# Psychobiology of Behaviour

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# Foreword

## Introduction and Guidance for the Study of the Book

This book is a comprehensive textbook of the psychobiology of behavior. It is written primarily for mental health professionals in general, doctors of various specialties outside mental health and students of medicine, psychologists and others who are interested in this topic. The editors apparently had in mind also particularly GPs who are increasingly faced with mental health or psychological or behavioral problems of their patients. Prof. Fountoulakis, who has written three chapters in this book, and the other authors had the vastly different tasks and needs of different groups in mind, considering multiple levels of details and depth.

Since the editors are both academic researchers and active doctors in everyday clinical practice, they could best meet the very demanding challenge of summarising the extensive research results in this field in a way that is digestible by the target group of readers.

A complete textbook, as the current one, needs to present the essence of things, but still the authors need to keep in mind that the era of sole authority has long passed. Any teaching text should provide, together with the essence, links to sources and data. In other words, no author is considered today a source unto himself/herself; he/she is rather the medium who carries knowledge to readers in a comfortable and practical way. Thus, a balance is needed between the inclusion of too many references, which would make the text too technical and difficult to read, and the inclusion of too few references, which would make the reader rely solely on the judgment and expertise of the author. The authors have tried to follow a middle line but seem inclined towards the first option. The approach is that it is much more important to show the reader the field of knowledge no matter how difficult and fuzzy it might be, rather than simply provide him with the conclusion.

This is obviously a difficult task. Currently, knowledge is increasing rapidly, and the sources one needs to scan are growing exponentially. New knowledge emerges constantly concerning neuroanatomy, neurophysiology, neuropharmacology, neuropsychology, behavior psychology, psychosocial research, etc. Still many of these recent developments should be incorporated within the existing theoretical and practical knowledge in the respective fields. The time when theoretical knowledge and keeping in line with recent developments was considered to be a hobby or an

extravagant intellectual exercise has long passed. In modern times, this is an important prerequisite for people working in the respective areas mentioned above.

The book follows the principle of an integrated approach. It looks from different angles at the complexity of the psychobiology of human behavior. This goal demands to include all kinds of knowledge, not only the evidence coming from the best designed empirical studies. A meaningful approach on the psychobiology of behavior cannot be restricted to the individual, but has to consider also the environment in all relevant aspects. Also conceptual issues should be discussed encompassing terms like psychological, behavioral, brain related, neurobiological, psychosomatic, etc. as well as the body-soul interaction. Finally, the intended better understanding of the psychobiology of human behavior shall help the mental help professionals and the doctors beyond this field to fulfil their mission which is primarily to help patients and their families.

Psychiatry/mental health have the unique characteristic that multiple perspectives could and should be taken into consideration in order to explain and understand the etiopathogenesis of mental disorders or in order to arrive at meaningful therapeutic tools. It is banal to repeat that humans are shaped by the interaction of their neurobiology with environmental events. What we need in the twenty-first century is to recognise the specific weight of different factors in the etiopathogenesis and the treatment tools. A vague bio-psycho-social model does no longer correspond to the state of the art of psychiatric/mental health research and practice. A better conceptualisation of mental illness is a pressing necessity today, and for this a deep understanding of the psychobiology of human behavior with all its dimensions, empirical results and theoretical conceptualisations is necessary.

Finally, this book deals with something which is indeed maybe the most challenging of all human desires: to understand human nature/human behavior itself. Whether such an understanding is possible is still a matter of philosophical debate; several philosophers argue that it is impossible for the human mind to fully understand itself since you need a higher level of functioning to understand a lower one. In this endeavor, the social and ideological and philosophical and religious philosophy itself is often embarrassing, one-sided and not always helpful for a deeper and meaningful understanding. For example, it was several centuries ago when Rene Descartes (1596–1650) proposed his mind-body dichotomy, better known later as the “Cartesian dualism”. With this Descartes provided the philosophical rationale for natural sciences and expelled metaphysical and religious explanations from the study of nature and the physical universe (res extensa), including the human body, but as a compromise he gave the mind (res cogitans) to religious beliefs and metaphysical ideas and preserved the concept concerning the divinity and immortality of the soul. These ideas, although are scientifically obsolete today, are much alive in lay culture and in the belief systems of groups of individuals and society in general, irrespective of specific religious and ideological or political inclinations or affiliations. This resilience of the Cartesian dualism has done much damage both in the

progress of psychiatry and in the way mental health and illness is perceived and accepted by the general public. Dualism can be traced at the roots of stigma and rejection as well as in the form of aggression towards patients, since according to such an understanding of the human nature, mental illness is a sign of moral weakness, sin or ill will. A modern and scientifically based psychobiology of human behavior might help to overcome some of these problems. Such a scientific psychobiology of human behavior provides valuable insights for all professionals in the field, but also for the people beyond.

