. In this process, drugs operate as instruments or technologies that reveal important causal regularities

underlying mental disorders. In the case of schizophrenia, the fact that typical antipsychotic drugs are dopamine antagonists facilitated the formulation of the original dopamine hypothesis that maintained that schizophrenia is caused by excessive dopamine activity. In depression, the fact that first generation antidepressants are monoamine agonists facilitated the formulation of the monoamine hypothesis that maintained that depression is caused by deficient activity of monoamine neurotransmitters.

The way in which pharmacological interventions facilitate the generation of neurobiological hypotheses exemplifies the interventionist kind of causal reasoning that has been examined comprehensively by James Woodward (2003). Woodward (2003, ch. 2) advocates a manipulability account of causation that maintains that variable *A* (e.g., excessive dopamine activity) is a cause of variable *B* (e.g., psychotic symptoms) if an intervention that can change the value of *A* (e.g., administering antipsychotic drugs that decrease dopamine activity) results in a corresponding change in the value of *B* (e.g., alleviation of psychotic symptoms). This account of causation is motivated, in part, to capture the role of experimentation in causal inference. On Woodward's view, experimentation is relevant to the generation of causal claims because these claims have implications concerning what would happen to *B* under appropriate interventions of *A*. This view indicates that scientists can distinguish genuine causal relationships between variables (from mere correlations) by way of experimental interventions (cf. Thagard 1999, chs. 7–8). From this perspective, pharmacological drugs can be viewed as facilitating the generation and formulation of causal hypotheses by providing a means of manipulating variables (e.g., neurobiological variables) that are causally relevant to the appearance of mental disorders.

A related but distinct experimental function of pharmacological drugs is to aid in the testing and confirmation of neurobiological theories. In this epistemic role, pharmacological interventions provide a crucial source of evidence for believing a neurobiological theory, or conversely, reasons for rejecting or revising a theory. For example, the revised dopamine hypothesis that maintains that schizophrenia is caused by a dysregulation of dopamine implies at least two sub-theses:

1. The positive (psychotic) symptoms of schizophrenia are caused by excessive dopamine activity in the mesolimbic pathway.
2. The negative symptoms of schizophrenia are caused by deficient dopamine activity in the mesocortical pathway (especially the prefrontal cortex).

Both of these sub-theses are supported by multiple lines of pharmacological research. For example, sub-thesis (1) is primarily supported by the findings that: (i) antipsychotic drugs that decrease dopamine activity in the mesolimbic pathway can alleviate positive symptoms, (ii) the antipsychotic effect of such drugs is directly correlated with dopamine blockade strength, (iii) typical antipsychotic drugs exert their influence by blocking D_2 dopamine receptors, and (iv) dopamine agonists that increase dopamine activity in the mesolimbic pathway can induce positive symptoms. Taken together, these various pharmacological findings constitute cogent evidence for believing sub-thesis (1).

The way in which pharmacological interventions aid in the confirmation of a neurobiological hypothesis is amenable to philosophical analyses that suggest that a hypothesis is better supported by evidence when multiple lines of independent research converge upon a unified hypothesis (e.g., see Wimsatt 1981, 2007, ch. 4; Hacking 1981; Franklin and Howson 1984; Culp 1994, 1995; Wylie 2002, ch. 14; Chang 2004, ch. 1; Staley 2004; Stegenga 2009; Soler et al. 2012). These analyses maintain that a scientific hypothesis or theory is "robust" (i.e., well-confirmed) when multiple lines of (at least partially) independent research all point to a common result. The revised dopamine hypothesis of schizophrenia is robust insofar as multiple lines of independent research support the theory that schizophrenia is caused by a dysregulation of dopamine in the mesolimbic and mesocortical systems. In this regard, it is important to state that pharmacological interventions only constitute one important part of a larger assemblage of research that contributes to the confirmation of a theory. For example, sub-thesis (2) of the dopamine hypothesis is supported by the findings that: (i) typical antipsychotic drugs, which decrease dopamine activity in the prefrontal cortex, exacerbate negative symptoms and cause cognitive impairment, (ii) atypical antipsychotic drugs, which increase dopamine activity in the prefrontal cortex, can alleviate negative symptoms, (iii) NMDA antagonists, which depress dopamine activity in the prefrontal cortex, cause cognitive impairment, (iv) the prefrontal cortex plays a role in speech, decision making, and goal-directed behaviors, which are all disrupted in schizophrenia, (v) cognitive impairment is associated deficient dopamine activity in the prefrontal cortex, (vi) schizophrenic patients perform poorly on cognitive tasks designed to measure functions promoted by the prefrontal region, and (vii) brain imaging studies demonstrate that schizophrenic patients fail to show activation in the dorsal prefrontal cortex while performing cognitive tasks (Kring et al. 2007, pp. 366–367; Carlson 2008, p. 466–467). Within this research, (i)–(iii) are obtained through interventions with pharmacological drugs, whereas (iv)–(vii) are obtained using alternative research methods (e.g., brain imaging studies, cognitive task studies). Similarly, the serotonin hypothesis of depression is supported by various pharmacological interventions, but it is also supported by research adopting alternative research methods (e.g., brain-imaging studies, post-mortem studies, tryptophan depletion studies). This clarifies the sense in which pharmacological interventions play an important—but only partial—role in facilitating the testing and confirmation of neurobiological theories of mental disorders (cf. Bechtel 2008, pp. 34–39).

An especially valuable epistemic role that pharmacological interventions play in psychiatric research is to promote the refinement, elaboration, and revision of neurobiological theories. In the development of neurobiological theories of schizophrenia and depression, pharmacological drugs played a central role in the elaboration and expansion of these theories. In this process, researchers used the known causal effects of various drugs to revise and refine neurobiological theories (e.g., the revision of the monoamine hypothesis to the serotonin hypothesis of depression). Moreover, knowledge about the different clinical profiles of various drugs—in conjunction with knowledge about different neurotransmitter systems in the brain—allowed researchers to identify distinct neurobiological causes for

different symptoms of mental disorders (e.g., the positive and negative symptoms of schizophrenia). An important technique that researchers utilized to gain such knowledge was the comparison of drugs with clinical profiles that varied in slight ways (e.g., having a weaker serotonin blockade effect, having a higher affinity for D_2 receptors), which allowed for causal inferences to be drawn based on the differential response of patients to such drugs.

The way in which pharmacological interventions facilitate the refinement and revision of neurobiological theories of mental disorders highlights the dynamic and interactive relationship between clinical contexts (applied science) and research contexts (pure science) in psychiatry. While pharmacological research is motivated primarily to design better pharmacological treatments in clinical contexts (e.g., creating drugs with fewer unwanted side-effects), the drugs that are developed often play a crucial role in assisting researchers to expand and revise existing neurobiological theories of mental disorders in research contexts. Martin Carrier (2004a, 2010) has argued that the aims of applied science (viz., pragmatic control)—which are embedded in a particular context of interests, values, and practical problems—do not necessarily compromise the aims of pure science (viz., knowledge acquisition). Moreover, he suggests that innovative discoveries in pure science often arise through applied research projects, which is a process he calls *application innovation* (Carrier 2004a, b, 2010). The ways in which neurobiological theories of mental disorders have been expanded and revised through applied research in pharmacology represents a particularly salient example of application innovation. Conversely, theoretical innovations in neurobiological research often feed back into applied contexts to facilitate the development of better pharmacological treatments (Thagard 2003, 2008). This highlights the manner in which applied and pure contexts in psychiatry stand in an interactive and complementary relationship.

27.5 Conclusion

This paper examined the ways in which pharmacological interventions with psychiatric patients have played a central role in the formulation, testing, and elaboration of neurobiological theories of schizophrenia and depression. In this process, pharmacological drugs function as experimental instruments that allow researchers to draw causal inferences about the neural pathways and activities responsible for the psychological and behavioral signs of mental disorders (e.g., delusions, feelings of sadness, cognitive impairment). This analysis also emphasized how innovative pharmacological developments in clinical contexts (i.e., in the development of pharmacological treatments for mental disorders) serve to further knowledge in research contexts (i.e., in the evolution of neurobiological theories of mental disorders). While the knowledge acquired in this process is not known with certainty or immune from revision, pharmacological interventions with clinical populations of psychiatric patients have provided an indispensable source of evidence in the articulation of modern biological theories of mental disorders.

Seen from a broader historical perspective, pharmacological interventions with psychiatric patients paved the path towards a physical understanding of mental disorders. In particular, the psychopharmacology revolution contributed to the downfall of psychoanalytic and dualist theories of psychopathology in the 1960s and 1970s, and it set the foundations for the emerging biological approach to psychiatry that would eventually supplant psychoanalysis. The psychopharmacological revolution—through its influence on neurobiology—also contributed to the idea that many psychological constructs examined by psychiatrists that were thought to be ineliminably "mental" (e.g., 'delusion,' 'sadness') could be explained and understood in physical terms. While this does not imply that social and psychological variables are unimportant in the study of psychopathology or the treatment of mental disorders, it does suggest that the attempt to study psychopathology purely at the level of a non-physical "mental realm" that is inaccessible by physical means is unlikely to promote progress in psychiatry or in the treatment of mental disorders.

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Chapter 28
Genetics of the Mind and Brain Disorders

Tatiana Popovitchenko and Mladen-Roko Rasin

Abstract In stark comparison to the elegance of mathematics, biology lies right at the edges of relative chaos, evading understanding at every turn often refusing to conform to theoretical hypotheses. To a biologist, this is the root of elegance. In particular, the irony of not being able to understand the mind remains enticing to both professional and amateur neuroscientists. Nevertheless, it would behoove the greater understanding of the mind and the disorders that afflict it to establish physical patterns. These can then be used in predicting the treatments that would be most effective.

Understanding of a system can begin with an understanding of its parts in a bottom-up approach. In the system of the mind, similar to any biological system, the "parts" can be the individual cells or organelles that make up a cell. We can also consider the fundamental parts the brain as genes in a code of deoxyribonucleic acid (DNA). A gene is the functional unit of heredity. The study of genetics encompasses both the structure and transmission of genes as well as the individual and combinatorial contributions of genes to development.

When the entirety of human DNA was sequenced by the Human Genome Project in 2003, the end of all genetic disorders, including the ones afflicting the brain, was predicted to be near. Despite the rapid increase in knowledge regarding the workings of genes, questions remain and cures are scarce to this day. While this is due in large part to the unpredicted complexity of gene networks, it is also reflective of the intricacy of the central nervous system (CNS). The CNS itself is a complicated system of networks that are spatiotemporally controlled and kept in balance by specific cell-to-cell contacts, neuromodulators, and electrical relays.

Yet, what is known today about disorders of the mind, and in particular the genetics behind them, provides many rich examples which we can explore to gain a deeper understanding of both of these topics. In this chapter, we will initially

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provide a perfunctory overview of genetics, and then delve into further detail by discussing two broad categories of genetic mind disorders: monogenic and polygenic. Throughout we will detail the biological forces driving both normal and abnormal neurodevelopment.

Keywords Physics • Mind • Neurodevelopment • Genetics • Monogenic • Polygenic • Fragile-X • Huntington's • Schizophrenia

28.1 Introduction

28.1.1 The Gene: A Driver of Development

Prior to a consideration of genetics in the brain, a short primer on the anatomy of a gene is necessary (Fig. 28.1). A **gene** is composed of deoxyribonucleic acid, DNA, which consists of four phosphate-bases linked by a sugar backbone: adenine, cytosine, guanine, and thymine (Fig. 28.1, left box). The region around the gene is known as the **locus** (also see Figs. 28.2 and 28.3, boxed regions). Genes are known to be composed of, in order from 5′ to 3′: a promoter, a 5′ untranslated region (UTR), a combination of exons and introns, a 3′ untranslated region (UTR), and a termination sequence recognized by RNA polymerase (Fig. 28.1, right box). DNA will be transcribed by RNA polymerase from the template strand (opposite the coding strand) into ribonucleic acid (RNA) or the pre-mRNA transcript. This is done base for base except for thymidine which is replaced with uracil in RNA (adenine in DNA paired to uracil in RNA). Introns are spliced out of the pre-mRNA and a 5′ cap and a 3′ poly-A tail are added to form the mature mRNA. Non-UTR Exons, in 5′ to 3′ sequential order, make up the coding region of a gene, or, the part of the gene that instructs protein synthesis. Coding of RNA into protein relies upon codons being recognized by the ribosome and matched with amino acids. Codons

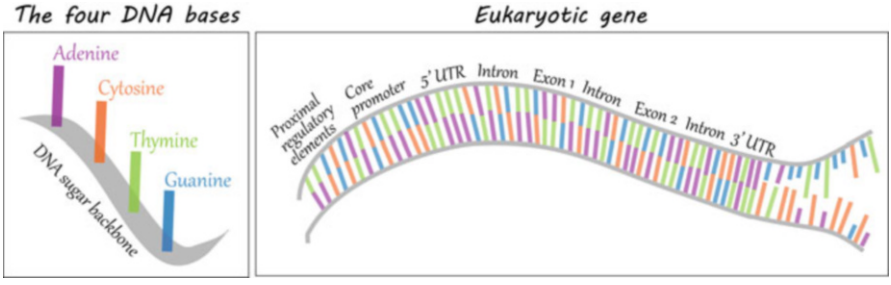

Fig. 28.1 The simplified anatomy of a eukaryotic gene is illustrated on the *right*. The four DNA bases are represented on the double stranded molecule according to standard base-pairing rules: adenine (*purple*) to thymine (*green*) and cytosine (*orange*) to guanine (*blue*)

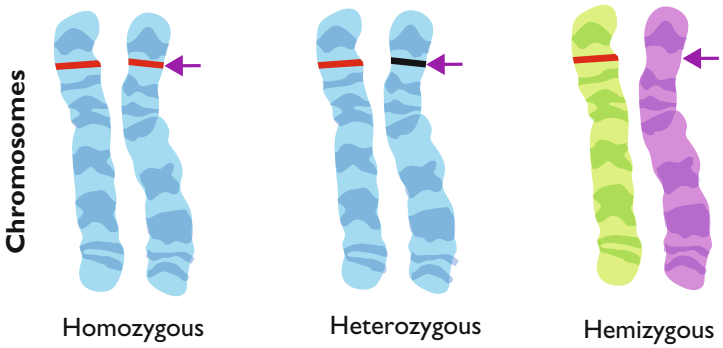

Fig. 28.2 Genotype variation is depicted at a gene locus (*red* and *black bars* indicated by the *purple arrow*). A homozygous locus will carry the same allele on both chromatids. The heterozygous variant has a different allele at the same locus (*black bar*). Sex chromosomes can vary in a hemizygous manner; the X chromosome (*green*) is different from the Y (*purple*), so one copy is present on the X and not on the Y, (lack of bar)

are composed of three nucleotides and are redundant to several amino acids; for example, the two codons UCA and UGC in mRNA will both cause the addition of a serine on the growing poly-peptide chain. This is known as codon **degeneracy**.

Genes are located on chromosomes (Fig. 28.2). **Diploid** organisms, such as humans, have two versions of each homologous chromosome called sister chromatids. One is inherited from the mother and the other from the father. With two versions of each chromosome come two versions of each gene called **alleles**. The combination of two particular alleles yields an individual's **genotype** (Fig. 28.2). An individual can be **homozygous** at an allele, meaning they have two copies of the same allele, or **heterozygous**, meaning they have two different versions of a gene. Without diverse alleles, humans would be homozygous for all genes, and this has been shown to be damaging on the organismal level as well as on the molecular level (e.g. through loss of heterozygosity (LOH) in cancer). Indeed, heterozygotes have an advantage over homozygotes at certain loci, for example, individuals that are heterozygous at the critical major histocompatibility locus (MHC). Have an advantage over homozygotes in their immune response (Penn et al. 2002; Sellis et al. 2011).

Different alleles arise because of changes to DNA through mutations, chromosomal rearrangements, and transposition events. Mutation events result in deletions, duplications and/or changes to single or multiple bases. Single base changes are sometimes called single nucleotide polymorphisms (SNPs, as seen in Fig. 28.3). The location and type of change will determine whether or not the change is noticed. For example, if a deletion or SNP occurs in an exon, it may be translated into protein; whereas a change in an intron is less noticeable generally, barring a mutation in an intronic regulatory region. Additionally, changes can occur in UTR regions and have equal chances of being benign or detrimental to the regulation of gene expression.

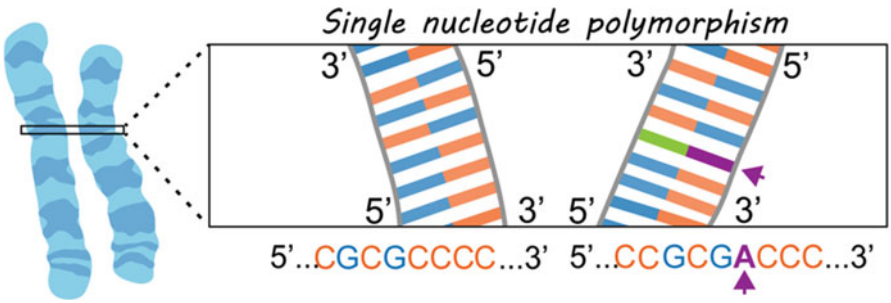

Fig. 28.3 A SNP has occurred at the base indicated by the *purple arrow*, nucleotide change is indicated *below box*. The chromosome is composed of two sister chromatids. Each chromatid is composed of a continuous strand of DNA, containing single alleles of the entire genome, and is complemented by an almost identical strand in the other chromatid. The two antiparallel strands in each chromatid (5′→3′ and 3′→5′) both contain genetic information. When comparing the chromatids, we can see a SNP (cytosine→adenine) has occurred in one in the chromatid on the right (*purple arrows*). This results in the generation of an allele unique from that contained on its sister chromatid. Thus, the genotype at this locus is heterozygous

This depends on whether or not the change occurs in a cis-regulatory element, which can be a protein or micro-RNA (miRNA) binding site. Single bases can be mutated as transversions (purine to pyrimidine) or transitions (purine to purine, A←→G, or pyrimidine to pyrimidine, C←→T). Additionally, the nature of the change will matter. If the sequence TCA is mutated to TCG, since both codons code for serine, no change will occur in final protein product. These kinds of mutations are called missense mutations. However, if the TCA codon is mutated to TGA, a so-called "stop" codon, the result will be a premature stop in the protein. This is known as a nonsense mutation. If the stop occurs within 50-55 nucleotides of the last exon, of the transcript, likely no major change is occurring; opposed to an early termination in the beginning of the protein, 50-55 nucleotides after the start of translation, which is more likely to have an impact on protein function. In most cases though, premature stops trigger a process called nonsense mediated decay (NMD) and the mutated transcript is never translated.

Other forms of mutation events are chromosomal rearrangements and transpositions. Chromosomal rearrangements include: (1) **translocation,** which is the break of a chromosome and then reattachment to a different one; (2) an **inversion,** which is a break that is reattached to the same chromosome, but in the other direction than it was originally attached; (3) **chromosome duplications**; (4) total loss of a piece of chromosome of or the entire chromosome (**aneuploidy**). Transposition events are caused by **transposons,** so called "jumping genes," and are common elements in humans. Briefly, transposable elements (TEs) can either excise themselves (autonomous TEs), or be excised (nonautonomous TEs), and reinsert into a different region of the genome. Again, where the reinsertion occurs will determine its effect – in the middle of an exon could be terrible for the fate of the protein while in a region between genes (intergenic region) could possibly be less so.

Mutations dictate the fitness of the individual and over time the evolution of the species. Importantly, genetic mutation is one of the only invariant forces in mind disorders, and can thus be contemplated in the context of Gauge theory. The human mutation rate at a single nucleotide has recently been approximated to 1.6×10^{-8} per generation (Lipson et al. 2015), which translates into about 33 SNPs per human genome. While the mutation rate itself varies from individual to individual, and the given value is an average calculation, the forces that introduce change into the genome seem to be more invariant than the genome itself.

28.1.2 Characteristics and Presentation of Genetic Disorders

Depending on interactions with other molecular partners, expression of the gene itself, and interaction of the organism with their environment, harmful alleles can cause disease at different rates (**penetrance**) and in different degrees of harmfulness (**expressivity**). Penetrance is particularly interesting from an epidemiological standpoint. For example, if an abnormal allele is observed to occur at a 10% penetrance in the population, 10% of individuals are at risk to develop that disorder. Gene penetrance has important implications for the analysis of **phenotype**, a consistent physical or behavioral manifestation of a disorder. Indeed, many abnormal genes confer a risk for disease. For example, if a child has a susceptibility gene for addiction and is raised in a family free of exposure to an addictive agent, addiction may not have a chance to present or develop. Though, even in a normal enviornment, the genetic forces can still arise in disease seem to be strong too based on recent studies (Agrawal and Lynskey 2008).

In order for the phenotype of a disorder to be understood, it must be studied on multiple levels. Mental health professionals define phenotypes by what they can observe in the patient, including the physical and behavioral manifestations of a disease. Clinical and basic research scientists will seek for a phenotype within the patient's brain's structure and molecular makeup: what brain regions are affected, which cells are malformed, and what molecular mechanisms have gone awry. The combination of both approaches allows for a distinct behavioral phenotypes to be characteristic of distinct neurodevelopmental disorders. For example, Down's Syndrome has a clearly defined chromosomal abnormality, an extra copy of chromosome 21, coupled to a multi-phenotype profiles, including intellectual disability. Collectively, today's stand is that people with a certain genetic make-up will have unique organismal and behavioral characteristics. While phenotypes can be analyzed on any level, from cellular to organismal, the diagnosis of brain disorders mainly depends on the conclusion of a human being because of the lack of laboratory tests specific for each disorder. This highlights the source of variability in psychiatric diagnosis as well as the need for rigorous standards and open communication amongst biomedical researchers.

28.1.3 Genes to Development

Our genomes ensure that the development of our systems proceed according to intrinsic programming. Cells progressively acquire their fates and go from naiveté to maturity in their journey from stem cells to their final differentiated state. Within this journey, there are many examples of symmetry and importantly of symmetry breaking.

One such example is the development of distinct cell subtypes within the neocortex. The first in the lineage of neocortical neural stem cells are called neuroepithelial cells. These cells will divide symmetrically to increase the pool of progenitors. Neuroepithelial cells will eventually be replaced by another type of neural stem cell called radial glia. Radial glia divide asymmetrically to give rise to themselves and to either an intermediate progenitor cell or a post-mitotic neuron. Ultimately, radial glia will sequentially give rise to distinct subpopulations of highly polarized projection neurons, astrocytes, and oligodendrocytes. Morphologically, radial glia (RG) have a fairly symmetrical structure and are an example of a bipolar cell. They consist of a cell body and two processes: one attached to the pial (basal) surface of the neocortex and the other to the ventricular zone surface (Fig. 28.4a) (Götz and Huttner 2005; Kwan et al. 2012).

After neurons are born from radial glia, quickly the bipolar symmetry is broken. The radial glial process dictates migratory path of the immature neuron into the

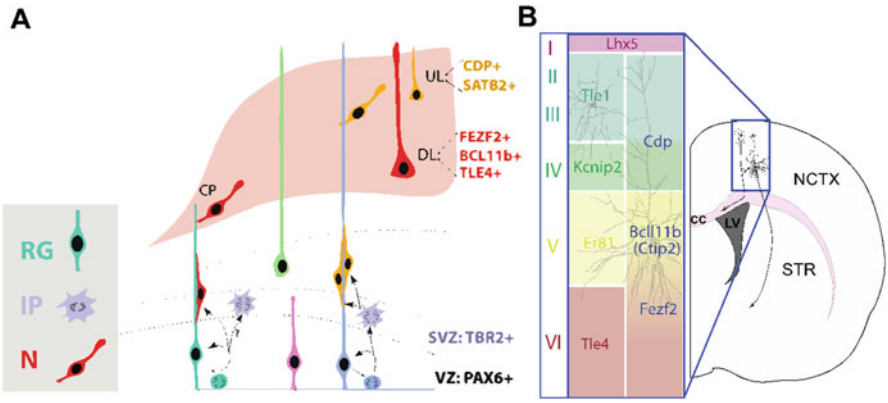

Fig. 28.4 Murine neocortical development. (**a**) Neural stem cells proliferate in the VZ and then the SVZ. Relevant genes expressed in region or cell type indicated on *right*. Adult neocortical six-layered lamination is detailed in (**b**) in the enlarged portion of the neocortex, boxed in blue, with distinct UL (layers 2–4) and DL (layers 5–6). Distinct neuronal dendritic morphologies for UL and DL are indicated, not to scale. Layers can be differentiated with labelling of transcription factors expressed in the cells of that layer, listed to the *left* of the box, as well as by transcription factors that span layers, leftmost labellings. The CC, composed of axons of intracortically projecting neurons, is highlighted in *pink*. Subcortically projecting axons are in *gray* (*arrowhead*). LV shown in *dark grey* directly under the CC. (*RG* radial glia, *IP* intermediate progenitor, *N* neuron, *VZ* ventricular zone, *SVZ* subventricular zone, *CP* cortical plate, *UL* upper layer, *DL* deep layer, *CC* corpus callosum, *LV* lateral ventricle, *STR* striatum, and *NCTX* neocortex)

cortical plate. Upon placement within the cortical plate, the leading process of the immature neuron will branch out into dendrites, while the trailing process will develop into an axon (Noctor et al. 2001). Unlike the radial glia processes, which are bipolar, the neuronal process will give rise to the multipolar and asymmetrical morphology of a mature neuron, and at each stage this morphology will be unique for each subtype being generated at that time and place (Fig. 28.4b). This kind of symmetry breaking is a well-stereotyped phenomena conserved through evolution (Lee et al. 2015).

Once a mature and highly-polarized morphology is achieved during development, neurons will incorporate into circuits and intermingle with glia and blood vessels to form a functional central nervous system. Though symmetry breaking occurred on the cellular level, one can imagine that symmetry is maintained on a larger scale systemically; much like asymmetrical puzzle pieces coming together to achieve functional symmetry. This may be achieved as neurons synapse via mostly axon-dendrite, and sometimes axon-axon or dendrite-dendrite, connections onto each other, while in parallel other cell types populate the neocortex, instilling a balance in the system as a whole. Further consideration of these balancing forces, especially the additional layer of regulation that extracellular signaling will add, includes the consideration of the protomap hypothesis (Rakic 1988).

Rigorous molecular biology has revealed the neocortex to be an excellent model for the adoption of heterogenous fates that incorporate to form a functional central nervous system. The molecular identities of many cells in the neocortex have been well-characterized and can be understood to define subpopulations. In particular, subpopulations of projection neurons may have functional homogeneity (Fig. 28.4). Additionally, there are distinct transcriptional programs with expression relatively restricted to a specific neocortical layer (see examples in Fig. 28.4b) (Molyneaux et al. 2007). It should be noted that many molecules have expression patterns that range several layers, which gives rise to combinatorial outcomes that increase the potential fates that can be acquired (Ravasi et al. 2010).

Many efforts at creating exhaustive transcriptomes of the neocortex have been undertaken and these studies reveal that molecular identities in fact do strongly predict function (Fig. 28.5a). While each subpopulation of neurons potentially has its own molecular characterization, we can also consider the broader expression profiles of single genes within the neocortex and the functional transcriptional networks they fit into. For example, those genes destined to be expressed in subcortically projecting neocortical neurons (Layers 5–6) will peak earlier than those to be expressed within intracortically projecting neurons (Layers 2–4) (Fig. 28.5a). These programs additionally highlight "inside-out" formation of the neocortex, deeper layer subcortically projecting neuronss are born before more superficial intracortically projecting ones.

Transcriptional profiling has revealed that while some genes, such as *FMR1*, have fairly consistent expression levels throughout life, others are high during prenatal development (*SATB2*, transcription factor), and still others peak during post-natal stages (*HTR3B*, serotonin receptor, Fig. 28.5b) (Kang et al. 2011). Both of these events, structural framework and specific gene expression profiles, are intriguing in the context of disease development. For example, studies of minicolumnar devel-

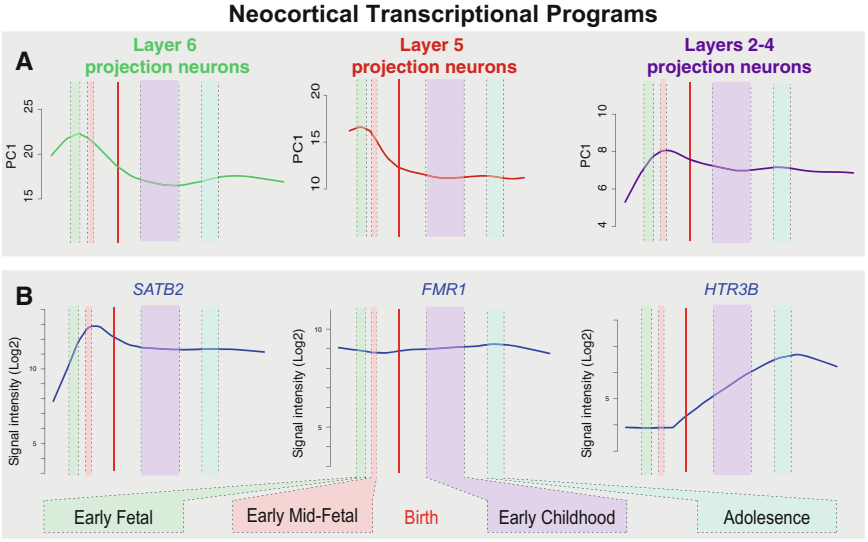

Fig. 28.5 Transcriptional Expression Patterns in Development (**a**) Certain genes will peak earlier, like those involved in Layer 6 and 5 neuron differentiation, others peak later such as those involved in upper layer formation. In (**b**), expression profiles shown for three genes: SATB2, FMR1, and HTR3B in the neocortex. These are representative genes for different patterns during development, i.e. high during fetal stages (SATB2), constantly maintained throughout life (FMR1), and peaks during adolescence (HTR3B). *Blue lines* are relative expression levels within the neocortex through time. The *red line* on each graph indicates birth. Generated using data freely available on the Human Brain Transcriptome Atlas (http://hbatlas.org/)

opment in autism have shown decreased space between minicolumns (Casanova et al. 2006). This suggests aberration during neuronal migration and positioning, which occurs in the prenatal stages of early fetal and early-mid fetal development (Fig. 28.5a). Meanwhile, the same type of measurement in brains of schizophrenics reveals no such structural abnormalities though cognitive decline is a common feature of both disorders (Casanova et al. 2008; Opris and Casanova 2014; Casanova et al. 2007).

A concrete mechanism of action has not been outlined for schizophrenia and given its polygenic origins, such an outline is unlikely. Onset of the disease correlates with genes that peak during the early childhood and adolescent developmental periods, i.e. HTR3B (Fig. 28.5b), including monoamine signaling systems (Opris and Casanova 2014; Casanova et al. 2007). Research has demonstrated that monoamine receptors have notably different functionality during development and during adulthood (Donaldson et al. 2013), further demonstrating temporal specificity of genetic programs. Moreover, a single receptor (5H1BR) can modulate distinct behaviors, such as impulsivity and aggression, through distinct pathways (Nautiyal et al. 2015). Insights from transcriptomic profiling underscore the necessity of tightly-regulated programs to produce symmetry throughout life.

If we consider a wild-type laminar pattern of the neocortex as one example of a functional symmetry, with all of its balancing forces, then the breaking of this

symmetry would result in a disruption of the neocortical processing powers. Such breaking does occur in nature and it has been hypothesized to be symptomatic of many cognitive and motor behavior disorders, including autism spectrum disorders (ASDs) (Hutsler et al. 2007; Stoner et al. 2014) and schizophrenia (Lewis and Levitt 2002; Behan et al. 2009). These and other studies underscore the delicate complexity of the neocortex and the forces that must constantly act throughout life to maintain its function. Further discussion of the topic can be found in other chapters of this book.

28.2 Monogenic and Polygenic Sources of Brain Disorder

Monogenic disorders are caused by the mutation of one gene. Intuitively then, **polygenic disorders** are ones caused by the interactions of multiple genes that have been mutated (Table 28.1).

Both monogenic and polygenic mind disorders have diverse temporal presentation; time is further discussed in Chap. 2 of this book as a possible Lagrangian. ASD and schizophrenia are polygenic disorders that manifest relatively early, between 2–6 and 18–30 in most individuals, respectively. On the other hand, disorders such as Huntington's, Alzheimer's, and Parkinson's, are typically diagnosed in the later stages of life, well past the third decade. Two relatively well-understood brain disorders are Fragile X syndrome, intellectual disability caused by a mutated Fmr1 gene, and Huntington's Disease, neurodegeneration caused by the mutation of the Huntingtin (HTT) gene. These are both monogenic disorders, and can both be caused by nucleotide-repeat mutations. They will serve as examples in the following sections of this chapter of how genetics influences the brain and its phenotypes, with a mention of schizophrenia as an example of a polygenic disorder.

Table 28.1 Monogenic and Polygenic disorders are shown

Monogenic		Polygenic	
Disease	*Gene*	*Disease*	*Genes*
Huntington's	HTT	Alzheimer's	APOE-e(2,3,4), APP, PS-1, PS-2
Fragile X	FXS	Schizophrenia	C4, COMT, DISC-1, NRG-1, 22q11.2
Neurofibromatosis	NF1, NF2	Parkinson's	LRRK2, PARK2, PARK7, PINK1, SNCA
Angelman	UBE3A	Autism	FOXP2, REELIN, SHANK3, PSD-95, NLGN-(3,4)
Rett	MECP2	Epilepsy	SCN1A, KCNC1,STX1B, ANO3, DNM-1
Tay-Sachs	HEXA	ALS	C9orf72, SOD1, TARDBP, FUS
Wilson's	ATP7B		
Tuberous Sclerosis	TSC1, TSC2		

Causative genes are indicated for monogenic disorders. Highly associated genes are indicated for polygenic disorders, though the lists are not exhaustive

28.2.1 Fragile-X Syndrome

Fragile X syndrome is the result of a mutated Fmr1 gene. Phenotypically, it results in intellectual disability, altered facial development, macroorchidism, as well as behaviors similar to those seen in autism. It disproportionally affects boys, about 2:1 (The Centers for Disease Control (CDC), 1 in 8000 affected males versus 1 in 4000 affected females.), most likely because it is an **X-linked** disorder. That is, the Fmr1 gene is located on the X chromosome. Males inherit an X chromosome from their mothers and a Y chromosome from their fathers; females inherit an X chromosome from both parents.

While this may seem unintuitive, as females have double the dose of the X chromosome after gene transmission, each female cell discourages the expression of one of these X chromosomes (seemingly randomly selected and established early-on in development) through a process called **X-inactivation.**

The classic visual example of X-inactivation is the heterozygous calico cat, all of which are female and have large patches of orange, black, and white color on their coats. Coat color is coded for on the X chromosomes of cats, with versions of black, orange, and a separate gene that interferes to form white. Each patch of color corresponds to a patch of cells derived from the same progenitor. That progenitor cell made a decision that turned the inactivated X into a **Barr body** by expression of the **X-Ist** RNA and its antisense **T-Six**. Barr bodies are composed of highly condensed DNA called heterochromatin, while normal chromosomes are composed of alternating regions of heterochromatic and euchromatic DNA, which has an open structure accessible to transcription factors of the cell (Depicted on chromosome in Fig. 28.2, lighter regions). With regards to Fragile X, this means that unless both the mother and the father are carriers for the *Fmr1* gene mutation, each cell in the female offspring has a 50% chance to be protected by the expression of the non-mutated chromosome if the mutated Fmr1 gene is in the Barr body. While X-inactivation accounts for most of the male-female difference in Fragile X presentation, it is not sufficient to form a complete understanding. Gender differences thus present a force of variation in the understanding of mind disorders.

Total loss of the *Fmr1* gene, a so-called **knockout**, is sufficient to cause a Fragile X phenotype in mice. In humans, several point mutations both in the untranslated regions as well as the coding region of the *Fmr1* gene are sufficient to cause intellectual disability such as that seen in Fragile X (Suhl et al. 2015). However, the most prevalent form of gene inactivation is not a full deletion, but rather, methylation of the *Fmr1* gene caused by an expanded trinucleotide region. The implicated trinucleotide is a CCG-repeat (also called CGG, when read in the opposite direction). Methylation of eukaryotic DNA occurs on cytosine and results in a conversion to 5-methylcytosine. It is a common form of gene repression (Fig. 28.6).

Trinucletoide CCG-repeats are found in the 5′UTR of the *Fmr1* gene in even unaffected individuals. The most common variant of Fmr1 was found to contain thirty CCG repeats in the 5′ UTR. If a variant has less than fifty-three repeats, it

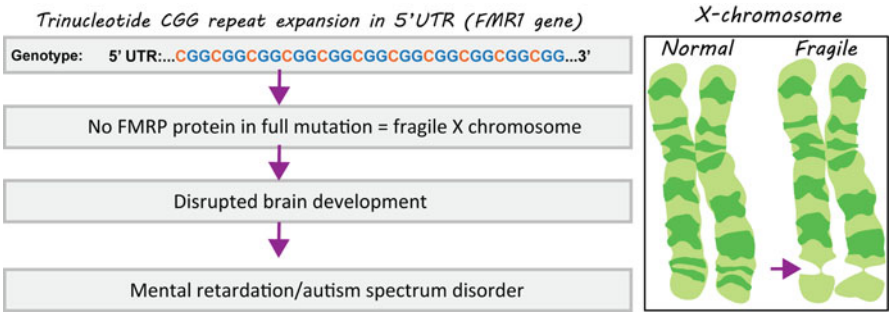

Fig. 28.6 Trinucleotide repeat expansion in Fragile X Syndrome is shown. The Fragile X chromosome is indicated in the *box* on the *right*. Progression of the disease from the expansion is shown in the *boxes* on the *left*

is considered **wild-type**, or, the most common version. Above 53 and below 200 repeats is known as a premutation allele. Above two-hundred is sufficient to activate methylation of the gene and as a result repress expression of it (Eichler et al. 1994). Both the premutation and the Fragile-X mutation differ from the wild-type. It is important to note that the classification of something as mutant or wild-type is not indicative of pathology, but rather of the rate of occurrence within a population-with so-called wild type alleles forming the majority of the allelic pool in a given population.

Premutation levels of the CCG-repeats are themselves risk-factors for carriers. Female premutation carriers are at risk for primary ovarian insufficiency (POI). This condition results in cessation of menses approximately 5 years earlier than average and occurs in 20% of female premutation carriers (Sherman 2000). The primary risk of the premutation is inheritance and further replication in the next generation. The expansion of repeats will occur and turn a premutation number of repeats into a Fragile-X disease associated number of repeats. The repeats are likely the result of polymerase slippage during replication (Richards and Sutherland 1994). The replication machinery is itself sensitive to repetitive sequences on both the **leading** and **lagging** strands. Replication of the lagging strand results in a series of **Okazaki fragments**, gaps between which must be repaired by the polymerase machinery. This is one source of expansion of the CCG-repeats. Additionally, non-disease associated variants contain periodic AGG-repeats, the presence of which have been suspected to minimize the risk of a expansion of the CCG-only regions implicit in FXS development (Jin and Warren 2000). CCG-repeats in the Fmr1 gene are predominantly found in the 5′- untranslated region (**UTR**). UTRs are parts of genes in the mRNA transcripts (Fig. 28.1) and are found at either end of the coding region, the 5′ end and the 3′ end. They are excluded from the final protein product, but have been found to contain important regulatory sites that can dictate translation of the coding region. In the case of Fmr1, the coding region is translated to form the Fragile X mental retardation protein (Fmrp). Fmrp has been found to be most highly expressed in the brain and testis.

Fmrp is a type of protein that has the ability to bind RNAs, thusly an **RNA-binding protein (RBP).** RNA-regulation by RBPs is similar to DNA-regulation by transcription factors. Transcription factors bind to sites in the enhancer/suppressor or promoter regions (Fig. 28.1). RBPs bind to binding sites in the UTRs of genes. These sites are collectively known as regulatory regions. With regards to transcription, this form of gene activation highlights an important aspect of eukaryotic biology. In prokaryotes, genes are constantly transcribed and translated, unless a metabolite or other signal represses transcription. Meanwhile, eukaryotic genes rest in a repressed state until activated by extracellular signals or regulatory factors like transcription factors.

Fmrp binds mRNA transcripts and represses them from encountering the ribosome and being translated into protein. Temporal regulation of this kind is important for precise expression of a transcript only when it is needed, such as at a synapse and in response to glutamatergic signaling via mGlu1 and mGlu5 (metabotropic glutamate receptors). Indeed, Fmrp in neurons plays an important role in neurotransmission through the binding of its target proteins.