More concretely, this book tries to cover in 13 chapters different aspects of the psychobiology of human behavior. The titles of these chapters are derived from different dimensions. Thus, we find chapters on more general/theoretical topics, for example, the "functional anatomy of the brain" (going much beyond that which is traditionally described as functional anatomy); on "basic vital functions and instincts"; on "genetics and behavior"; on "the contribution of sociology, ethology and other disciplines"; on "psychophysiology and psychosomatics"; on "psychobiology and psychoanalysis"; etc. The other topics that focus on special aspects of behavior alterations are, for example, "temperament-personality-character", "sexuality" "sleep and dreams", "substance abuse", "biological psychiatry and psychopharmacology" and "aging". All the chapters are well written and rich in the thoughtful presentation of empirical data as well as in considering the respective theoretical frameworks. One is impressed how much knowledge is available in the field of neurobiology of human behavior. On the other hand, one understands that in spite of all this knowledge, it is very difficult to condense all this into a unified complex theory. We see primarily facets of a theory of human behavior, but nevertheless this is already quite a lot, and we should be thankful to the authors for their excellent contributions.

To go a bit more in detail, I will briefly mention the first chapter, the one on functional anatomy, written by one of the editors. It offers much more than we would expect reading the short title. It starts with a general introduction and historical perspective, discussing issues like "brain" and "mind", historical findings of descriptions of the brain and brain-related therapeutic interventions, the humoral pathology of Hippocrates, the mind-body dichotomy proposed by Descartes, the phrenology of Gall and others and concepts of the modern brain anatomy. In the following section, a comprehensive description of the basic anatomy and physiology of the brain is presented, describing all the brain lobes and subcortical structures, the cellular structure, the neurophysiology as well the localisation and function of the neurotransmitters (the latter in much detail).

To mention another chapter as an example which describes another world, I select the chapter on ethology, evolutionary psychology, sociobiology and evolutionary psychiatry. Already the title underlines that this chapter deals with a very complex field, involving very different scientific approaches. First some definitions, short descriptions and historical remarks on each of these approaches are presented. Then a special focus is on evolutionary psychology, a very rich section

encompassing among others environment of evolutionary adaptiveness, life history theory, evolution of emotion, mating and parenting, evolution of language, personality, etc. Furthermore, two sections describe evolutionary social psychology and sociobiology. Finally, a chapter on Darwinian (evolutionary) psychiatry follows. All this is described in many details, with a deep understanding, but also with a lot of critical reflections.

Altogether a very interesting book, which hopefully will find many readers!

1 May 2018

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# About the Editors

**Kostas N. Fountoulakis, M.D.,** is Professor of Psychiatry at Aristotle University of Thessaloniki, AHEPA University Hospital, in Thessaloniki, Greece.

**General Background**

Dr. Fountoulakis received his medical degree (1989), performed his residency in psychiatry (1998) and earned his doctorate in psychiatry (1999) at the Aristotle University of Thessaloniki and served as Research Fellow in the Department of Psychiatry, Division of Neuropsychiatry, at the University of Geneva in Switzerland.

**Research and Teaching Topics**

Dr. Fountoulakis' areas of clinical and research interest are reflected in the topics that he teaches: general psychiatry, biological psychiatry, psychopharmacology, mood disorders, schizophrenia and personality disorders. He has co-authored more than 400 papers, and more than 250 of them are published in international journals such as the *The Lancet, The BMJ, The American Journal of Psychiatry, British Journal of Psychiatry, Biological Psychiatry, International Journal of Neuropsychopharmacology, Journal of Affective Disorders, Schizophrenia Research, Psychiatry Research, Bipolar Disorders* and the *Annals of General Psychiatry*, among others, with over 10,000 citations and $h = 50$ (Publish or Perish).

He has authored or co-authored a number of chapters in books. He has authored the book *Bipolar Disorders: An Evidence-Based Guide to Manic Depression* (Springer-Verlag 2015) and edited the WPA book *Advances in Psychiatry*.

Dr. Fountoulakis is Editor in Chief of *Annals of General Psychiatry* and has served as Section Editor of *Current Opinion in Psychiatry* as well as Guest Editor in other international journals.

**Membership in Scientific Associations**

He was the Chair at the ISNP and at times was Chair of several sections of the World Psychiatric Association. He served as Chair of the CINP Credentials and Membership Committee (2010–2012) and is an active Member of a number of national and international professional organisations and Peer Referee for the Cochrane Collaboration.

**International Awards**

He has received a number of national and international research awards, including the 2012 Kraepelin-Alzheimer Medal of the University of Munich and the 2015 Excellence in Education Award of the WFSBP.

**Since 2014, he is Honorary Member of the WPA.**

**Ioannis Nimatoudis** is Professor of Psychiatry at the Aristotle University of Thessaloniki, Greece, and Head of the 3rd Department of Psychiatry at the same university.

He received his medical degree from the Aristotle University of Thessaloniki in 1979 and completed his residency in Psychiatry–Neurology in 1984. Since 1990, he has been an active member in Psychiatric Reform and rehabilitation in Greece, and specially devoted to the "Leros Programme" of the Regulation 815/84 of the EU. During 1991–2003 he served as Scientific Coordinator of rehabilitation units in Thessaloniki under the auspices of the NGO "Society of Mental Health and Social Rehabilitation", in collaboration with the Ministry of Health and the EU.

He has supervised, as part of a three-member committee, nine Ph.D. researches, four of which were completed successfully, as part of a three-member committee. He is currently the main Supervisor in four Ph.D. researches that are in process. He is responsible for organising elective courses in Neuropsychiatry; he participates in education programmes of other medical universities in Greece and is responsible for organising educational workshops in international conferences. His main research interests lie in neuropsychology, psychopharmacology, psychopathology and evaluation of psychiatric services. He served as Member of the organising committee of 13 international and 13 national conferences. He is an active Member of 11 national and international scientific societies. He has participated in 83 Greek and international scientific conferences and in 58 round tables, lectures and seminars as invited speaker. He is Author or Coauthor of more than 250 papers presented in conferences or published in national and international scientific journals.

# The Human Connectome: Functional Anatomy of the Brain

1

Kostas N. Fountoulakis, Ioannis Nimatoudis, and Xenia Gonda

## 1.1 General Introduction and Historical Perspective

Trying to describe the way the human brain functions is a great challenge. Trying to describe how the human mind functions is an even more difficult endeavor. There is a difference between the words "brain" and "mind." The word "brain" is of Germanic origin and probably is analogous to the Greek word *εγκέφαλος* (enkephalos, meaning what is inside the skull). On the other hand, the respected word in the Latin is cerebrum or cerebro which come from the Proto-Indo-European "keres" or "ceres." This root is related to a number of words with different meanings but some common line of concept in their development, including "top of the head," daughter (in Greek *κόρη*), female goddess, cereal, "soft tender and grayish-like cooked cereal," etc. The etymology of the word "mind" comes from the Latin word "mens" which is related to the Greek words *μένος* (menos) and *μήνις* (minis) which both mean anger. It is also related to the verb *μένω* (meno = stay) and thus reflects a condition in which the state of the mind is stalled because of intrusion of anger and intense emotions. Interestingly, in ancient Greek the word *μήνις* also means crescent and thus relates the states of the mind with the phases of the moon. The Greek word for month

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(which corresponds to moon phases) is *μήνας* (minas), while the Latin word is mensis. This group includes also the words "menses" and "menstrual," and thus they possess both a temporal/cyclical and an emotional meaning. The word *μαινάς* (= maenad) used for women who participated in the orgiastic rites of God Dionysus and *μηνίσκος* (meniscus of the knee) have a similar etymology. The equivalent Greek word for mind is *νους* which is of unknown etymology but probably is related to the Latin word.

Essentially the brain is the anatomical formation, the organ in which the processes that constitute and give birth to the mind take place.