In exploring the biology of Fragile X syndrome, the importance of genetic threshold becomes clear. Evolution is often thought of in terms of fitness and what mutations enhance or suppress one's ability to transmit their genes to the next generation. Yet, mutations occur mostly indiscriminately along the genome, including in exons, regulatory regions, and intergenic regions and can indeed be beneficial, harmful, or neutral. Theoretically, harmful mutations result in either early cessation of development and involuntary abortion or damage the fitness of the individual. Beneficial mutations would increase fitness. What about neutral mutations? Seemingly, the first repeat of the CCG trinucleotide sequence was a neutral mutation, and indeed its replication fifty more times was not enough to warrant negative effects on the individual. Yet, once it hit a certain threshold, fitness began to be challenged through POI in females and ataxia in both genders; the same replication event a hundred and fifty more times results in a very harmful mutation and a full-blown pathological outcome.

28.2.2 Huntington's Disease

Fragile X is one example of a disease caused by a trinucleotide repeat expansion. Of the twenty disorders caused by expansion of repeats, another well-known monogenic example is Huntington's Disease (HD). The trinucleotide expansion diseases are grouped into those that occur in non-coding regions, such as FXS, and those that occur in coding regions, such as HD. Other examples of CAG/polyglutamine repeat diseases like HD are spinocerebellar ataxia and spinal and bulbar muscular atrophy. All affect the central nervous system, are slowly progressive, are dominant, and show a correlation between increasing expansion size and disease severity. The CAG/polyglutamine repeats, as in the FXS CGG expansion, can expand when

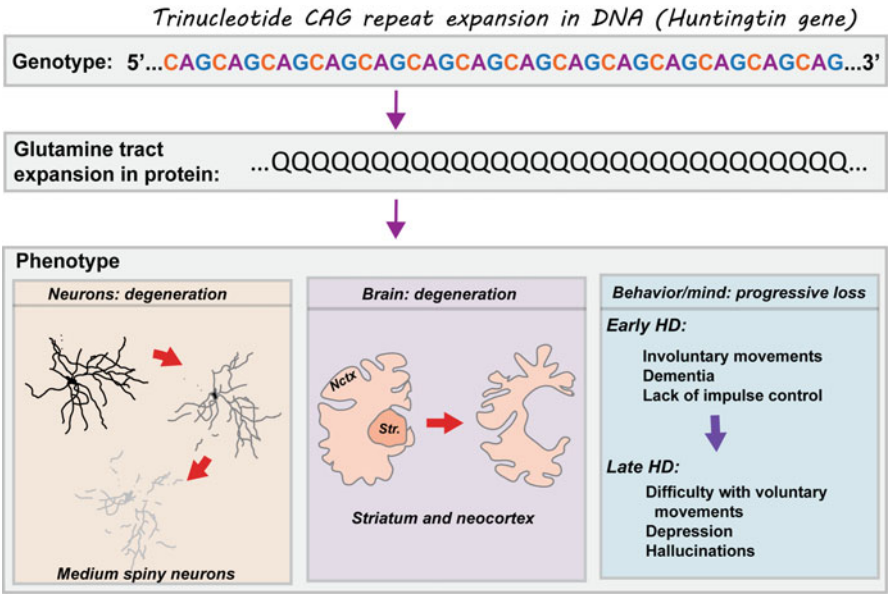

Fig. 28.7 Genotype versus phenotype in Huntington's Disease. HD is caused by a trinucleotide repeat expansion. This would be seen in the genotype (*top grey box*), which molecularly results in a glutamine (PolyQ) tract. The resultant phenotype is dependent on the level of observation, from cellular (*beige box*), organ (*purple box*), and systemic (*blue*)

transmitted from parent to child, and once a certain threshold is reached, the benign expansion turns pathological (Usdin 2008).

HD is the result of a CAG repeat, which when translated results in a glutamine, polyQ, tract (Illustrated in Fig. 28.7). PolyQ tracts in the N-terminus of the protein, arising from mutation in exon 1, are postulated to undergo post-translational proteolysis and form short aggregates that will accumulate and cause neurotoxicity (Mangiarini et al. 1996; Petersén et al. 2001; Martin et al. 2015; Saudou and Humbert 2016). HD is an **autosomal dominant** disease; the Huntingtin (HTT) gene is located on chromosome 4, an autosome and is inherited dominantly. The **dominant** pattern of inheritance, seen in every generation, is the result of the dominant negative action of the mutant protein on the wild type protein in heterozygotes. Dominant negative mechanisms involve the interference of a mutant version with the wild type one. In HD heterozygotes, the mutant polyQ repeats aggregate both with themselves and with the wild type versions of the gene. The nucleotide expansion is thus a **gain-of-function**, as a new ability not seen in the wild type version is acquired (Saudou and Humbert 2016). By contrast, a **recessive** allele would be masked by the action of a dominant version; the pattern of inheritance would be every other generation.

HD has some similarities to FXS; for example, gender seems to play a role in the inheritance of the disease. Expansion of the trinucleotide repeat is understood

to occur from the male germ line. This is postulated to be the result of more cellular divisions in spermatogenesis versus oogenesis (Keightley 2012). The age of the father at the time of conception is another susceptibility factor in HD, as well as in the general acceleration of the *de novo* mutation rate (Kong et al. 2012). Phenotypically, HD manifests as a triad of symptoms, including progressive movement deterioration, cognitive deficit, and psychiatric presentations of irritability and depression. It manifests much later than FXS with a disease onset between 25 and 55 years (median age is 38); although some juvenile cases exist which notably led to the discovery of the inverse correlation between repeat number and age of onset (Mangiarini et al. 1996). HD is fatal within 10–20 years after symptom onset.

The Huntingtin (HTT) protein is known to have over 300 interacting partners involved in diverse pathways from cellular dynamics to neurotransmission (Saudou and Humbert 2016). In contrast to Fmr1, expression of HTT is ubiquitous in different tissues. Yet, neurons face the greatest risk during disease progression. Several theories have been posited as to why, including the increased energy demands of the brain. Therein lies the mystery as to what the basis of selective vulnerability at the cellular level is in HD.

The GABAergic medium spiny neurons in the striatum are always the first to succumb to degeneration (Fig. 28.7, phenotype). This is thought to be due to the toxic effects of high dopamine signaling from caudal substantia nigra neurons. Dopamine signaling causes aggregates to form in wild type neurons *in vitro,* whereas in HD, the already energetically run down neurons accelerate the formation of aggregates and add to the neurotoxic load (Petersén et al. 2001). After the death of the striatal neurons, the corticostraital pathways lose their targets and the cortical neurons will degenerate next as a result (Papoutsi et al. 2014).

The reliance on connectivity is an essential concept to understand in neurobiology. Neurons will live and die based on whom they do and do not connect with. This is a theme seen in HD, as well as other neurodegenerative disorders such as Parkinson's Disease (PD). However, circuits are flexible to a degree in a demonstration of compensatory mechanisms. This is one hypothesis as to why diseases like HD and PD can go unnoticed for decades after their cellular onset (Papoutsi et al. 2014). Late-presenting disorders such as HD are an example of the compensatory mechanisms, or tendency towards symmetry under homeostatic mechanisms the genetically programmed brain can undertake (Papoutsi et al. 2014; Morcom and Johnson 2015). One recent hypothesis suggests a degree of resilience to the onset of neurodegenerative conferred by a cognitive reserve; however, this does not affect the severity of the disease once compensation can no longer account for the damage (Barulli and Stern 2013; Papoutsi et al. 2014; Andrews et al. 2015; Morcom and Johnson 2015).

HD is often referred to as the most curable incurable brain disorder. This is evidenced by the foundational and prolific amount of research surrounding HD. In summary, HD is caused by increased number of CAG repeats in the HTT gene on Chromosome 4. Everyone with a large enough repeat expansion (>40) will get HD; everyone with HD has the repeat expansion in HTT. 36–39 CAG repeats in HTT results in lower penetrance and later onset than those with 40+ CAG repeats.

The specific neurons affected in the disease have been elucidated. The medium spiny neurons of the striatum targeting brain region that coordinates movement. The second group of neurons to succumb to degeneration are those in the cerebral cortex that controls cognitive functions. Despite the preponderance of biomedical and mechanistic evidence, no cure exists. This further highlights the necessity of a novel approach in understanding mind disorders; a void that can be filled by an application of gauge theory.

28.2.3 Schizophrenia: Insight into Polygenic Disease

Schizophrenia is the classic example of a disorder that has clear genetic influence and yet not one consistent cause or even phenotype. Schizophrenia is thought to primarily affect neurons of the prefrontal neocortex, a recent structural acquisition in mammals (Rakic 2009). Generally, schizophrenia is characterized by the presence of both positive (hallucinations, delusions) and negative (depression, catatonia) psychiatric symptoms. For years we have known that the prevalence of schizophrenia is 10% in families and 1% in the general population. The identical twin of a schizophrenic patient has a 40–50% risk, suggesting a genetic component to the disorder.

The genetic influence in schizophrenia became clear with the identification of a single gene mutated in three different family studies. In the early 1990s, the Disrupted in Schizophrenia (DISC-1) gene was found to be mutated in family studies. DISC-1 is the result of a translocation of the long arm of chromosome 1 to the short arm of chromosome 11(Blackwood and Muir 2004). In a Golgi-staining study of the DBZ (DISC1-binding zinc finger protein) model, an increased number of spines was observed despite a decrease in total dendritic length in cortical pyramidal neurons (Koyama et al. 2015), creating a structural imbalance.

Schizophrenia risk has also been associated with the mutation of miR-137 (micro RNA 137) (Sullivan et al. 2012). miRs enact genetic silencing, which can take place at the transcriptional (silencing of the initiating transcription factor) or post-transcriptional (silencing of the gene itself) levels. The mechanism by which they operate is very similar to **RNAi** (RNA interference). RNAi refers to the artificial introduction of double-stranded RNA by scientists, but miRs operate as an intrinsic mechanism for gene silencing. Via this mechanism, miR-137 has been found to downregulate several genes, including complexin-1, NSF, and Synaptotagmin-1, and consequently has been implicated in fine-tuning of synaptic formation and plasticity (Siegert et al. 2015). One can imagine how miR-137 may play a protective role in schizophrenia, and when mutated crosses the threshold of pathogenicity.

While discovery of associated genes in case studies can provide insight to a subset of patients, the approach lacks mechanistic insight and broad applicability. Studies of a larger scale have been conducted called **genome wide association studies (GWAS)**. Curiously, the Major Histocompatibility (MHC) locus, a locus which contains genes that code for complement proteins of the immune system, has been repeatedly identified in these studies (Sullivan et al. 2012). This too had been lacking mechanistic insight, until a study identified that the copy number of the complement component 4 (C4) gene in MHC II was strongly correlated with the incidence of schizophrenia. The group found that copy number of C4 was influenced by the presence of a human endogenous retrovirus sequence (HERV, a type of transposon) within two isoforms of the gene (C4A and C4B). They correlated C4 haplotype with schizophrenia risk and found a high association. C4 was shown to be involved in synaptic pruning, suggesting a mechanism for the increased number of spines in schizophrenia neurons (Sekar et al. 2016). In addition to highlighting the vast polygenic complexity of psychiatric disorders, this example suggests that with the evolution of new technologies and the rigorous application of empiric testing, we can acquire new perspectives.

28.3 Conclusions

The monogenic and polygenic disorder(s) discussed here exemplify the complexity of neurobiology. There are many invariants acting in these examples, including the human mutation rate, evolution and fitness, and time. Additionally, homeostasis is the ever-present balancing force in any cell, with the concept of compensation acting as a permutation of homeostatic mechanisms.

Though monogenic disorders are the result of single faulty genes, their effects are counteracted by enough forces for development to continue; this suggests an asymmetry introduced by mutation and balanced back to symmetry by homeostasis. Polygenic diseases are a subtler manifestation with many interacting and non-interacting molecules affected in these diseases on the genomic level. Hypothetically, if each mutation introduces an asymmetry, then each must have one or more counteracting forces for the system to be maintained. This understanding of mutation is interesting when we consider the reoccurring theme of disease threshold in mind disorders. In both monogenic and polygenic disorders, gender is another force that introduces variability into the system. Gender and the unique roles it plays in disease progression are understudied, but can be considered yet another asymmetry or as a gauge field in itself. Finally, the perspective one takes is essential. Just as a phenotype is dependent on the level observed, so too is the definition of pathology in disease. FXS is largely analyzed on the cellular level, while HD is characterized by specific circuit degeneration, and schizophrenia a combination (Despite the diversity of approach, it is the least understood of the three.). Any definition of the components of a gauge theory will have to take this concept into consideration.

While this chapter explores the known genetic aspects of brain disorders and their development, Chap. 2 details the applicability of Gauge theory in further understanding the complexity of the brain and the disorders that affect it. Also of note to consider is that this chapter reviews the essentials of molecular genetics, however, the field of population genetics, driven by the mathematical understanding of transmission genetics, is largely left untouched. In conclusion, we hope that the concepts and disorders conveyed in this chapter motivate the reader to both appreciate the chaos of biology as well as strive to build on this through a perspective grounded in physics.

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Chapter 29
The Spiritual Brain: Science and Religious Experience

Andrew Newberg

Keywords Mind • Spiritual • Religious • Brain • Cortex • Disorder • Experience • Physics • Connectome • Grid cells

29.1 Neurologically Oriented Definitions of Religion and Spirituality

Until the late eighteenth century, religions, particularly in the West, were defined by their sacred texts and dogmatic formulations. Friedrich Schleiermacher, in the late eighteenth century, was one of the first scholars that attempted to define "religion" by switching from a doctrinal emphasis to a more cognitive, visceral, or intuitive one. Schleiermacher defined religion as a "feeling of absolute dependence." Since his day most attempts at a general definition of religion have relied heavily on emphasizing the intuitive, emotional, or visceral elements rather than the doctrinal ones. This shift has important implications for bringing a neuroscientific approach to the study of religion. However, this also results in a neuroscientific approach to both religious and non-religious spirituality and spiritual experiences. In fact, as the definitions have evolved, the distinction between spirituality and religiousness has become much more complicated.

Emile Durkheim, in his *The Elementary Forms of the Religious Life* (1926), describes religion as nothing more than a transform of society. Thus, religion is nothing more than a natural consequence arising from communities of people. On the other hand, Sigmund Freud viewed religious behaviors and spiritual feelings in terms of a projection of various intrapsychic dynamics, often with a psychopathological perspective. For Freud, religion was a way of satisfying various psychological shortcomings. Psychologist B.F. Skinner described religious beliefs in terms of hopes and expectations based on previous experiences.

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At the turn of the twentieth century, scholars began to devote themselves to the phenomenology of religious and spiritual experiences on their own terms. William James engaged religious experience from a scientific perspective attempting to describe and analyze the large variety of different types of experiences (James 2002). These experiences included those that were more natural and "normal" as well as those that were more related to pathology such as schizophrenia or seizures. Rudolf Otto, in *The Idea of the Holy*" (1917), defined the essence of religious awareness as awe, described as a mixture of fear and fascination before the divine and referred to as a *mysterium tremendum et fascinans*. Such an approach began to get at a dominant form of Western mysticism but was not so applicable to Eastern religions or to primitive ones.

A more recent attempt at defining religion and spirituality, specifically from a scientific perspective, was elaborated as part of a consensus conference of scientists studying the physical, psychological, and neuroscientific aspects of religion and spirituality (Larson 1998). These were described in the form of criteria rather than a true "definition." The criteria for spirituality were listed as the subjective feelings, thoughts, experiences, and behaviors that arise from a search or quest for the sacred. In this definition, "search" referred to attempts to identify, articulate, maintain, or transform, and "sacred" referred to what the individual perceives as a divine being, ultimate reality or ultimate truth. The criteria for religion included the criteria for spirituality and/or included a search for non-sacred goals (such as identity, belonging, meaning, health, or wellness) in the context of spiritual criteria. In addition, a religion required that "the means and methods of the search receive general validation and support from within an identifiable group of people." These criteria were meant to be operationalized for scientific analysis such that religious and spiritual experiences could be evaluated as part of an experimental paradigm while preserving the essential nature of the experiences.

Ultimately, definitions of spirituality and religiousness can arise from numerous sources including religious, anthropological, sociological, neurological, or medical (Newberg 2014). How successful any definitions ultimately may prove to be will depend on both the religious perspective of such definitions and how well scientific methods can actually be performed on the basis of such definitions. But it must also be remembered that definitions that rely on cognitive, emotional, and perceptual constructs may inherently miss what is truly spiritual. If spirituality indeed merges human beings with something supernatural, then the scientific approach may only be able to measure the effects of spirituality rather than spirituality itself.

29.2 The Neurological and Psychiatric Correlates of Spiritual Experiences

In considering a neurocognitive approach to the study of religious and spiritual experiences, it is important to consider the various avenues towards attaining such experiences (d'Aquili and Newberg 1999). Experiences may arise from following

sacred texts, various rituals, practices such as meditation or prayer, drug and other induced states, near death experiences, or certain medical conditions. It is also important to identify the components of these experiences including cognitions, emotions, and experiences. For example, many of these experiences consist of a decreased awareness of the boundaries between the self and the external world. Such experiences can also lead to a sense of oneness between other perceived individuals thereby generating a sense of community. At the extreme, unitary experiences can eventually lead to the abolition of all boundaries of discrete being, thus generating a state of absolute unity.

It should be noted that the experiences of group rituals and individual meditation or prayer practices have a certain degree of overlap such that each may play a role in the other. In fact, it may be that human ceremonial ritual actually provides the "average" person access to spiritual or mystical experience ("average" in distinction to those who regularly practice intense contemplation such as highly religious monks or nuns).

Religious and spiritual experiences associated with meditation, prayer, and spiritual rituals have been described in the biomedical, psychological, anthropological, and religious literature. Specific descriptions in religious texts can date back several thousand years. More recently, there has been a growth in the number of studies that have examined the neurophysiological and physiological correlates of such experiences and we will focus on these in the next section of this chapter. From an evolutionary perspective, it is likely that such experiences became possible with the development of various structures in the brain of early primates and eventually of *Homo sapiens*. This level of brain development was accompanied historically by an explosion of religious traditions that have continued to permeate human societies since prehistoric times. In light of this evolutionary pattern, neurobiological and neuropsychological correlates of religious and spiritual experiences have begun to be identified. Furthermore, by considering other relevant studies in neurobiology, a more complex model of neurophysiological events during religious and spiritual experiences can be developed. More specifically, brain function can be considered in relation to its interconnection with other body physiology that can be mediated by the autonomic nervous system as well as the neuroendocrine system. A consideration of this relation between cognitive processes in the brain and the autonomic nervous system may yield a more complete understanding of a variety of spiritual experiences ranging from "awe" to intense mystical states. Thus, from the current literature, a foundation for the development of a neuropsychological model can be considered in order to guide future studies in the neurobiology of religious and spiritual experiences. The use of state-of-the-art brain imaging techniques that can now measure various neurotransmitter systems, as well as other physiological measures, can be applied to investigate brain function during experiences such as meditation, prayer, and ritual experiences. It is interesting that the complex design and execution of such imaging techniques utilizes an array of physics concepts including radioactivity, electromagnetism, radiofrequency emission and detection, and high level electronics in order to capture the mechanisms of the brain. It should also be noted that while the focus in this chapter will be on neurophysiological

correlates of religious and spiritual phenomena, there is a physical underpinning of each of these processes. Neurotransmitters evoke subsequent changes in ion concentrations and electrical currents in the neuron. Neuronal activity can be observed as electrical activity. And there are fascinating questions as to which processes ultimately lead to a concept of consciousness or mind. Is human consciousness the result of neuronal firing, neurotransmitter function, electrical activity, neuronal network connectivity, or something more than just the biological processes of the brain? Much future research will be needed to elucidate these questions.

A number of people use hallucinogenic agents to help induce intensive spiritual experiences. Since it has long been observed that drugs such as opiates, LSD, and stimulants can sometimes induce spiritual experiences, careful studies of the types and characteristics of drug-induced spiritual experiences, perhaps utilizing modern imaging techniques, may help elucidate which neurobiological mechanism are involved in more "naturally derived" spiritual experiences. Some studies related to the use of such hallucinogenic agents have already been performed and have revealed that these experiences are as intense, if not more intense, than more "naturally occurring" spiritual experiences. However, a more extensive study of such agents, particularly in relation to religious and spiritual experiences is required. Comparing this paradigm to naturally occurring spiritual phenomena may allow for a better distinction of pathologic and non-pathologic spiritual experiences. There are obvious ethical and legal considerations with studies such as these (although studies outside of the United States may be more possible). However, subjects who have had pharmacologically induced spiritual experiences can be studied using radioactive analogues of such agents as a means of determining the concentration of receptors and their agonists. Another related approach would be to study the effects of drug withdrawal on spiritual experience.

Neuropathological conditions including seizure disorders, particularly in the temporal lobes, brain tumors, and stroke, have been associated with spiritual experiences or alterations in religious beliefs. For example, temporal lobe epilepsy has been associated with hyperreligiosity and religious conversions (Bear and Fedio 1977). Psychiatric disorders such as schizophrenia and mania also have been associated with spiritual experiences and religious conversions (Grover et al. 2014). Delineating the type of pathology and the location of that pathology will aid in determining the neurobiological substrate of spiritual experience. Thus, neuropsychiatric disorders can be an effective tool for the neuroscience of spiritual experience.

Research on pathological conditions has classically been used to elucidate the normal functions of biological systems. Spiritual experiences in psychiatric and neurological disorders may be central to the identification of largely nascent neurobiological systems that subserve "normal" spiritual experience. This presents a crucial distinction to the historic psychiatric implication that spiritual experience is an expression of psycho- or neuro- pathology. This provides a framework in which normal spiritual experience can occur in pathological and normal conditions and pathologic spiritual episodes might occur in individuals with or without psychopathological disorders. However, care must be taken to avoid referring to

spiritual experience only in pathological terms or associated with pathological conditions as well as not reducing spiritual experiences only to neurophysiological mechanisms.

29.3 A Neurophysiological Model of Religious and Spiritual Experiences

The model described below is a summary of a previously described model which now incorporates recent neuroimaging, neurochemical, neuropathological, hormonal, and physiological studies (Newberg and Iversen 2003). The purpose of this model is to provide a framework from which many different types of religious experiences and practices can be considered and compared. As shown in Fig. 29.1, the model begins with the prefrontal cortex and suggests a number of complex interactions with the thalamus, posterior superior parietal lobe, limbic system, and autonomic nervous system. A number of structures involved are also part of other networks such as the default mode network and the reward system network. These networks likely play a role in spiritual experiences as part of this larger model. Furthermore, a number of both excitatory and inhibitory neurotransmitters can now be proposed to play a role in such practices and experiences. Dopamine, serotonin, acetylcholine, and several other molecules may be associated with various phenomenological aspects of such experiences and these are also considered in this model. It would be anticipated that depending on the specific spiritual practice, tradition, and individual involved, the specific mechanisms might be somewhat different. Thus, this network of brain structures might be activated in different ways and starting with different structures depending on a variety of circumstances. By focusing on the phenomenology of spiritual practices and experiences, this model provides information regarding the diversity of experiences, along with their various sensory, cognitive, and affective elements. The model was initially developed utilizing information from studies primarily on meditative practices due to the relatively large amount of data available. However, this model can similarly be applied to many different types of spiritual practices and experiences.

29.3.1 Activation of the Prefrontal and Cingulate Cortex

Most spiritual practices such as meditation or prayer require some degree of sustained attention. This can be either on a visualized object, a mantra, prayer, or other spiritual focus. Brain imaging studies suggest that willful acts and tasks that require sustained attention are initiated via activity in the prefrontal cortex (PFC), particularly in the right hemisphere (Ingvar 1994; Frith et al. 1991; Posner and Petersen 1990; Pardo et al. 1991). The cingulate gyrus has also been shown to be

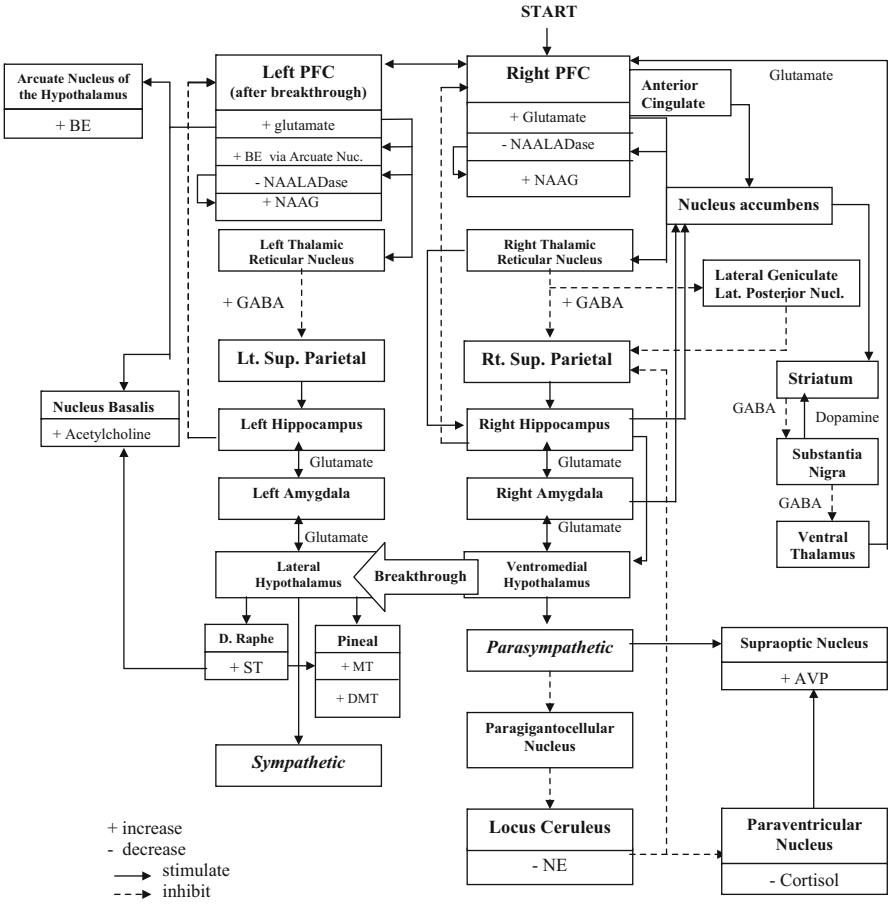

Fig. 29.1 Updated model of neurophysiological processes associated with spiritual practices such as meditation or prayer. The model is based specifically on concentrative practices (i.e. mantra meditation or focused prayer). Other practices might involve different interactions and structures

involved in focusing attention, probably in conjunction with the PFC (Vogt et al. 1992; Fox et al. 2016). Spiritual practices that require intense focus of attention likely begin with activation of the PFC (particularly on the right) as well as the cingulate gyrus. This notion is supported by brain imaging studies of volitional types of meditation that show increased activity in the PFC (see Fig. 29.2) and anterior cingulate (Newberg et al. 2001; Fox et al. 2016). More recent studies have also shown increased functional connectivity in between the frontal lobe and temporal regions that are part of the default mode network (Panda et al. 2016). Therefore, many spiritual practices appear to start by activating the prefrontal and cingulate cortex associated with the will or intent to focus on a sacred object. This frontal lobe activity may also change throughout the course of the practice, particularly toward peak experiences, something we will consider later.

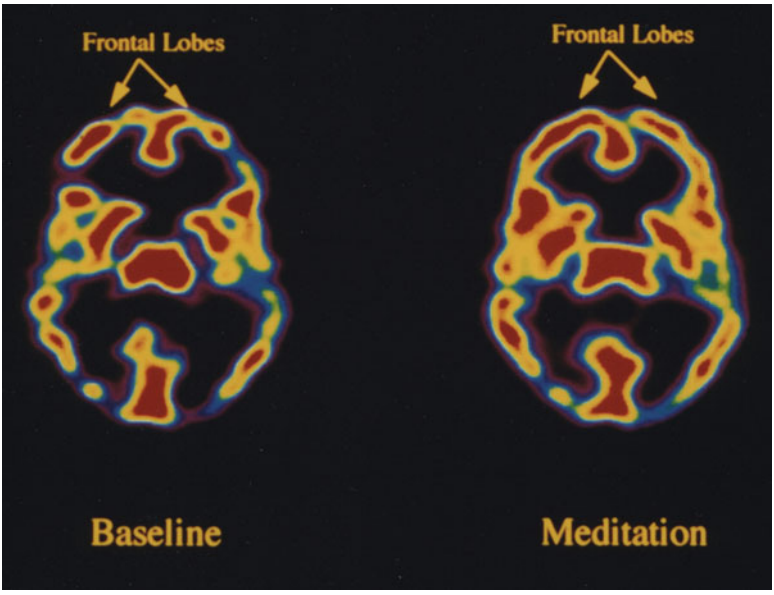

Fig. 29.2 SPECT scan during meditation showing increased cerebral blood flow in the frontal lobe areas during meditation

29.3.2 Thalamic Activity

The thalamus is a major relay in the brain which connects other structures as well as communicates "higher order" processing to the areas of the brain that subserve emotion and ultimately regulate various physiological processes. Early animal studies showed that the PFC, when activated, innervates the reticular nucleus of the thalamus (Cornwall and Phillipson 1988), particularly as part of a more global attentional network (Portas et al. 1998; Langner and Eickhoff 2013). Such activation may be accomplished by the PFC's production and distribution of the excitatory neurotransmitter glutamate which the PFC neurons use to communicate among themselves and to innervate other brain structures (Cheramy et al. 1987). The thalamus itself governs the flow of sensory information to cortical processing areas via its interactions with the lateral geniculate and lateral posterior nuclei and also likely uses the glutamate system in order to activate neurons in other structures (Armony and LeDoux 2000; Smith et al. 2014). The lateral posterior nucleus of the thalamus provides the superior parietal lobe with the sensory information it needs to determine the body's spatial orientation (Bucci et al. 1999; Miller et al. 2014).

When excited, the reticular nucleus releases the inhibitory neurotransmitter gamma aminobutyric acid (GABA) onto the lateral posterior and geniculate nuclei, cutting off input to the superior parietal lobe and visual centers in proportion to the reticular activation (Destexhe et al. 1998). During spiritual practices such as

meditation, because of the increased activity in the PFC, particularly on the right, there should theoretically be a concomitant increase in the activity in the reticular nucleus of the thalamus. While brain imaging studies of meditation have not had the resolution to distinguish the reticular nuclei, several SPECT studies did demonstrate a general increase in thalamic activity that was proportional to the activity levels in the PFC (Newberg et al. 2001; Manuello et al. 2016). This is consistent with, but does not confirm the specific interaction between the PFC and reticular nuclei. If activation of the right PFC causes increased activity in the reticular nucleus during a spiritual practice, the result may be decreased sensory input entering into the superior parietal lobe. This has been supported by a magnetic resonance spectroscopy study which demonstrated an increase in GABA in the brain during yoga meditation (Streeter et al. 2007). Another study using transcranial magnetic stimulation also supported a release of GABA during meditation along with inhibitory effects in the cortex (Guglietti et al. 2013). This functional deafferentation related to increased GABA would mean that fewer distracting outside stimuli would arrive at the visual cortex and superior parietal lobe enhancing the sense of focus during the meditative practice.

Thalamic involvement during spiritual practices and experiences may also be related to the alteration in the sense of realness and clarity frequently reported during such experiences (Newberg and Waldman 2016). Since the thalamus is intimately involved in the establishment of our consciousness, along with our sensory representation of reality, since both of these are altered during spiritual experiences, it is no surprise that the thalamus activity would be altered. There is also evidence of more permanent changes occurring in the thalamus as the result so extended exposure to spiritual practices. Such a permanent change thalamic activity, particularly related to asymmetric function, might help explain the long term consequences of spiritual experiences. These long term consequences include changes in how a person perceives his or her occupation, relationships, meaning and purpose in life, and religiousness (Newberg and Waldman 2016).

It should also be noted that the dopaminergic system, via the basal ganglia, is believed to participate in regulating the glutamatergic system and the interactions between the prefrontal cortex and subcortical structures. In addition, dopamine is the primary neurotransmitter involved in the reward system of the brain. An increase in dopamine would therefore be associated with positive, possibly euphoric, emotions. Several studies support the notion that there is a release of dopamine during spiritual practices. For example, the only PET study using a radioactive dopamine analogue showed that there was an increased release of endogenous dopamine during Yoga Nidra meditation (Kjaer et al. 2002). They hypothesized that this increase may be associated with the gating of cortical-subcortical interactions that leads to an overall decrease in readiness for action that is associated with this particular type of meditation. A more recent study has demonstrated increased activity in the nucleus accumbens which modulates dopamine activity in the brain (Ferguson et al. 2016). In new data from our laboratory, we have also found a change in the dopaminergic system resulting from a 1 week spiritual retreat of intense meditation and prayer (Fig. 29.3). Again, the results suggest that the dopamine system is affected and

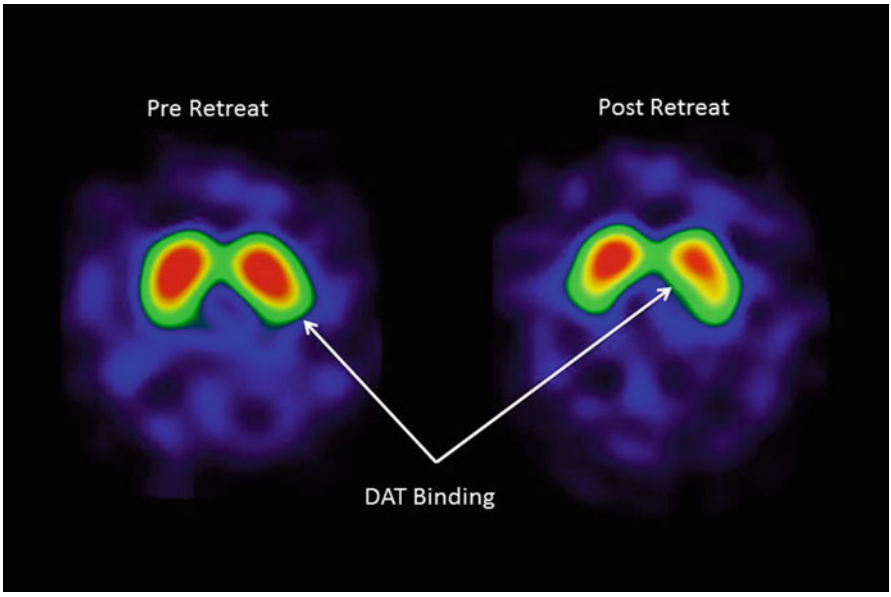

Fig. 29.3 Results showing decreased dopamine transporter binding (*arrows* showing reduced *red* activity) after undergoing a 7 day spiritual retreat suggesting a "priming" for dopamine release

may even prime the brain for spiritual experiences. Future studies will be necessary to elaborate on the role of dopamine during meditative practices as well as the interactions between dopamine and other neurotransmitter systems.

29.3.3 Superior Parietal Lobe Function

Studies have indicated that the posterior superior parietal lobe is involved in the analysis and integration of higher-order visual, auditory, and somaesthetic information (Adair et al. 1995; Joseph 1990; Hui et al. 2014). It is also involved in a complex attentional network that includes the PFC and thalamus (Fernandez-Duque and Posner 2001). Through the reception of auditory and visual input from the thalamus, the superior parietal lobe is able to help generate a three-dimensional image of the body in space, provide a sense of spatial coordinates in which the body is oriented, help distinguish between objects, and exert influences in regard to objects that may be directly grasped and manipulated (Mountcastle et al. 1980; Lynch 1980). These functions of the superior parietal lobe might be critical for distinguishing between the self and the external world. It should be noted that a recent study has suggested that the superior temporal lobe may play a more important role in body spatial representation (Karnath et al. 2001), although this has not been confirmed by other reports. However, it remains to be seen what

is the actual relationship between the parietal and temporal lobes in terms of the spatial representation of the self and how that representation is affected during spiritual experiences. More recent studies exploring the default mode network, particularly the posterior subnet that includes the posterior cingulate, occipital and temporal lobes, have revealed suppressed function associated with meditation and the alterations in the sense of self (Fingelkurts et al. 2016).

Regardless, deafferentation of these orienting areas of the brain appears to be an important concept in the physiology of spiritual practices and experiences. If, for example, deafferentation of the superior parietal lobe by the reticular nucleus's GABAergic effects, the person may begin to lose their usual ability to spatially define the self. Such a notion is supported by clinical findings in patients with Balint's syndrome in which parietal lobe damage results in marked difficulty orienting themselves in three dimensional space (Caminiti et al. 2010). The effects of meditation are likely to be more selective and do not destroy the sense of self, but alter the perception of it. Deafferentation of the superior parietal lobe has also been supported by several neuroimaging studies (see Fig. 29.4) demonstrating decreased activity in this region during intense spiritual practices (Newberg et al. 2001, Newberg and Iversen 2003; Herzog et al. 1990–1991). Further, our earlier SPECT study of meditation showed a correlation between increasing activity in the thalamus and decreasing activity in the superior parietal lobe. The implication is that the more individuals increased the activity in their PFC, the more they deafferented the superior parietal lobe. Hence, one might suggest that with deeper and more intense focus during a spiritual practice, the individual is more likely to attain unitary states.

It is also possible that the parietal lobe, in conjunction with other brain structures, is involved in establishing the overall sense of self and how that self orients to the

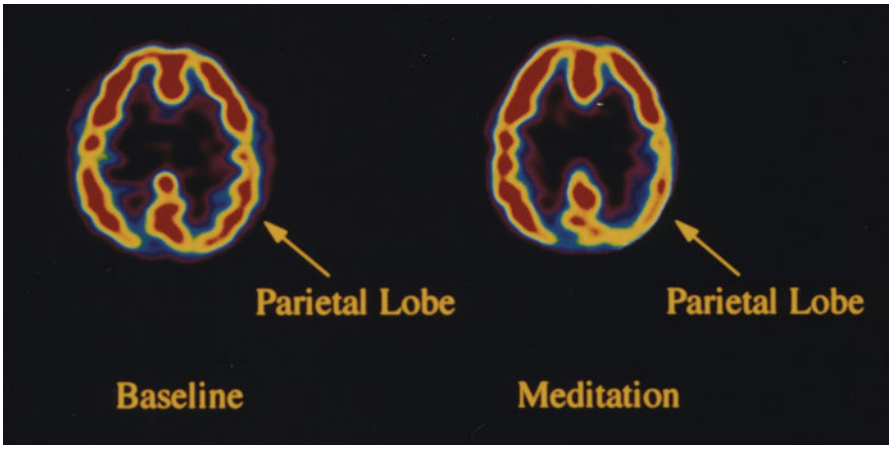

Fig. 29.4 SPECT scan of meditation showing reduced cerebral blood flow during meditation in the parietal lobes consistent with the loss of the sense of self

rest of the world. Some recent work on a type of cell called "grid cells", that appear to be particularly located in the hippocampus, has shown how they are associated with navigating the self through the world in a spatial manner (Sanders et al. 2015). Although no studies have explored grid cells with respect to religious or spiritual experiences, it is possible that they are associated with some of the important elements of these experiences, especially with respect to the sense of self and the relationship between the self and God or the universe in a spiritual context.

29.3.4 Hippocampal and Amygdala Activation During Spiritual Practices

In addition to activity in the cortical-thalamic network, spiritual practices might also be expected to alter activity in the limbic system given the intensity of the associated experiences and their strong emotional content. Stimulation of limbic structures has also been associated with eliciting experiences similar to those described during spiritual practices (Fish et al. 1993; Saver and Rabin 1997). The hippocampus acts to modulate and moderate cortical arousal and responsiveness, via rich and extensive interconnections with the prefrontal cortex, other neocortical areas, the amygdala, and the hypothalamus (Tao et al. 2016; Joseph 1990). The ability of the hippocampus to stimulate or inhibit neuronal activity in other structures likely relies upon the glutamate and GABA systems respectively (Armony and LeDoux 2000). In our neuropsychological model of meditation, we have suggested that during meditation, there is partial deafferentation of the right superior parietal lobe (Newberg and Iversen 2003). This deafferentation could further result in stimulation of the right hippocampus because of the inverse modulation of the hippocampus in relation to cortical activity. If, in addition, there is simultaneous direct stimulation of the right hippocampus via the thalamus (as part of the known attentional network) and mediated by glutamate, then we suggest that a powerful recruitment of stimulation of the right hippocampus occurs. Right hippocampal activity may ultimately enhance the stimulatory function of the PFC on the thalamus via the nucleus accumbens which is capable of gating neuronal input from the PFC to the thalamus via dopamine's modulatory effects (Newman and Grace 1999).

The hippocampus and amygdala reciprocally interact with each other such that they complement and interact in the generation of attention, emotion, memory, and certain types of imagery (Kreiman et al. 2000; Abe 2001; Desmedt et al. 2015). It seems that much of the prefrontal modulation of emotion is via the hippocampus and its connections with the amygdala (Poletti and Sujatanond 1980). Because of this reciprocal interaction between the amygdala and hippocampus, we have suggested that activation of the right hippocampus during meditation likely stimulates the right lateral amygdala as well. The results of the fMRI study by Lazar et al. support the notion of increased activity in the regions of the amygdala and hippocampus during meditation (Lazar et al. 2000). Other studies of spiritual practices have also reported changes in amygdala and hippocampus activity (Engström et al. 2010; Peres et al. 2012).

29.3.5 Hypothalamic and Autonomic Nervous System Changes

It is known that the hypothalamus is extensively interconnected with the limbic system. Stimulation of the right lateral amygdala has been shown to result in stimulation of the ventromedial portion of the hypothalamus with a subsequent stimulation of the peripheral parasympathetic system (Davis 1992). Increased parasympathetic activity should be associated with the subjective sensation first of relaxation, and eventually, of a more profound quiescence. Activation of the parasympathetic system would also cause a reduction in heart rate and respiratory rate. All of these physiological responses have been observed during meditation (Jevning et al. 1992; Amihai and Kozhevnikov 2015; Bharshankar et al. 2015).

Typically, when breathing and heart rate slow down, the paragigantocellular nucleus of the medulla reduces its innervation of the locus coeruleus (LC) in the pons. The LC produces and distributes the stress neurotransmitter, norepinephrine (NE, Foote 1987), that increases the susceptibility of brain regions to sensory input by amplifying strong stimuli, while simultaneously gating out weaker activations and cellular "noise" that fall below the activation threshold (Waterhouse et al. 1998). Decreased stimulation of the LC results in a decrease in the level of NE (Van Bockstaele and Aston-Jones 1995). The breakdown products of catecholamines such as NE and epinephrine have generally been found to be reduced in the urine and plasma during meditation (Walton et al. 1995; Infante et al. 2001) which may simply reflect the systemic change in autonomic balance. However, it is not inconsistent with a cerebral decrease in NE levels as well. During a meditative practice, our model suggests that reduced firing of the paragigantocellular nucleus cuts back its innervation of the locus ceruleus, which is known to densely and specifically supply cortical areas such as the superior parietal lobe with NE (Foote 1987). Thus, a reduction in NE would decrease the impact of sensory input on the superior parietal lobe, contributing to its deafferentation.

The locus coeruleus would also deliver less NE to the hypothalamic paraventricular nucleus. The paraventricular nucleus of the hypothalamus typically secretes corticotropin-releasing hormone (CRH) in response to innervation by NE from the locus coeruleus (Ziegler et al. 1999). This CRH stimulates the anterior pituitary to release adrenocorticotropic hormone (ACTH) (Livesey et al. 2000). ACTH, in turn, stimulates the adrenal cortex to produce cortisol, one of the body's stress hormones (Davies et al. 1985). Decreasing NE from the locus ceruleus during spiritual practices would likely decrease the production of CRH by the paraventricular nucleus and ultimately decrease cortisol levels. Most studies have found that urine and plasma cortisol levels are decreased during meditation practices (Jevning et al. 1978; Sudsuang et al. 1991; Buttle 2015) supporting the notion that there is an overall decrease in cortisol secretion. A more recent report suggested that meditation practices that enhance awareness reduce cortisol via a hippocampal modulation (Lau et al. 2015).

The drop in blood pressure associated with increased parasympathetic activity during spiritual practices might be expected to relax the arterial baroreceptors leading the ventral medulla to decrease its inhibition of the supraoptic nucleus of the hypothalamus. In certain circumstances, this lack of inhibition can cause the supraoptic nucleus to release the vasoconstrictor arginine vasopressin (AVP) which would increase blood pressure back to normal levels (Renaud 1996). AVP has also been shown to contribute to the general maintenance of positive affect (Pietrowsky et al. 1991), decrease self-perceived fatigue and arousal, and significantly improve the consolidation of new memories and learning (Weingartner et al. 1981). One study did show that plasma AVP increased during meditation (O'Halloran et al. 1985). Increased AVP might contribute to a decreased subjective feeling of fatigue and increased sense of arousal. It could also help enhance the individual's memory of any spiritual experience obtained, perhaps partly explaining how spiritual experiences are remembered and described in very vivid terms.

29.3.6 PFC Effects on Other Neurochemical Systems

As a person continues to perform a spiritual practice, there should be continued activity in the PFC associated with the persistent will to focus attention. In general, as PFC activity increases, it produces ever-increasing levels of glutamate in the brain. Increased glutamate can stimulate the hypothalamic arcuate nucleus to release beta-endorphin (Kiss et al. 1997). Beta-endorphin (BE) is an opioid produced primarily by the arcuate nucleus of the medial hypothalamus and distributed to the brain's sub-cortical areas (Yadid et al. 2000). BE is known to depress respiration, reduce fear, reduce pain, and produce sensations of joy and euphoria (Janal et al. 1984). That such effects have been described during meditation may implicate some degree of BE release related to the increased PFC activity. Meditation has been found to disrupt diurnal rhythms of BE and ACTH, while not affecting diurnal cortisol rhythms (Infante et al. 1998). However, it is likely that BE is not the sole mediator in such experiences during meditation because simply taking morphine-related substances does not produce equivalent spiritual experiences. Furthermore, one very limited study demonstrated that blocking the opiate receptors with naloxone did not affect the experience or EEG associated with meditation (Sim and Tsoi 1992).

Glutamate activates N-methyl d-Aspartate receptors (NMDAr), but excess glutamate in synapses can kill these neurons through excitotoxic processes (Albin and Greenamyre 1992). We have proposed that if glutamate levels approach excitotoxic concentrations during intense states of meditation, the brain might limit its production of N-acetylated-alpha-linked-acidic dipeptidase, which converts the endogenous NMDAr antagonist N-acetylaspartylglutamate (NAAG) into glutamate (Thomas et al. 2000). The resultant increase in NAAG would protect cells from excitotoxic damage. There is an important side effect, however, since the NMDAr inhibitor, NAAG is functionally analogous to the disassociative hallucinogens

ketamine, phencyclidine, and nitrous oxide (Jevtovic-Todorovic et al. 2001). These NMDAr antagonists produce a variety of states that may be characterized as either schizophrenomimetic or mystical, such as out-of-body and near-death experiences (Vollenweider et al. 1997).

29.3.7 Autonomic Nervous System Activity

In the early 1970s, Gellhorn and Kiely developed a model of the physiological processes involved in meditation based almost exclusively on autonomic nervous system (ANS) activity, which while somewhat limited, indicated the importance of the ANS during such experiences (Gellhorn and Kiely 1972). These authors suggested that intense stimulation of either the sympathetic or parasympathetic system, if continued, could ultimately result in simultaneous discharge of both systems (what might be considered a "breakthrough" of the other system). Several studies have demonstrated predominant parasympathetic activity during meditation associated with decreased heart rate and blood pressure, decreased respiratory rate, and decreased oxygen metabolism (Travis 2001). However, a recent study of two separate meditative techniques suggested a mutual activation of parasympathetic and sympathetic systems by demonstrating an increase in the variability of heart rate during meditation (Peng et al. 1999). The increased variation in heart rate was hypothesized to reflect activation of both arms of the autonomic nervous system. This notion also fits the characteristic description of meditative states in which there is a sense of overwhelming calmness as well as significant alertness. Also, the notion of mutual activation of both arms of the ANS is consistent with recent developments in the study of autonomic interactions (Hugdahl 1996).

29.3.8 Serotonergic Activity

Activation of the autonomic nervous system can result in stimulation of structures in the lateral hypothalamus and median forebrain bundle which have been shown to produce both ecstatic and blissful feelings when directly stimulated (Olds and Forbes 1981). Stimulation of the lateral hypothalamus can also result in changes in serotonergic activity. In fact, several studies have shown that after meditation, the breakdown products of serotonin (ST) in urine are significantly increased suggesting an overall elevation in ST during meditation (Walton et al. 1995). Serotonin is a neurotransmitter that influences the flow of visual associations generated in the temporal lobes (Joseph 1990). The cells of the dorsal raphe produce and distribute ST when stimulated by the lateral hypothalamus (Aghajanian et al. 1987) and also when activated by the prefrontal cortex (Juckel et al. 1999). Moderately increased levels of ST appear to correlate with positive affect, while low ST often signifies depression (Van Praag and De Haan 1980; Newberg et al. 2005). This

relationship has clearly been demonstrated with regard to the effects of the selective serotonin reuptake inhibitor medications which are widely used for the treatment of depression. It should also be noted that several clinical studies have found that meditative and related spiritual practices can lower depressive symptoms. The relationship between spiritual practices and decreased depression supports a overall role of serotonin in such practices. However, neuroimaging studies specifically designed to explore the relationship between serotonin and spiritual practices and experiences are needed.

When cortical ST receptors (especially in the temporal lobes) are activated, the stimulation can result in a hallucinogenic effect. Tryptamine psychedelics such as psylocybin and LSD seem to take advantage of this mechanism in producing their extraordinary visual experiences (Aghajanian and Marek 1999). The mechanism by which this appears to occur is that ST inhibits the lateral geniculate nucleus, greatly reducing the amount of visual information that can pass through (Funke and Eysel 1995; Yoshida et al. 1984). If combined with reticular nucleus inhibition of the lateral geniculate, ST may increase the fluidity of temporal visual associations in the absence of sensory input, possibly resulting in unusual, hallucinatory-like, imagery that has been described during certain spiritual states.

Increased ST levels can affect several other neurochemical systems as well. An increase in serotonin has a modulatory effect on dopamine suggesting a link between the serotonergic and dopaminergic system that may enhance feelings of euphoria (Vollenweider et al. 1999), frequently described during spiritual states. Serotonin, in conjunction with the increased glutamate, has been shown to stimulate the nucleus basalis to release acetylcholine which has important influences throughout the cortex (Manfridi et al. 1999). For example, increased acetylcholine in the frontal lobes has been shown to enhance attention and in the parietal lobes enhance spatial orienting without altering sensory input. While no studies have evaluated the role of acetylcholine in meditation, it appears that this neurotransmitter may enhance the attentional component as well as the orienting response in the face of progressive deafferentation of sensory input into the parietal lobes during spiritual practices. Increased serotonin combined with lateral hypothalamic innervation of the pineal gland may lead the latter to increase production of the neurohormone melatonin (MT) (Moller 1992). Melatonin has been shown to depress the central nervous system and reduce pain sensitivity (Shaji and Kulkarni 1998). During meditation, blood plasma MT has been found to increase sharply (Tooley et al. 2000) which may contribute to the feelings of calmness and decreased awareness of pain (Dollins et al. 1993). Under circumstances of heightened activation, pineal enzymes can also synthesize the powerful hallucinogen, 5-methoxy-dimethyltryptamine (DMT) (Monti and Christian 1981). Several studies have linked DMT to a variety of mystical states, including out-of-body experiences, distortion of time and space, and interaction with supernatural entities (Strassman et al. 1996; Strassman and Clifford 1994). Hyperstimulation of the pineal at this step, then, could also lead to DMT production that can be associated with the wide variety of mystical-type experiences associated with that hallucinogen.

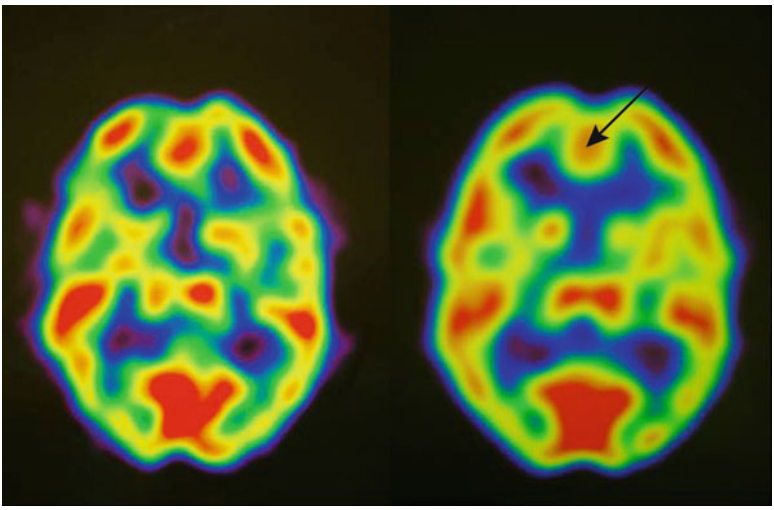

Fig. 29.5 SPECT scan results comparing religious singing (**a**) and speaking in tongues (**b**) showing reduced frontal lobe activity during speaking in tongues

29.3.9 Hypofrontality in Spiritual Experiences

Depending on the circumstances, either prolonged meditation or prayer practices, or other types of spiritual practices might ultimately lead to sharp reductions in frontal lobe activity. We have observed such decreases in Pentecostal speaking in tongues and Brazilian mediums in trance (see Fig. 29.5); Newberg et al. 2006; Peres et al. 2012). In each of these practices, the practitioner perceives his or her own will dissipating and feel "taken over" by the experience. Hypofrontality has also been reported in other altered states of consciousness such as creative states or flow states (Dietrich 2004). We have argued that the decreased frontal lobe activity may result either from the inability to continue the sustained attention during a particular practice such as meditation, or from reciprocal modulation by the hippocampus, thalamus, or limbic system. It may also be the case that meditation or prayer practices "prime" the brain for spiritual experiences by first augmenting frontal lobe activity before the subsequent decrease in activity. This change in activity from initially elevated to subsequently reduced could be sufficient to enable the person to experience being taken over or surrendering to the experience. Such mystical or enlightenment states also result in permanent transformations in various cognitive and emotional processes (Newberg and Waldman 2016). This ability to shift neuronal activity may result from the sudden shifts in frontal lobe function during these spiritual practices and experiences.

29.4 Future Directions

This field of study, sometimes referred to as "neurotheology", can pursue many different approaches such as studies of the substantial array of spiritual practices including meditation, prayer, rituals, and specific practices from a wide range of traditions and within traditions. Studies can also explore the impressive array of religious and spiritual experiences ranging from mild experiences to mystical ones. The study of particular circumstances associated with intense experiences such as near death states, pathological conditions, or drug induced states are also ripe for future investigation.

Future studies will also be able to take advantage of the many new developments in the field of cognitive neuroscience. Studies might consider utilizing the most advanced techniques in neuroimaging including projects such as the Human Connectome Project (Smith 2013) which evaluates with great detail the intricate interconnectedness of brain structures. Studies of the resting brain and the default mode network can determine how the functional connectivity of different structures is related to religious and spiritual phenomena. And there is the potential for many studies designed to explore the different neurotransmitter systems in the brain and how they are associated with various practices and experiences. Finally, efforts should be made to better assess the phenomenological and psychological elements of religious and spiritual experiences. Determining the most effective means of evaluating how these experiences affect cognitive, emotional, sensory, and behavioral domains are essential to understand any neuroscientific results.

The future is bright and virtually unlimited regarding studies of the neurobiological correlates of religious and spiritual phenomena.

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Chapter 30
The Neurobiology of Moral Decision-Making, Embodied Cognition and the Case of Tolerance

Diana Stanciu

Abstract Key findings from brain imaging research on the neurobiological correlates of moral decision-making in both healthy and impaired persons generated major changes in the philosophical methodology for the study of moral decision-making, which thus became considerably more integrated into a broader interdisciplinary field. This opened the way to its study from a new perspective: that of embodied cognition, which challenges the traditional scientific understanding of cognition as based primarily on mental representation. The supporters of embodied cognition propose a view on moral decision-making that is less of a computational and representational type, relying primarily on mental representations, and more of an enactive embodiment type, relying on sensory-motor contingencies and habitual embodied intersubjective factors. This can also have useful applications in explaining moral decision-making that encourages or, on the contrary, discourages prosocial behaviour and tolerance, as the case study in the last part of this article will show.

Keywords Embodied cognition • Mental representation • Conscious intention • Empathy • Agency • Moral decision-making • Moral relativism • Prosocial behaviour • Tolerance • Neurobiological correlates of decision-making

30.1 The Neurobiology of Moral Decision-Making

The philosophical methodology for the study of the mind has radically changed in the last two decades. While the twentieth century was dominated by a research programme that used a priori methods to address foundational questions, the philosophical study of the mind has recently become considerably more integrated

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into the broader interdisciplinary field of cognitive science (Knobe 2015). The empirical studies seem to have become dominant and many of them report original experimental results. More importance is also being ascribed to evaluative beliefs and subjective concerns (Kahane 2016).

Generally, while both the normative and the descriptive domains of morality have been taken into account, as Fig. 30.1 shows, several brain regions have actually been ascribed an important role in moral decision-making (Heinzelmann et al. 2012).

Moreover, key findings from brain imaging research on moral reasoning in people displaying antisocial behavior were integrated into a neural moral model of antisocial behavior. Areas found to be functionally or structurally impaired in antisocial populations include dorsal and ventral regions of the prefrontal cortex, amygdala, hippocampus, angular gyrus, anterior cingulate and temporal cortex. Regions most commonly activated in moral judgment tasks consist of the polar/medial and ventral prefrontal cortex, amygdala, angular gyrus and posterior cingulate. Specialists suggest that the rule-breaking behavior common to antisocial, violent and psychopathic individuals can be generated by impairments in some of the structures subserving moral cognition and emotion (dorsal and ventral prefrontal cortex, amygdala and angular gyrus) (Raine and Yang 2006) – see also Fig. 30.2. Furthermore, the study of psychopathic traits may be able to offer some insight into the brain functioning during moral decision-making when a deficit in emotional response is present (Glenn 2010) – Fig. 30.3.

In this train of thought, philosophers and neuroscientists seem to have been working together to delineate the neural correlates of moral decision-making as precisely as possible (Greene et al. 2001, 2004; Opris and Bruce 2005; Kahane et al. 2012; Shenhav and Greene 2014). But many have also argued that data from neuroscience only emphasise the impact of conscious rational processes in moral decision-making (and thus of consequentialism) and rather neglect the impact of sometimes automatic emotional processes (and thus of deontological theories) (Singer 2005; Levy 2011).

Then, moral decisions and social relationships are often characterized by strong feelings of ambivalence that can represent a catalyst for emotional distress and health-related problems. The anterior cingulate cortex has been identified as a key brain region in monitoring conflicting information, but the neurobiological substrates of ambivalence processing are still widely unknown. For instance, the effects of the neuropeptide oxytocin on neural and behavioral correlates of ambivalence may be quite substantial and may also influence moral decision-making (Preckel et al. 2015) – see Fig. 30.4 – but further research needs to be done on that.

It was also noted that diminished emotional processing and reduced empathy have been associated with unusual high rates of utilitarian responses in moral judgments. But the effects of diminished emotional processing and empathy on moral decision-making have been only partially considered – it was only demonstrated that several neurological patient populations, including those suffering from traumatic brain injury, appear to produce an abnormally 'utilitarian' pattern of judgments to moral dilemmas (Rowley et al. 2017) and that empathy and alexithymia can modulate emotional reactions to moral decision (Cecchetto et al. 2017) – see Fig. 30.5.

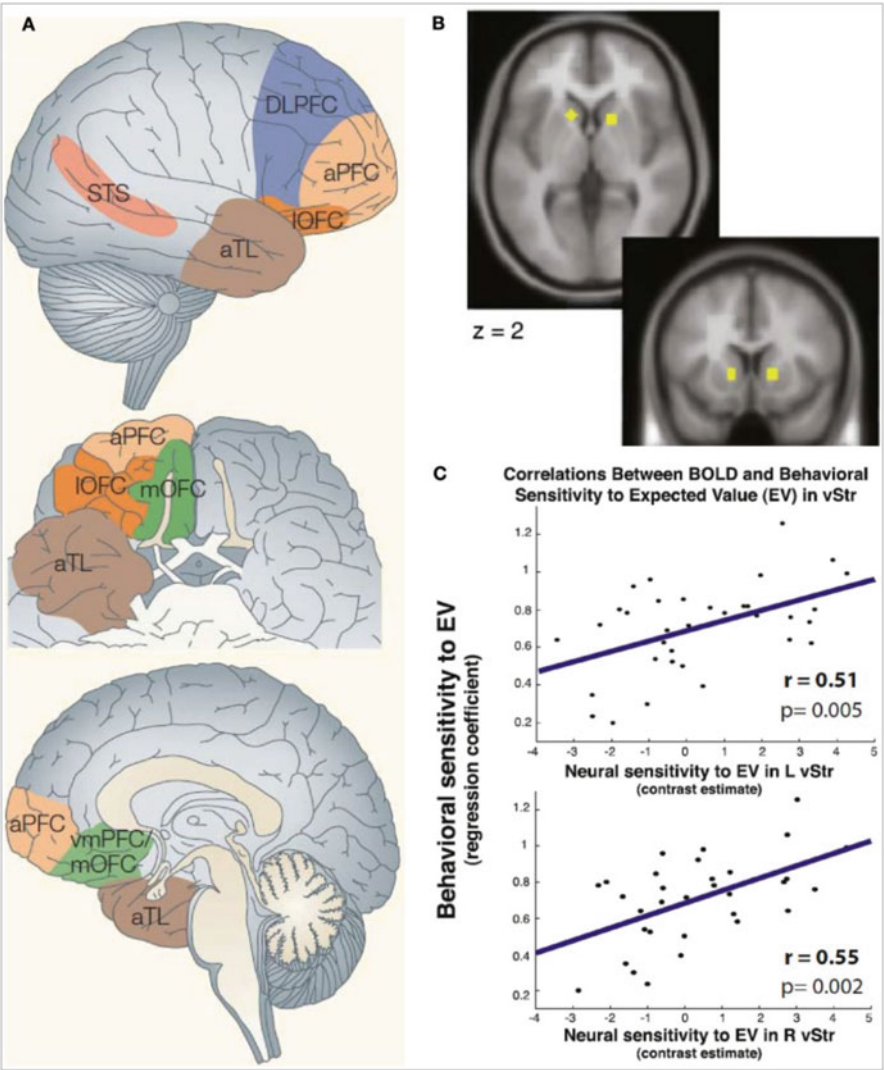

Fig. 30.1 Brain regions implicated in moral judgment and decision-making. (**a**) Cortical regions. Note that the posterior cingulate cortex and the angular gyrus (temporoparietal junction) have also been implicated in moral judgments. *aPFC* anterior prefrontal cortex, *aTL* anterior temporal lobe, *DLPFC* dorsolateral prefrontal cortex, *lOFC* lateral orbitofrontal cortex, *STS* superior temporal sulcus, *vmPFC* ventromedial prefrontal cortex (Adapted with permission from Moll et al. 2005). (**b**, **c**) Example for striatal involvement in moral decision-making. The task employed moral dilemmas. In each trial, subjects rated how morally acceptable it was to save a group of individuals from death with a known probability rather than a single individual with certainty. Across trials, group size, and probability varied. Group size and probability should be multiplied to compute the expected number of lives saved. (**b**) Regions in ventral striatum previously identified by Knutson et al. (2005) as processing reward value. (**c**) In the regions shown in (**b**), individual neural sensitivity (contrast estimates of activation increases) correlated with behavioral sensitivity (beta estimates in rating) to the expected number of lives saved (Adapted with permission from Shenhav and Greene 2010). This finding is in line with the notion that moral functions can be underpinned by neural mechanisms that have originally evolved for different functions, such as reward processing (Tobler et al. 2008) (Courtesy of: Heinzelmann et al. 2012)

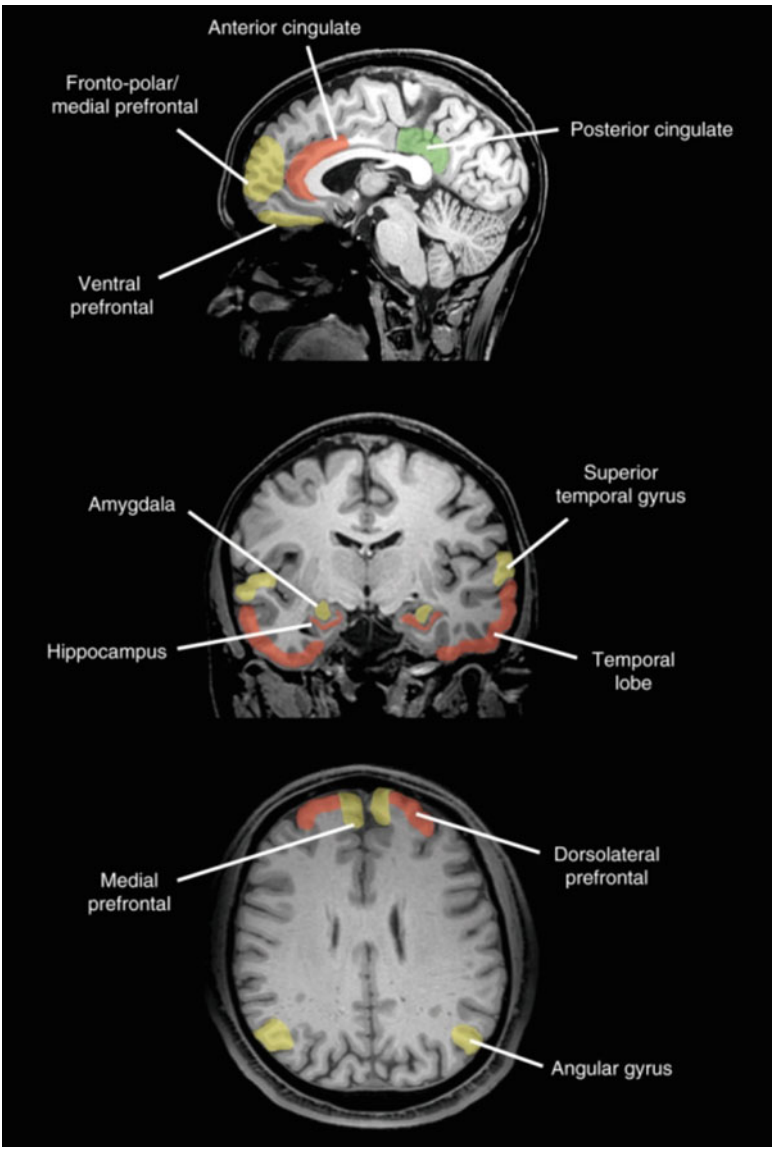

Fig. 30.2 A schematic diagram of brain regions impaired only in antisocial groups (*red*), activated only in moral decision-making (*green*) and regions common to both antisocial behavior and moral decision-making (*yellow*) (Courtesy of: Raine and Yang 2006)

However, the distinction between 'utilitarian' and deontological concerns in moral decision-making has lately been deemed rather uncertain. The alleged 'utilitarian' outlook can often be better explained in terms of commonsensical moral notions when sacrificial dilemmas are discussed (Kahane 2015). Thus, despite the fact that 'utilitarian' judgments in moral dilemmas still dominate current research

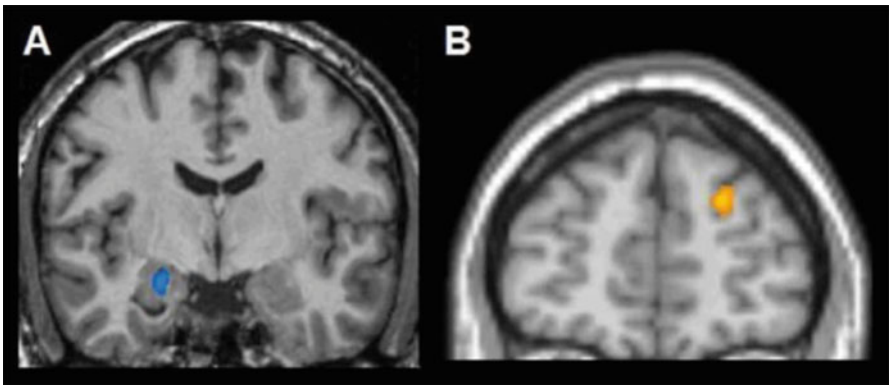

Fig. 30.3 A summary of the findings by Glenn et al. (2009), Glenn and Raine (2009). Psychopathy scores were negatively correlated with activity in the amygdala during emotional moral decision-making (**a**), but positively correlated with activity in the dorsolateral prefrontal cortex (**b**) (Courtesy of: Glenn 2010)

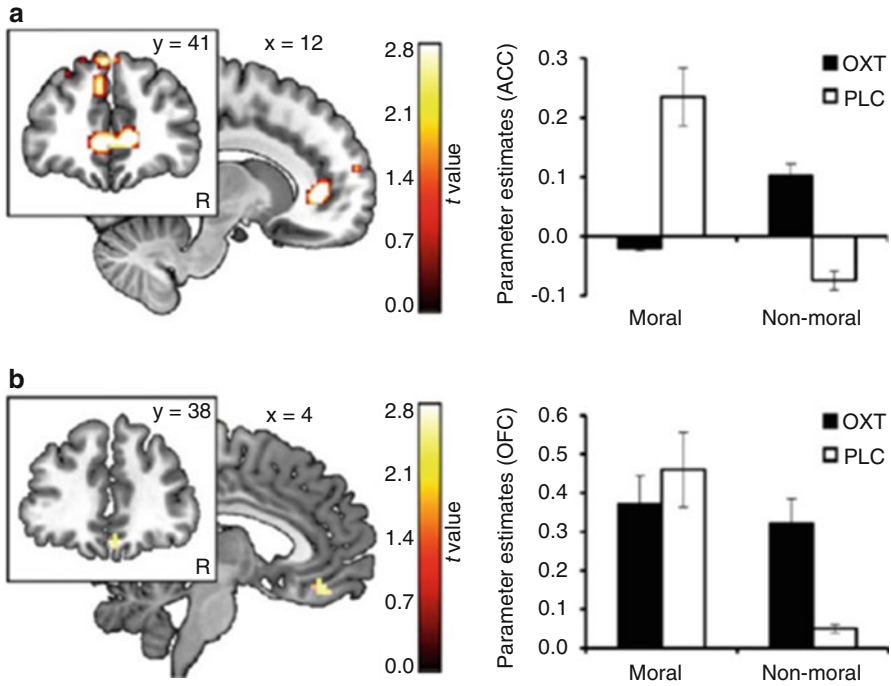

Fig. 30.4 Oxytocin (OXT) effects on moral decision-making (Experiment 1). OXT compared with placebo (PLC) significantly reduced brain activity in the anterior cingulate cortex (**a**) and orbitofrontal cortex (**b**) during the evaluation of moral dilemmas. *Error bars* indicate the standard error of the mean (SEM). Abbreviations: *ACC* anterior cingulate cortex, *OFC* orbitofrontal cortex, *OXT* oxytocin, *PLC* placebo (Courtesy of: Preckel et al. 2015)

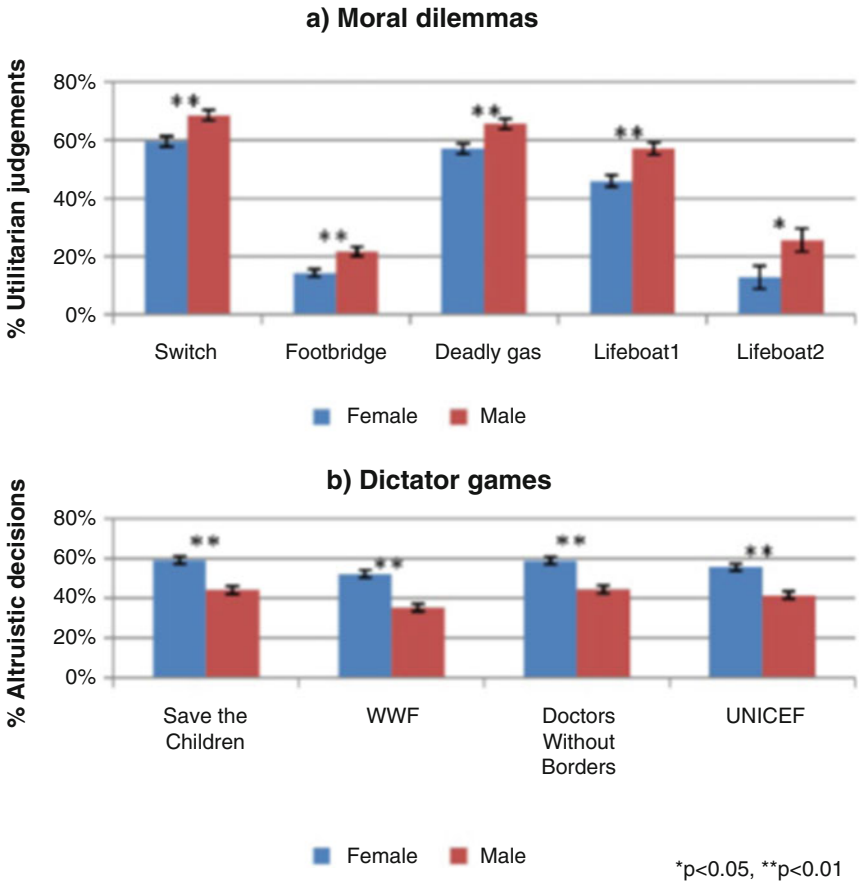

Fig. 30.5 Gender differences in (**a**) moral judgements and (**b**) altruistic behavior (Courtesy of: Tinghög et al. 2016)

(Crockett 2013; Lotto et al. 2013, etc.), they seem to be only remotely related to the utilitarian impartial concern for the greater good, that is, to a genuine utilitarian approach to ethics (Kahane et al. 2015).

A certain terminological vagueness has also been noted (Kahane and Shackel 2010) and the standard explanation on the possible neural mechanisms that correlate positively with the consequentialist and, respectively, deontological moral judgments has lately been challenged. For instance, brain areas formerly associated with cognitive processes were found to be related to deontological judgments (Borg et al. 2006) and, moreover, the contents of the moral judgments (either consequentialist or deontological) seem to have become irrelevant; the intuitive vs. counterintuitive difference in moral judgments became especially important instead (the intuitive moral judgments being associated with activations in the visual and premotor cortex and the counterintuitive ones with activations in the rostral anterior cingulate cortex – Kahane et al. 2012). But the possibility that individuals intuitively favor

certain moral actions over others and that significant interactions between gender, for instance, and the intuitive versus reflective decision-making can be observed is still insufficiently proved (Tinghög et al. 2016).

Additionally, in developmental psychology and social neuroscience, the fundamental nature of moral and social cognition lies in general computational processes such as attention, approach-avoidance, social valuation, and decision-making rather than in fully distinct, dedicated neural regions for morality (Decety and Cowell 2017). The very contrast between 'rational/cognitive' and 'emotional' processes in the research on moral judgment has lately been challenged by psychologists and the division between action-based and outcome-based value representation considered to provide the ideal framework for a dual-system theory has been preferred (Cushman 2013). Then, the fact that moral judgments depend on conscious reasoning from explicitly understood principles has also been challenged and the need to consider the unconscious appraisal system that mentally represents the causal and intentional properties of human action has been emphasised (Hauser et al. 2007). Then, in a social–functionalist perspective, distinctions were drawn among specific moral emotions both regarding the antecedent appraisals and the consequent actions and judgments related to them (Hutcherson and Gross 2011). This was later explained by the possibility that morality be unified at the functional level, but not at the cognitive level – 'as vehicles are unified by shared function rather than shared mechanics' (Greene 2015). The moral foundations theory has been developed as an alternative to such views and as a more pliable theory to a wide variety of behavioral and neuroimaging investigations of moral cognition (Clifford et al. 2015).

30.2 Embodied Cognition, Moral Decision-Making and Agency*

The above-mentioned findings on the neurobiology of moral decision opened the way to the study of decision-making from a new perspective: that of embodied cognition, which challenges the traditional scientific understanding of cognition as based on mental representation. According to this traditional conception, mental representations are symbolic structures with linguistic and combinatorial properties that act as vehicles for contents and can explain intelligent behavior (Fodor and Pylyshyn 1988).

This traditional view of cognition as based on mental representation has turned out to be particularly unfit for integrating the new discoveries in the neuro-

*Material in this section draws from the following works in the Stanford Encyclopedia of Philosophy: (1) Robert A. Wilson and Lucia Foglia, 2015, "Embodied Cognition", Winter 2015 Edition, URL = https://plato.stanford.edu/archives/win2015/entries/embodied-cognition/; (2) Karsten Stueber, 2014, "Empathy", Winter 2014 Edition, URL = https://plato.stanford.edu/archives/win2014/entries/empathy/; and (3) Markus Schlosser, 2015, "Agency", Fall 2015 Edition, URL = https://plato.stanford.edu/archives/fall2015/entries/agency/

science of moral decision-making since it asserts that mental representations: (1) are autonomous from perceptual systems and bodily action; (2) contain only propositionally organised knowledge; (3) are used for motor programmes that are independent from cognition.

In contrast, the supporters of embodied cognition propose a view on moral decision-making that is less of a computational and representational type, relying primarily on mental representations (see more on that in Aizawa 2007; Chemero 2009; Adams 2010; Shapiro 2011) and more of an active embodiment type relying on sensory-motor contingencies and habitual embodied intersubjective factors (such as facial expression, posture, movement and gestures) (see more in Varela et al. 1991; Thompson and Varela 2001; Noë 2004; Gallagher 2005).

For instance, it has been demonstrated that gesturing during conversation facilitates both communication and language processing (McNeill 1992). Similarly, vision is often action-guiding and bodily movement and the feedback it generates are actually better integrated into visual processing than the traditional models of vision had suggested before (O'Regan and Noë 2001). Then, the so-called 'mirror neurons' fire not only during action, but also during observing others undertaking the same action (Rizzolatti and Craighero 2004). Moreover, people are often able to perform several cognitive tasks (e.g. remembering something) more effectively when they use parts of their bodies and even parts of their environments to simplify the cognitive processing (Donald 1991).

Developed primarily as part of research programmes on artificial intelligence (Clark 1997), embodied cognition is actually only a paradigm (together with embedded and extended cognition) (Robbins and Aydede 2009) of a more general view – on situated cognition – that maintains the significant causal or physically constitutive role both of different aspects of the agent's body and of its natural, social and cultural environment. This new paradigm accounts for the numerous empirical data that recently demonstrated that sensorimotor activity and central cognitive processing are more dependent on one another than previously thought and that bodily activity can certainly constrain, distribute, and regulate neural activity (Clark and Chalmers 1998; Farrer et al. 2003; Leube et al. 2003; Wilson 2004; Tsakiris et al. 2007; Clark 2008; Menary 2010).

Situated cognition in general can be quite valuable an interpretation for those studying moral decision-making since it can bring new insights on prosociality and empathy within the context of the debates on folk psychology regarding our mindreading capacities, as an intersubjectively accessible practice in which agents predict and explain the actions and emotions of other agents (Goldman 2006; Stüber 2012). Quite relevant are here also the distinctions between different types of empathy: basic and reenactive (Stüber 2006) or mirroring and reconstructive (Goldman 2011). The basic or mirroring empathy involves the findings on 'mirror neurons' (Gallese 2003; Rizzolatti and Craighero 2004; Rizzolatti and Sinigaglia 2008; Iacoboni 2011) while the reenactive or reconstructive empathy, as a higher level of mindreading, in which we understand others' behavior in more complex social contexts, involves more complex neuronal areas such as the medial prefrontal cortex, temporoparietal cortex, and the cingulate cortex (Kain and Perner 2003; Frith and Frith 2003; Goldman 2006).

The valuable impact the paradigm of embodied cognition has on moral cognition and decision-making is thus to offer a more comprehensive framework beyond the rationalist model in moral thought and behaviour (which, even when it took into account emotions and bodily states, preferred to assert the ultimate importance of reasoning in moral decision-making – e.g. Kohlberg 1969). In fact, it is due to this new paradigm of embodied cognition that several social intuitionist models claim that moral judgments can be the result of affective components as well. In fact, affective concerns have actually come to be considered pervasive in moral judgments, a role that formerly escaped researchers' attention and was in fact masked by the emphasis on conscious reflection (Haidt et al. 1993; Greene and Haidt 2002).

For instance, experimental literature offered numerous examples in which disgust and repugnance (involving explicit physical components and changes) could also represent an emotion of social rejection, thus becoming relevant also for the field of moral cognition and decision-making (Prinz 2004; Niedenthal et al. 2005). Moreover, several experiments show that the feeling of disgust induced by a bad smell or dirty room makes moral judgments more severe. For instance, heterosexual individuals offered more negative evaluations of their gay and lesbian peers when exposed to an unpleasant odour in the room than when the odour was absent (Schnall et al. 2008; Inbar et al. 2009). Likewise, the feeling of anger can modify moral cognition and decision-making. For instance, anger manifested due to a traffic incident before going to work lead to an increased reliance on prejudice when interviewing a job candidate afterwards (DeSteno et al. 2004).

Embodied cognition also provides a valuable paradigm for empirical research that goes beyond the standard theory of action, which states that one can only act intentionally if one has the right functional organization – in which certain mental states and events (intentions, beliefs, desires, etc.) cause the right events (e.g. certain movements) in the right way. According to this standard theory of action, the exercise of agency consists in the instantiation of the right causal relations between agent-involving states and events (Davidson 1980; Brand 1984; Dretske 1988; Mele 2003; Enç 2003). Opponents of the standard theory argue that an agent's capacity to initiate action cannot be reduced to acting intentionally and for specific reasons and that agency may be spontaneous – for no reason and without prior intent (Lowe 2008). Action can thus be discussed both in terms of metabolic self-maintenance and of 'adaptive regulation' of the agent to the environment (Varela et al. 1974).