## 1.2 Basic Anatomy and Physiology of the Brain

### 1.2.1 Gross Morphology

At the macroscopic level, the central nervous system includes the spinal cord, the medulla oblongata (responsible for vital autonomic functions), the pons, the cerebellum (which is responsible for motor function), the midbrain (coordinates visual and auditory reflexes and controls sensory and motor functions), the diencephalon (includes the thalamus and the hypothalamus), and the brain hemispheres. Another description includes three parts of the human brain: the hindbrain (medulla, pons, and cerebellum), the midbrain, and the forebrain (thalamus, hypothalamus, and hemispheres). The midbrain and hindbrain are also called the "brain stem" (Fig. 1.1).

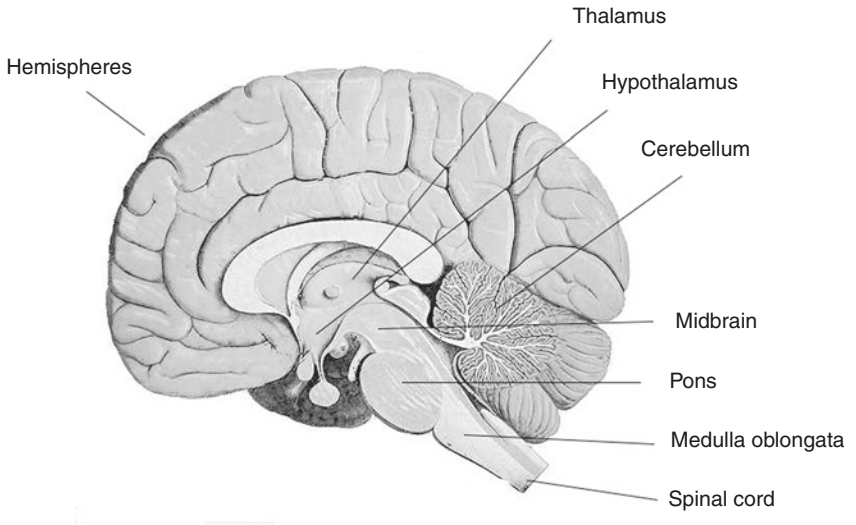


**Fig. 1.1** The human brain and its parts

The connections between the brain areas and structures are many and complex but not infinite. Some are but others are not reciprocal, some are uni- and other bi-directional, some are convergent (gather information from many sources to a single point), while others are divergent (distribute information from a single source to many recipients), some are hierarchical (they transfer the information from a to b then to c followed by d), while others are parallel (they transfer information from a1 to b1 and then to c1, and the same information travels from a2 to b2 and then to c2).

There is also a relative differentiation and specialization of specific brain areas to carry out a specific function. The spinal cord receives bodily sensory information and contains motor neurons responsible for both voluntary and reflex movements of the trunk and limbs. There are 31 spinal nerves serving these functions. The brain stem includes functions pertaining to sensory (e.g., hearing and taste) and motor (e.g., balance) systems as well as autonomic function (cardiac output, blood pressure, eye pupil reflex, etc.). There are 12 cranial nerves functionally analogous to the spinal nerves responsible for the sensory information and movement of the head, neck, and face. In the brain stem, there is the reticular formation which influences the arousal level. The medulla participates in the regulation of blood pressure and respiration, and it is also involved in taste, hearing, and maintenance of balance as well as the control of neck and facial muscles. The pontine nuclei relay information about movement and sensation from the cerebral cortex to the cerebellum, and also they are involved in respiration, taste, and sleep. The midbrain provides important linkages between the cerebellum, the basal ganglia, and the cerebral hemispheres. The cerebellum is the part of the brain which contains a far greater number of neurons and synapses than any other part. It receives somatosensory and motor information, and it is important for maintaining posture, coordinating head and eye movements, and fine-tuning the movements of the muscle. It is important in learning motor skills but also in language and other neurocognitive functions. The diencephalon contains the thalamus and hypothalamus. The thalamus determines whether sensory information will reach conscious awareness in the neocortex. It participates in the integration of motor information from the cerebellum and the basal ganglia and subsequently transmits the processed result in the cortex. The hypothalamus regulates several bodily vital behaviors that are essential for homeostasis and reproduction including eating, drinking, maternal behavior, and circadian rhythms.

The cerebral hemispheres constitute the largest region of the human brain and are concerned with perceptual, motor, and higher cognitive functions, including memory, emotion, and decision-making (Ungerleider 1995). They include the cerebral cortex (2–4 mm thick), the underlying white matter, the basal ganglia (responsible for the control of fine movement), the amygdala (where mood is generated), and the hippocampus (responsible for memory). Each hemisphere is divided into four anatomically distinct lobes (frontal, parietal, temporal, and occipital) each hosting different functions. Their surface is full of infoldings whose crests are called gyri, while the grooves are called sulci. These infoldings serve the purpose to increase the surface of the brain (and the gray matter) while keeping the overall

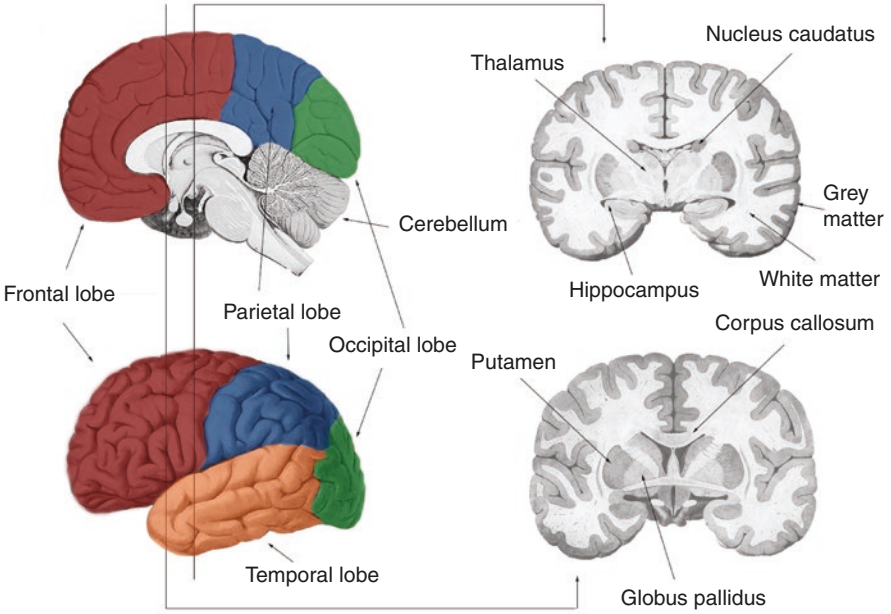


**Fig. 1.2** Brain lobes and subcortical structures

volume as small as possible. The major gyri and sulci are stable across persons, and they hold specific names (Fig. 1.2).

An important characteristic of the functioning of the hemispheres is that each hemisphere function is primarily related to sensory and motor function of the opposite (contralateral) half of the body, and hemispheres although they are similar in appearance are not similar or symmetrical in function (Kandel 2000).

The two hemispheres are interconnected by the corpus callosum, which is essentially a thick set of fibers (the largest of the commissures) that connect symmetrical and similar regions of the left and right sides of the brain.

### 1.2.2 Cellular Structure

The basic unit of the brain is the nerve cell. The brain includes an extraordinary number of nerve cells at the order of 100 billion ($10^{11}$). These cells are mainly divided into two broad categories: the nerve cells (neurons) and the glial cells (glia). Glial cells outnumber neurons 10–50:1, and their name comes from the Greek word *γλοια* (meaning glue).

They are further divided into microglia and macroglia. Microglia are phagocytes mobilized in case of injury and infection of certain diseases. Macroglia include oligodendrocytes which are located in the brain, Schwann cells which are located in the peripheral nervous system, and astrocytes. Oligodendrocytes provide the brain