Therefore, the embodied and enactive approaches to cognition assert that many instances of human agency can be explained without the ascription of representational mental states (Chemero 2009; Hutto and Myin 2014). On the one hand, they postulate a basic 'online' skillful and even effortless engagement with the environment, without conscious deliberation, reasoning, or planning (the so-called 'skilled coping'), which can be observed in habitual actions such as driving a car or in verbal exchanges. On the other hand, judgments about one's agency are postulated as 'offline' and usually post-act. They are thus subject to various biases that may distort the interpretation of one's own agency (Gallagher 2007; Synofzik et al. 2008).

All this can also be related to the dual-process (or dual-system) theories of decision-making. According to such models, there are two types of mental processes (or systems) that underlie decision-making and agency: one is characterized as automatic, effortless, and heuristics-based, and the other as conscious, deliberate, and rule-based. Dual-process models of decision-making have been used in many areas of research and they challenge the traditional view in philosophy that there is only one mechanism (or faculty) of practical reason that supports a reason-based agency (Evans 2008; Keren and Schul 2009). However, there is no consensus on the details of the dual-process model – especially regarding the modalities in which the two processes (or systems) interact: top-down influence of the conscious and deliberate processes on the automatic ones, interactions of the two types of processes, interferences only in some cases, switching from one type to the other, etc. Further research is needed in this respect.

30.3 The Neurobiology of Moral Decision-Making and the Embodied Cognition in the Case Study of Tolerance*

From the point of view of clinical neuroscience (I am very grateful to Prof. Mihai Moldovan, from the University of Copenhagen, for specific information on this), tolerance has been traditionally introduced through the pharmacological concept of drug tolerance, defined as a decreasing response to repeated constant doses of a drug. When extended to the brain system level, the concept has usually been referred to as 'habituation', which is a form of adaptive behavior (or neuroplasticity) in which the brain reduces its response to a repeating stimulus, independent of sensory adaptation or fatigue. This form of non-associative learning has been extensively explored in connection to attenuation of pleasure responses and the reward system of drug addicts (Lingford-Hughes et al. 2010). Nevertheless, more recently it became apparent that a similar process could also occur in the context of chronic pain of various causes (Baliki et al. 2014). Specifically, the long term repetition of unpleasant pain stimuli was found to cause a plastic change in a particular brain network, known as the default mode network (DMN). Intriguingly, the DMN activity was also found to be critically involved in the social understanding of others (Li et al. 2014). It is therefore reasonable to hypothesize that the search for the brain network responsible for the tolerance for the unpleasant others' behavior should start from the DMN level.

*Material in this section draws from the following works in the Stanford Encyclopedia of Philosophy: (1) Maria Baghramian and J. Adam Carter, 2016, "Relativism", Winter 2016 Edition, URL = https://plato.stanford.edu/archives/win2016/ entries/relativism/; (2) Markus Schlosser, 2015, "Agency", Fall 2015 Edition, URL = https://plato.stanford.edu/archives/fall2015/entries/agency/; and (3) Karsten Stueber, 2014, "Empathy", Winter 2014 Edition, URL = https://plato.stanford.edu/archives/win2014/entries/empathy/

Furthermore, recent advancements in brain surgery offer an unprecedented source of human intracerebral electroencephalographic (EEG) recordings from various brain networks including DMN (Duncan et al. 2013). The DMN is constituted from a set of synchronous brain regions that are deactivated during stimulus processing / task performance (Raichle et al. 2001). Cortical network mapping (e.g. for epilepsy surgery) typically involves the assessment of effective connectivity using responses to single pulse electrical stimulation. The epilepsy patient population is particularly relevant here because temporal lobe epilepsy and surgery are known to alter the DMN (Doucet et al. 2014) and postoperative changes in behavioral tolerance could also be expected.

Moreover, from the clinical standpoint, epilepsy is the most common serious neurological disorder and this high prevalence explains why the patients are often both the targets and the perpetrators of inter-personal intolerance. Numerous studies have demonstrated that social stigma is one of the main factors affecting the quality of life in this population and that programmes determining social integration and acceptance can positively impact the course of the disease (Bautista et al. 2014).

But the issue of tolerance is also crucial in moral decision-making and prosocial behaviours nowadays, when societies are more and more confronted with religious intolerance and fundamentalism, discrimination, xenophobia, violence, terrorism, etc. despite numerous non-discriminative public policies devised in accordance to the United Nations' Universal Declaration of Human Rights (10 Dec. 1948) and to the Declaration of Principles on Tolerance (16 Nov. 1995). The emphasis on toleration as a social principle that should be both educated and legally enforced in democratic states without a thorough study of tolerance as an individual capacity/volition, of its epistemological context and of the cognitive and affective decision-making processes upholding or undermining it, clearly turns out to be insufficient.

And here embodied cognition and the above-mentioned neurobiology of decision-making may be of considerable help in the case study of tolerance. I refer here to 'tolerance' as a mark of prosociality – that is, as one's 'capacity' or 'willingness' to accept and accommodate what one perceives as different, unpleasant or annoying opinions, beliefs, rights, and behaviors in order to maintain social concord. That can be examined in connection to 'toleration' – the social, cultural, religious and political 'practice' through which the capacity or willingness to tolerate is exercised.

Nowadays, the specialised literature on tolerance as prosocial behaviour based on moral decision-making remains still indebted to the long-established historically-oriented pattern in studying this issue (and the related one of toleration) (Horton 1994; Laursen and Nederman 1997; Israel 1999; Zagorin 2003; Marshall 2006; Kaplan 2007; Stanciu 2009, 2013; Forst 2012; Walker 2013; Morton et al. 2016; Paulmann et al. 2016; Warman et al. 2016, etc.). Moreover, this kind of historical literature concentrates primarily on the early modern period while neglecting numerous more recent developments. Thus, tolerance and toleration have been examined especially in relation to the early modern period as an issue raised by three main causes: (1) the religious, social, economic and political conflict generated by the Reformation; (2) the Enlightenment, with its 'triumph of rationalism'; and (3)

the development of experimental science in the sixteenth to seventeenth centuries (cf. Ashcraft 1992). Indeed, the early modern period brought forth a number of important theories on toleration, among which three became paradigmatic: Baruch Spinoza's *Tractatus Theologico-Politicus* (1670), Pierre Bayle's *Commentaire Philosophique* (1686) and John Locke's *A Letter Concerning Toleration* (1689). But a solid theoretical approach of the issue of tolerance and moral decision-making, doubled by solid empirical research also became necessary and can become possible within the paradigm of embodied cognition.

A few specific issues can be singled out in this respect: (1) whether moral relativism can constitute a suitable context for a theoretical study of tolerance; (2) whether tolerance can involve agency without conscious intention and what kind of decision-making processes that would involve; (3) whether tolerance is related to embodied cognition rather than to computationalism in social cognition and practice and whether and how it is associated with empathy (which, alongside tolerance, promotes prosociality) in this respect.

30.3.1 Tolerance and Moral Relativism

The main issue here is represented by the standards of reasoning and the procedures of justification that could support tolerance. The study of tolerance can be thus integrated within the context of the twentieth-century debates on moral relativism (more on this issue in Wong 2006; Rachels 2009; Velleman 2013; Carter 2016). According to moral relativism, standards of reasoning and procedures of justification are the products of various conventions and frameworks of assessment and their truth claims and authority are confined to their specific contexts (local cultural norms, individual standards, specific epistemic systems or practices etc. – more on that in Kusch 2002). In fact, the supporters of relativism in general often cite tolerance as a normative reason for being relativists. Its critics, on the other hand, insist that one can accommodate diversity and lack of agreement at a higher level of generalization (Foot 1982). Furthermore, the supporters of moral relativism see it as a proof of tolerance, open-mindedness and anti-authoritarianism, but its critics think that it undermines the very bases of ethics. Within this epistemic and ethical context, understanding tolerance at a psychological level, as an individual capacity and volition, should also involve the so-called 'paradox of tolerance' – the situation in which a tolerant person holds antagonistic views towards 'intolerance', and hence is intolerant of it for the sake of self-preservation – as presented in Popper, *The Open Society and Its Enemies* (1945), with more moderate variants in Rawls, *A Theory of Justice* (1971) and Walzer, *On Toleration* (1997).

30.3.2 Tolerance and Conscious Intention in Decision-Making and Agency

The main questions here are: whether tolerance can involve agency without conscious intention and what kind of decision-making processes are involved. When being tolerant to others' opinions, rights, behaviours, etc., one displays a specific sense of agency (more on agency in Neth and Müller 2008). But whether one's reasons and conscious intentions determine the way one acts (Wegner 2002; Malle 2004) when being tolerant or tolerance is simply a matter of basic empathy is still to be established. Likewise, the emotional component of this conscious/unconscious agency still needs to be discussed (more on consciousness and agency in Custers and Aarts 2010 and on emotion and consciousness in Engelen 2014).

It may thus happen that tolerance is either the rather unconscious and secondary outcome of an automatic goal pursuit, a sub-routine used for higher goals and long-term intentions (more on automatic actions in Adams 2010; Clarke 2010) or the higher goal and long-term intention itself or both of these altogether. In the last case, the decision-making process that leads to tolerance may be best described by dual-process theories of decision-making, which propose two types of mental processes: an automatic one and a conscious one (Evans 2008; Keren and Schul 2009). In this respect, tolerance may also involve a mixed sense of agency: both the 'online', basic one that does not require conscious intention and the 'offline' post-act judgment that can be sometimes distorted or illusory (as quoted above, Gallagher 2007; Synofzik et al. 2008).

The question is, in fact, to what extent we are reason-responsive (at least in the first instance) when tolerance is required/ advisable. As noted above, consistent empirical evidence that supports situationism suggests that our agency is often influenced by situational and morally irrelevant factors even when there are significant moral reasons to act otherwise (Nelkin 2005; Schlosser 2013; Vargas 2013). One possible solution would be to discuss tolerance in the context of the dual standpoint theories, in which agency is explained from both a practical and a normative standpoint (Nagel 1986; Korsgaard 1996; Bilgrami 2006). However, the dual standpoint theories have been questioned in as much as they may involve contradictory viewpoints on free will (Nelkin 2000) and this should also be taken into account.

30.3.3 Tolerance, Embodied Cognition and Empathy

The question here is whether tolerance is triggered by embodied cognition rather than by computationalism, that is, by embodied notions and also by automatisms and habits established during social practice rather than by rationally construed mental representations.

Quite helpful for a better understanding of the sense of agency involved in tolerance could also be the recent work on empathy and prosocial behaviors (German 'Einfühlung' – feeling into) in psychology and philosophy (Decety and Meltzoff 2011; Engelen and Röttger-Rössler 2012). Particularly useful could also be the latest discoveries in experimental psychology facilitated by computational modeling and neuroimaging (Lockwood 2016). Thus, if we refer to empathy within the context of the debates on folk psychology regarding our mindreading capacities, as an intersubjectively accessible practice in which agents predict and explain the actions and emotions of other agents (Goldman 2006; Stüber 2012), we can establish its impact on the type of agency involved in tolerance. One should also take into consideration here the distinctions between different types of empathy mentioned above: basic and reenactive (Stüber 2006) or mirroring and reconstructive (Goldman 2011). The basic or mirroring empathy involves the neuroscience findings on 'mirror neurons' (Gallese 2003; Rizzolatti and Craighero 2004; Rizzolatti and Sinigaglia 2008; Iacoboni 2011) while the reenactive or reconstructive empathy, as a higher level of mindreading, in which we understand others' behavior in more complex social contexts, involves different neuronal areas such as the medial prefrontal cortex, temporoparietal cortex, and the cingulate cortex – Kain and Perner 2003; Frith and Frith 2003; Goldman 2006). Such discoveries from cognitive neuroscience can be employed in order to explain the dual standpoint type of agency and the dual-process decision-making theories that can be related to tolerance.

Besides the useful insights the work on empathy can offer for such an attempt, tolerance can also be discussed within the framework of more complex embodied forms of social cognition leading to instances of direct perception and the ability to match separate actions into larger narrative or cultural frameworks (Zahavi 2010; Stüber 2012; Seemann 2011; Gallagher 2012).

Finally, tolerance can also be studied within the wider framework of situated cognition (with its different paradigms: embodied, embedded or extended cognition), which generally maintains the significant causal or physically constitutive role of both different aspects of the agent's body and its natural, social and cultural environment (as noted above, Clark and Chalmers 1998; Farrer et al. 2003; Leube et al. 2003; Wilson 2004; Tsakiris et al. 2007; Clark 2008; Menary 2010). Various theorists of situated cognition have developed the hypothesis that even the representation of emotion concepts is grounded in bodily simulations. Thus, emotion concepts related to intolerance such as 'disgust', 'fear' or 'anger' could not be abstractly defined since they are representations embedded in bodily feelings that generate meaning (more on the embodiment of emotions and on emotion concepts in Niedenthal et al. 2014 and Oosterwijk and Barrett 2014). Intolerant attitudes may indeed represent a direct, automatic and prereflexive type of agency (based on the rejection of 'the other') that is somewhat similar to our motor behaviours and, even if moral cognition is also required here, the affective judgments involved may incorporate patterns of bodily interaction with the environment (Casasanto 2014) that may be difficult to rationalise and educate unless both empirical and ethical studies are involved.

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Chapter 31
Insights into the Animal's Mind

Gabriel Predoi, Iulian Raus, Florica Barbuceanu, and Ioan Opris

Abstract Although it was believed that the mind is an "exclusive ability" of human beings, many animals possess excellent perceptual and cognitive skills that sometimes surpass those of humans. For example, sensory abilities such as sight, hearing, and smell are much better developed in some animals than in humans. Also some animals are capable of using tools, to live in a hierarchical society, and to develop empathy towards animals of different species (Striedter 2013). Here, we discuss cognitive features in animals with small brain, as well as, in animals with larger brains. To understand animal's mind, this chapter examines the animal's brain from structural (anatomy: brain size, connectome and modularity, i.e. lamination and minicolumns) and functional (learning, cognition, and mind) perspectives.

Keywords Animals • Learning • Mind • Brain • Memory • Animal cognition

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31.1 Introduction

For a long time it was believed that mind is an "exclusive ability" of human beings. Surprisingly, it was found that many animals possess excellent perceptual and cognitive skills. For example, sensory abilities such as sight in golden eagle, hearing in elephant, and smell in bear are much better developed than in humans. To determine the roots of cognition in animals it is a very challenging task that employs both facets of knowledge (learned and unlearned) to orient perception, learning, and the encoding of environmental features. A top ten of the most intelligent animals with high cognitive abilities has been compiled (see some of their brains in Fig. 31.1) (Mota and Herculano-Houzel 2015). Such animal list must begin with nonhuman primates (orangutans, chimps, and monkeys). Monkeys are able to solve certain problems and are able to have emotions, too. Next, in the list are: elephant, dolphin/whale, crow, parrot, pig, dog/wolf/fox, cat, squirrel, and octopus. The elephant can learn how to paint and seems to cry when any member of the herd dies. The dolphin makes various "pranks like other animals" for their own fun. The whale has the largest brain and may feel anxiety, joy, and parental love. Dogs can count up to five, they are jealous and never forget if one hurts them. They can

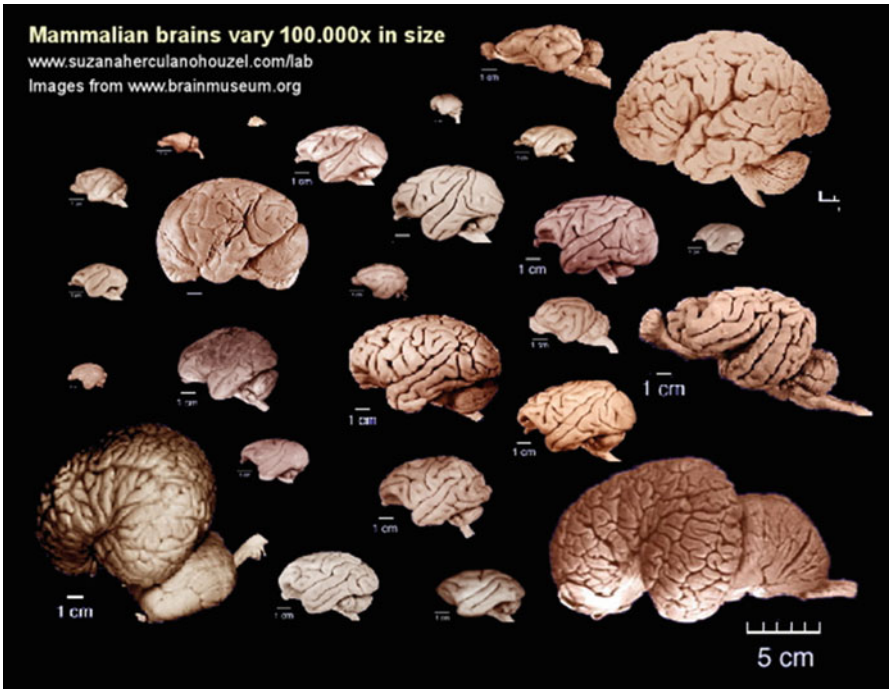

Fig. 31.1 Mammalian representation of brain size. Brain size varies over 5 orders of magnitude (With permission from Herculano-Houzel 2009)

understand human language and even respond to some questions by mastering some suggestive gestures (Cheney and Seyfarth 1998). The pig loves to listen to music and performs well in video games. Crows can use different tools to obtain food (Amant and Horton 2008). The parrot can answer you when you ask him if he wants food or water. The wolves have a hierarchical society with alpha male and female in leading roles. Foxes are cunning, having a reputation for being very intelligent. Cats like to be independent and show caution before crossing the street Amant and Horton (2008). The squirrels have very good memory and make traps for thieves. Thus, in the fall, squirrels bury the nuts in hundred places and during winter they easily remember where the nuts were hidden. Octopuses can memorize different shapes and even can open a jar.

To understand animal's mind, we start with the first step by looking into the animal's brain *structur*e (Herculano-Houzel 2011) (anatomy: brain size, connectome, and modularity, i.e. lamination and minicolumns (Mountcastle 1997; DeFelipe 2011) and *function* (cognition and mind) perspectives (Goldman-Rakic 1996; Arnsten 2013; Opris and Casanova 2014).

31.1.1 Anatomical Substrate of Animals Mind

The anatomical organization of animal's brain can be discussed in several steps. First, many anatomical investigations provide data about brain size, from the smallest to the largest animal on the Earth (DeFelipe 2011; Herculano-Houzel 2011). In these animal brains, the existence of connection pathways between brain regions is examined *in vivo* by using either traditional tracing methods or diffusion-based imaging (Shanahan 2012). These data provide information for a connectivity matrix covering the major cortical areas of the animal's neocortex, or even the entire forebrain. This connectivity matrix is, in fact, the animal's brain structural *connectome* (Beul et al. 2015). The resulting connectivity matrix is then analyzed using advanced mathematical concepts to characterize brain's complex networks (i.e. graphs), in order to reveal its large-scale interconnections. A number of topological features of such networks include the sparse network and the meso-level microcircuits defining cortical modularity (Opris and Casanova 2014; Sporns and Betzel 2016). A modular network (dealing with the local processing) can be partitioned into subsets of nodes (modules) that are densely connected internally but only sparsely to other subsets (Chunga et al. 2016). Cortical modules betray the existence of a functional specialization.

31.1.2 Animal's Cognition

What Is Cognition in Animals? The concept of cognition in animals was introduced in neuroscience (through comparative psychology) to characterize the mental (memory, emotion, behavior) abilities of animals (Kandel 2007). It includes studies of

operant conditioning and learning in animals, but has also been strongly influenced by research in ethology and behavioral ecology.

Do Animals Have Cognitive Abilities? Cognitive abilities are mental skills required by the animal to carry out a given behavioral task. These abilities deal more with the mechanisms of how animals learn, remember, pay attention, rather than with the actual knowledge. Animal cognition is the label given to a modern approach to the mental capacities of non-human animals.

Do Animals Have Feelings? Animals do have feelings because they can be trained to do some peculiar tasks. The foundation of training animals is based on mixing negative emotions with unwanted behavior and positive emotions with wanted behavior.

How Do Animals Think? Thinking ability refers to the use of mental activities and skills to perform tasks involving learning, remembering, making decisions or paying attention, and more. Most animals have the ability to perceive their environment and to experience pleasure and suffering, although they may interpret/understand these features in various ways (Grieves and Jeffery 2017). Animals are 'conscious' just like humans, meaning that, they are aware of their surroundings (Duncan 2006). Animals have different "levels of consciousness", some animals having "higher levels" of thinking/planning ability than others (Dawkins 2014). For example, the crows from New Caledonian are able to learn how to make and use various tools and, when given the choice, select the ones appropriate for a given task (Kenward et al. 2006). Lower "levels of consciousness allow species to experience sensations and emotions, without being aware of concepts like time and space.

Below are some examples of ways that "animals can think differently" than people:

- When an animal is injured, it may react in a different way than when it is healthy. For example, mice can hide their pain, because when "showing weakness" it may mean they "could get eaten" by an eagle (Martinez et al. 1999).
- An animal "may not be able to explain uncomfortable experiences to itself", in the way that humans can. This means that they "may feel more frightened and unsure" about experiences, "similar to how a child may react when it gets hurt" (Bearzi and Stanford 2008).
- Animals can enjoy similar types of experiences like humans do. For example, a mother deer may enjoy time with its new born calf, or a dog feels comfortable when lying down in the sunshine!

Although it was previously assumed that only humans possess the ability to think, science discovered the impressive cognitive abilities of animals. Animals as diverse as apes, dolphins, and birds use tools to acquire food and water (Boesch and Boesch 1990). Apes, dolphins, dogs and parrots "can understand some basic human language" (Shettleworth 2010). Other animals "demonstrate empathy and altruism". Some animals have even "demonstrated a degree of self- awareness", i.e. knowing that they are individuals that are "separated from others and from the environment

(Couchman et al. 2010). Apes, elephants, and dolphins can all recognize, that "the image in the mirror is a reflection of their own body" (Prior et al. 2008).

We may not understand precisely how an animal thinks, but what is important is to appreciate that many of these animal species, are conscious, being capable to feel emotions such as pleasure or pain. The Cambridge Declaration on Consciousness states that: "*The absence of a neocortex does not appear to preclude an organism from experiencing affective states. Convergent evidence indicates that non-human animals have the neuroanatomical, neurochemical, and neurophysiological substrates of conscious states along with the capacity to exhibit intentional behaviors. Consequently, the weight of evidence indicates that humans are not unique in possessing the neurological substrates that generate consciousness. Non-human animals, including all mammals and birds, and many other creatures, including octopuses, also possess these neurological substrates"* (Bekoff 2012).

31.2 The Anatomy of Animal Brains

Do All Animals have a Neocortex? The six-layer microarchitecture of the cortex appears to be a distinguishing feature of mammals, but it is not present in any other animals. There is some debate, however, as to the cross-species nomenclature for neocortex.

31.2.1 Brain and Size

The increase in the size and complexity of animal (especially in mammals) (Herculano-Houzel 2011) and human brains opened the gate to a grandiose development of mental skills. This "expansion of the brain allowed the addition of neuronal microcircuits" with a "similar basic structure", which "enhanced the complexity of the human brain" and contributed to its unique abilities (DeFelipe 2011). However, there are fundamental differences even between distinct mammalian species.

Brain Size and Intellectual Capabilities The absolute brain size of great apes has increased more three times-from an average of 450 cm^3 in *Australopithecus* to 1345 cm^3 in *Homo sapiens* (DeFelipe 2011). Human encephalization can be evaluated quantitatively by an "encephalization quotient (EQ)" (Jerison 1977, 1985). This is a ratio calculated based on evaluations of brain and body weight compared to the expected brain weight, using the cat as the "standard" for mammals (EQ = 1) (Herculano-Houzel 2011). Thus, EQ values bellow or above 1 indicate a relative brain size that is less or more what would be expected. Using this EQ measure in fossil specimens, values of 2.5 (for *Australopithecus afarensis* more than 3 million years old) and respectively 6 (*Homo sapiens*, more than 200,000 years old) have been calculated (Marino 1998). The EQ of modern humans is between 7.4 and 7.8, being the highest EQ of all the mammals. Accordingly, it is assumed that the

EQ is a good predictor of intelligence. Nevertheless, there are many exceptions, like dogs (relatively intelligent creatures) and squirrels that have very similar EQs (1.1 and 1.2, respectively). Similarly, New World capuchin monkeys have EQs (2.4–4.8) higher than chimpanzees (2.2–2.5) and gorillas (1.5–1.8) but their intelligence is less (Roth and Dicke 2005).

Some Features of Cortical Circuits

Comparative Studies Knowing that brain's architecture consists of different functional modules whose size varies based on species-specific behavior, the allometric relationship of brain parts to the overall size provides some insight into how the brain scales across species (see for a review DeFelipe 2011). As expected, there is huge variability in brain size across different mammalian species (Fig. 31.2). This variability ranges from the smallest mammal's brain on Earth (insectivorous pygmy shrew and the bumblebee bat, both with a similar body weight of 2–3 g) that weighs approximately 0.06 g, up to 9.2 kg for the brain size of the sperm whale (50,000 kg body weight). Moreover, animals with *similar brain weight* (blue whale, 6 kg, elephant, 5 kg) have huge body weight difference: the blue whale (*Balaenoptera musculus*; the largest animal on Earth) weighs 100,000 kg, compared to the Indian elephant (*Elephas indicus*), that weight only 5000 kg. By contrast, animals with similar body weight (gorilla, 160 kg vs. dolphin, 150 kg), have major brain size differences: the brain of gorilla weighs only 0.5 kg compared to the brain of the striped dolphin (*Stenella coeruleoalba*) that weighs 1.2 kg.

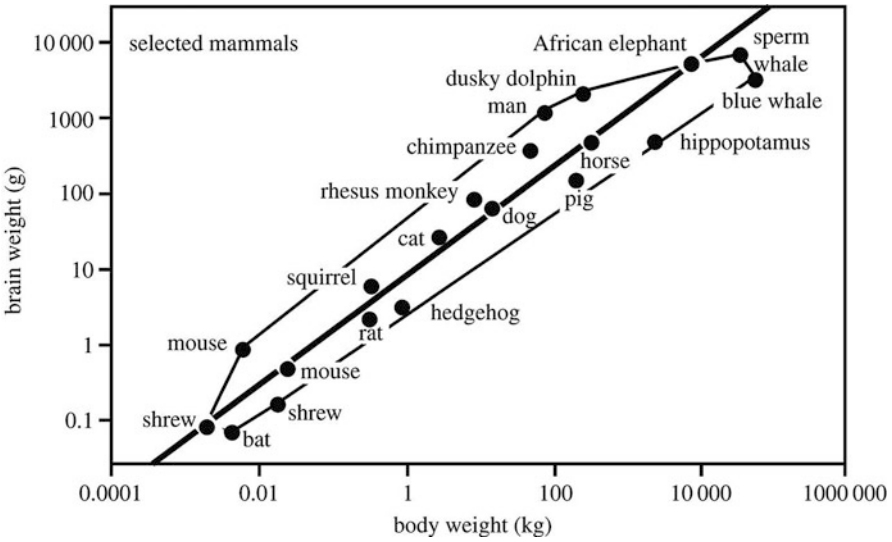

Fig. 31.2 Relationship between brain size and body weight (With permission from Dicke and Roth 2016)

31.2.2 Brain Lamination

Despite the broad variability in brain size across mammalian species, "there is little variation in the thickness of the cerebral cortices" that varies relatively little between brains of different sizes. The variation observed within a given brain is "similar to that found between species of different brain size" (DeFelipe 2011). In a valiant effort, Javier DeFelipe compared the thickness of lamination (see Fig. 31.3) of frontal, parietal, and occipital cortices across nine species, including the mouse,

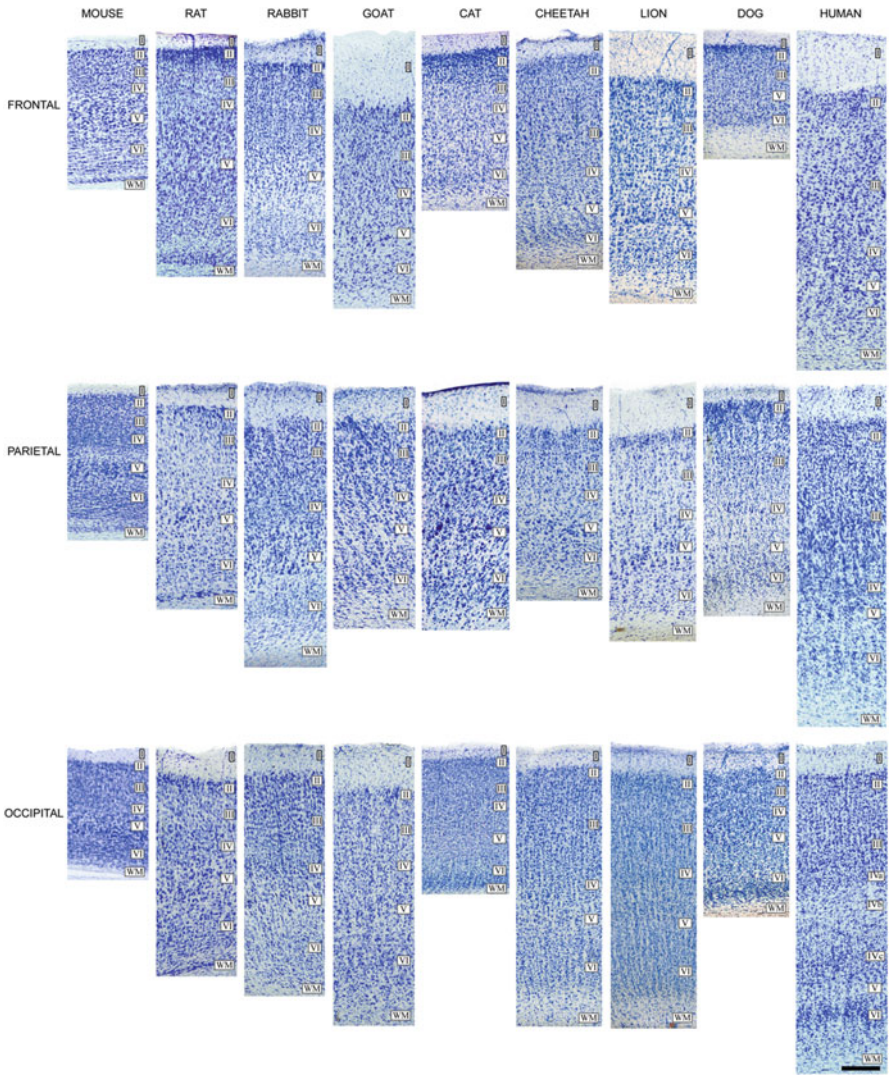

Fig. 31.3 Cortical lamination in animal brains (With permission from DeFelipe 2011)

rat, rabbit, goat, cat, cheetah, lion, dog, and human. As pointed out by DeFelipe (2011), the thickest part of the cerebral cortex is in the *human motor cortex*, which can reach up to 4.5 mm, in striking contrast with cortex in the depths of the fissures that may only be 1 mm thick. Also, there are marked differences across brain areas where, for example, the thickness of dog's frontal cortex is 0.8 mm, while the thickness in parietal cortex is 1.6 mm. Regardless of the several thousand times difference between the brain size of whales and that of pygmy shrew, there seems to be no difference in the basic lamination pattern of cerebral cortex in the pygmy shrew (0.4 mm thickness), and in whales (less than 2 mm thick). Furthermore, the appearance of the cellular components in Nissl-stained sections is generally similar in all cortices. Another observation stemming from the lamination thickness of frontal cortex is that the supra-granular layers in humans are the thickest across all species shown in Fig. 31.3. Altogether, these observations suggest that the increased brain size may be regarded as the main developmental drive across species.

31.2.3 Animal Brain Connectome

A connectome is a structural map of the "wiring diagram" of neural connections in the animal brain (DeFelipe 2010). More broadly, an animal connectome would include the mapping of all neural connections within an animal's nervous system. The visualization of the detailed anatomic structures of the mouse brain is obtained from a diffusion MRI tractography of the mouse brain and comparison with neuronal tracer data in Fig. 31.4.

Fig. 31.4 (continued) is +0.5. The exemplified hrFM were reconstructed at $15.6 \times 15.6 \times 50\ \mu m^3$ resolution, matching the thickness of the histological tissue slices. Acronyms: *aca* anterior commissure anterior part, *cg* cingulum, *cc* corpus callosum, *CPu* caudate putamen, *ec* external capsule, *lo* lateral olfactory tract. With permission from Laura-Adela Harsan et al. PNAS 2013, 110: E1797-E1806. The connectome in the rodent brain. A probabilistic tractography connectivity matrix for the mouse brain. Relative connectivity estimates that 148 anatomic regions are displayed with a $\log_{10}$ scale color map (top *left*). Tractography seeds (*rows*) and targets (*columns*) are organized based on their developmental origins as indicated by colored surface renderings of parent structures along the *top* and *left* side of the figure (With permission from Chen et al. 2015)

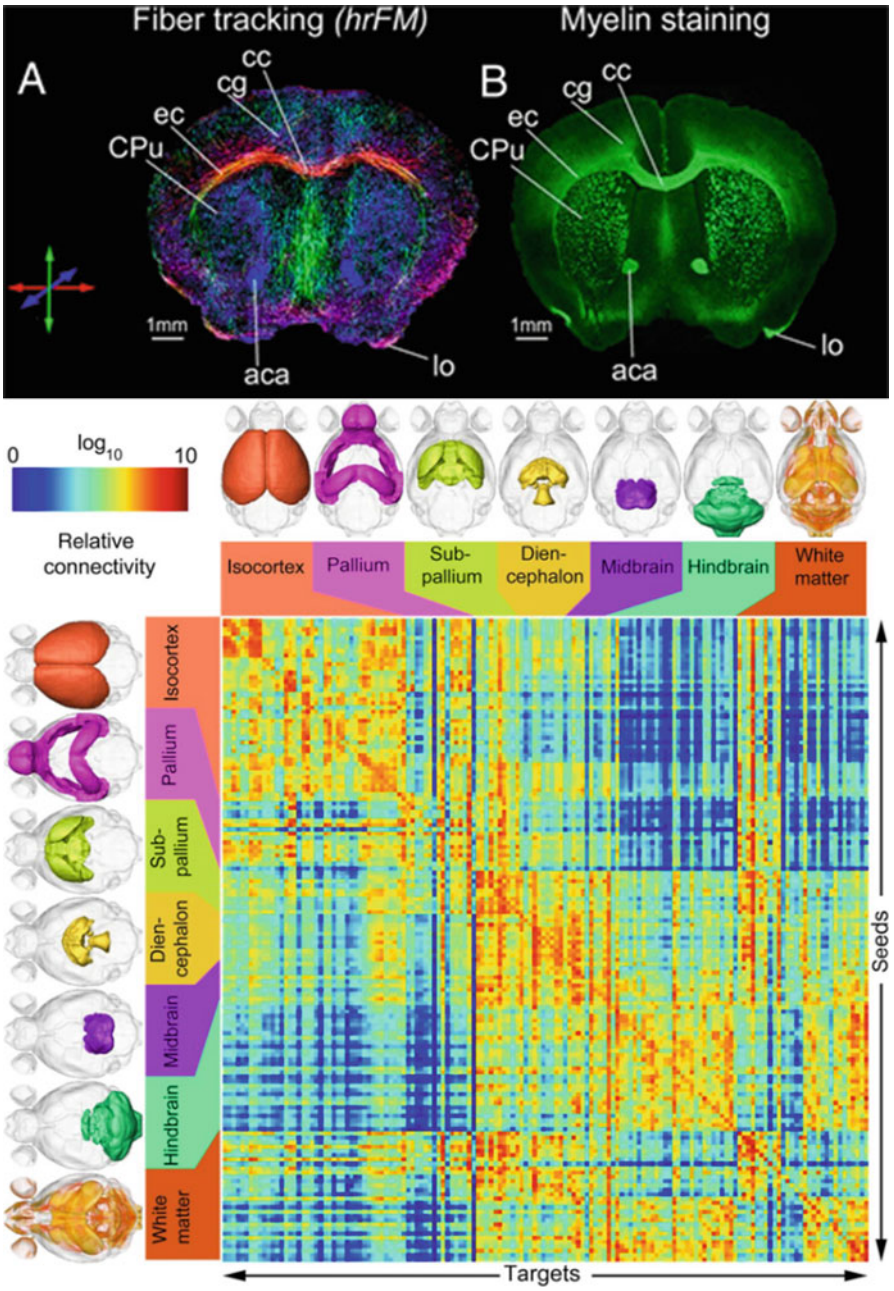

Fig. 31.4 (**a, b**). Living mouse brain connectional anatomy. High-resolution fiber maps (hrFM) generated from the global fiber tracking data and their qualitative comparison with immunofluorescent myelin staining. High qualitative resemblance of hrFM with myeloarchitecture is observed at three different rostro-caudal positions across the mouse brain. (A,B) Distance from bregma

31.3 Animal Cognition

31.3.1 Rationale

Looking from a historic perspective to understand animal cognition, Descartes argued that all animals behave like "machines" (i.e. "simple reflex devices") that do not think because they lack language ability (Rumbaugh et al. 1996). From another perspective, Darwin came up with a totally different view on animal behavior, by defending their ability to think, even in the absence of language (Thierry 2010). Contrary to Descartes's view, today it is well documented, that "animals use their thinking ability to represent events and objects in their environments" (Grieves and Jeffery 2017). Surprising insights into the animals mind and their communication abilities provide "ample evidence that animals do think" (Larkin 2013). If animals think, the next question to ask is: what does this imply about their brains? **"**If an animal turns out to think in a similar way as we do, did the animal develop a brain similar to humans? Or is the animal able to come up with the same kind of thought but with a completely different brain?" (Prior et al. 2008).

31.3.2 Animals Cognitive Functions

The spectrum of animal cognitive functions is quite broad. Here, are shown some examples of such functions with the neural correlates of animal's mind.

Human Face Recognition in Dog

Dogs have a complex social relationship with humans. One fundamental clue in support of this claim is the manner in which dogs pay close attention to human faces in order to guide their behavior. For example, they recognize their owner's emotional state using visual cues (Cuaya et al. 2016). To understand how dogs' brains perceive human faces, Cuaya and his colleagues trained seven dogs to remain awake, still, and unrestrained inside an MRI scanner (Fig. 31.5), while their brain was scanned using functional magnetic resonance imaging (fMRI).

A visual stimulation paradigm was used to compare animal's brain activity elicited by human faces versus everyday objects. Cuaya's experimental results are showing significant brain activation related to the perception of faces, mainly in the bilateral temporal cortex, with no significant brain activity change to everyday objects. Cuaya's results are consistent with reports in humans and other animals like primates and sheep that suggest a high degree of conservation of ventral visual pathway for face processing. This study confirms the role of the temporal cortex as node in the circuitry of social cognition in dogs (Cuaya et al. 2016).

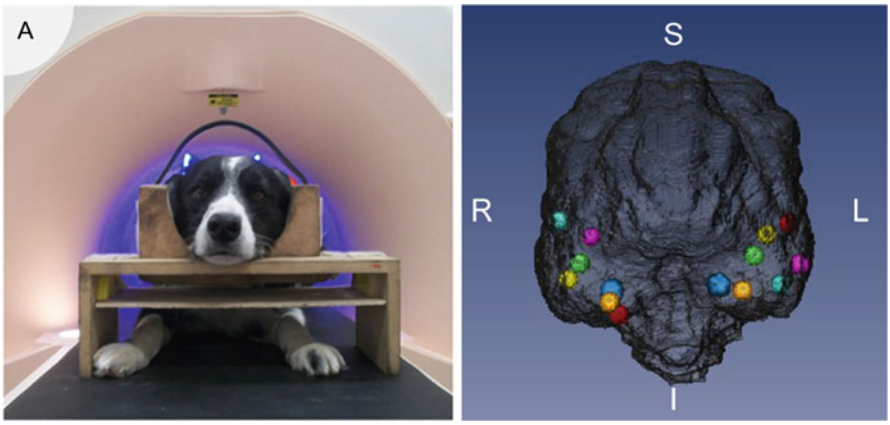

Fig. 31.5 *Left*: A dog trained in the fMRI scanner. *Right*: Location of the most sensitive region for faces in the temporal cortex (With permission from Cuaya et al. 2016)

Elephant's Memory

A question like: *Do elephants never forget?* may be an exaggeration, but nevertheless, the elephants rank among the smartest animals on the planet. Elephants have the largest brains of all terrestrial mammals, weighing around 5 kg (see Fig. 31.6) for an adult animal (Conger 2017; Shoshani et al. 2006).

Although the brain size alone cannot tell us how effectively the brain works, nevertheless, it can provide a salient hint about the power of elephant's memory.