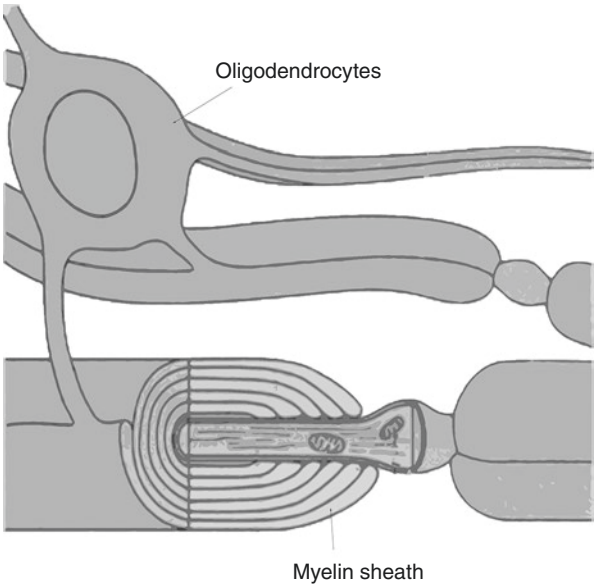


**Fig. 1.3** Oligodendrocytes and the myelin sheath (from Bunge 1968)

with structure and support and separate and also insulate neurons with a myelin sheath by wrapping their processes around the axons (Fig. 1.3) (Bunge 1968). Some of glia cells (astrocytes) place end feet on the walls of blood vessels where they cause the formation of tight junctions between endothelial cells, thus creating the blood-brain barrier which isolates blood vessels from the brain and prevents various substances to enter the brain.

The nerve cells share more or less a similar structure throughout the brain. They include four morphologically defined regions (Fig. 1.4):

(a) The cell body, which contains the nucleus (with the genes and the DNA), the endoplasmic reticulum where proteins are synthesized, and the mitochondria which constitute the power stations of the cell, the places where energy is produced and manipulated.
(b) The dendrites are short processes which arise from the cell body and serve the connection with neighboring cells.
(c) The axon is a single and very long dendrite which extends far away from the cell body. It is the main conducting unit and serves as communication with distant neurons. It can carry signals up to 3 m away. The axons are wrapped with a myelin sheath stemming from oligodendrocytes. This sheath isolates them from one another. In this way the electrical phenomena occurring in one axon do not spread to neighboring axons and cells.

The cerebral cortex is organized into six cell layers (Felleman and Van Essen 1991). Layer I (molecular layer) is an acellular layer occupied by dendrites and axons of the cells located deeper in the cortex. Layer II (external granule cell layer)

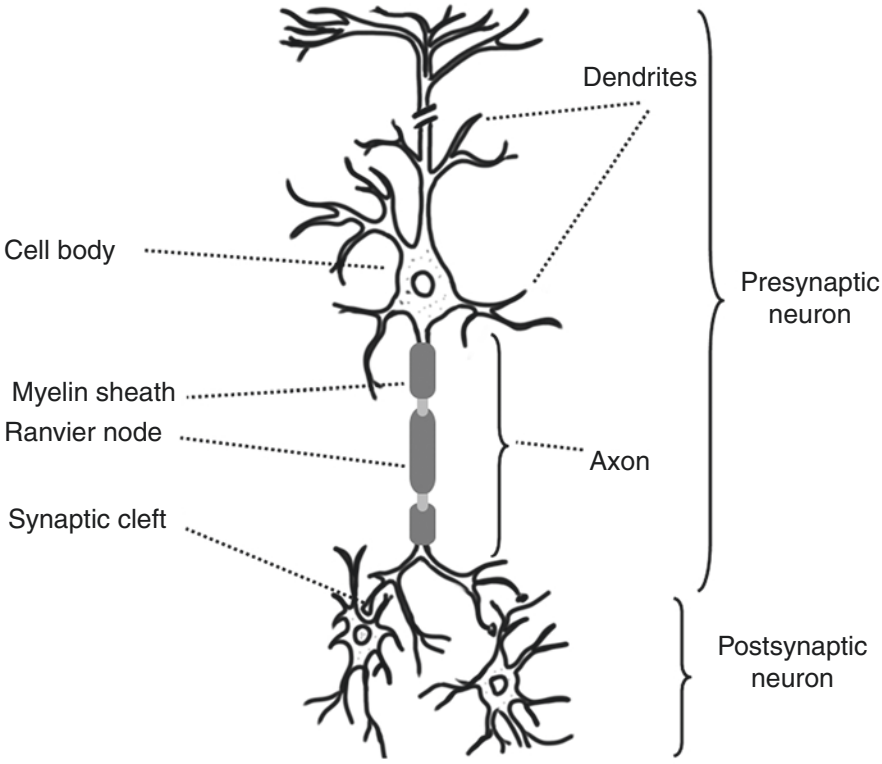


**Fig. 1.4** Presynaptic neuron and its components

is comprised of small spherical cells called granule cells. Layer III (external pyramidal cell layer) contains a variety of cell types, many of which are pyramidally shaped; layer IV (internal granule cell layer), like layer II, is made up primarily of granule cells, layer V (internal pyramidal cell layer) contains mainly pyramidally shaped cells that are typically larger than those in layer III, and layer VI (polymorphic or multiform layer) is a heterogeneous layer of neurons.