As shown in Sect. 31.2, an animal's intelligence has been related to it's encephalization quotient (EQ). Thus, the higher the ratio of brain-to-body-mass, the smarter the animal is supposed to be and vice versa. For example, humans have an average EQ above 7, elephants of 1.88 and pigs around 0.27 (Shoshani et al. 2006). Female elephants, as the leaders of matriarchal elephant herds, show signs of better memory, alerting their herd if a potential danger arises or if a feeding ground is recognized (Herculano-Houzel et al. 2014; McComb et al. 2011). An elephant's memory encodes information necessary for survival, such as foraging locations and family members identification, in the same manner that human working memory systems selectively discard or transfer data for long-term memory storage (or future retrieval) (Hart et al. 2008). There is clear evidence that elephants have an excellent ability to remember relevant spatial details about their environment for a very long time.

Executive Decision Making in Sheep and Goat

The Sheep Compared to macaque monkeys, the sheep seems to have a similar brain size, but not the same level of intelligence, and therefore, sheep is not typically used for testing in pre-clinical cognitive studies (Morton and Avanzo 2011). However,

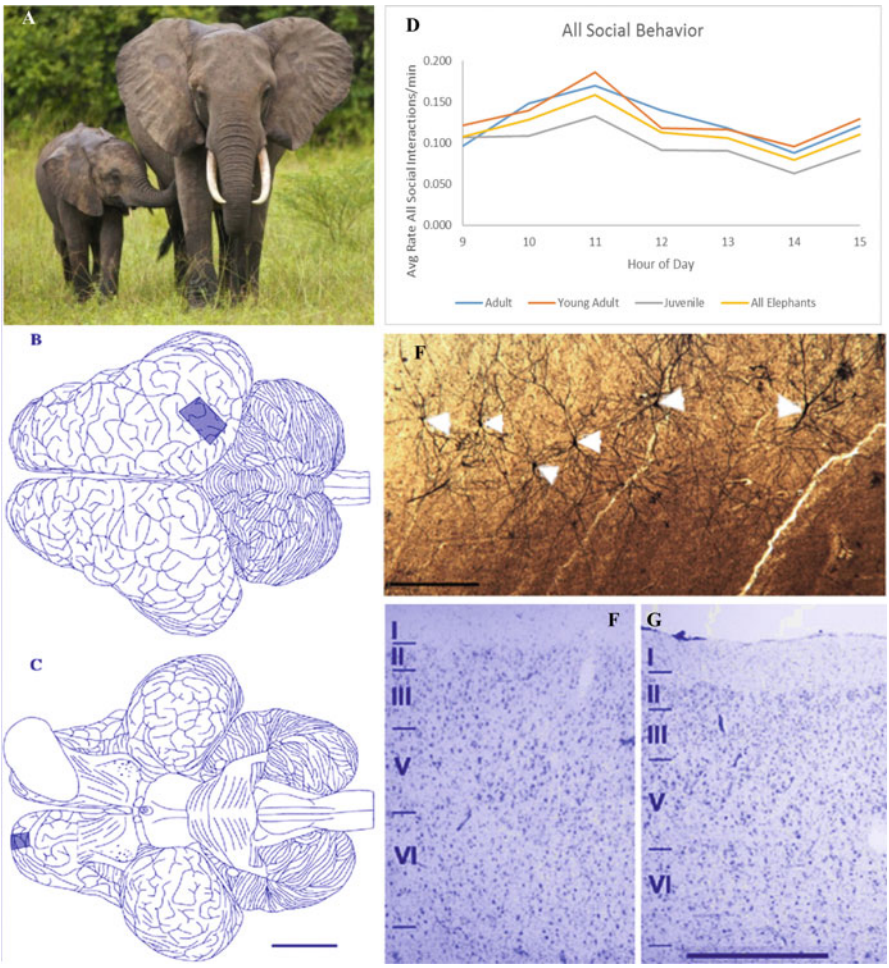

Fig. 31.6 The neural substrate of elephant's mind. (**a**) Elephant and calf. (**b, c**) Elephant brain: superior (**b**) and **c** inferior (**c**) views of the elephant brain illustrating the relative position of sampled tissue blocks (*shaded areas*) for the occipital and frontal regions, respectively. Scale bar 5 cm. (**d**) Social behavior of elephants (Redrawn from Jeffrey 2017). (**f, g**) Photomicrographs of Nissl-stained cortex from frontal (**b**) and occipital (**c**) cortex with labeled layers. Note that the elephant appears to lack a well-developed layer IV. Scale bar 1 mm (Adapted from Jacobs et al. 2010)

because cognitive decline is a key therapeutic target in Huntington Disease (HD), the sheep model of HD needs to be evaluated with feasible testing with cognitive function. Morton and Avanzo (2011) tested sheep's ability to perform cognitive tasks (discrimination learning, reversal learning, and attentional set-shifting) involving the executive function. The significant findings show that, sheep not only could perform tests of discrimination learning and reversals, but they could also perform

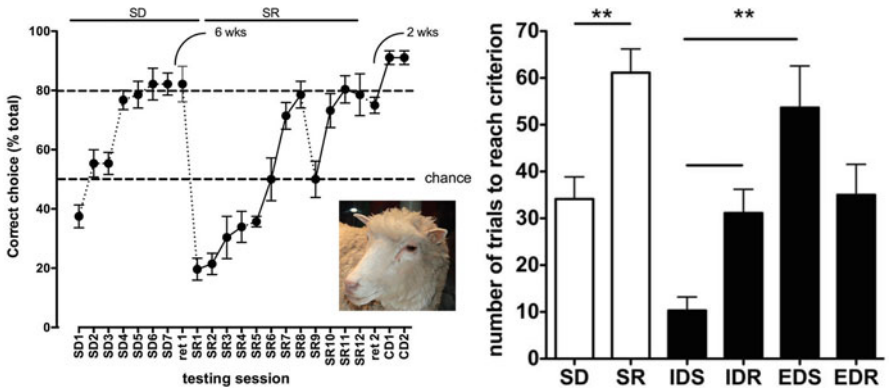

Fig. 31.7 *Left*: Performance of sheep in the two choice discrimination task. Each point represents the mean (± SEM) number of correct choices made in each set of eight discriminations. Where points are joined by solid lines, the sets of discriminations were tested on the same day. Where points are joined by *dotted* lines, testing was conducted on a different day. *SD* simple discrimination, *SR* simple discrimination reversal, *Ret1* first retention trial, *CD* compound discrimination *IDS* intradimensional shift, *IDR* intradimensional shift reversal, *EDS* extradimensional shift, *EDR* extradimensional shift reversal. *Right*: Comparison of number of trials to reach criterion in different stages of the task (With permission from Morton and Avanzo 2011)

the set-shifting tasks that are relevant for cognitive dysfunction in humans. Sheep performance on the set-shifting task mirrored that seen in humans and macaques, demonstrating that this animal can perform cognitive tasks that are useful for HD testing (Fig. 31.7).

The Goat In certain situations, animals can use their environments to decide/select based on particular sources of information (personal or social). Animals living in groups may benefit from information based on the behavior of other individuals. Indeed, social information is obtained much faster and at low cost compared to personal information, thus increasing foraging efficiency (Baciadonna et al. 2013). However, individual information becomes more reliable than social information when food locations change during the season or when food is randomly distributed. When testing in goats (*Capra hircus*) the use of conflicting information (personal versus social), during a foraging task, it was found that goats relied more on personal than social information (when both types of information were available and in conflict). This implies that goats are selective herbivores that rely on personal rather than social information to find randomly distributed resources in highly changing environments.

The Bird's Mind

The cognitive faculty of humans is not the exclusive ability of mammals, but also of the birds (Fig. 31.8) that seem to be endowed with memory, face recognition, and executive control functions, as recent research highlights in corvidae and gray

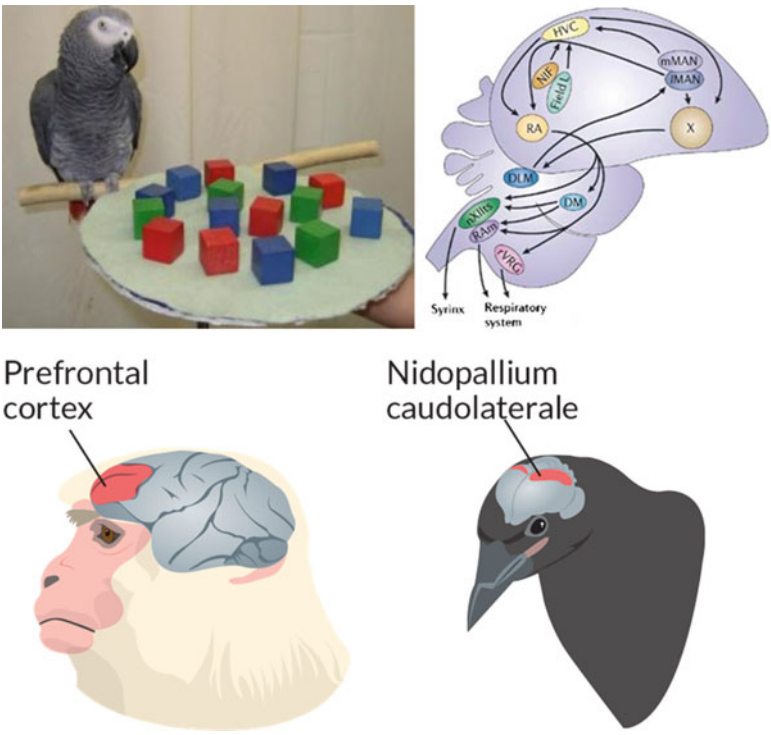

Fig. 31.8 *Upper left*: *Gray* parrot on a perch with colored objects in front of it. *Upper right*: Schematic diagrams of parasagittal view of the songbird brain. Songbirds have an elaborate network of interconnected forebrain nuclei that form an interface between auditory input (which converges on field L, the primary auditory projection region in the avian forebrain) and vocal output, which is produced in the syrinx, the avian vocal organ. The network of forebrain nuclei includes *DLM* nucleus dorsolateralis anterior, pars medialis, *DM* dorsomedial nucleus of the midbrain nucleus intercollicularis, *HVC* high vocal center, *lMAN* lateral magnocellular nucleus of the anterior nidopallium, *mMAN* medial magnocellular nucleus of the anterior nidopallium, *NIF* nucleus interface of the nidopallium, *nXIIts* tracheosyringeal portion of the nucleus hypoglossus, *RA* robust nucleus of the arcopallium, *RAm* nucleus retroambigualis, *rVRG* rostro–ventral respiratory group, *X* Area X (Adapted, with permission, from Bolhuis et al. Nature Reviews Neuroscience 7, 347–357 (2006))

parrots (Seyfarth and Cheney 1997; Pepperberg 2002, 2013; Marzluff et al. 2012; Veit and Nieder 2013; Veit et al. 2015; Bolhuis and Gahr 2006).

(a) *Working memory***.** The concept of working memory dealing with the ability of brain to retain past information for online processing, in order to guide goal-directed behavior was recently tested in corvidae (Veit et al. 2015).

Corvidae songbirds have remarkable high-level cognitive capabilities (Veit et al. 2015). To demonstrate that neurons in the avian brain process working memory in a behaviorally relevant manner, Veit and his colleagues trained four carrion crows (Corvus corone) on a delayed match-to-sample task that required the birds to

remember a visual stimulus for a delayed comparison (Veit et al. 2015). The activity of bird's neurons in the nidopallium caudolaterale (NCL, a pallial association area of the avian endbrain) was recorded while the birds performed the cognitive task. Many NCL neurons encode visual stimuli in "sustained" delayed activity and store this information after the stimulus disappeared. Such selective delay activity suggests that NCL neurons in corvidae brain encode visual working memory for short-term processing of visual information.

(b) *Rule based decisions.* Veit and Nieder (2013) tested corvidae in flexible rule-based decisions by recording single-unit activity from NCL neurons. The widespread firing activity in NCL represents the behavioral rules, becoming weaker in error trials, thus predicting the crows' behavioral decisions. This suggests that NCL cells are "mirroring the executive control functions of primate prefrontal cortex" (Veit and Nieder 2013).

(c) *Human face perception***.** Crows can remember certain human faces for years after just one encounter. Marzluff's and colleagues have shown via *in vivo* imaging of crow's brain the circuits underlying the perception of human faces (Marzluff et al. 2012). Such findings demonstrate that, similar to humans, crows use visual mechanisms to recognize human faces by integrating visual information with emotion.

(d) *Abstract representation in parrot*. Research in the gray parrot (*Psittacus erithacus*), demonstrated that one male parrot, named Alex, understood number symbols as abstract representations, in ways comparable to those of apes and young human children (Pepperberg 2013). The parrot appeared to learn these concepts in ways more similar to humans than to apes. According to Pepperberg (2002, 2013), the parrot Alex, "labeled more than 50 different objects, 7 colors, 5 shapes, about 6 quantities, 3 categories (color, shape, material) and uses 'no', 'come here', 'wanna go X' and 'want Y' (X and Y being appropriate location or item labels)". The parrot combined the above labels to "identify, request, comment upon or refuse more than 100 items and to alter his environment". This unique parrot exhibits capacities that were "presumed" to be limited to humans or nonhuman primates (Pepperberg 2002, 2013).

Cognitive Abilities of Dolphins and Whales

Dolphins The dolphins are well-documented as intelligent animals. Dolphin's large brain (Fig. 31.9) is structured for awareness and emotion. From structural perspective, the dolphin brain seems even more complex than the human brain (Bearzi and Stanford 2008; Marino et al. 2007). Folding is more, but this does not make it more complex). Dolphins are capable of mimicry and spontaneous imitation of humans (Kuczaj and Yeater 2006). An adult dolphin male copied the diver who came to clean the water tank portholes by picking up a seagull feather in the tank and stroking the glass with it. A calf dolphin, when he saw a man smoking on the other side of the glass, swam back to her mother, took a mouthful of milk, returned

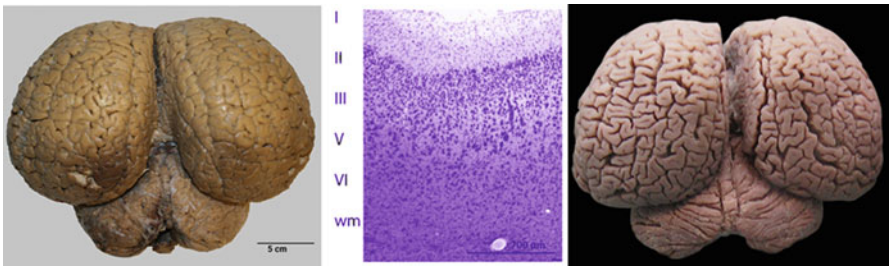

Fig. 31.9 *Left***.** Representative image of a long-finned pilot whale brain center: Laminar organization of the whale's neocortex. *Right*: Dolphin brain. Acronym (*wm* = white matter) (With permission from Mortensen et al. 2014)

to the porthole and blew a cloud of milk towards the window, exactly replicating the cigarette smoke (Safina 2015). Surviving skills like dolphin calves copying their mother's feeding techniques closely in the wild are not surprising.

Whales During courtship and migration, male whales sing songs which can be heard over dozens of kilometers. In the South Pacific, whales regularly alter their songs, with novelties moving eastward over time. A song that appears 1 year among whales feeding near eastern Australia will be heard the next year around New Caledonia (1500 km to the east). The year after the whale song gets to Tonga, and so on until it reaches French Polynesia that is 6000 km away. Another song will be started in Australia, in the meantime. There seems to be no environmental or genetic underpinning for this, the succession of songs seems a matter of fashion, or whale's "cultural change on a vast scale" (Derbyshire 2011).

31.4 Insights into the Animal's Mind

31.4.1 Transfer of Memory in Rats

A unique feature of memory-transfer in rats was demonstrated by Deadwyler et al. (2013) when patterns of successful information encoding were derived online from well-trained animals ("donor") during long-delay memory trials and delivered *via* online electrical stimulation to synchronously tested naïve animals ("recipient"), never before exposed to the memory delay feature of the task (Fig. 31.10). By transferring such memory trained (donor) animal hippocampal firing patterns *via* stimulation to coupled naïve recipient animals, their task performance was facilitated in a direct "donor-recipient" manner. This provides the basis for utilizing extracted appropriate neural information from one brain to induce, recover, or enhance memory related processing in the brain of another subject.

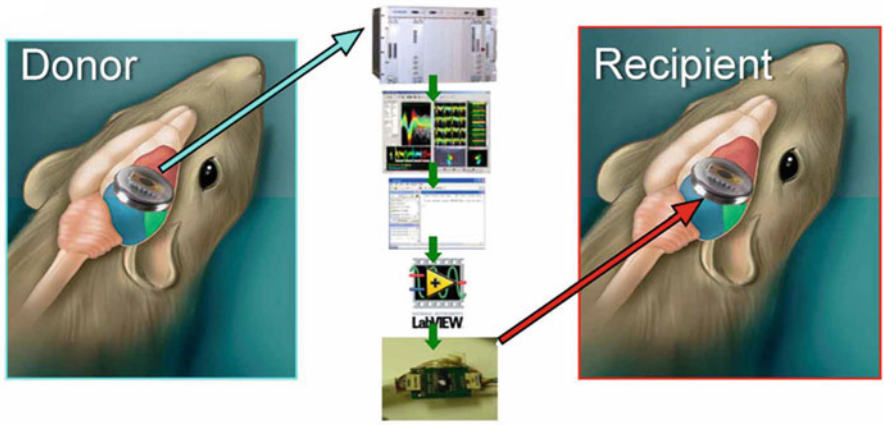

Fig. 31.10 Transfer of memory from one well trained rat (donor) to a naïve rat (recipient). Recordings were obtained online from donor rats with validated effective stimulation patterns in CA1. Naïve animals (recipients) were only trained to perform the memory task in sequence without exposure to extended delay intervals interposed between task phases requiring completion of the nose poke response on the opposite wall (*red* middle diagram) (With permission from Deadwyler et al. 2013)

31.4.2 Social Cognition in Animals

Social behavior is perceived as a "set of interactions" among the individuals of the same group/species. A rich spectrum of social behaviors occurs among animals. One reason of "why do animals help others at the potential cost of their own survival and reproduction?" is that social behavior is "adaptive", meaning that social behavior ultimately enhances an animal's "chances to survival and fitness", including its lifetime reproductive success (McGlynn 2010) One example of how social behavior is adaptive is "aggregation against predators". Living in groups involves a balance of conflict and cooperation, which is mediated by the costs and benefits associated with living socially. From the Neuroeconomics perspective, one can predict that "social cooperation" will be favored when the benefits of living socially exceed the costs and risks of social life. Two features of social behavior are beneficial: altruism and reciprocity, and both of which involve synergy (McGlynn 2010).

Social groups are formed to increase the probability of survival and reproduction of group/species members. One can distinguish two categories (Fig. 31.11) of social animals: a) *highly social animals*, such as packs of wolves, school of fish, and herds of herbivores, and b) *asocial animals*, like polar bears, that rarely interact to each other.

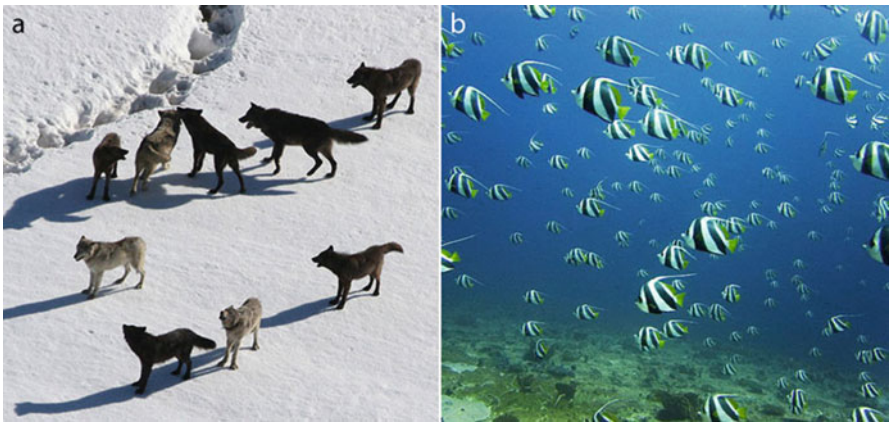

Fig. 31.11 Social groups which have formed to improve the probability of survival and reproduction of individual members: pack of wolves (**a**) and school of fish (**b**) (With permission from McGlynn (2010))

An *altruistic* act of one member of the group increases the welfare of another member at the cost of the member who performs the act. For example, ground squirrels, may warn other members of their group about a predator, with the risk to attract predator's attention upon the member giving the warning call. Such risky behavior benefits other members of the squirrel's group. *Reciprocity* assumes a permutation of altruism act by other members, and in fact, enables the existence of altruism. The long term benefit of altruistic behavior can outweigh its costs, being ultimately measured in on an animal's lifetime reproductive success.

Conclusion To conclude, contrary to expectations, animals possess excellent perceptual and cognitive skills that sometimes surpass those of humans. This is likely because animal cognition in mammals relies on the modular arrangement of the neurons in the cerebral cortex that allow the emergence of various aspects of the mind (attention, memory, decision making or motor planning). Moreover, animals are capable of using tools, to live in hierarchical society, and to develop empathy towards animals from different species. Comparing social interaction of individuals with the interaction of molecules one can easily realize that the species that have a hierarchy are more advanced than those that do not have a social interaction. The physics of the mind of animals captures the unique organization across many scales of living and nonliving matter emerging from the low molecular level to the cellular, systems/cognitive and social levels.

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Chapter 32
Blood-Brain Barrier and Cognitive Function

Ana-Maria Zăgrean, Bogdan Ianosi, Cosmin Sonea, Ioan Opris, and Leon Zăgrean

Abstract The blood-brain barrier (BBB) is the highly specialized and selective crossing area between blood and brain, essential for brain homeostasis and functioning, formed by the endothelial cells of the cerebral microvasculature in a rich and intimate cooperation with the neighboring cells and local signaling factors from both the brain and blood sides. Its distribution throughout the brain is following the brain cytoarchitectonic patterns, each capillary serving the adjacent neurons in a privileged neurovascular interplay that ultimately responds to the manifestation of brain functions, scaled from the cellular to the system level. At the edge of our understanding, cognition stands for what makes us humans and needs the cooperation of the entire body functioning to assist homeostatic favorable conditions for its manifestation. The cerebral endothelial system is operating at this interfacing point, modulating its own phenotype in accordance with various conditions to which the organism and brain are exposed, responding with changes in its permeability and signaling processes. In this chapter we will briefly describe the multicellular assembly of the neurovascular unit from which the BBB emerges, and its contribution

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to the brain homeostasis by dynamic neurovascular and neurometabolic coupling processes. Further, we will refer to the principal morphologic and functional features of the BBB from which its specific properties arise, making it not just a physical selective barrier, but also a metabolic, neuroimmune and endocrine interface. We will touch on the physiological implications of BBB and neurovascular coupling on high brain functions and cognition, in normal or disease-associated conditions.

Keywords Blood-brain barrier • Neurovascular unit • Neurovascular coupling • Neurometabolic coupling • Cognition • Brain diseases • Cerebral endothelial cells • Cerebral microcirculation • Neuroenergetics • Aging

32.1 Introduction

The blood-brain barrier (BBB) is a dynamic and selective interface between blood and brain, constituted by the specialized endothelial cells of the brain microcirculation, escorted by perivascular cells, pericytes, glial cells, neurons, in a complex cooperation. Within this cellular establishment that form functional neurovascular modules, BBB governs communication between brain and blood and counteracts the fluctuations in the composition of blood and brain interstitial fluid to maintain a precisely regulated brain microenvironment, essential for a reliable neuronal signaling (Abbott 2013).

The brain has a high metabolic rate and uses about 20% of the available oxygen for maintaining its normal functioning and cognition (Siesjo 1978). The proper brain delivery of oxygen and glucose, as main metabolic substrate, is sustained by a continuous blood flow in all cerebral capillaries, tightly regulated by neuronal activity in a process known as functional hyperemia. Secondary to neuronal activation there is a transition of low-flow to high-flow capillaries, described as functional recruitment (Akgoren and Lauritzen 1999; Kuschinsky and Paulson 1992; Paulson 2002), resulting in a more homogeneous flow into the capillary bed (Kleinfeld et al. 1998; Vogel and Kuschinsky 1996).

Cerebral blood flow and cerebral metabolic rate of oxygen are locally controlled by the synaptic activity, an effect modulated by perivascular pericytes, astrocytes and neurons (Attwell et al. 2010; Mathiesen et al. 2011). The rate of oxygen consumption is especially high in the frontoparietal cerebral cortex, where the processes of neural synchrony that encodes specific cognitive functions or item of information within highly interactive neuronal networks (cognits) is supported by a metabolic demanding synaptic activity accompanied by an adequate neurovascular dynamic (Ardestani et al. 2016).

BBB is critically involved in brain processes responsible for perception, motor activity and cognitive functions by timely responding to the high metabolic rates in neurons and astrocytes during neuronal activity, a relation based on neurovascular, neurometabolic and neurobarrier couplings (Magistretti 2000; Leybaert 2005). This partnership, manifested especially at the level of gray matter, is supported by the

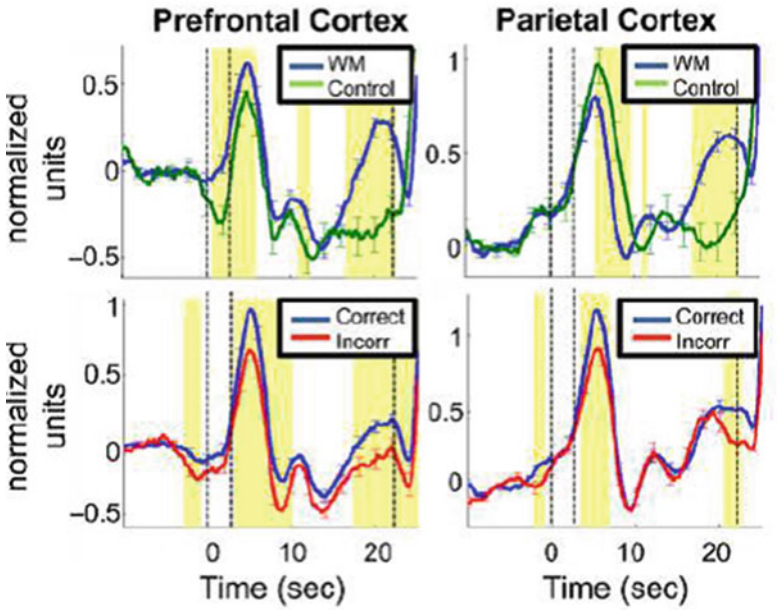

Fig. 32.1 Near infrared Spectroscopy (NIRS) amplitude during task performance of one monkey. Each plot is standardized with respect to its own baseline. The *top pair* of panels depicts the mean NIRS time course for working memory (WM) and control task trials, whereas the *lower pair* does the same for correct and incorrect performance. *Highlighted segments* indicate significant difference between the two conditions ($p < 0.05$ on a cluster permutation distribution from 5000 iterations). *Error bars* denote variance computed across trials. *Vertical dotted lines* demarcate the stimulus (cue) epoch at $t = 0–2$ s, and the choice stimulus at $t = 22$ s (With permission from Ardestani et al. 2016. ©2016 by the Massachusetts Institute of Technology, published by the MIT Press)

differences in the capillarization of the cerebral cortex laminae, corresponding to their cytoarchitectonic patterns, as extensively described in Bar (1980).

For example, Ardestani et al. have recently shown neuromodulation of frontoparietal neurovascular dynamics (Fig. 32.1) in the working memory of nonhuman primates (Ardestani et al. 2016).

There seems to be a direct relationship between the lamination of the cortex and the cerebral blood volume, and between blood oxygenation and brain functions (Frostig et al. 1990; Attwell et al. 2010; Hall et al. 2014). In Fig. 32.2 Huber et al. (2015) shown cortical profiles of cerebral blood volume (CBV) and blood oxygenation level-dependent (BOLD) signal, non-invasively and simultaneously. They used a method based on slice-selective slab inversion of vascular space occupancy (VASO) at high magnetic field (7T). This allowed them to capture layer dependent CBV responses in humans. VASO may thus play an important role in revealing top-down or afferent-efferent stimulus processing in the brain using layer-dependent fMRI.

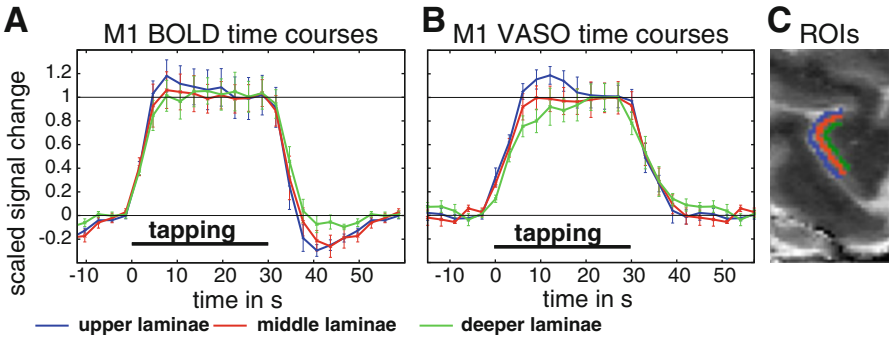

Fig. 32.2 Layer-dependent vascular space occupancy (VASO) and blood oxygenation level-dependent (BOLD) signal time courses. Time courses for BOLD (**A**) and VASO (**B**) signal at different cortical depths. Compared to the amplitude of the total signal change, the differences in time courses for different cortical depths are relatively small. There is a tendency of stronger BOLD signal overshoot and undershoot at the cortical surface. An overshoot approximately 10 s after stimulus onset is also clearly visible in VASO, while the post-stimulus signal does not show a clear laminar signature. Cortical depth-dependent differences in signal time courses could potentially reflect: local differences in neural activity, different neurovascular coupling, or different macrovascular contributions for different cortical laminae. For the sake of clarity, only three time courses are depicted corresponding to: cortical surface, middle cortical laminae, and deep cortical laminae. The respective ROIs are depicted in panel (**C**) for a representative subject (With permission from Huber et al. 2015)

Next, we will present the BBB features that make it a highly active interface in the neurovascular assembly and will touch on the physiological implications on high brain functions. Further, the concurrence of BBB breaks in some neurological conditions evolving with cognitive impairment will be exemplified.

32.2 The Blood-Brain Barrier of the Neurovascular Units: A Dynamic Interface

32.2.1 The Neurovascular Interface

Brain processes, from the simplest manifestation of excitability to higher cognitive functions, delicately rely on the elaborated functional interconnections and signaling between neurons, perivascular astrocytes, microglia, pericytes, extracellular matrix and the endothelial cells from the abundant cerebral microvascular territory in the gray matter. These cell types are integrated in dynamic multicellular functional modules, called neurovascular units (NVUs), as shown in Fig. 32.3. The short diffusion distance between neurons and capillaries (~8–25 μm) enables one NVU module to serve just a small number of neurons (Abbott 2004).

The NVU functions as a complex and dynamic brain-vessel-blood interface, with an essential role in the maintenance of cerebral homeostasis by formation of the

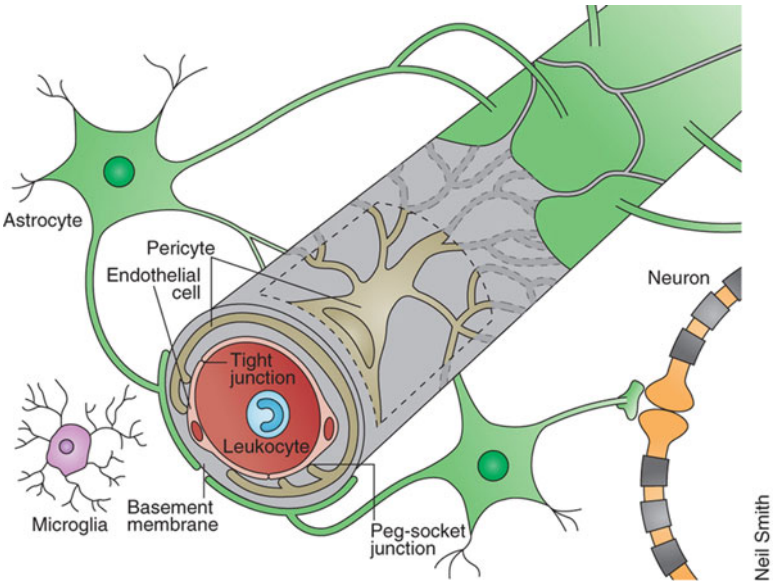

Fig. 32.3 The BBB is part of the NVU, which represents an elaborate interplay of central and peripheral cells. Vascular endothelial cells sealed by tight junctions constitute the BBB. The endothelium's abluminal surface is covered by a basement membrane in which pericytes and their processes are embedded. Direct intercellular crosstalk between endothelial cells and pericytes are implemented by peg-socket junctions. Astrocytes extend foot processes that encircle the abluminal side of the vessel to an extent of nearly 100%. Neurons and microglia are considered members of the NVU as they interact with core elements of the BBB and influence barrier functions. Peripheral blood cells, including leukocytes, also participate in this cellular interplay as they modulate BBB functions under pathological conditions such as inflammation (Reprinted by permission from Macmillan Publishers Ltd: Nature Medicine, Obermeier et al. 2013)

BBB and by timely adjusting local cerebral blood flow to the actual needs within the process of neurovascular coupling. The intimate interaction and interdependence between all cellular components of the NVU, contribute to the diverse brain functions, therefore the function of each cell type is important in the context of the whole community of cells comprising the neurovascular microdomains. Similarly, a dysfunction of one NVU cell type (endothelial cell, pericyte, perivascular astrocyte, microglia or neuron) is finally accompanied by NVU dysfunction, with BBB opening, microvascular impairment and alteration in brain microenvironment, synaptic activity, neuronal excitability etc., resulting in various brain pathologies like stroke, hemorrhage, vasogenic edema, epilepsy, brain edema, tumors, trauma, infection, inflammation, neurodegenerative disorders, with different levels of cognitive impairment (Schoknecht et al. 2015; Ghosh et al. 2015; Zlokovic 2008). Understanding the multicellular crosstalk in the NVU is important for developing new, cell-targeted therapeutic strategies aiming to maintain the BBB function (Attwell et al. 2015). More data on cerebral microvasculature, neurovascular coupling and cerebral blood flow is described in Chap. 33 (A. Domschke, F. Bohm).

Components of the NVU – astrocytic endfeet, pericytes, microglia and neurons – have an essential role in inducing and preserving the BBB phenotype. To exemplify the dynamic reciprocal support between the cellular components of the NVU, it's worth to mention the modulatory effects of cerebral endothelial cells on neuronal cells, as well as on neural stem cells and neurogenesis, by secretion of growth factors like vascular endothelial growth factor (VEGF), brain-derived neurotrophic factor (BDNF) and nerve growth factor (Ward and Lamanna 2004).

Pericytes surrounding capillaries are contractile cells that have recently been shown to respond to neuronal activation by vasodilation faster than arterioles (Hall et al. 2014), functioning as highly sensitive sensors of neurovascular coupling. Pericytes are found in a ratio of 1:3 with endothelial cells and communicate with them through gap junctions (Pardridge 1999). This direct cellular networking enables the transmission of the hyperpolarizing vasodilatory signals towards arterioles, thus significantly contributing to local blood flow distribution at microcirculation level. Pericytes also contribute to formation of BBB basement membrane. Recent studies associate pericyte deficiency with increased BBB permeability to water and to low- and high-molecular mass compounds, such as cholesterol, whose passage across the BBB increases in both directions (Saeed et al. 2014).

Within NVU, the polarized perivascular astrocytes strategically bridge cerebral microvessels and adjacent neurons, promoting neurovascular coupling through a lively traffic of molecules and ions and metabolic processes, as reviewed in Obermeier et al. (2013) and Cabezas et al. (2014). Remarkably for the complexity of integration of neural activity and vascular network, the protoplasmic astrocytes within gray matter are organized in non-overlapping domains and are interconnected by gap junctions constituting a functional syncytial network that may contact about 160.000 synapses (Cabezas et al. 2014). The extracellular K^+ increases generated by sustained synaptic activity, enters into the perisynaptic segment of astrocytes triggering an electrochemical gradient that leads to K^+ efflux at distant perivascular astrocytic endfeet. This mechanism of K^+ spatial buffering towards the perivascular space is facilitated by the inwardly rectifying Kir4.1 channel present in high density in the perivascular astrocyte membrane (Abbott 2002). Astrocytes also uptake K^+ by route of Na^+, K^+-ATPase and Cl^- cotransporter NKCC1, enabling a reversed spatial K^+ buffering when neuronal activity diminishes or ends, thus preventing K^+ loss from the brain through the low permeability endothelial route (Amiry-Moghaddam and Ottersen 2003).

Synaptic activity engages release of high amounts of neurotransmitters, especially glutamate, that need to be recovered fast to keep the synapse homeostasis, by a Na^+-driven cotransport into the adjacent astrocytes. The increased intracellular ionic concentration osmotically drives water and determine astrocyte swelling. Water is then redistributed towards the perivascular space and interstitial fluid by the aquaporin 4 (AQP4) present in high density at the perivascular astrocytic membrane (Abbott 2002).

The neurobarrier coupling, as a signaling within NVU from neurons to endothelial cells, can be exemplified by histamine or other transmitters released from the nerve endings consecutive to neuronal activity that act on the endothelial cells

to increase glucose transport into the brain and to transiently modulate the TJs to facilitate the passage into the brain of various growth factors and antibodies (Abbott et al. 2006). Importantly, signaling at NVU determine Ca^{2+} waves into the astrocytic syncytium transmitted via astrocyte-endothelial cell gap junctions and purinergic transmission to endothelial cells. Here, Ca^{2+} signaling further causes activation of different signal transduction pathways, resulting in cytoskeletal proteins' phosphorylation, TJ opening (Abbott et al. 2006) and vasodilation through nitric oxide (NO) production. In inflammatory conditions, NO produced in high amounts through inducible NO synthase increases the permeability of the BBB (Sloan et al. 2012).

The neuronal-astroglial-pericyte-endothelial cell crosstalk, without mentioning the immune cells, governs the dynamic changes in the interstitial fluid and volume transmission, promotes the synaptic homeostasis and synaptic plasticity, to respond to the continuous requirements for a coordinated activity of neuronal networks involved in the higher cognitive functions. Recent functional neuroimaging studies based on changes of local hemodynamics during neural activity are investigating the physiology of neurometabolic-neurovascular coupling in search for a suitable dynamic model to capture specific mechanisms, as recently reviewed by Huneau et al. (2015). Pathological conditions such as cerebrovascular and degenerative disorders associating with NVU disruption, alter the continuous adaptation of blood supply to local energy needs at the cerebral level (Huneau et al. 2015).

32.2.2 What Makes the Endothelium of the Cerebral Microcirculation a Physical and Functional Interface

Particularly to the brain, endothelial cells form a continuous cellular layer being interconnected by high density, high resistance tight junctions (TJs) intermingled with adherens junctions.

The distribution of TJs in the cerebral microvascular endothelium (more at capillary level then at the arteriolar and venule levels) give a certain heterogeneity in the tightness of the barrier and depends on the interaction of endothelial cells with astrocytes and pericytes (Wilhelm et al. 2016). The endothelial layer is surrounded by an extracellular matrix and pericytes, further covered on more than 90% of its surface by glial endfeet processes, constituting the glia limitans perivascularis (McArthur et al. 2016), as shown in Fig. 32.4.

The BBB is freely permissive for oxygen, carbon dioxide, and small neutral lipophilic substances (<500 Da), such as narcotics or alcohol. These molecules cross BBB as a consequence of their concentration gradients through transient gaps in the cell membrane formed by continual motion of the membrane phospholipids' tails (Abbott 2004). However, brain endothelial cells have cell membranes more enriched with cholesterol that enhance their resistance to passive transmembrane passage (Aänismaa et al. 2008) and strictly controls the entry and exit of hydrophilic molecules between blood and brain. Thus, BBB restricts the entrance into the

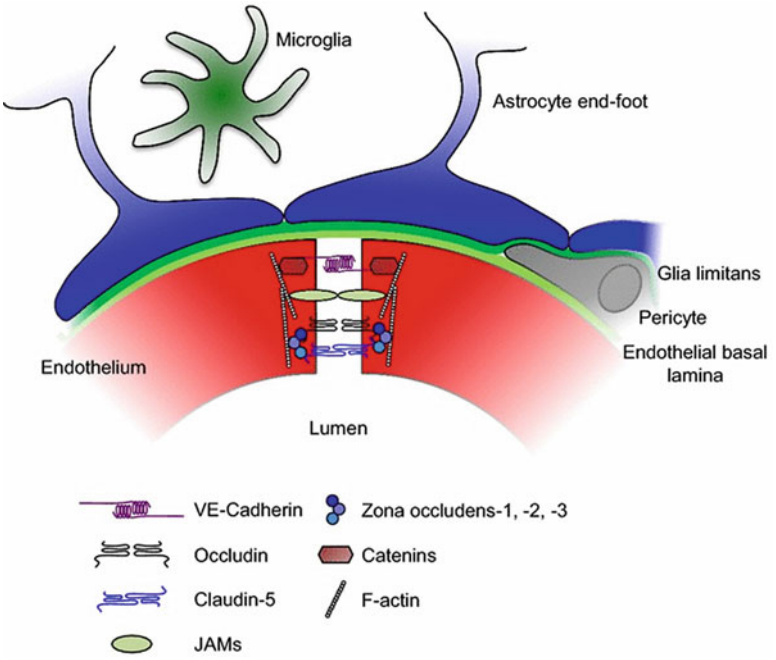

Fig. 32.4 Schematic depiction of the principal molecular and cellular components of the neurovascular unit that regulate inter-endothelial permeability, and thereby provide the foundation of the blood–brain barrier. *JAM* junctional adhesion molecule (With permission from McArthur et al. 2016, under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/)

brain of hydrophilic drugs, plasma proteins (albumin), blood cells and harmful compounds and preventing the loss of substances from the brain. One example of protein crossing from the brain to the blood, with diagnostic value for an altered BBB, is protein S-100, synthetized in increased amounts in the damaged nervous tissue (e.g., stroke, severe head trauma, brain tumors, multiple sclerosis, etc.). The blood level of S-100 is used as a sensitive although not specific marker for early detection of BBB integrity disruption and neuronal injury (Sendrowski et al. 2004).

Through specialized carrier-mediated transport systems, placed in a polarized apical and basolateral pattern (Wolburg et al. 2009), the brain endothelial cells translocate ions, glucose, amino acids, other nutrients essential to life and energy metabolites. Through active efflux transporters, mostly represented by ATP-binding cassette (ABC) efflux transporters (P-glycoprotein and multidrug resistance-related proteins) located on their luminal and abluminal membranes, cerebral endothelial cells prevent accumulation of xenobiotics, impedes the entry of therapeutic drugs and remove molecules from the brain into the blood.

The BBB has a low hydraulic conductivity and water takes more the transcellular route then the paracellular pathway across the endothelial layer (Choi and Kim 2008), even it has few or no aquaporin 1 (AQP1) as the other endothelial territories

constitutively have (Nielsen et al. 1993; Abbott 2002). In the brain, AQP1 is present just at level of choroid plexus, ependyma and pia (Nielsen et al. 1993). This particular configuration alters Starling's forces in the brain, as ions retained in the vascular lumen counterbalance the water movement due to hydrostatic pressure. This supplementary control of water and osmotic active particles movement across the BBB is essential in the brain, considering its limited capacity for expansion within the rigid skull and the fact that water is also generated within the brain from the glucose metabolism accompanying neuronal activity at a rate of ~28 nl/g min^{-1} (Rapoport 1976). A failure in the BBB control on osmoregulation causes vasogenic edema and increases the intracranial pressure, triggering severe neurologic complications and even death (Cipolla 2006).

The cerebral endothelium restricts and regulates the entry into the brain of large hydrophilic peptides and proteins (e.g. signaling molecules, growth factors) by receptor-mediated and adsorptive transcytosis (Abbott 2002). By restricting the peptide transport, BBB limits the brain innate immune response and the proliferative potential of its microenvironment (Abbott 2004). The low pinocytotic activity of endothelial cells is maintained by factors released from perivascular astrocytes (Petty and Lo 2002). All these features greatly increase the trans-endothelial electrical resistance from 2–20 Ohm/cm^2 in peripheral capillaries, to about 1500–2000 Ohm/cm^2 in cerebral endothelium (Petty and Lo 2002; Abbott 2002). Through concurrent transport mechanisms, BBB maintains lower concentration of proteins, K^+ and Ca^{2+}, and higher levels of Mg^{2+} in the brain interstitial fluid comparatively with plasma concentrations, to enable an appropriate synaptic and axonal signaling.

More than a physical barrier endowed with a specific transport system, the BBB also acts as a metabolic/enzymatic barrier through ecto-enzymes (peptidases and nucleotidases) and intracellular enzymes (monoamine oxidase and cytochrome P450, 1A and 2B) that modifies molecules in transit (e.g., metabolize biologic active molecules, inactivate neuroactive and toxic compounds) (Abbott 2002; Zlokovic 2008). Also, glutathione, a ubiquitous thiol with essential cellular functions, contributes to endothelial barrier preservation by protection against oxidative injury and control of cell proliferation in post-injury endothelial repair (Li et al. 2012).

Additionally, the BBB is a regulatory endocrine interface between the peripheral tissues and central nervous system (Banks 2012a, b), with multiple roles in hormonal regulation, feeding behavior, gut-brain crosstalk or sleep, with important effects on behavior and cognitive processes.

Moreover, the BBB works as an interface for the neuroimmune crosstalk, by recruitment of leukocytes, enabling an immune surveillance, while mitigating inflammation and cellular injury (Abbott et al. 2010). Considering the complex interactions between leukocyte and vascular cell surface (e.g. adhesion molecules, signaling through cytokines, etc.) it was recently proposed that circulating leukocytes together with the glycocalyx of the cerebral endothelium, could be incorporated in an "extended NVU" (Neuwelt et al. 2011).

BBB is more permeable at the level of circumventricular organs (CVOs), because of fenestrations and discontinuous TJs, in relation to the function of these highly specialized brain areas (area postrema, median eminence, neurohypophysis, pineal

gland, lamina terminalis and subfornical organ), which necessitate communication with the blood (e.g., hormones release and transport). However, CVOs have a limited surface area of only 1/7500 to 1/5000 of the BBB and are endowed by other barrier restrictions through particular glial cells, tanycytes and ependymal cells, that limit the diffusion of the circulating substances just into the CVO (Ueno 2007). Another examples of more permeable endothelial layer than the BBB are blood-CSF barrier, formed by the choroid plexus, discussed in Chap. 34 (I. Cherian and M. Beltran), and the blood-spinal cord barrier, with less numerous intercellular TJs and pericytes (Bartanusz et al. 2011).

Understanding the complex system of the brain microvascular endothelium, its development and maintenance during life, its interaction with the other components of the NVU and how it continuously and precisely deals with the extraordinary dynamics of concurrent blood and brain factors and events, is important for further understanding of the seen and unseen performance of the brain, in physiological and altered conditions.

Paracellular Tightness of Cerebral Endothelium and Its Role

As soon as the structures of the central nervous system develop during the embryonal life, the capillaries from where they derive their blood supply already form TJs between their endothelial cells. Finally, the surface of endothelial cells in the brain microvasculature is entirely in contact with the adjacent endothelial cells through apical TJs and basolateral adherens junctions (e.g. cadherins, catenins), to prevent passive movement into the nervous tissue of various compounds carried through the blood flow (Tietz and Engelhardt. 2015). The tightness of the intercellular contacts is enough to restrict even the passage of small ions (e.g. Na^+, Cl^-). Adherens junctions are not just accompanying TJs, but they are essential for TJs formation early in development and further for their maintenance in adults (McCaffrey et al. 2007; Wolburg and Lippoldt 2002). Dysregulation of tight junction proteins, that make BBB more permissive for paracellular transport, accompanies acute (e.g. ischemic stroke, seizure, hypertension, eclampsia) or chronic (e.g. multiple sclerosis, Alzheimer's disease) brain diseases.

TJs consist in a complex of transmembrane integral proteins, claudins, occludin and junction adhesion molecules (JAMs), and cytoplasmic accessory proteins (Fig. 32.4). Claudins contribute to the tightness of paracellular barriers and form through their extracellular loops interendothelial pores that enable bidirectional water passage along the length of the junction (Stamatovic et al. 2008; Tang and Goodenough 2003).

Claudins and occludin are attached by cytoplasmic anchoring proteins, such as zona occludens proteins 1, 2 and 3 (ZO-1, 2 and 3) (Furuse et al. 1993), which bind them to the actin cytoskeleton (Wolburg et al. 2009) to maintain the TJ structure. Also, occludin contributes to preservation of the endothelial cytoskeleton (Chiba et al. 2008), mediates endothelial response to inflammatory conditions and apoptosis by inhibiting mitogen-activated protein kinases (MAPK)

and Akt signaling pathways (Murata et al. 2005). Occludin, claudin-5, and ZO-1 are sensitive indicators of the BBB functional state. The matrix metalloproteinases (MMP2, MMP9) released from brain cells and leukocytes degrade occludin, claudin-5 and extracellular matrix when increased. MMPs have physiological roles in axonal growth, synaptic plasticity, and vascularization, but their increased activity in inflammatory conditions, cerebral ischemia/hemorrhage or neurodegenerative diseases conducts to disruption of BBB and NVU, and leads to cognitive impairment (Weekman and Wilcock 2016). The therapeutic inhibition of MMPs to reduce BBB permeability and edema after stroke should be carefully considered during a short therapeutic window, as MMPS are also involved in the repair processes (e.g. neuroblast migration, neuronal plasticity) (Zhao et al. 2006).

JAM-1 and JAM-3 are members of the immunoglobulin (Ig) superfamily present in the cerebral microcirculation, that contribute to the development of cerebral endothelial cells polarity (Rehder et al. 2006), bind to ZO-1, localize with actin and are involved in regulating leukocyte passage through BBB (Itoh et al. 2001).

An important aspect for various physiologic and pathologic conditions, the complex apparatus of the TJs at the level of BBB is finely regulated by extracellular and cytoplasmic factors, such as Ca^{2+} and protein kinases, influencing the strength of intercellular adhesion and the anchoring to TJ transmembrane proteins to the endothelial cytoskeleton (Hawkins and Davis 2005).

Annexin A1 (ANXA1), normally expressed in the cerebral microvascular endothelial cells near the intercellular contact areas of the cell membrane, is a calcium-dependent phospholipid binding protein, that maintains endothelial TJs and has an anti-inflammatory activity by limiting leukocyte migration, as described in McArthur et al. 2016. ANXA1 is expressed in brain endothelial cells beginning with fetal development and is downregulated in aging, when paracellular BBB transport is increased. ANXA1 is involved in neurological diseases like Alzheimer's disease, stroke or multiple sclerosis, conditions that could benefit from its use in various therapeutic strategies to reverse the coexistent BBB damage.

Specialized Transcellular Transport Through the Blood-Brain Barrier

The BBB controls the bidirectional transcellular transport in five main ways: carrier mediated transport, efflux carriage, ion transfer, fluid-phase endocytosis, receptor-mediated transport and adsorptive-mediated passage (Zlokovic 2008; Chen and Liu 2012; Vidu et al. 2014) (Fig. 32.5).

Specific carrier transporter systems of the BBB are used to transport hexoses (e.g. glucose, galactose), amino acids (neutral, basic and acidic amino acids), monocarboxylic acids (lactate, pyruvate and ketone bodies), amines, purines, nucleosides, and vitamins (Zlokovic 2008). These substances passage in and out the brain by facilitated diffusion depends on their concentrations and on brain needs.

The major glucose carrier of the brain endothelial cells and perivascular astrocytes is GLUT-1, an insulin-insensitive and saturable bidirectional transporter, that mediates facilitated diffusion of glucose down the concentration gradient, both at

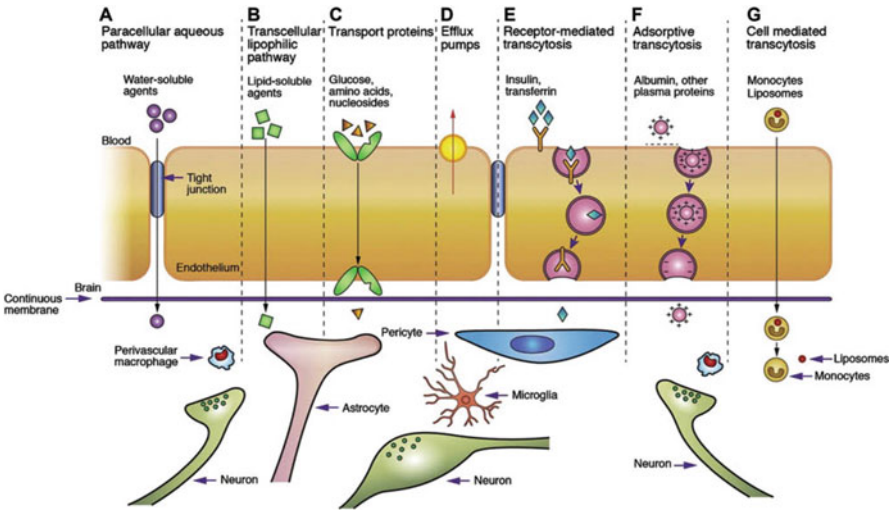

Fig. 32.5 Transport routes across the blood–brain barrier. Pathways "a" to "f" are commonly for solute molecules; and the route "g" involves monocytes, macrophages and other immune cells and can be used for any drugs or drugs incorporated liposomes or nanoparticles. (Adapted with minor changes from Advanced Drug Delivery Reviews, Vol 64 (7), Yan Chen and Lihong Liu, Modern methods for delivery of drugs across the blood–brain barrier, P. 26, 2012, with permission from Elsevier)

the luminal and the abluminal membranes of the endothelial cells (Boado and Pardridge 1993). By the neurometabolic coupling process described by Magistretti (2000, 2009), glucose uptake and glycolysis is stimulated by activation of Na^+-K^+-ATPase via the sodium-coupled glutamate uptake consecutively to synaptic activity. Endothelial GLUT-1 is locally upregulated in response to sustained or repeated energy demanding processes, especially cognitive functions. Also, endothelial GLUT-1 activity and expression is either increased or decreased in different environmental conditions like chronic hypoglycemia and hypoxia (Simpson et al. 1999; Boado and Pardridge 2002) or hyperglycemia, respectively, through an astrocyte-to-endothelial cell communication involving a neurobarrier coupling (Leybaert 2005).

The excitatory amino acid transporters 1–3 (EAAT1–3) are located mainly abluminal, to move EAA (glutamate, aspartate) out of the brain, using an abluminal Na^+ gradient created by Na^+-K^+-ATPase activity. Na^+-dependent glutamate transporters move glutamate out of the brain against a high concentration gradient (less than 1 μM in the interstitial fluid compared to about 100 μM in the plasma). The timely uptake of glutamate from the interstitial fluid is essential for a homeostatic neuronal signaling and, together to the recently discussed GABA efflux from the brain to the circulating blood (Takanaga et al. 2001), contribute to the excitability-inhibition balance in the brain.

The BBB has specific large neutral amino acid transporters (LAT1) for amino acids that are essential for brain metabolism and neurotransmitter synthesis: tyrosine, phenylalanine, tryptophan, valine, leucine, isoleucine, methionine and threo-

nine. LAT1 are expressed both on luminal and abluminal side of endothelial cells and assist a Na^+-independent facilitative bidirectional transport of essential amino acids. The competition between these amino acids on the same transporter and the lower affinity of tryptophan, make brain serotonin, melatonin and niacin, that have tryptophan as precursor, more sensitive to changes in plasma amino acids (O'Kane and Hawkins 2003).

The monocarboxylic acid transporters (MCT-1, MCT-2) of the BBB, at luminal and abluminal sides (Pardridge 2007a, b; Abbott et al. 2010), carry into the brain energy substrates like ketone bodies (β-hydroxybutyrate and acetoacetate), pyruvate and lactate, consistent with their concentration gradients (Simpson et al. 1999; Zlokovic 2008). With half the transport efficiency of glucose, lactate enter the brain to serve as a fuel in case plasma glucose is low or plasma lactate is high (Barros 2013). Lactate is also produced by the neuronal cells and used as a preferential metabolic substrate during intense neuronal activity (Schurr et al. 1999; Riske et al. 2017). Interestingly, low L-lactate availability at critical time points during learning was shown to have a negative impact on memory formation (Newman et al. 2011) and association of an intestinal pathology accompanied by blood accumulation of the D-isomer of L-lactate has negative effect on memory (Hanstock et al. 2010). More recently L-lactate is investigated as a signaling molecule that influences neuronal activity through various mechanisms (Mosienko et al. 2015).

The P-glycoprotein transporter on endothelial luminal surface impedes drugs, glutamate or potential neurotoxic molecules, including bilirubin, to enter from the bloodstream into the brain (Li et al. 2012). Some treatment failures in neurological and psychiatric disorders could be explained by upregulation of P-glycoprotein transporters in pathological conditions (Potschka 2010).

The lipophobic molecules passage across BBB can take the route of endocytotic vesicles with low rate of no more than 5–10 vesicles/μm^2 (Sukriti and Begley 2005). Fluid-phase endocytosis enables macromolecules to pass into the brain and the plasma membrane to recycle (Broadwell et al. 1988). In this case, transported molecules do not bound to the cell surface and are internalized in an indiscriminant way. The rate of fluid-phase endocytosis is low, but increases in pathologic conditions (e.g. acute hypertension, ischemic stroke) contributing to brain injury (Cipolla 2006). In this way plasmin, thrombin and albumin entering the brain determine inflammation, activation of glia, cell injury, epileptogenesis and apoptosis. Absorptive endocytosis is the route followed by molecules that bind to glycocalyx or carbohydrate moieties, while receptor-mediated endocytosis transport specific molecules/ligands that bind to a receptor on the endothelial cell surface and determine the receptor–ligand complex to internalize (Serlin et al. 2015).

The BBB receptor-mediated endocytosis is the blood to brain route for neuroactive peptides which have important roles in the brain, some being also produced in the brain: leptin, insulin, insulin-like growth factor, transferrin, chemokines, cytokines and high-/low-density lipoprotein (Zlokovic 2008). The satiety hormone leptin and gastrointestinal hormones, especially insulin and the hunger hormone ghrelin, act beyond the periphery and, by crossing the BBB act on their neuronal receptors located at the hypothalamus and in other brain regions, regulating various

neuronal activities, influencing neuronal survival and exerting profound effects on feeding behavior and multiple cognitive functions (Banks 2008). It was shown that deficiency in insulin signaling in the brain is associated with Alzheimer's disease (Marques et al. 2013).

The receptors on the brain endothelial cells exhibit binding sites for various signaling molecules from the blood or released by the cells of NVUs. These receptors are coupled to an intracellular machinery that mediate BBB modulation. One example is insulin binding on its receptor that enable its transport across BBB, but also influence the BBB transport rate of various compounds, like the serotonin precursor tryptophan, leptin or the antiviral drug azidothymidine (Banks 2008). Also, inflammatory mediators like bradykinin or histamine when present in high concentrations can transiently modulate the TJs and increase BBB permeability, possibly contributing to cerebral edema (Abbott et al. 2006).

Depending on the brain requirements, the endothelial cells modulate receptors expression, with impact on cognitive function. One example is leptin receptor expression and leptin transport rate that changes in distinct brain regions with circadian rhythms and the plasma concentration of adrenaline, estrogens, insulin, glucose and triglycerides (Kastin and Akerstrom 2001; Banks 2004; Xing et al. 2015). Also, leptin increases the BBB transcytosis of the urocortin, a peptide belonging to the corticotropin-releasing factor family involved in appetite and reaction to stress, across the BBB (Skelton et al. 2000; Pan et al. 2004; Abbott et al. 2006).

A recently studied form of transport, the exosomes are small (∼30–100 nm) extracellular vesicles, carrying diverse cellular compounds (e.g. mRNAs, miRNAs, proteins, lipids) which are secreted by cells, including neurons, astrocytes and oligodendrocytes. Exosomes can act on cells in the immediate microenvironment or diffuse and enter the circulatory system. They are internalized by recipient cells through endocytosis. Exosomes generate a distinctive cell-cell communication system with important role in the brain physiology and pathology. Exosomes are currently studied for their diagnostic and therapeutic potential in the central nervous system (Andras and Toborek 2016).

32.2.3 Transport of Nutrients Across the Blood-Brain Barrier

Nutrients availability in the brain is imperative to meet the high neurometabolic and neuroenergetic requirements for the continuous processing of information and cognition. The nutrients obtained from ingested food breakdown into the digestive system, such as amino acids, sugars, vitamins, fatty acids and minerals are essential for the survival of all cells, and are transported to the brain via the bloodstream and further, ingress through the BBB to nourish the brain (Banks 2012a, b).

Among the most typically transported nutrients across the BBB is glucose, which is the primary fuel for cells of the human body, especially for the brain. Various

sugars found in carbohydrates (e.g., fruits, vegetables) are among the main providers of glucose in the bloodstream.

The bloodstream also transports myriad proteins (representing the building blocks of cells) that are comprised of different amino acids, each of them conveying a different function to the body and brain. Among the most vital roles played by the amino acids relates to the synthesis of neurotransmitters, which modulate most functions of the nervous system (Campos-Bedolla et al. 2014). The facilitated transport of amino acids across the BBB interface involves carrier molecules (see Fig. 32.5), which furnish a transport carrier for the amino acids and specific pathways to access the brain.

Dietary changes can cause changes in the availability of neurotransmitter precursors in the brain and influence neurotransmitters synthesis (Wurtman 1987). Thus, a diet depleted of aromatic amino acids lowers their brain concentration and reduces the synthesis and the release of neurotransmitters derived from them, particularly serotonin from tryptophan and catecholamines (dopamine, norepinephrine, epinephrine), derived from tyrosine and phenylalanine. The aromatic amino acids depletion is accentuated by the competition on the same transport system (LAT1) with branch-chained amino acids (e.g. leucine, isoleucine, valine), especially when these are supplemented in the diet (Fernstrom 2005). Tryptophan, an essential amino acid available only in the diet and precursor of serotonin (Haleem 2012), melatonin, tryptamine and kynuramines, acts as an important element of brain-gut axis. Low tryptophan availability in the bloodstream and consecutive low transport across the BBB (Fernstrom 2013), depletes brain serotonin and determine behavioral changes (e.g. depression, impulsivity), insufficient control of the pain threshold (e.g. migraines) and cognitive impairment (e.g. deficits in verbal reasoning and in episodic and working memory), deficits that could be reversed by tryptophan supplementation (Jenkins et al. 2016). Also, it was shown that mutations in Slc7a5, a solute carrier protein for the branched-chain essential amino acids at the BBB result in neurobehavioral abnormalities associated with autism spectrum disorder in mice (Tarlungeanu et al. 2016).

In addition to glucose and proteins, the human body degrades fats into primary components, i.e. fatty acids (including omega-3 and omega-6). Deficiencies in fatty acids are related to the development of Alzheimer's disease, according to Cardoso et al. (2013).

Other nutrients that cross the BBB include vitamins and minerals, along with water. Some vitamins also cross the BBB unimpeded, while others, as B vitamins (e.g. vitamin B-6, folate and vitamin B-12), essential in brain metabolism and neurochemical synthesis, require dedicated active transport mechanisms across the BBB, that guarantee B vitamins brain concentrations higher than those in the blood (Kennedy 2016). Low B-vitamins intake prone to hyperhomocysteinemia, causing oxidative stress, endothelial injury, blood vessels inflammation and BBB impairment, with a high risk of ischemia, mild cognitive impairment and dementia (Stanger et al. 2014).

Ions, such as sodium, potassium, calcium, and chloride, flow in the bloodstream and cross the BBB via passive/facilitated diffusion, to contribute to the homeostasis of the interstitial fluid that occupies about 20% of the brain volume (Sykova and Nicholson 2008). Part of interstitial fluid water comes from the glucose metabolism in the brain cells and passes through the aquaporin 4 (AQP4) water channels present in the membrane of astrocytes perivascular endfeet (Abbott 2004).

Water could be perceived as a nutrient and its role is critical for the proper functionality of the body and brain. Faraco et al. (2014) recently described the deleterious effects of water deprivation on neurovascular and cognitive function, by altering the mechanisms regulating the cerebral circulation, mechanisms involving vasopressin, endothelin-1 and oxidative stress (Faraco et al. 2014).

Glucose, amino acids and long-chain fatty acids, ingress and egress cells via their concentration gradient with the assistance of substance-specific carriers (proteins), which form channels or "pores" within cell membranes.

Certain nutrients, encompassing disaccharides (e.g., sucrose, maltose, etc.), oligosaccharides (e.g., raffinose), polysaccharides (e.g., starch), triglycerides, some nonessential fatty acids and cholesterol cannot cross the BBB. For some of these nutrients the BBB uses the mechanism of facilitated diffusion, which depends on a carrier. In case of lipoprotein-bound cholesterol from the blood, its restricted passage through BBB is crucial for maintaining cholesterol metabolism in the brain, where cholesterol is mainly synthetized de novo in neurons and astrocytes, at different rate during development, to serve vital cellular functions (e.g. enters in the myelin composition and give its insulatory properties), while excess cholesterol is transported out of the brain as oxysterols (Saeed et al. 2014). An altered cholesterol metabolism in the brain was associated with cognitive deficits in elderly and with neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, Huntington's disease (Zhang and Liu 2015).

Disruption of BBB integrity has been shown to be involved in the mechanisms connecting diet, obesity, cognitive decline and various neurodegenerative diseases. The hippocampus dependent memory formation is negatively affected by Western diet (Kanoski 2012) by a mechanism linked with a decreased expression of TJ proteins (claudin 5 and 12) (Kanoski et al. 2010). Also, increased BBB permeability was associated with accumulation of amyloid B (pathological hallmark of Alzheimer's disease) in the hippocampus following extended exposure to a high cholesterol diet (Hsu and Kanoski 2014).

The blood glucose levels influence BBB function. In the context of diabetes, TJ proteins (ZO-1, occludin and claudin-5) are down regulated, changes associated with oxidative stress, increased cerebral neovascularization, decrease of transporters (e.g. P-glycoprotein, GLUT-1) and thickening of the capillary basal membrane. These changes have been correlated with an increased risk for neurodegenerative disease such as AD (Prasad et al. 2014).

32.2.4 Blood-Brain Barrier and Ageing

In normal aging, but also in Alzheimer Disease, there are significant cerebral changes concurrent with low cerebral metabolic rate for oxygen and glucose and low cerebral blood volume. These aging-related changes, confirmed through sensitive neuroimaging methods, consist in decrease in microvascular density, pericytes deficiency and deterioration in global and local measures of cerebral blood flow (about 4 mL/min/year) (Marques et al. 2013; Stoquart-ElSankari et al. 2007).

The functions of the BBB decrease with aging through an increase in BBB permeability with albumin and IgG leakage that contributes to pathological alterations (e.g. white matter lesions) (Popescu et al. 2009). An increased production of ROS and proinflammatory cytokines (e.g. TNFα) in endothelial cells was associated with memory and learning impairment in ageing (Fukui et al. 2001; Popescu et al. 2009; Enciu and Popescu 2013; Elahy et al. 2015). Also, aging was correlated with an increase in the soluble platelet-derived growth factor receptor β (sPDGFRβ), an established marker of the pericytes (Armulik et al. 2010), and a decrease in TJ proteins (mostly occludin-1) (Elahy et al. 2015). Moreover, a limited exclusion of toxic substances from the brain corresponds to a decreased activity of the BBB P-glycopotein efflux transporter (Popescu et al. 2009).

A recent MRI study, using an advanced dynamic contrast-enhanced magnetic resonance imaging protocol, showed an age dependent decrease in the BBB function in the hippocampus, particularly in the CA1 region and DG, but not the CA3 region (Montagne et al. 2015). No significant BBB changes during aging were found in cortical (e.g., frontal and temporal cortex) or subcortical (e.g., thalamus, striatum) regions, except for the caudate nucleus. These changes were found both in individuals with normal cognitive abilities and in subjects with mild cognitive impairment that presented a more accelerated impairment of BBB. Biochemical studies showed an increased CSF/plasma albumin ratio that correlates with the loss of cognitive function in individuals with mild cognitive impairment (Montagne et al. 2015).

32.2.5 Blood-Brain Barrier and Physical Activity

It is a known that physical activity induces cognitive function improvement in all ages, especially in elderly who are susceptible to neurodegenerative disorders, but just recently the responsible molecular and cellular mechanisms began to be revealed. These mechanisms involve trophic factors including BDNF and IGF-I (Phillips et al. 2014).

The BBB enzymes, including monoamine oxidase, have protective and detoxifying roles to protect the synaptic activity from catecholamines and other neuroactive molecules, whose plasma concentration increase during exercise (Abbott 2002).

Protein S-100 was found to be acutely elevated in the plasma as response to exercise, especially in hot environments or by lack of fluid ingestion, through possibly hyperthermia, increase in serotoninergic activity, elevated circulating ammonia and epinephrine, and increased production of inflammatory cytokines (Watson et al. 2005).

However, it must be noted that exercise has many other effects on the BBB, for example an increase in angiogenesis to supply the demand of oxygen and glucose (Nierwinska 2008).

There have been studies showing that exercise could attenuate some of the BBB dysfunction in neurological diseases such as Multiple Sclerosis – through what is thought to be a global effect of exercise by reduction of systemic inflammatory proteins (TNF α, IFN-gamma, IL17, IL6, MCP-1 and expression of PECAM-1) (Souza et al. 2017). Other results in a mouse model showed that regular exercise could change the expression of junction proteins like claudin-5, occcludin and ZO-1, in cerebral endothelial cells, which functions beneficially in early stages of brain metastases (Wolff et al. 2015).

32.2.6 Blood-Brain Barrier and Stress

Stress is an important factor that plays a key role in the development of cognitive impairment and neuropsychiatric disease (Chrousos 2009). Recently, stress-related neuropsychiatric diseases have been shown to associate with BBB dysfunction, progression in neuroinflammation and neuronal death (Shanta et al. 2016), as described below in this chapter. Accumulating evidence suggests that stress accompanied by dysfunctional BBB is a major contributor in diseases such as Alzheimer's (Wilson et al. 2006), major depression disorder (Najjar et al. 2013), schizophrenia (De Klerk et al. 2011), and cognitive impairment secondary to obstructive sleep apnea (Lim and Pack 2014). Agents released during neural activity like histamine, glutamate, leptin, Ca^{2+}, adrenaline and serotonin act on receptors and transporters expressed on endothelial cells and astrocytes, thus modulating capillary diameter, local blood flow, GLUT-1 expression and tightness of TJs (Santha et al. 2016).

Previous studies revealed that stress increases BBB permeability in rodents (Fotti Cuzzola et al. 2013) and in humans (Hanin 1996), resulting in disturbances of CNS homeostasis and neuronal death. A recent study showed that exposure to acute stress for 1 day and chronic stress for 3–21 days in Wistar rats, induced a morphological alteration in TJ proteins, claudin-5 and occludin, as well as in the expression of GLUT-1 in the frontal cortex and hippocampus. These changes occurred in a time dependent manner, indicating capillary endothelial cell damage after 1-day acute stress, as well as edema in astrocytes and thicker, irregular capillary basal membranes after 21 days (Santha et al. 2016).

32.3 Blood-Brain Barrier in Disease

32.3.1 The Blood-Brain Barrier in Psychiatric Disease

The exact cause of most psychiatric diseases is currently unknown. One of the hypotheses put forward for the development of psychiatric disorders is a dysfunctional BBB. More and more clinical evidence point at least to a dysfunctional BBB for schizophrenia and depression (Shalev et al. 2009). Confirmation of BBB impairment in psychiatric disease is weakened by a lack of standardized animal models for human psychiatric disorders, as well as a lack of standardized modalities of studying the BBB disorders in living individuals. The use of dynamic contrast enhanced MRI could overcome this problem. Although this technique has proven valuable in studying intracranial neoplasms, identifying risks for hemorrhage in stroke patients and BBB dysfunction in Alzheimer's disease (Heye et al. 2014), there has not been to date a systematic use of this protocol in assessing psychiatric patients.

The intensity of symptoms and the course of disease in patients with depression seem to correlate with proinflammatory mediators (IL-1, IL-2, Il-6, TNF alpha and C Reactive Protein) (Dantzer et al. 2008). An inflammatory state is shown to weaken the BBB. Also, CSF to serum albumin ratio is altered in patients with psychiatric disease (Bechter et al. 2010). Other evidence of BBB dysfunction in major depression comes from increased levels of serum markers, like protein S-100B (Schroeter et al. 2008).

Through PET CT studies it was shown that depression and antidepressant treatment modulates the function of the multidrug efflux transporter P-glycoprotein. Reduced expression or function of P-glycoprotein may facilitate BBB permeability to neurotoxic substances (De Klerk et al. 2010).

Although the role of the BBB remains uncertain in the development of psychiatric disease, the problem of psychiatric drugs crossing the BBB remains a classic. This has been such a problem that 98% of the developed drugs failed to enter clinical studies because of poor BBB penetration (Pardridge 2007a, b). Numerous novel techniques are being developed in pharmacological research to elude the BBB. These include MRI guided low intensity focused ultrasound (Rezayat and Toostani 2016), osmotic disruption of the BBB and even magnetic guided nanoparticles (Kong et al. 2012).

An increased BBB permeability and neuroinflammation were associated with autism spectrum disorders. The metabolic profile of these patients is consistent with an impaired capacity for methylation and increased oxidative stress (low plasma concentrations of methionine, S-adenosyl-methionine, homocysteine, cysteine, total glutathione and high concentrations of S-adenosylhomocysteine, adenosine, and oxidized glutathione). Recently it was shown that autism patients show an altered expression of genes associated with BBB integrity and increased neuroinflammation, with possible involvement of an impaired gut barrier integrity (Fiorentino et al. 2016).

32.3.2 The Blood-Brain Barrier in Encephalopathies

One of the most common situations at in the emergency room or in the intensive care unit is a disturbance of consciousness in patients that are febrile. This could range from impaired attention, confusion, to delirium, stupor and even coma. The septic encephalopathy is the most frequent encephalopathy in the ICU (Bleck et al. 1993). One of the mechanism through which this happens is a breakdown of the BBB. This was shown through an elevated protein level in CSF of septic patients (Young et al. 1992).

In a porcine model of caecal peritonitis it was demonstrated that the disruption of the BBB was partly due to a severe perimicrovessel edema and disruption of associated astrocyte end-feet that were grossly swollen. This lead to neuronal injury, insufficiently explained through the decreased cerebral blood flow in sepsis and likely caused by the circulating inflammatory mediators that gain access through the dysfunctional BBB to the brain parenchyma possibly initiating apoptosis (Davies 2002). Although the ultrastructure of cortical microvessel endothelial cells seems intact, their function might be compromised. An increase in pinocytosis was described as a result of endotoxaemia (Clawson et al. 1966).

One of the other systems that likely play a role in the dysfunction of the BBB in sepsis is the adrenergic system. A beta-2 receptor agonist (Dopexamine) was shown protective against sepsis induced perimicrovessel edema and an alpha-1 adrenoreceptor agonist Methoxamine was shown to produce the edema even in the absence of sepsis (Davies 2002).

Patients with uremia often show neurological symptoms such as clouding of consciousness, disturbed sleep patterns, tremor, asterixis and even coma and death. Uremia leads to an increased permeability of the BBB as well as an electrolyte imbalance: K^+ transport is increased whereas Na^+ transport is impaired. There is also an increase in brain osmolarity in acute renal failure due to urea concentration and in chronic renal failure due to the presence of idiogenic osmoles in addition to urea (Siegel et al. 1999). This phenomenon was known since 1962, when Freeman et al. work, conducted in patients in uremic state and control, has shown a higher CSF/blood ratio for urea nitrogen, uric acid and phosphorus in uremic patients, corresponding to a BBB disrupted integrity confirmed by an elevated CSF/Blood ratio to sodium bromide (Freeman et al. 1962). This disruption of the BBB integrity may lead to increased permeation of guanidino compounds, guanidinosuccinic acid, methylguanidine, guanidine and creatinine, that may contribute to the epileptic and cognitive symptoms accompanying uremic encephalopathy, like hyperexcitability. Although the current indications and guidelines for dialysis currently consider urea and creatinine, which are neurologically inert, perhaps the other compounds that are increased in uremic states, guanidine compounds, should be considered and monitored in the future.

32.3.3 The Blood-Brain Barrier and Stroke

The BBB disruption is one of the main ways acute ischemic stroke (AIS) leads to complications, most of all the dreaded hemorrhagic transformation (HT) as well as the building of edema around the necrotic tissue. There is a direct correlation between the degree of BBB disruption and risk of HT (Kassner and Merali 2015), with consequences for the acute stroke treatment. In a recent study (Leigh et al. 2016) (DEFUSE-2) it was shown that the degree of BBB disruption calculated on MRI using dynamic susceptibility contrast correlated with the amount of HT. This correlation has shown itself independent of the time of onset or the route of administration of thrombolytics used since it was constant in all groups (IV, IA and IV+IA therapy). The consequence of this trial is that in the future subgroups of patients that could benefit from therapy could be identified and receive therapy beyond the well-established window of opportunity (4.5 h) for AIS. The DEFUSE-3 trial is now underway; researchers will use imaging data to select patients for endovascular therapy up to 16 h after stroke onset.

The pathophysiology of acute ischemia and BBB disruption is dictated through the activation of proteases. A biphasic opening of the BBB has been described. The first phase of the BBB disruption occurs through the activation of MMP-2 and this phase was shown to be reversible. The second disruption is irreversible and occurs through the activation of MMP-3 and MMP-9. The latter could also be activated directly through tPA. This activation of proteases occurs mostly through inflammatory mediators (Yang and Rosenberg 2011) and is altered in patients which present systemic inflammation from a biphasic model to a continuous disruption (Mccoll et al. 2008). Also, a temporary dysfunction of the BBB may contribute to epileptogenesis (Ciurea et al. 2015).

A current study I-STROKE (Hughes 2016) is looking currently at modulating the opening of the BBB to prolong the window of opportunity in treating stroke. The use of imatinib (a tyrosine kinase inhibitor already available in the use against certain tumors) has been shown to slow down the opening of the BBB in the acute stroke phase.

32.4 Conclusions

The BBB is a highly dynamic and selective endothelial interface within the neurovascular assembly, interface on which the brain homeostasis and neuronal signaling depend. The NVU microdomains are subject to endlessly multiple crosstalk between neurons, astrocytes, pericytes, microglia and endothelial cell, to timely adjust the local cerebral blood flow to the actual metabolic needs within the processes of neurovascular and neurometabolic coupling.

The preferred transcellular route of transport through the BBB supports the ions, water and nutrients availability in the brain, imperative to meet the high

neurometabolic and neuroenergetic requirements associated with a continuous information processing and cognition. Thus, any temporary or long-term change in BBB structure and functioning, resulting in an altered permeability, selective transport and signaling, can have paramount physiological and pathological implications on brain functions and finally on cognition. The BBB breaks associated with various neurological conditions generally evolve with neuroinflammation and cognitive impairment. The difficulty of therapeutic interventions in various neurologic conditions associating BBB dysfunction and impaired cognition, keep BBB and neurovascular coupling at the forefront of research, in a continuous ride to find preventing and curing strategies to elude BBB break and NVU dysfunction.

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Chapter 33
Application of a Conceptual Nanomedical Platform to Facilitate the Mapping of the Human Brain: Survey of Cognitive Functions and Implications

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Abstract This chapter will explore the application of a conceptual nanomedical entity called the Vascular Cartographic Scanning Nanodevice (VCSN) to facilitate the ultrahigh resolution mapping of the human brain. The VCSN would comprise a highly sophisticated and completely autonomous ~1 μm in diameter nanomedical device, whose purpose would be to safely ingress, scan and image the entire human vasculature (down to the level of the smallest ~Ø3 μm lumen capillaries), followed by egress. In operation, likely thousands to tens of thousands of VCSN units would work in parallel to transmit cumulatively scanned spatial data to "outbody" computers, which would render the entire vasculature of a patient in high resolution three dimensional format. This capability would enable physicians and surgeons to "fly-through" all imaged areas via a joystick and computer display, generate full body holographic renderings, or inspect the entire vasculature in intimate detail through virtual reality. The human brain contains close to 100 billion capillaries within the neocortex, which serve to deliver a dedicated blood supply to each of the $\sim 23.9 \times 10^9$ individual neurons that support approximately 164 trillion synapses. Hence, it is plausible that the spatial coordinates of every neuron within the neocortex might be inferred from VCSN scanning data, to create an ultrahigh density map of the brain. This map might have significant utility and implications for the diagnosis, and treatment of various cognitive disorders, and potentially, toward the development of future cognitive augmentations, including the capacity for enhanced learning.

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33.1 Introduction

It has been commonly recognized that there are a total of ∼100 billion neurons within the human neocortex, with each neuron facilitating up to 15,000 synaptic contacts (∼6700 on average) with other neurons. The neocortex of an average 50 year old human male is estimated to contain ∼164 trillion synapses (Brotherson n.d.; Pakkenberg and Gundersen 1997). According to another estimate, the number of synapses within the cerebral cortex is ∼0.15 quadrillion, or about trillion synapses per cubic centimeter of cortex (Drachman 2005). Cumulatively, it is thought that there are ∼150,000–180,000 km of myelinated nerve fibers within the white matter of the brain (by age 20), which serve to intimately interconnect all of these neuronal constituents (Drachman 2005). A new, and purportedly more accurate, cell counting technique, referred to as the isotropic fractionator (Herculano-Houzel and Lent 2005), has arrived at a significantly lower number of neurons (∼16.3 billion) in the human neocortex in conjunction with ∼60.8 billion glia (Herculano-Houzel and Lent 2005; von Bartheld et al. 2016). The isotropic fractionator method begins with the homogenization of brain tissues at the level of destroying only the cell membranes but not nuclear membranes. Thus, a nuclear suspension is attained, which is then DNA-stained for improved imaging and immunostained to highlight the neuron-specific (NeuN) antigen, which facilitates the differentiation of neuron nuclei from other cell nuclei. Subsequently, aliquots are extracted from the nuclear suspension and counted via a fluorescence microscope in a hemocytometer. Equivalent and more rapid results for the differentiation of immunolabeled nuclei may also be acquired through flow fractionator, which involves the use of a flow cytometer (Collins et al. 2010; Young et al. 2012; Herculano-Houzel 2011).

We propose that the spatial coordinates of all neurons in the human brain might be precisely determined through the generation of an ultrahigh resolution map, which may be enabled by employing a conceptual nanomedical Vascular Cartographic Scanning Nanodevice (VCSN). In the future, this capacity may facilitate the further elucidation of the physiological makeup, and hence, the physics that underlies various cognitive functionalities. It is conceivable that this highly detailed spatial data might have significant benefits for patient outcomes in terms of demarcating the precise locations, morphologies, and physiological perimeters of brain domains to enable dramatically improved diagnostics and therapeutics. Further, toward the augmentation of specific cognitive capabilities, encompassing sensorial perception, memory, learning, and potentially information processing speeds. We will explore each of these possibilities below.

33.2 Cognitive Constituents

33.2.1 Survey of Brain Cell Species

The quantification of the cellular compositions and their arrangement within the various regions of the human brain is critical toward our full understanding of its development and plasticity, myriad neurological and psychiatric diseases, and aging, as well as fundamental and higher cognitive functions and the elucidation of their underlying physics. Over the last five decades, it was surmised that the human brain housed approximately 100 billion neurons and one trillion glial cells, with a ratio of glia to neurons of 10:1. As described above, a new cell quantification technique, referred to as isotropic fractionator has significantly revised these earlier numbers and purports that the glia to neuron ratio in the human brain is actually less than 1:1, with a population of glial cells of under 100 billion (von Bartheld et al. 2016).

It should be clarified that for most brain cell quantification studies, different neuron cell types, sizes, and morphologies with variable dendritic or axonal configurations are grouped together; as are glial cells, which are not differentiated between astrocytes, oligodendrocytes, and microglia. Further challenges to the accurate determination of cell numbers in the human brain is its significant biological variability and the complexities involved with the investigation of various human tissues. Three primary strategies that have been employed (aside from the latest isotropic fractionator technique) to deduce the populations of brain resident cells include: (a) counting of stained cells or their nuclear constituents in histological sections; (b) calculation of cell numbers via DNA extraction and the quantification of total DNA content; (c) counting of cell nuclei in suspension subsequent to the homogenization of brain tissues (von Bartheld et al. 2016).

33.2.2 Whole Brain

The latest estimate, derived from the isotropic fractionator technique, for the total number of neurons in the entire human brain ranges from ∼67 to 86 billion (Azevedo et al. 2009; Andrade-Moraes et al. 2013), while it is estimated that the total number of non-neuronal glial cells is ∼85 billion; inclusive of ∼20–25 billion endothelial cells (von Bartheld et al. 2016; Azevedo et al. 2009). Below are more detailed estimates for the various structures of the brain.

33.2.3 Cerebral Cortex and Cerebellum

Most studies aimed at quantifying the number of neurons within the cerebral cortex have typically included only the gray matter and not the underlying white

matter. These estimates have ranged from 1.2 to 32 billion neurons (Pakkenberg and Gundersen 1997; Donaldson 1895) for the complete cortex, with most in the range of from 10 to 20 billion neurons (Pakkenberg and Gundersen 1989; Koch 2004). This aligns well with the new estimate of ∼16.3 billion neurons in the cerebral cortex derived from the isotropic fractionation technique (Table 33.1) (Azevedo et al. 2009). Comparatively, the population of neurons in the white matter is quite small at ∼250–1000/mm^3, which comprises less than 1% of the glial cell population at 20,000–200,000/mm^3 (García-Marín et al. 2010). Non-neuronal cells of the cerebral cortex, such as endothelial cells, which line the interior surfaces of blood and lymphatic vessels, make up approximately 30% of the non-neuronal cell population. For comparison, the endothelial cell population in the white matter is slightly lower than that of the gray matter (10–20%) (Bahney and von Bartheld 2014). This leaves a new estimate for the glial cell population of the cerebral cortex via isotropic fractionation at ∼60.8 billion, and sets the glial cell/neuron ratio for this portion of the brain at ∼3.8 (Table 33.1) (Azevedo et al. 2009).

Estimates ofspecific cell types that comprise the cerebellum include Purkinje cells (26×10^6), granule cells (granule neurons) (75.2×10^9) (Kiessling et al. 2014), total neurons (54×10^9) (Andrade-Moraes et al. 2013), glial cells (3×10^9) (Andersen et al. 1992), non-neuronal cells (15.4×10^9) (Andrade-Moraes et al. 2013). Interestingly, there is a far higher (nearly fourfold) population of neurons that resides within the cerebellum (∼69 billion, or 80.2% of brain neurons) in contrast to the neocortex (∼16 billion, or 19.0% of brain neurons) (Table 33.1), which appears counterintuitive when we consider the higher cognitive processes that operate within the neocortical substrate to be manifest as the brain's crowning evolutionary achievement. One would surmise that the highest concentration of cognitive horsepower (in the form of neurons) would reside here. As Barton observes, "The volume of a brain region is potentially related to cognitive capacities to the extent that it correlates with more functionally meaningful variables such as numbers of neurons and synapses." It is thought, however, that the cerebellum has been underestimated as per its contribution to the cognitive function of the brain, and over the last decade significant evidence has been garnered to elucidate its much more extensive role (Barton 2012). The involvement of the cerebellum is now thought to encompass (from Barton (2012)) emotion (Colibazzi et al. 2010; Tavano and Borgatti 2010), non-motor associative learning (Bellebaum and Daum 2011), working memory and mental rehearsal (Bellebaum and Daum 2011; Leiner 2010), verbal working memory and other language functions (Tavano and Borgatti 2010; Leiner 2010; Schmahmann and Sherman 1998; Steinlin 2008; Leggio et al. 2011), spatial and episodic memory (Schmahmann and Sherman 1998; Leggio et al. 2011; Rochefort et al. 2011), event prediction (Forster and Brown 2011), empathy and predicting others' actions (Ramnani and Miall 2004; Gazzola and Keyser 2009; Schulte-Ruther et al. 2007; Singer et al. 2004), imitation (Jackson et al. 2005), planning and decision-making (Schmahmann and Sherman 1998; Ito 2008; Strick et al. 2009), individual variation in cognitive performance (Hogan et al. 2011), and cognitive developmental disorders including autism (Steinlin 2008; Shukla et al. 2010). Thus, in response to why there are so many neurons in the cerebellum,

Table 33.1 Brain region glia and neuron populations

Brain region	Weight (grams)	Total cells (billions)	Glia (billions)	Neurons (billions)	Glia/neuron ratio
Cerebral cortex (GM+WM)	1232.93 (+/− 233.68)	77.18 (+/− 7.72)	60.84 (+/− 7.02)	16.34 (+/− 2.17)	3.76
(81.2% of brain mass)					
(19.0% of brain neurons)					
Cerebellum	154.02 (+/− 19.29)	85.08 (+/− 6.92)	16.04 (+/− 2.17)	69.03 (+/− 6.65)	0.23
(10.3% of brain mass)					
(80.2% of brain neurons)					
Basal ganglia + diencephalon + Brainstem	117.65 (+/− 45.42)	8.42 (+/− 1.50)	7.73 (+/− 1.45)	0.69 (+/− 0.12)	11.35
(7.85 of brain mass)					
(0.8% of brain neurons)					
Whole brain	1508.9 (+/− 299.14)	170.68 (+/− 13.86)	84.61 (+/− 9.83)	86.06 (+/− 8.12)	0.99

Adapted from Azevedo et al. (2009)
GM grey matter, *WM* white matter

Barton suggests, "The answer suggested here, based on converging comparative and experimental evidence, is that the cerebellum and cortico-cerebellar networks are key components of systems enabling the control, organization and comprehension of complex sequences involved in both technical and social intelligence, and, ultimately, language." (Barton 2012; Barrett et al. 2012; Sterelny 2012; Fitch 2011).

33.2.4 Brainstem, Diencephalon, and Striatum

The combined number of cells, as determined by the isotropic fractionator for this relatively diminutive brain region, has amounted to 700 million neurons and 6.6–7.7 billion non-neuronal cells, with a glial cell to neuron ration of 10:1 (Azevedo et al. 2009; Andrade-Moraes et al. 2013). The brain stem, which houses various neuron nuclei and fibers, along with the diencephalon and striatum, constitute approximately 2–8% of the total brain volume; however, they contain only 1% of the neurons in the brain (Azevedo et al. 2009). Estimates of the number of neurons in various brain stem structures have been determined to be: reticular formation (5.2×10^6 neurons) (Blinkov and Glezer 1968), corpora quadrigemina (inferior colliculi:1.2×10^6 neurons) (Blinkov and Glezer 1968), lateral geniculate nucleus (one side – ranges from 570,000 (Balado and Franke 1937) to 3.5×10^6 (Selemon and Begovic 2007)), supraoptic nucleus (75,000 neurons) (Blinkov and Glezer 1968), paraventricular nuclei (85,000 neurons) (Blinkov and Glezer 1968), mammillary bodies (medial nuclei) (800,000 neurons), anteroventral and medial nuclei of thalamus (1.3×10^6 neurons) (TPS et al. 1957), basal ganglia (816×10^6 neurons) (Karlsen and Pakkenberg 2011), striatum (100×10^6 small neurons and 570,000–670,000 large neurons) (Schroder et al. 1975), anterior striatum (7.8×10^6 neurons) (Weise et al. 2015), globus pallidus (~700,000 neurons) (Thörner et al. 1975), subthalamic nucleus (286,000–306,000 neurons) (Lange 1975), substantia nigra (500,000–600,000 neurons) (Mann 1986), and locus coeruleus (32,000–38,000 pigmented neurons) (Mouton et al. 1994; Ohm et al. 1997). The population of glial cells in the striatum and globus pallidus was estimated to be 400×10^6 and $63–82 \times 10^6$, respectively (Schroder et al. 1975; Thörner et al. 1975).

Since numerous psychiatric and neurological conditions (e.g., schizophrenia, autism spectrum disorders, mood disorders, depression, and Alzheimer's disease), have been associated with uncharacteristically high numbers of glial cells, or glial cell:neuron ratios, a capacity for the detailed elucidation of the spatial coordinates of specific cell types within the brain may facilitate far more precise diagnoses and subsequently, more efficacious therapies.

33.2.5 The Microvasculature of the Human Brain

The dense microvasculature of human brain is comprised of an estimated ~100 billion capillaries, which have a combined surface area of ~20 m^2 and a total length of ~400 miles. Intercapillary distances in the brain are typically ~40 μm, which accommodates enough space for two neurons; hence, each individual neuron within the neocortex is perfused by a dedicated blood vessel (Pardridge 2011). The average perfusion of blood within the brain amounts to 54 ± 12 ml of blood per 100 g of brain tissue per minute (Kety et al. 1948). Mancini et al. who compared cerebral blood flow between multiple sclerosis patients and healthy controls, found that the median longest cerebral circulation time (CCT) in patients with MS was 6.47 s (range: 3.29–29.24 s) in contrast to the healthy control subject CCT (5.54 s, range: 2.57–7.63 s). The median CCT of MS patients was 5.76 s (range: 2.64–17.51 s), in contrast to 5.01 s (range: 2.57–7.06 s) for the healthy control subjects (Mancini et al. 2012).

The neocortex, which has a median thickness of 2.5 mm, is perfused by arterioles and venules that typically penetrate to its center, while a certain percentage extend through into the white matter. The majority of neocortex penetrating arterioles range from Ø15 to Ø40 μm; with the largest being Ø240 μm. Neocortex penetrating venules have a mean diameter of Ø110 μm (Duvernoy et al. 1981). Arteriole vessel density is 385.1/mm^3, whereas venule vessel density is 281.2/mm^3 (Cassot et al. 2010).

It remains that there has been negligible elucidation of the relationship between the topology of the microvasculature and the overall distribution of blood and oxygen in the neocortex. The spatial resolution of current imaging strategies (e.g., perfusion MRI) still far exceeds that of microvascular elements; thus, it continues to be a significant challenge to quantify the connection between the microvasculature and total perfusion in the brain (El-Bouri and Payne 2016). An additional vexing factor relates to the randomly configured cerebral capillaries that exhibit no discernible geometric coherence (Hadjistassou et al. 2015).

33.2.6 The Glymphatic System

The glymphatic system (Fig. 33.1) comprises a dedicated perivascular system formed by astroglial cells that extends throughout the human brain with the purpose of exchanging solutes, as well as the clearance of metabolic waste byproducts (e.g., beta-amyloid peptides) and toxins from the central nervous system via the cerebrospinal fluid. This recently discovered system (Iliff et al. 2012) is more profusely active during sleep, where initially, the cerebrospinal fluid flows into the para-arterial space and subsequently into an interstitial space via aquaporin 4 (APQ4) water channels (Xie et al. 2013). During the various phases of sleep an exchange proceeds between cerebrospinal and interstitial fluids that is driven by

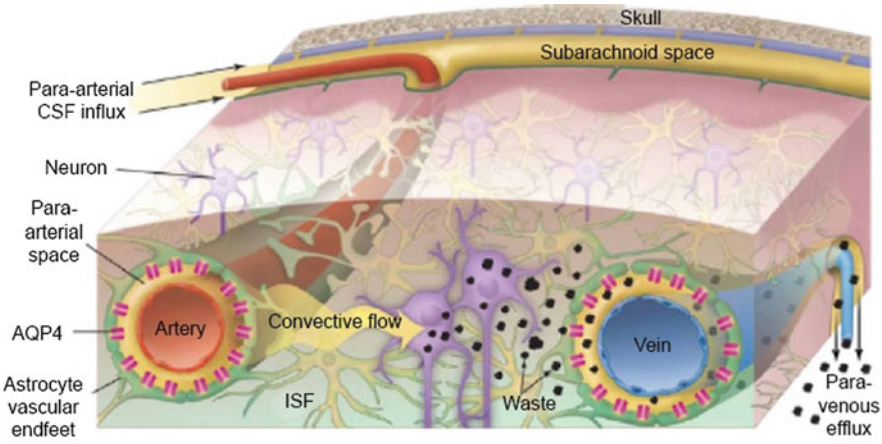

Fig. 33.1 The glymphatic system depicting para-arterial and para-venous pathways (From Velasco-Aguirre et al. (2015). Permission for use granted by Creative Commons License)

rhythmic vascular pulsations, which diverts wastes from the arteries to the veins and then into the paravenous space (Eugene and Masiak 2015; Underwood 2013). In the sleep state the interstitial space has been observed to increase by ~60%, thereby facilitating the clearance of toxic cellular wastes (Jessen et al. 2015). Further to the elimination of metabolic wastes, the glymphatic system also enables the distribution of substances such as amino acids, glucose, growth factors, lipids, and neuromodulators throughout the brain (Ross and Poirier 2004).

The functionality of the glymphatic system has been observed to decrease dramatically as the result of injury and due to aging. In terms of aging, this knowledge is critical, as aging constitutes the most prominent risk factor for neurodegenerative diseases. It has been surmised that the faltering functionality of the glymphatic system in aging humans may contribute to the aggregation of various proteinaceous materials that proceed to impede the flow of, or block, the glymphatic pathways, which subsequently prevents the system from properly cleansing the brain of toxic metabolic wastes. This situation likely sets the stage for all prominent neurodegenerative conditions (Takalo et al. 2013).

33.3 Cognitive Physics and Energy Flows

Leithner and Royl explored the intimate neovascular coupling that exists between cerebral blood flow (CBF) and neuronal activity (Leithner and Royl 2014). The CBF possesses a highly dynamic capacity for the continuous and highly sensitive delivery of oxygen to brain tissues (where its fluctuating demand is adjusted for

almost instantaneously), along with less readily responsive glucose transfer. As the researchers state, "Brain activity, especially synaptic transmission, is highly energy demanding and the brain generates the majority of its ATP via the oxidative metabolism of glucose." (Howarth et al. 2012; Hall et al. 2012). The human brain typically utilizes six molecules of oxygen for every glucose molecule, and when blood traverses the cerebral capillaries, the oxygen extraction (via diffusion) fraction ranges from ~30% to 50%; in contrast to the glucose extraction fraction that is significantly lower at ~10% (Frackowiak et al. 1988; Poulsen et al. 1997; Aanerud et al. 2012; Madsen et al. 1999). The cerebral cortex utilizes three to five times the oxygen than does white matter (Siesjö 1978).

There are also significant differences in the concentrations of oxygen versus glucose in the brain. The levels of oxygen storage molecules (e.g., neuroglobin) that are present in the cortex are quite low (<1 nmoL/mL), which translates to a low average oxygen content in the brain (30 nmoL/mL) (Burmester et al. 2000; Hayashi et al. 1983). The concentration of glucose in brain tissue, however, is much higher at 1000–4000 nmoL/mL (Madsen et al. 1999). Hence, the cerebral metabolic rate of oxygen in the brain at ~30 nmoL/mL/s, would be sustained for only 1 s, if the vascular oxygen supply were to abruptly stop, in comparison with several minutes for the cerebral glucose metabolism rate, at from 4 to 7 nmoL/mL/s, were the glucose supply (not oxygen) suddenly cease. Interestingly, the authors put forward that the, "The physiologic blood flow response to increases in neuronal activity is very fast, initiated by an incompletely understood coupling mechanism involving several molecules, neurons, interneurons (Cauli and Hamel 2010), astrocytes (Filosa and Iddings 2013), endothelial cells, and possibly pericytes (Fernandez-Klett et al. 2010; Hamilton 2010; Peppiatt et al. 2006), (the 'neurovascular unit'), which signal changes in brain activity to nearby blood vessels in a feed-forward manner (Lecrux and Hamel 2011; Lauritzen et al. 2012; Iadecola and Nedergaard 2007; Attwell et al. 2010). Additionally, they state that, "The temporal dynamics of the CBF response thus suggest a close relation to oxygen rather than glucose availability." (Leithner and Royl 2014).

Since the human brain is primarily driven by glucose derived metabolic energy, an intimate association might be made between localized cerebral blood flow and glucose metabolism by neurons. This localized consumption of glucose may thus be translated to specific neuronal, synaptic, and presynaptic activity by virtue of the requirement of glucose for membrane potential preservation and ion gradient restoration. Jueptner and Weiller state that, "More than 85% of cerebral glucose is used by neurons (mainly presynaptic axon terminals), while the remainder may at least partly account for metabolic processes in glial cells. Monitoring of regional cerebral blood flow with PET or fMRI thus mainly reflects neuronal and more specifically (pre-) synaptic activity." (Jueptner and Weiller 1995).

33.4 Conceptual Vascular Cartographic Scanning Nanodevice (VCSN)

We propose here a conceptual nanomedical Vascular Cartographic Scanning Nanodevice (VCSN) platform (Fig. 33.2) that might facilitate the generation of ultrahigh resolution mapping of the human brain. Spatial data may be acquired via nanoscale capacitive ultrasound elements or radically scaled down time-of-flight LIDAR-type measurements. The VCSN would comprise a highly sophisticated and completely autonomous ~1 μm in diameter nanomedical device, whose purpose would be to scan and image the entire human vasculature, down to the level of the smallest (~Ø3 μm lumen) capillaries. In operation, likely thousands to tens of thousands of VCSN units would be ingressed into the patient and work in unison to transmit cumulatively scanned spatial data to "outbody" computers, and subsequently egress the patient. The acquired spatial data would enable the rendering of the entire vasculature of patients in ultrahigh resolution for display in multiple three dimensional formats. This capability would enable physicians and surgeons to "fly-through" all imaged areas via a joystick and computer display, generate full body holographic renderings, or inspect the entire vasculature in intimate detail through virtual reality.

Once developed, the VCSN technology might enable the mapping of the full extent of the microvasculature of the brain (Fig. 33.3) in ultrafine detail. Secondary, maps might be compiled of what is known as the glymphatic system (as described above), which is exclusive to the brain, and comprised of a series of cerebrospinal fluid carrying channels that are formed by glial cells, which surround both the cerebral arteries and veins. This system has analogous functionality to that of the lymphatic system that operates in the rest of the body to remove waste materials, in that it cleanses the brain of neural toxins (Iliff et al. 2012). Cumulatively, these detailed spatial data could be correlated and extrapolated to assist in elucidating the identification, location, three dimensional spatial arrangement, and activities of specific neuronal species, dendrites, synapses, and glial cells. It may be possible that linkages to particular brain structures, their organization and cognitive functionality might be inferred via the spatial configurations of arterial blood supply, venous blood drainage, and glymphatic networks. Associations to specific neuronal activity might also be drawn through the calculated supply and metabolism of oxygen and glucose molecules via these pathways.

33.4.1 VCSN Constituents and Perceived Operation

Listed below is a summary of VCSN constituents, excerpted from the book *Nanomedical Device and Systems Design: Challenges, Possibilities, Visions*, and their envisaged functionality:

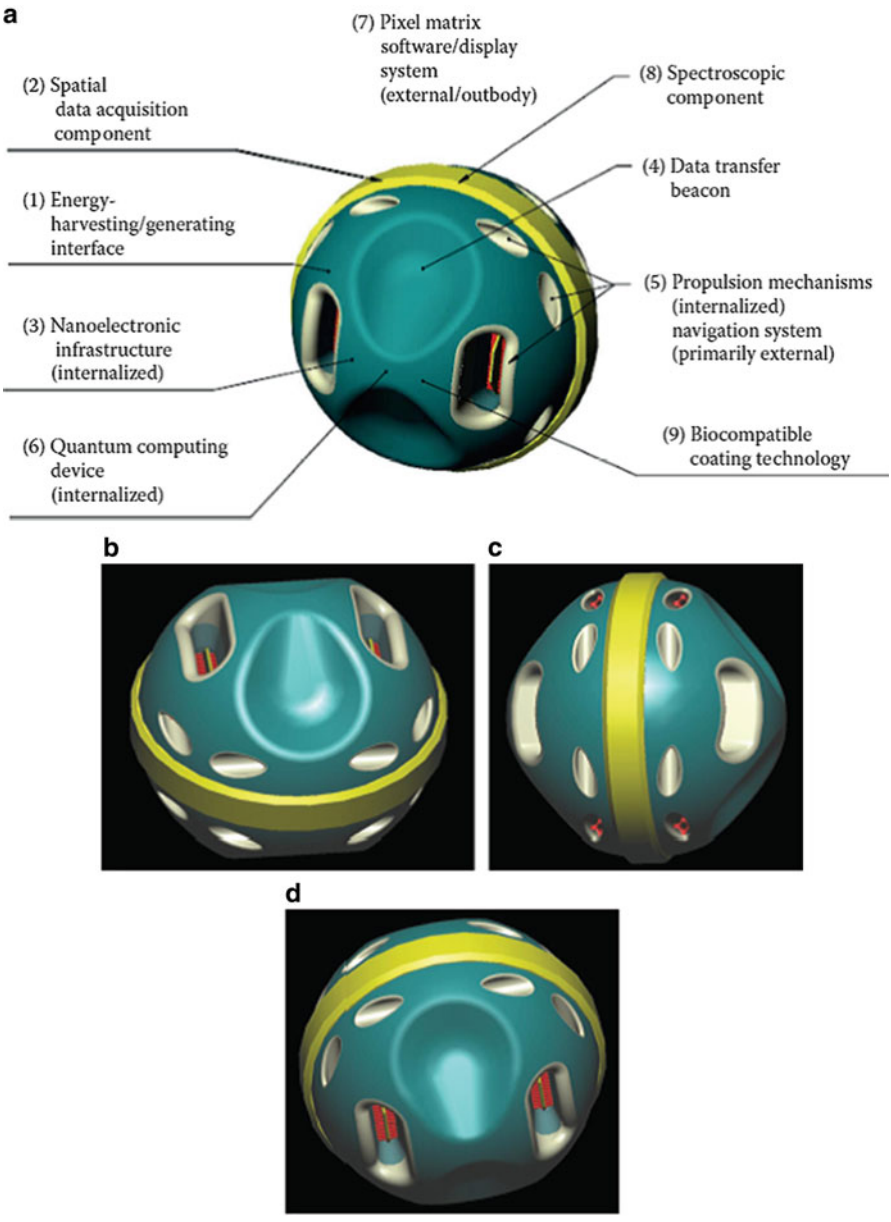

Fig. 33.2 (**a**) Anatomy of conceptual Vascular Cartographic Scanning Nanodevice (VCSN), (**b**–**d**) VCSN in various orientations (©CRC Press/Taylor Francis Group. Certain VCSN related text and images are excerpted from a chapter that was previously published by CRC Press in 2013 in the book entitled: *Nanomedical Device and Systems Design: Challenges, Possibilities, Visions*, and appears here with kind permission of CRC Press/Taylor Francis Group)

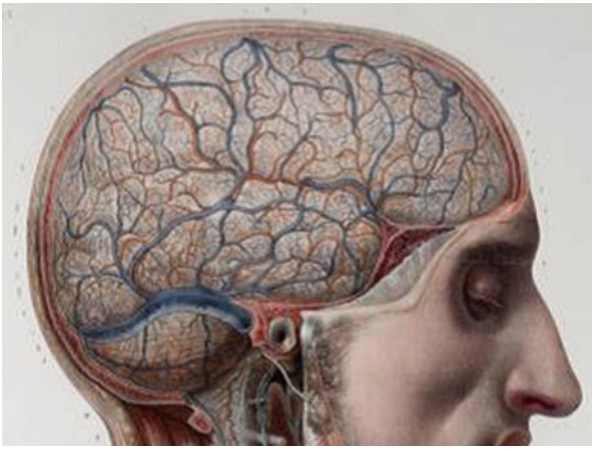

Fig. 33.3 Depiction of peripheral brain vasculature (From Bourgery, M.J., *Traité complet de l'anatomie de l'homme*, C. Delaunay, Paris, France, 1831–1854. Permission for use granted by Creative Commons License)

1. *Energy-harvesting/generating components.* Constitute the primary and auxiliary power-harvesting/generating sources for all primary, secondary, and multiple redundant VCSN systems. These mechanisms might harvest and catalyze readily available molecular biofuels (e.g., glucose, hydrogen) from the in vivo environment, and convert them into electron flow. There are many additional potential nanoscale energy harvesting and generating technologies (e.g., thermopiles, piezoelectronics, hydrostatics, and biomimetic entities and processes) that will be worthy of exploration...
2. *Spatial data acquisition component*. Functions as the spatial data acquisition signal emitter and receiver that will constitute the scanning mechanism. With this component as well, several potential technologies exist, or might be extrapolated (e.g., capacitive ultrasound, nanoscale time-of-flight LIDAR), which will warrant serious investigation . . .
3. *Nanoelectronic/nanophotonic infrastructure.* Conveys and modulates the electrical current and photonic streams that enable myriad critical VCSN functions (e.g., propulsion, onboard navigation controls, computing, and communications) including the emission and reception of scanning pulses from the spatial data acquisition array, and to facilitate the transfer of acquired spatial information to a data transfer beacon for transmission to outbody computers for final processing, image reconstruction, and display. Various nanoelectronic/nanophotonic components and conveyance conduits such as highly conductive carbon nanotubes, organic/inorganic nanowires or conductive polymeric nanofibers, and nanoscale chalcogenide (photoconductive glass)-derived optical nanofibers might electronically and photonically interconnect and interface all nanodevice elements . . .
4. *Data transfer beacon.* Transmits collected spatial data to an "outbody" receiver, which is interfaced with the Pixel Matrix (PM) image reconstruction system. It is also utilized as the primary communications node for receiving external

commands as well as for inter-nanodevice coordination. In addition, it would serve to lock onto an external homing signal upon completion of the scanning procedure, or for emergency egress from the patient.

5. *Propulsion and navigational systems.* Endows the nanodevice with autonomy in vivo and enables travel in any orientation and direction while within this environment. Movement is initiated and guided by transmitted command signals under external computer control via a dedicated "NanoNav" navigation system, perhaps akin to a miniaturized GPS system. An onboard computer (quantum or possibly DNA based) will assist in this regard by emanating positional coordinate feedback data.
6. *Nanoscale computation.* Enables the capacity for command data storage, working protocols, and spatial data backup at a high level of redundancy for fail-safe nanodevice operation, propulsion, and navigation including internal, inter-device, and external communications. This component might be manifest as a solid-state quantum computer or an organized biomolecular device comprising restriction nuclease and ligase hardware working in conjunction with software-encoded DNA duplex arrays. Alternatively, all optical nanoscale computing may be implemented to reduce the cumulative thermal footprint that may conceivably be generated by possibly millions of in vivo nanodevices.
7. *Pixel Matrix (PM) display system.* Translates acquired spatial data into digitized display format with ultrahigh image resolution. Each endothelial wall target "hit" that is initiated and measured by onboard ultrasonic transducer arrays (or other selected spatial data acquisition mechanisms) would be represented by a pixel, assigned to a calculated position in 3D space on a display. This software might also have the capacity for discerning vascular wall thicknesses so as to facilitate aneurysm detection via the isolation of secondary echo signatures from the spatial data set.
8. *Spectroscopic component.* Elucidates the chemical composition of scanned entities so as to accurately differentiate plaque deposits and lesions from healthy (background) vascular endothelial or lymphatic constituents by utilizing mass spectroscopic analysis. This capability may assist in the whole-body mapping and compositional analysis of pathogenic aggregates, regardless of their makeup (e.g., vascular plaques, neurological beta amyloid plaques, lipofuscin, cholesterol, and oxysterols).
9. *Biocompatible coating technology*. Endows nanodevices with reliable stealth qualities so that they may circumvent any level of immune response while they operate in vivo, through the utilization of inert and biocompatible materials (e.g., diamondoid, sapphire materials) as the main building materials of nanodevices, or via the use of bioinert diamondoid or polymeric thin film coatings.

Note: VCSN constituents, as defined in Nanomedical Device and Systems Design: Challenges, Possibilities, Visions (Boehm) (CRC Press), (Boehm 2013) *may be enhanced with biocompatible sensor patches as described by Domschke (see Sect. 33.6.1. for further details).*

33.4.2 VCSN Spatial Data Acquisition and Brain Mapping Procedure

A prescribed assemblage of VCSN units, dedicated to traversing the vasculature of the brain might be ingressed into the patient via hypodermic injection, ingestion as syrup or pill, a dermally applied patch, or topical gel. As it seems logical to scan of the complete vasculature of the body in obtaining brain circulatory data, it would be a matter of isolating the spatial data sets that are obtained from the brain for detailed scrutiny, utilizing the Pixel Matrix display platform. Since the paravascular network of the glymphatic system is in such intimate proximity to cerebral arterial and venous pathways, it might be imaged as well as an overlay, via the isolation of derivative echo signatures, and may serve to assist with the generation of a more finely detailed rendering of the brain. The VCSN's would scan the vasculature and glymphatic channels of the brain "on the fly" as they transit through these systems in massively parallel fashion, hence the timeline for the arterial/capillary/venous mapping procedure should not require longer that the median cerebral circulation time. Freitas recommends a conservative speed limit of ∼1–2 cm/s for nanodevices that are traversing the circulation (Freitas 1999).

Egress protocols for the VCSN may include that, subsequent to scanning operations, they be naturally excreted from the brain and body through the glymphatic/lymphatic systems. The simplest, most direct and rapid egress strategy might be through the digestive or urinary tracts. Other options may include their self-guided migration to sweat pores, hair follicles, or finger/toe nail beds, where they would power down and be slowly egressed (as inert entities) through these pathways. Boehm suggests a (conceptual) more deliberate and rapid egress strategy:

> *A hypothetical egress method that might be instituted subsequent to a nanomedical diagnostic or therapeutic task could involve the initiation of an external homing signal, perhaps generated by a dermally applied nanodevice "retrieval patch," which would trigger an autocommand for all nanodevices to immediately travel to the signal source. Once in range of the patch, nanodevices will burrow up from the deeper epidermal layers to the surface of the skin whereupon they might be adsorbed to a specifically nanoengineered undersurface of the patch for subsequent removal. Contingent on the extent of nanodevice and infrastructural sophistication, this conceptual procedure might be completed within tens of minutes.* (Boehm 2013)

33.5 Aligning Cerebral Spatial Data with Cognitive Health and Functionality

Specific physiological and cognitive functions may be correlated to certain physiological and morphological domains of the human brain, and assigned to particular species of cells within those domains. We propose that in the future, it might be possible to precisely infer the type and quality of cognitive functionality, as gleaned from the spatial locations, orientations, and operational status of various types of

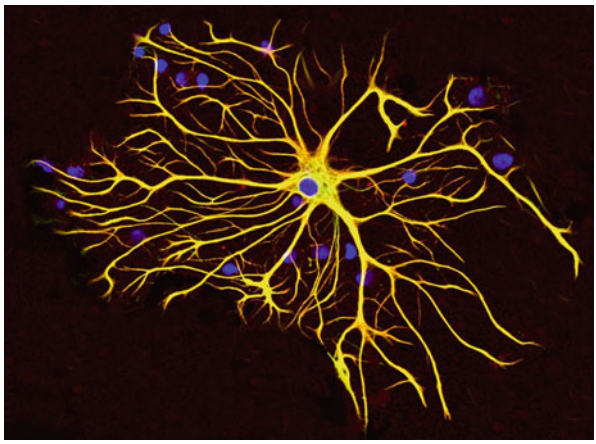

Fig. 33.4 Astrocyte cell grown in stained tissue culture. Image was acquired using a confocal microscope (EnCor Biotechnology laboratory. Image created by Gerry Shaw. Permission granted by Creative Commons License)

brain cells and synapses, which are demarcated by exquisitively detailed VCSN 3D maps of the cerebral microvasculature and glymphatic system. These data may subsequently assist in the rapid diagnoses of myriad cognitive conditions, and/or facilitate the development of efficacious targeted therapeutic strategies. The VCSN might be further endowed to include integrated nanosensors (Sect. 5.1) that have the capacity to identify and monitor (via the successive VCSN administrations) the concentrations of a range of cognitive-specific metabolites, localized pH, and blood pressure.

For example, star-shaped astrocytes (Fig. 33.4) comprise specialized glial cells serve as substrates for the spatial stabilization of neurons, with each astrocyte having its own distinct/non-overlapping domain. These cells are endowed with multiple fine extensions and endfeet, which intimately interface with and mediate both neuronal synapses and the cerebral microvasculature. Single astrocytes in the cortex or hippocampus may interrelate with multiple neurons, several hundred dendrites, and >100,000 synapses (Bushong et al. 2002; Halassa et al. 2007; Ogata and Kosaka 2002). They are the most abundant of the glial cells in the human brain and outnumber neurons five to one. It had previously been surmised that astrocytes were relatively passive cells, which were responsible for general cerebral housekeeping tasks. However, new research over the last several decades has elucidated much more extensive and versatile role for astrocytes in both the development and maintenance of the human brain (Mishra 2017). Through their communications with neurons and intimate association with synapses, astrocytes have the capacity to monitor and directly alter synaptic function (via the release of gliotransmitters such as glutamate, purines (ATP and adenosine), GABA, and D-serine); hence, they can control synaptic transmission between neurons (Chung et al. 2015; Sofroniew and Vinters 2010). Further, signals emanating from astrocyte endfeet may dilate or constrict blood vessels, thereby titrating blood flow, and hence, the flow of oxygen and nutrients within the brain in association with synaptic activity (Sofroniew and Vinters 2010).

Reactive astrogliosis refers to a process through which astrocytes directly respond to any insult imparted to the CNS, and has emerged as a "pathological hallmark of CNS structural lesions." In this reactive state, astrocytes have a vast molecular arsenal at their disposal, albeit progressive changes are manifest in response to the level of severity of a particular injury to the CNS via "a finely gradated continuum", which are "context-dependent" (Sofroniew and Vinters 2010). Therefore, it may be of significant value if the health, cognitive performance, and functional status of specific brain regions may be determined through the detection of molecular level influxes into, and pressure of the microvasculature (via VCSN nanosensors) as relates astrocyte functionality. This information might be precisely correlated with VCSN acquired spatial data (time stamped) in the provision of an overlay of the molecular composition of blood for any defined segment/s of the cerebral microvasculature. In turn, these data may inform more accurate diagnoses and facilitate improved therapies.

The human brain possesses a significant inherent capacity for plasticity, and indeed, is in a perpetual state of flux across the human lifespan. Further, the mechanisms that underlie brain plasticity also undergo change over the course of a lifetime. Current technologies utilized for the elucidation of brain plasticity include transcranial magnetic stimulation (TMS), which may operate in conjunction with other neuroimaging platforms such as electromyography (EMG), electroencephalography (EEG), or functional magnetic resonance imaging (fMRI) (Freitas et al. 2013). The capacity for the generation of an ultrahigh resolution 3D map of the human brain would likely serve as a useful tool for further clarifying the mechanisms of brain plasticity, as well as to assist with the correlation of various alterations in cerebral physiology to specific disease states. Comparative maps, which might be generated sequentially over time, may also enable the monitoring of physical brain changes and to formulate prudent interventions if deemed necessary.

The prognosis for the decrease of cerebral cells and the loss associated cognitive abilities as we age is rather bleak. It is estimated that approximately 9.5% of the cortical neurons in the human brain is lost between the ages of 20 and 90 (Pakkenberg et al. 2003), which represents a decline of close to ~85,000 neurons per day (1 neuron per second). At our oldest, ~40–50% of myelinated nerve fiber length is lost, while vascular perturbations may exacerbate brain tissue loss, and hence, cognitive function (Drachman 2005). Moreover, the formation of toxic proteinaceous aggregates (e.g., amyloid plaques, tau, Lewy bodies) may give rise to serious cognitive impairments including Alzheimer's, Parkinson's and various other dementia's (Arbor et al. 2016; Arendt et al. 2016; Falkenburger et al. 2016).

A highly detailed cerebral map may enable a better understanding of the processes involved with cerebral cell loss and why they occur, allowing for the development of preemptive interventions to perhaps slow, or ideally, negate these cumulative deficits. In terms of cerebrally toxic proteinaceous aggregates, it has recent been proposed that the distinctive morphologies of tau aggregates may be employed to determine specific types of dementia, which particular brain regions will be impacted, and how rapidly the disease will propagate (Kaufman et al. 2016).

Hence, it is conceivable that the spatial coordinates of particular tau protein strains may be inferred by metabolites that are exclusively associated with specific strains, as well as being differentiated via the same process.

33.6 Prospective Applications of VCSN 3D Ultrahigh Resolution Brain Maps

There will likely be myriad prospective beneficial medical applications derived from the ultrahigh resolution three dimensional cerebral maps generated by the conceptual VCSN system. Many of these applications will undoubtedly enhance our understanding of cognitive functionality, while assisting with the detailed demarcation of domains within the brain where particular cognitive operations proceed. We explore a number of these potential applications below.

33.6.1 Advanced Cerebral Diagnostics and Monitoring

Proper cognitive function is based on physiological and biochemical homeostasis. The ultrahigh resolution mapping of the human brain in combination with the monitoring of brain/cognitive-specific metabolites offers the capacity for advanced diagnosis and the potential for specific cognitive-domain treatment opportunities. Metabolite monitoring may be facilitated through the integration of chemical nanosensors with the VCSN mapping devices. Examples of key analytes that are associated with biochemical homeostasis include lactate, glucose, CO_2, O_2, and pH. An imbalance of these analytes is associated with cognitive disorders such as major depressive disorder (MDD), and anxiety disorders, both of which cause cognitive impairment.

The core symptoms of acute MDDs are cognitive complaints, such as the diminished ability to think or concentrate and/or indecisiveness (Lam et al. 2014). Suboptimal remission rates and the persistence of cognitive deficits contribute to functional impairment in MDD, inviting the requirement for the development of mechanistically novel and domain specific treatment approaches (Bortolato et al. 2015). High levels of both CO_2 and lactate alter pH balance, and may generate acidosis that influences neuron functionality through pH-sensitive receptors, which continue to be discovered**.** Acidosis is associated with panic attacks and anxiety disorders (Wemmie 2011).

Since synaptic plasticity is related to glucose levels (Diano 2015), suitable VCSN-integrated nanosensors for the detection of lactate and pH, as well as glucose measurements, might be fabricated from stimuli responsive hydrogel matrices with embedded sensing receptors. Biocompatible stimuli responsive sensing hydrogels are described by Domschke et al. (Domschke et al. 2006; Domschke 2010). The

non-electrical changes of the physical properties of stimuli-responsive hydrogels may be converted to an electrical signal through the use of appropriate transducers such as magnetoelastic sensors (Richter et al. 2008).

Constant blood pressure is key for physiological homeostasis, which allows for the sufficient supply of oxygen. Significantly reduced resting cerebral blood flow, predominantly in left-sided medial prefrontal cortical and subcortical regions, is related to depression (Phillips et al. 2015). A time-resolved VSCN-integrated nanosensor capacity may be envisaged that enables acquired spatial data to be overlaid with highly localized blood flow pressure data for any site within the cerebral vasculature (Wang et al. 2015; Mohammad Haniff et al. 2014).

Comprehensive cumulative spatial and/or physiological data acquisition and monitoring would constitute a significant step toward a holistic understanding of the anatomical and functional superstructure of the brain as a whole organ. Biopolymeric superstructures create new functionalities that individual components do not possess (e.g., the *quaternary structure* of multiply-folded protein forms lead to enablement of enzymatic activity, hemoglobin, ion channels, etc.). Likewise, the overall anatomical superstructure of the brain gives rise to capabilities that are far beyond the functions of individual synapses. Over time, cumulative whole brain data monitoring may allow for the derivation of typical individual patterns of functional and/or anatomical brain modifications that relate to pathology and/or neuroplasticity alike. These collective whole brain patterns would be a considerable step forward in the elucidation of holistic brain function.

33.6.2 Augmented Sensorial Perception

The classic five senses are vision (sight), audition (hearing), tactile stimulation (touch), olfaction (smell), and gustation (taste). Other sensory modalities are the vestibular sense (balance and the sense of movement) and proprioception (the sense of knowing one's position in space), along with time (the sense of knowing where one is temporally as relates to activities). A further modality that has garnered increasing attention is the capacity for electromagnetic sensing (the perception and connection to endogenous and external electromagnetic fields). Living cells, tissues, and organisms have the ability to produce electrical fields, sense and respond to the fields. Endogenous DC electric fields (EFs) are important, fundamental components involved with development, regeneration, and wound healing (Messerli and Graham 2011). These modalities, which may be closely aligned with social intelligence, are well-known at the cellular level; however, they await the elucidation of central sensory processing mechanisms in the human brain. An additional potential sensing mechanism of the brain is magnetosensing, which is connected to the visual-spatial processing apparatus, and is known from animals that utilize the Earth's magnetic field to facilitate orientation and navigation. Recent studies have suggested the potential for a similar mechanism that involves human cryptochrome (CRY 2), which is heavily expressed in the retina (Foley et al. 2011).

Historically, sensory processing associated with the different senses has been thought to occur predominantly in distinct lobes of the brain, referred to as projection areas. Projection areas compromise domains in the four lobes (frontal, parietal, temporal, occipital) of the brain where sensory processing occurs (Pirotte et al. 2008). Recent studies have indicated a complex model as opposed to a single purpose system, toward multifaceted systems. An example is the visual-spatial processing that comprises of a diverse set of processing pathways that mediate both spatial perception and visually guided action across multiple cortical areas within the frontal, temporal and limbic lobes (Kravitz et al. 2011). There are approximately 20 retinal ganglion cell (RGC) types that may be classified via morphological, molecular, and functional criteria. Each type of RGC participates in distinct retinal circuits and projects to a specific set of targets within the brain including the primary image-forming nuclei such as the lateral geniculate nucleus (LGN), the visual portion of the thalamus, and the superior colliculus (SC), located in the roof of the midbrain, which coordinates rapid eye movement (Erskine and Herrera 2014; Coombs et al. 2007; Schmidt et al. 2011). Each multifaceted sensor system is coordinated with other sensory systems, accounting for what is known as multisensory integration which is central to adaptive behavior, in that it allows us to perceive a world of coherent perceptual entities derived from the totality of all sensory input (Lewkowicz and Ghazanfar 2009).

Understanding multisensory integration is critical toward understanding how different sensory modalities interact with one another and alter each other's processing, organization and growth (Stein and Rowland 2011). The prospect of ultrahigh resolution 3D brain mapping enabled through the development of advanced nanomedical images systems such as the VCSN, opens a door to understanding the nuances and subtleties of complex multisensory integration processes and coherent perceptual entities generated by holistic brain functions. By utilizing VCSN generated brain maps/models as a template, it might be possible to begin to consider the nanomedical augmentation of the senses, and various aspects thereof. These capabilities may not only potentially significantly improve the lives of patients who have either been born with major sensory deficits (blindness, deafness) or have experienced damage to sensory systems, but enable the possibility for considerably expanding our innate sensory perceptions and range.

33.6.3 Augmented Learning and Memory

Regions of the brain associated with learning include the prefrontal cortex (learned emotional responses to perceived threats); hippocampus (spatial learning, navigation, initiation and processing of fear response); amygdale (mediates emotional learning and fear conditioning); thalamus (spatial learning, initiation and processing of fear response), and the cerebellum (motor learning) (Wood et al. 2012; Whitlock et al. 2006; Fonseca 2013; Liu et al. 2016; Fiez 2016). Domains in the human brain associated with memory consolidation include the hippocampus, which serves

as the core site of episodic memory, and is currently hypothesized to mediate the encoding and retrieval of both conscious and unconscious episodic memories (Züst et al. 2015). The dorsolateral prefrontal cortex (DLPFC) is recognized as containing the critical neural mechanisms that facilitate working memory, though there is negligible knowledge available as relates to the specific neural elements and pathways involved. The cerebellum also contributes to the processing of procedural and working memory (Mandolesi et al. 2001), and it was recently discovered that the introduction of higher levels of gamma-aminobutryic acid (GABA) in the DLPFC may ameliorate deficits in the working memory (Yoon et al. 2016). Other portions of the brain that are involved with memory include the temporal lobe, which plays a key role in the development of long term memories, and the medial temporal lobe, which is engaged in episodic and declarative memory. Embedded within the medial temporal lobe is the limbic system (where the hippocampus resides), which is also host to other brain structures that are engaged in memory processing. These include the amygdala, cingulate gyrus, thalamus, hypothalamus, epithalamus, mammillary body, and other organs (Izquierdo et al. 1993). It is conceivable that future nanomedical devices may be targeted to specific sites in the brain (that have been demarcated by VCSN maps), which are deficient in certain molecules that may facilitate learning and memory (molecular engrams) (Fuxe and Borroto-Escuela 2016; Fuxe et al. 2014; Borroto-Escuela et al. 2015), to modify molecular assemblies, or increase the levels of specific molecules toward their enhanced functionality.

Neuroplasticity pertains to the brain's capacity to form new neural connections, and be influenced by the environment, which proceeds most prolifically during the formative years of childhood and adolescence, while the brain is still malleable. It is suggested that during critical periods of brain development, the neural circuits that relate to mental states and behaviors are being sculpted, and thus, they are particularly sensitive to the effects experiential events. One aspect of the brain's plasticity is structural; in animals, and likely in humans as well, the perineuronal net, which is a cartilage-like matrix, develops around neurons and blocks them from further physical changes, whereas other aspects operate within the molecular realms.

The extracellular matrix (ECM) of the central nervous system regulates numerous events during brain development (e.g., neurogenesis, gliogenesis, neurocircuitry formation), as well as in adulthood, which impacts damage responses, plasticity, and regeneration. Substantial changes in the quantity and the composition of the ECM occur during cognitive development. At the conclusion of critical periods, that is, temporal windows during development when experience-dependent neuronal plasticity is heightened, a specialized ECM structure, referred to as the perineuronal net (PNN), deposits around many types of neurons, to assist with the stabilization of newly established neuronal connections (Carulli et al. 2016). The structure of the PNN, cellular origin of PNN components, PNN binding elements, and the primary functions of PNN in the regulation of plasticity (at the single circuit, cellular, and synaptic level) and neurological conditions in which the PNN is altered, are being increasingly elucidated, and may soon reveal opportunities for the reopening of windows of plasticity in the adult brain.

In terms of molecular associated plasticity, studies are already confirming that drugs such as valporate may have the ability to reopen the plasticity window (Gervain et al. 2013). A further example reveals evidence for reversing an epigenomic state of a gene that is established through behavioral programming (Weaver et al. 2004). However, Friedman alludes to the possibility that there might be a shadowy aspect to reopening the vault. It appears that the developmental strategy of the brain to integrate finite sensitive periods may be a prudent strategy. This is because plasticity requires significant energy in order to sustain the dynamism of neural circuitry. The limiting of plasticity may actually shield the brain from vividly re-exposing earlier traumas and negative events that we would rather keep obscured in deep neural crypts. Further, our personalities are intertwined within this neural circuitry; hence, we risk modifying the very essence of ourselves (Friedman 2016). The careful comprehensive monitoring of the brain through methodical and sequential VCSN mapping, might guide investigations into the reopening of these cognitive windows to assist in elucidating energy efficiencies, and the safety aspects of future neuroplasticity research.

33.6.4 Augmented Cognitive Information Processing

General information processing capacity (IPC) in mammals is optimized in humans and is determined by a number of factors, including cortical neuron population, neuron packing density, interneuronal distance, and axonal conduction velocity (Dicke and Roth 2016). Information processing in the human brain is distributed across and involves interactions between multiple forebrain structures, encompassing the cortex, basal forebrain, basal ganglia, and dorsal thalamus, with the prominent role being performed by the cerebral cortex. Higher cognitive, executive, and communicative operations, inclusive of language and vocal learning, are enabled by this complex neural architecture (Lefebvre 2012; Petkov and Jarvis 2012). The emergence of potential ultrahigh resolution 3D brain maps rendered by the VCSN with overlaid chemical data may lead to the possibility that some aspects of cognitive information processing might be enhanced to a certain degree.

The augmentation of the IPC in the brains of patients with Alzheimer's, or those with a host of other neurodegenerative conditions might be accomplished by precisely increasing the number of neurons and glial cells in the neocortex though the introduction of additional neuron and glial stem cells, thereby also increasing neuronal packing density. Using the VCSN map/model as a guide, the appropriate populations and species of neuronal and glial stem cells might be accurately introduced to specific sites of the brain that clearly indicate deficits in the numbers of these cells. This might be done subsequently to the prepatory precision degradation and removal of beta amyloid plaques, tau proteins, and lipofuscin aggregates at these sites. The hope would be the reestablishment of healthy brain tissues to replace those that have been ravaged by disease. The possibility of adding more neurons to healthy brains would likely be ill-advised. As mentioned above, in the healthy

brain, intercapillary distances of ~40 μm only allow space enough for two neurons between them, which define and physically constrain interneuronal distance and packing density.

Hence, it appears that the potential augmentation of cognitive information processing in healthy brains might, for example, be achieved by increasing intracortical information processing speeds through enabling higher axonal conduction velocities. Two strategies employed by nature to achieve this end are to decrease the interior resistance of axons, and/or to decrease the trans-fiber capacitance. Resistance is lower in larger diameter axons (e.g., in the giant squid axon) since resistance decreases as the square of diameter (Hartline and Colman 2007). As Hodgkin observed, "This increases conduction speed in proportion to the square root of the interior diameter." (Hodgkin 1954). Lowering the transverse capacitance between the interiors and exteriors of nerve fibers by increasing axonal insulation efficacy also enables more rapid conduction. This is accomplished through the establishment of a multilayered lipid based myelin sheath, (Fig. 33.5) which prevents the leakage of current (Hartline and Colman 2007). It might be possible that nanomedical biomimetic analogs that incorporate these strategies might be developed in the future toward enhancing the speed of cognitive information processing. It is conceivable that future nanomedical enhancements may cumulatively serve as a portal of sorts, which enables the fine manipulation of electromagnetic fields; thus facilitating augmented sensitivity and communicative information exchanges through these energy fields with other individuals and life forms, and the external environment at large.

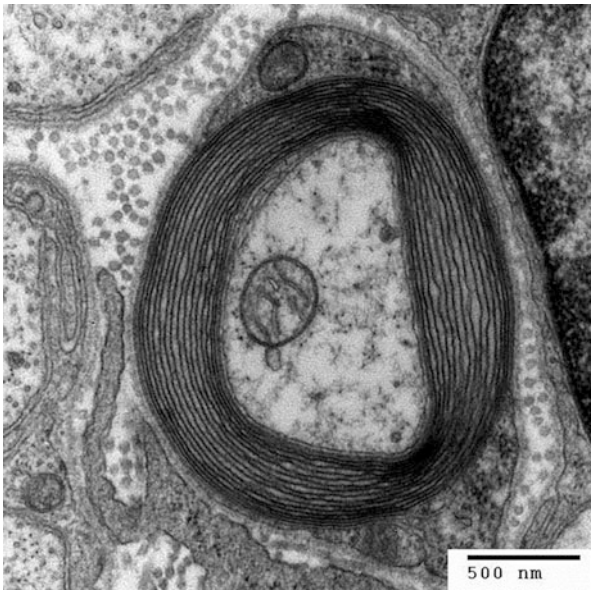

Fig. 33.5 Transmission electron micrograph of cross-section of myelinated axon (Image credit: Electron Microscopy Facility at Trinity College, Hartford CT. Permission granted by Creative Commons License)

As observed by Boehm, the cognitive enhancement of the human brain and the potential implications thereof, are not to be taken lightly, and warrants serious consideration:

> *Nanomedicine may well evolve capacities for enabling the first incremental nascent steps toward potential finely controllable and clinically safe cognitive enhancement. However, these capacities will likely be tempered, as they should, by intelligent moral and ethical considerations, hopefully arriving at clarity in regard to what the true motivators should be behind various forms of cognitive augmentation. A broad review culminating in consensus as to what the essence and core values of humanity and humanness should be is warranted, as well as how we are to perceive and conduct ourselves with respect to the prospect of having an ever-increasing influence over the human brain, the human condition, and human evolution itself.* (Boehm 2013)

Note: Further to the above, the establishment of a new set of stringent operational protocols will be required in order to ensure the safety and highly efficient functionality of nanomedical devices, in conjunction with high resolution monitoring, and standardized procedures for nanodevice recycling and assurance of downstream environmental compatibility.

Cognitive communications involving thousands of distinct species of neurons in the human brain are mediated by ~100 unique types of neurotransmitters, and action potentials along axons typically range from ~2 to 400 km/h via neural spikes (Eliasmith and Anderson 2003). A wide variety of "nootropics" (cognitive enhancers) may be introduced by targeted nanocarriers, such as liposomes, that interact with neuronal receptors, ion channels, nerve growth factors, enzymes, etc. (Froestl et al. 2012). The precise delivery of compounds that act to increase the stimulation of neurons, amplify the efficacy and robustness of synapse firing, and augment the accessibility of neurotransmitters (e.g., acetylcholine, norepinephrine, serotonin, gamma-aminobutyric acid [GABA], glutamate, dopamine [DOPA]) might also be possible. These nanotherapeutics might significantly assist with the mitigation of depression and anxiety, in addition to influencing executive function, memory, mood, libido, appetite, and sleep (Farah et al. 2004).

33.7 Implications for the Future of Human Cognition

Once the capacity for the safe mapping of the brain attains the level of sophistication that allows us to precisely spatially locate and image the physiological parameters of virtually all domains that are associated with every aspect of cognition, we will possess a very potent tool against every type of degradative cognitive condition that the brain is subject to. Further, the various cells types that operate within these domains might also be identified, which may enable the formulation of very precisely targeted therapeutic interventions. Beyond the realms of diagnostics and therapeutics, might be possibilities for the optional nanomedically-mediated augmentation of certain cognitive facilities, including memory, sensory acumen, learning capacities, and cognitive information processing speeds. It is very likely,

and indeed anticipated, that the prospects for the implementation of these capabilities will be thoroughly scrutinized in terms of their safety, moral, ethical, societal, and legal implications. For instance, might one group of individuals who have undergone a specific enhancement procedure be considered as having advantages over unenhanced individuals? Will these cognitive augmentation procedures be made economical enough, as they should, to be available for all, rather than for just a privileged few? These critical issues are beyond the scope of this chapter; however, they will certainly warrant much careful and meticulous consideration and discussion. The above said, the broad availability of positive cognitive enhancements may cumulatively facilitate the further progress of the human species toward improved problem solving in addressing the myriad serious issues that currently confront and challenge us, (e.g. global warming, disease/epidemic eradication, complex conflicts, environmental degradation, clean energy development, clean water/advanced desalination, sustainable food supplies, etc.). These cognitive capacities might also assist us in the discovery of new and unprecedented technologies, and enable significant further advancements in space exploration, and the propagation of the human species across the solar system, and far beyond.

33.8 Conclusion

It is proposed that in the relatively near future (~10–30 years) the generation of ultrahigh resolution 3D cerebral maps might be possible through the use of advanced autonomous nanomedical devices. A conceptual Vascular Cartographic Scanning Nanodevice (VCSN) is described that might, in conjunction with perhaps thousands to tens of thousands of identical nanodevices, map the entire microvasculature, as well as glymphatic system of the human brain. The VCSN may also be endowed with several classes of integrated nanosensors for the detection and quantification of chemicals, analytes, pH, and physiological parameters such as blood pressure. Future surgeons and/or physicians might subsequently have the capability to safely "fly though" the entire vasculature/microvasculature, and glymphatic system of the human brain via a joystick and computer display to scrutinize for any indications of imminent aneurysms, for example.

These highly detailed digital maps/models would be available in a number of other formats as well, including in holographic and virtual reality. Significantly, it is conceivable that it may also be possible that the spatial proximity of various types of cell populations in the brain (e.g., neurons, glial cells, etc.), and perhaps even individual cells, may be inferred through the localized (time stamped) analyses of metabolites and other interactions that occur with the microvasculature and glymphatic system, which might be correlated to specific cognitive domains/functionality. Prospectively, in addition to the further elucidation of fundamental cognitive mechanisms, these data could be of vast benefit for patients, as they may facilitate considerably enhanced and accurate diagnostics, therapeutics, and monitoring to more efficaciously address myriad brain conditions. Ultrahigh

resolution brain mapping will likely reveal yet undiscovered holistic functions and capabilities that are derived from the superstructures of trillions of collaborative elements in the brain. A deeper understanding may be envisioned for these functions that extend well beyond our bodies to include abilities to communicate directly with the external electromagnetic energy fields of other living beings, as well as the ambient environment.

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Chapter 34
A Unified Physical Theory for CSF Circulation, Cooling and Cleaning of the Brain, Sleep, and Head Injuries in Degenerative Cognitive Disorders

Iype Cherian and Margarita Beltran

Abstract Cerebrospinal fluid (CSF) from the basal cisterns transits into the brain through spaces that surround the vascular system of the brain; the so-called paravascular spaces (Virchow Robin Spaces), or paravascular pathway, which surround the arteries, veins, and capillaries. The passage of CSF through these paravascular spaces is driven by the cardiovascular and respiratory systems, and is more active at night during sleep. Their cumulative function is presumed to include the clearance (or "cleaning") of metabolic wastes, which likely contributes to counteracting metabolic heat, via the "cooling" of the brain. This paravascular CSF transport system might be implicated in CSF shift edema that occurs in head injuries; hence, it may be the rationale behind why opening the cisterns to atmospheric pressure through cisternostomy, quickly decreases post-traumatic brain swelling. When this paravascular system is blocked or becomes somehow dysfunctional, the "cleaning" and "cooling" functions of this system may be impaired or completely stopped. This could result in the accumulation of metabolic wastes that cannot be removed within these spaces. In addition, a faulty brain cooling system might play a role in the modification of the molecular structures of proteins, thereby making them more difficult to be removed by the flow of CSF, thus aggravating the situation. Therefore, this may be a common underlying mechanism for many neurodegenerative disorders, and an aggravation factor for others. This avenue appears to be novel and promising toward the elucidation and treatment of a host of diseases.

Keywords Virchow Robin spaces • Paravascular pathway • Cleaning • Cooling • Cisternostomy • Degenerative CNS diseases

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34.1 Introduction

The full scope of the purpose and functions of the cerebrospinal fluid (CSF) has likely been underestimated and misunderstood for many years. Classically, the primary function of CSF was believed to be to enable buoyancy, to prevent the brain from losing its shape. However, this does not explain the reason behind the daily secretion of 500 ml of CSF, and the refreshing of its entire volume ∼4 to 5 times each day. If the CSF was meant solely for buoyancy, why is it required to be changed so frequently?

There are further questions which come to the fore when one begins to ponder the mysterious ways in which the brain functions. How, for instance, does the brain release excess metabolic heat, or byproducts, when a blood brain barrier is in place? What is the rationale behind anyone to sleep for 4 h or more, and what are the changes take place during this time that makes one wake up refreshed and with an uncluttered mind? To throw some light to these queries it is necessary to explore new insights into this field.

The understanding of the dynamics of CSF has evolved significantly since the classic bulk flow theory was described more than a century ago. The classic view of CSF production by the choroid plexus, unidirectional circulation from the ventricles to the craniospinal subarachnoid space, and absorption in the Pacchioni granulation is no longer considered as valid.

Fresh CSF is still believed to be secreted through the epithelium of the choroid plexus under determined conditions (Linninger et al. 2016). However, according to new theories, the formation and absorption of CSF may rely mainly on the hydrostatic pressure and osmotic forces that exist between the capillaries on one side, and the interstitial fluid (IF) and CSF on the other. It appears that continuous bidirectional fluid exchange between IF and CSF takes place, leading to the net formation of CSF (Oreskovi ć and Klarica 2010; Maraković et al. 2010; Chikly and Quaghebeur 2013). This new theory implies that a constant shift of fluid proceeds between the IF and CSFn and from there to the neurovascular bed. The exchange between IF and CSF into the brain parenchyma is made possible due to the presence of paravascular spaces that are filled with CSF, which communicate with CSF in the subarachnoid space. This system has recently been referred to as the "glympathic system" (Iliff et al. 2012, 2013), which comprises the anatomical space that is enclosed between perivascular astrocyte end feet and the vascular wall (Rangroo Thrane et al. 2013). The paravascular system that guides the CSF has been proven to clear interstitial proteinaceous waste from the brain interstitium (Iliff et al. 2012, 2013); primarily in the paravenous side (paravenular efflux) (Iliff et al. 2012). This clearing is regulated by AQP4 water channels that are located in the end feet of astrocytes limiting with the vascular wall (Iliff et al. 2012).

Contingent on solubility and molecular dimensions, metabolic wastes may enter the paravascular space and egress the brain via CSF outflow from the subarachnoidal spaces (SAS) through the perineural pathways of the cranial and spinal nerves (Johnston et al. 2004; Wagshul and Johnston 2013). Alternately, they may traverse

the regular lymphatic vessels that surround the dural sinuses and meningeal arteries into the systemic lymphatic system (Louveau et al. 2015; Aspelund et al. 2015), or pass through the bloodstream.

These new understandings of CSF and the empirical experience of the corresponding author in the opening of cisterns of patients with severe head trauma (Cherian et al. 2013, 2016a, b) have prompted a novel hypothesis on CSF hemodynamics and function with a global perspective, as described in previous papers (Beltran and Cherian 2016; Cherian and Beltran 2016). According to this view, CSF plays an essential role in clearing metabolic waste from the brain parenchyma and acts as a local buffer of metabolic heat under normal physiological conditions (Wang et al. 2014). It is tempting to speculate that the impaired performance of CSF inflow or outflow through the glymphatic system might lead to alterations in the regulation of localized temperatures, with a potential role in the malformation of proteins, while impeding the clearance of pathologic proteins, and thus, promoting the onset of neurodegenerative disorders.

The paravascular system comprises the anatomical connection between the interstitial fluid (ISF) and vascular system of the brain, and it is almost in direct continuity with the subarachnoid space. The functional impairment of the paravascular system appears to be an underlying condition of the aging human brain (Kress et al. 2014), which has also been related to various CNS disorders, such as neurodegenerative disorders that are brought on by the accumulation of misfolded, prion-like proteins (e.g., Alzheimer's, or amyloid angiopathy) (Iliff et al. 2012; Dunning et al. 2013; Gallina et al. 2015; Simka 2015), normal pressure hydrocephalus (Gallina et al. 2015; Greitz 2006; Silverberg et al. 2003), postraumatic encephalopathy (Simka 2015; Iliff et al. 2014), or neuroinflammatory disorders, such as multiple sclerosis (Simka 2015). Furthermore, the presence of the paravascular system would explain the advantages of cisternostomy over decompressive craniectomy, in the treatment of acute brain trauma (Cherian et al. 2013; Cherian and Beltran 2016).

34.2 Discussion

The corresponding author serendipitously uncovered the fact that opening cisterns in severe head trauma had the effect of abating severe brain swelling, while drastically reducing the requirement for decompressive hemicraniectomies (Cherian et al. 2013, 2016a, b; Cherian and Munakomi 2013). His decade long work on this, led him to believe that CSF was ingressing to the brain through the Virchow Robin spaces, (Fig. 34.1) producing a condition which has been recently termed as CSF shift edema (Cherian and Beltran 2016). Although this concept was not accepted initially, research on the glymphatic system by Iliff et al. categorically proved that CSF was indeed going into the brain through the Virchow Robin spaces, or paravascular spaces, and that this pathway was critical for clearing the brain of metabolites (Iliff et al. 2012, 2013).

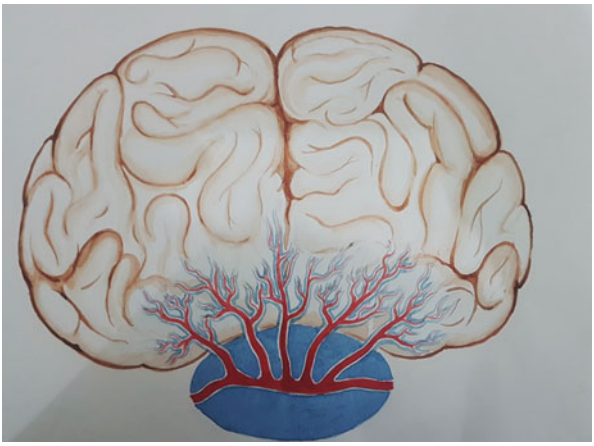

Fig. 34.1 Artistic representation of the brain, cisterns, Virchow-Robin spaces, and blood vessels within the cisterns. Note that the Virchow-Robin spaces travel around the blood vessels from the cisterns into the brain. The paravascular pathway through which the CSF flows could communicate into the brain parenchyma, indicating that the paravascular pathway persists with the bifurcation of the brain vessels

The glymphatic system branches along the course of the arteries, arterioles, capillaries, and venules, transporting CSF to wherever blood is brought, and this CSF interacts with the end feet of glia and indirectly with neurons. CSF-ISF exchange has been shown to drive the removal of exogenous molecules from the interstitial spaces of the brain (Iliff et al. 2012, 2013) controlled primarily by water pore transport (aquaporins), specifically aquaporin type 4 (AQP4) (Iliff et al. 2012; Papadopoulos and Verkman 2013).

34.3 Paravascular CSF Delivery Mechanism

The primary CSF delivery mechanism, from the subarachnoid space into the paravascular system and along the paravascular space, appears to be arterial pulsatility (Linninger et al. 2016; Iliff et al. 2013), coupled with brain compliance (Kress et al. 2014). When arterial pulsatility (Fig. 34.2) is preserved and there is perivascular compliance, a certain degree of successive physical brain compression and expansion events occur, wherein the brain behaves somewhat akin to a sponge by virtue of the cycle-dependent systolic-diastolic circulatory movement of blood through the brain (Yamada et al. 2013). This reciprocal movement influences the flow of fluids in the brain parenchyma to initiate a "pumping" effect of CSF around the vessels. These movements are driven by physiological oscillations of arterial and venous blood during craniospinal blood circulation, which are influenced by respiration, body activity, and posture (Orešković and Klarica 2014).

The impairment of this "pumping" effect in the paravascular system may occur due to loss of arterial wall elasticity, as seen for instance in small vessel disease, or as a consequence of low craniospinal compliance that impedes the expansion of the arteries, as can be seen in normal pressure hydrocephalus, glyosis (Kress et al. 2014), or postraumatic hypertension. This would result in a decrease of CSF turnover that hinders the clearance of metabolites (Kiefer and Unterberg 2012)

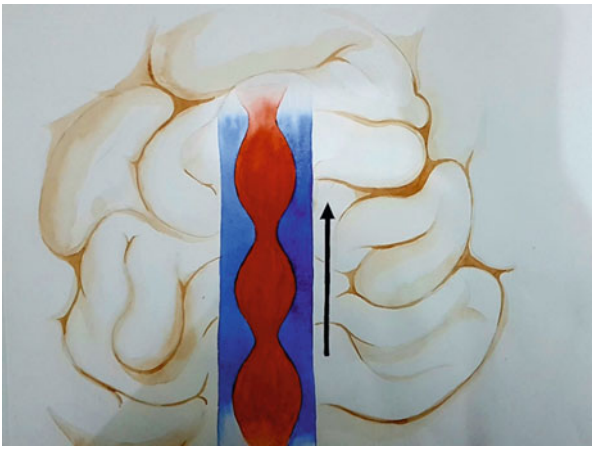

Fig. 34.2 Showing the graphical representation of pulsations in the artery and veins being the driving force to the CSF in the paravascular pathway

and generates excess metabolic heat, thereby contributing to the pathogenesis of neurological diseases.

It has been demonstrated that with age, a decline in the exchange efficiency between CSF in the paravascular spaces and ISF appears to be related to a reduction in the vessel wall pulsatility of intracortical arterioles and widespread loss of perivascular AQP4 along the penetrating arteries (Kress et al. 2014). This "stiffening" of vessel walls concurrent with age, leads to a lack of drainage of amyloid peptides, which may deposit in the paravascular pathways as cerebral amyloid angiopathy (CAA). These deposits act to block the drainage of ISF along the paravascular spaces resulting in loss of homeostasis of the neuronal environment that may contribute to neuronal malfunction (Weller et al. 2009; Kida 2014). In our opinion, the loss of localized temperature control by the paravascular pathway may play a role in the modification of proteinaceous components, which are very sensitive to subtle changes in temperature. These structural changes in molecular geometries might disturb solubility and thus the drainage of this metabolic waste, giving rise to a vicious circle.

The glymphatic system is highly dependent on pressures, where the primary controller of water transport between the paravascular and interstitial spaces is AQP4 (Kress et al. 2014), which mediates the bidirectional transport of water in response to passive osmotic and hydraulic pressure gradients (Agre 2006). This means that an increase of pressure in the glymphatic system would produce the passage of fluid toward the interstitial space until the pressure in both compartments is equalized.

It must be clarified that AQP4 is not present in the limiting membrane of the ventricular wall; however, the end feet of astrocytes that limit with the subarachnoid space, at the surface of the brain within the pia mater, present this transporter. The dependence of AQP4 to pressure gradients in both senses might be the underlying mechanism leading to the recently described "shift edema" following trauma (Cherian and Beltran 2016), and also would explain the advantages of

cisternostomy over craniectomy for the treatment in the short and long term follow up of the patients (Cherian et al. 2013). Subsequent to subarachnoid hemorrhage, red blood cells are confined to the subarachnoid space, and do not enter the VRS as pial membranes between the PVS and the SAS prevent the exchange of large molecules (Hutchings and Weller 1986).

Moreover, the difference in hydrostatic and osmotic pressure between the arteries and veins under normal physiologic conditions transports water and molecules in a way that water emanates from the arterial side and molecules enter toward the venous side along with soluble waste, which elucidates why the reabsorption of metabolic waste occurs in the venous side (paravenular efflux) (Iliff et al. 2012). This translates to there being a movement of fluid that would literally act as a cleaning shower for the brain. This might explain why the brain is the only organ in the human body were the main arteries and veins do not run parallel in location, but run totally opposite. The primary arteries lie in the ventral and central side of the brain, whereas the principal veins run in the dorsal and lateral side of the brain. In addition, the disposition of white matter tracts may assist with directing the movement of molecules and fluid as they create an anisotropic field that facilitates the direction of fluid and molecules toward the main veins.

Should the pressure within the venous side increase, the arteriovenous pressure gradient will decrease, and the clearance of metabolites may be disturbed. Abnormalities of the venous system have been implicated in a variety of neurological disorders, including multiple sclerosis (MS), leukoaraiosis, vascular dementia, and normal-pressure hydrocephalus (NPH) (Beggs 2013). It may be the case that the malfunction of the glymphatic system might also be implicated in the pathogenesis or evolution of these diseases.

In consideration of the influence that arterial and venous pressures have on the dynamics of fluid flow through the paravascular system, we hypothesize that breathing may have a potential role in the regulation of the clearing and cooling of the brain, (Fig. 34.3) as it would increase the movement of fluid through the brain and thus improve the clearance and transport of molecules, and because through breathing, the CSF is cooled, the cooling effect of the glymphatic system would therefore be increased. During inspiration venous return increases due to a decrease in the right atrial pressure.

34.4 Sleep

The brain clearing mechanism regulated by AQP4 appears to be at its zenith during the night. Exchanges between interstitial fluid and CSF have been demonstrated to be more active during sleep due to an expansion of the extracellular space, being increased by ~60 % during sleep (Xie et al. 2013), particularly in the lateral position (Lee et al. 2015). Therefore, the restorative properties of sleep may be linked to increased glymphatic clearance of the metabolic waste products that are generated by neural activity in the awake brain. This might underpin the beneficial effects

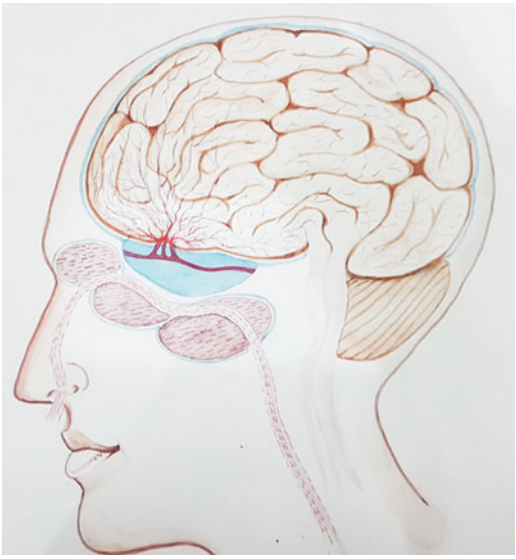

Fig. 34.3 Artistic representation of air that enters the sinuses to cause the evaporation of water within the sinuses, thereby cooling them, which in turn cools the suprasellar cisterns that abut them

of sleep, which would entail the clearance of all metabolic byproducts (almost as if the brain had a shower after a tiring day). This would also explain jetlag, and the problems with lack of sleep. However, to believe that this system is active only at night would be erroneous. It is known, for instance, that the CSF is secreted continuously at a rate of 0.3 ml per second. The requirement for this secretion may be explained by the fact that the CSF is engaged with the cooling and cleaning of the brain on a 24 h basis.

Hence, within the brain there is a supportive network that includes the vessels that supply nutrients, and the paravascular system which likely undertakes the cooling and cleaning tasks in the support of this humongous supercomputer. The glial framework enables this system to interact with multiple inputs while maintaining its own inner sanctum. One must also understand and appreciate that this entire computing system, inclusive of its cooling and cleaning systems, weighs just 1,500 g and is enclosed within our cranial cavity.

The paravascular system, its cleaning and cooling possibilities, their hindrance leading to many disorders, as well as potential corrective measures have not yet been investigated in detail. There have been reports of a bacteriophage being introduced into the olfactory system of a mouse, which resulted in the reversal of Alzhiemer's symptoms. It might very well be the case that the phage travelled into the cisterns through the perineural space of the olfactory nerve and proceeded to clear away the blocked paravascular system. The scope of this line of thinking is truly immense and might constitute a significant paradigm shift. We hope that we have touched on a concept that might be a game changer.

The paravascular system may aptly be referred to as "The tree of life", in that this system provides the cooling and cleaning of the brain via CSF, and thus maintains a very intricate and evolved system. The branching/bifurcation of vessels in the brain along with its paravascular system, the bronchioles in the lungs, the venules of the

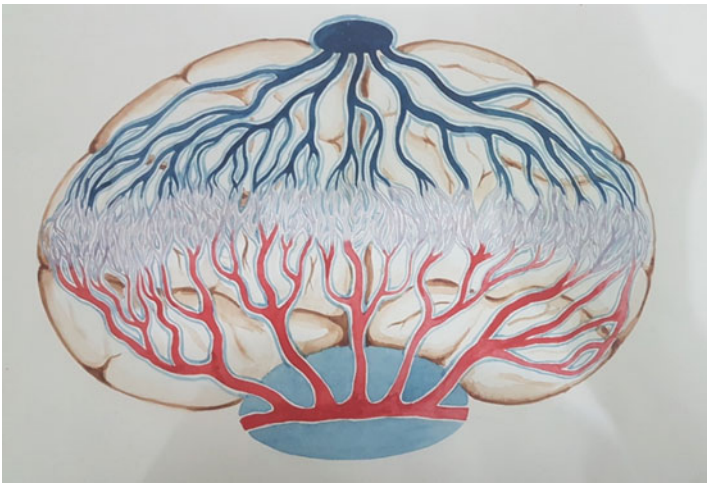

Fig. 34.4 Artistic representation that depicts the persistence of the paravascular system through the arteries, arterioles, capillaries, venules, and veins. This indicates that just as there is a vascular cast of the brain, there is a paravascular system cast as well

leaves, trees, and almost any fractal branching that takes place in nature seems to follow similar patterns, which might be explained by a relatively simple equation known as the Mandelbrot set, named after the mathematician who discovered this key. The paravascular system branches along the entire vascular tree throughout the brain, thus following the vascular cast (Fig. 34.4) of the brain, and may indeed be even more intricate than the vessels, since the limiting dimension of the capillaries is $\sim$3 μ in diameter, which is just large enough for a red blood corpuscle to squeeze through.

34.5 Cisternostomy

The author has been involved with the microsurgical opening of the cisterns in cases of severe head injury in order to reverse CSF shift edema. This procedure assists with avoiding decompressive hemicraniectomy in most instances of severe head injury and has been discussed in detail in previous publications. Since this surgical procedure works, it led the author to investigate the paravascular system in further depth, as well as CSF shifts, and subsequently the likely functionality of the paravascular system.

34.6 Future Directions

It has been observed that a bacteriophage (M13) injected into the olfactory system was able to revert Alzhiemer's disease in rats. Unfortunately, the direction of this research has been modified to having this phage being injected in an intravenous fashion. If one would inject this phage into the cisterns, the bacteriophage would likely proceed to degrade and clear aggregated material within the paravascular system, to fully reopen the pathway. This might serve as a new therapeutic strategy toward addressing myriad neurodegenerative diseases.

34.7 Future Experimental Design

Further experimental work in this area will include the injection of paramagnetic nanoparticles into the suprasellar cisterns of mice, porcine, or baboon models, where the movement of these nanoparticles may be observed with a T 1 W 3 T MRI. This work will serve to prove or disprove our hypothesis that the paravascular pathway extends throughout the brain.

34.8 Conclusion

The paravascular system is the fluidic interface that connects cells and vessels within the brain, which has likely not been investigated in any detail due to its diminutive dimensions and challenges that encumber its study, either in vivo or ex vivo. We propose that the functions of the paravascular system are critical for the homeostasis of the brain, and any disturbance of this system may give rise to neurological disorders through divergent mechanisms. Decreased intracranial compliance leads to increased transmantle pressure and thus affects the arterial perfusion of the brain, provokes venous congestion, and impairs the movement of fluid along the paravascular spaces of the brain (Greitz 2006). If AQP4 localization is lost (e.g., in reactive astrogliosis, the aging brain, or following trauma or ischemia), or if the CSF outflow is reduced as a consequence of either CSF flow obstruction, cerebral artery pulsatility inefficiency, cerebrospinal venous insufficiency, or lymphatic disorders (Brinker et al. 2014), localized perivascular CSF recirculation may be impaired.

Disclosure of Interests The authors declare no conflict.

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Correction to: The Neurobiology of Moral Decision-Making, Embodied Cognition and the Case of Tolerance

Diana Stanciu

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In chapter 30, below mentioned footnotes have been added to sections 30.2 and 30.3, as the book was mistakenly published without this content.

*** Material in this section draws from the following works in the Stanford Encyclopedia of Philosophy: (1) Robert A. Wilson and Lucia Foglia, 2015, "Embodied Cognition", Winter 2015 Edition, URL = https://plato.stanford.edu/archives/win2015/entries/embodied-cognition/; (2) Karsten Stueber, 2014, "Empathy", Winter 2014 Edition, URL = https://plato.stanford.edu/archives/win2014/entries/empathy/; and (3) Markus Schlosser, 2015, "Agency", Fall 2015 Edition, URL = https://plato.stanford.edu/archives/fall2015/entries/agency/ (for section 30.2)

*** Material in this section draws from the following works in the Stanford Encyclopedia of Philosophy: (1) Maria Baghramian and J. Adam Carter, 2016, "Relativism", Winter 2016 Edition, URL = https://plato.stanford.edu/archives/win2016/entries/relativism/; (2) Markus Schlosser, 2015, "Agency", Fall 2015 Edition, URL = https://plato.stanford.edu/archives/fall2015/entries/agency/; and (3) Karsten Stueber, 2014, "Empathy", Winter 2014 Edition, URL = https://plato.stanford.edu/archives/win2014/entries/empathy/ (for section 30.3)

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