The projection neurons typically have pyramidally shaped cell bodies and are located mainly in layers III, V, and VI with glutamate being their primary neurotransmitter, while local interneurons are located in all layers and use GABA as their primary neurotransmitter.

### 1.2.3 Neuronal Action Potential

The communication among neurons is achieved through electrical signals, called "action potentials." These potentials constitute an "all-or-none" phenomenon which does not decay and travels to distant targets and is periodically regenerated.

At rest all neurons maintain a difference in the electrical potential on either side of the cell membrane, which is about −65 mV on average and is called "resting potential." This potential depends on the unequal distribution of ions and particularly of $Na^+$ and $K^+$, as well as on the selective permeability of the cell membrane to $K^+$ alone. This potential is maintained by the $Na^+$-$K^+$ pump which pumps $Na^+$ out of the cell and $K^+$ in. When the resting potential increases, the phenomenon is called hyperpolarization, and it is considered to be inhibitory since the neuron's ability to produce an action potential is reduced. On the contrary, when the resting potential decreases, then the phenomenon is called depolarization, and since it enhances the ability of the neuron to produce an action potential, it is considered to be excitatory.

The action potentials are initiated at the "hillock" which is the specific region of the cell body where the axon originates and where ion channels are denser. While the action potential is a long-distance signal, the neuron produces also a number of local signals in the form of receptor or synaptic potentials, which typically spread only for a few millimeters. While action potential is an "all-or-none" phenomenon, the local potentials could be graded, based on the amount of chemical neurotransmitter released and the duration these molecules are active in the synaptic cleft. On the contrary, the action potential carries information only in terms of frequency of potential generation and duration.

However, while the amplitude of the action potential is an "all-or-none" phenomenon, the duration is not, and this duration of the action potential determines the amount of $Ca^{2+}$ that flows into the terminal, with more $Ca^{2+}$ flowing into the cell after prolonged action potentials (Smith and Augustine 1988). In this frame, the steady-state $Ca^{2+}$ influx is enhanced by depolarization and decreased by hyperpolarization, and vice versa the action potential is modulated by voltage-sensitive $Ca^{2+}$ channels (Baker et al. 1971).

Intense activity alters synaptic effectiveness since a high-frequency sequence of action potentials is followed by a period during which action potentials produce successively larger postsynaptic potentials. The very high frequency in the production of action potentials (even up to 1000 $s^{-1}$ in some neurons) is called "tetanic stimulation" and leads to a significant increase in the size of the potentials in the postsynaptic neuron, a phenomenon which is called "potentiation." Often this increase persists even after the resolution of the tetanic stimulation, and this perseveration is called "post-tetanic potentiation" and usually lasts several minutes, but it can persist for more than an hour (Erulkar and Rahamimoff 1978).

On the contrary, when one neuron causes a hyperpolarization in the cell body or the dendrites of another, in this way it decreases the likelihood that the postsynaptic cell will fire. This is called "postsynaptic inhibition." When through a contact on the axon terminal of another cell, it reduces the amount of the released transmitter by the second cell (presynaptic neuron) with a third cell as a target (postsynaptic neuron); this action is called "presynaptic inhibition," while when it increases the amount of the neurotransmitter, it is called "presynaptic facilitation." In sensitized neurons, a high-frequency sequence of action potentials could result in tetanic stimulation. The increase in size of the postsynaptic potentials during tetanic stimulation

is called potentiation. The increase that persists after tetanic stimulation is called post-tetanic potentiation (Erulkar and Rahamimoff 1978).

One very interesting feature is that presynaptic neurons keep records of their activity in the form of residual $Ca^{2+}$ in their terminals. This eventually leads to the strengthening of the presynaptic connection that persists for many minutes. Thus, post-tetanic potentiation is followed by an even longer-lasting process, which also depends on $Ca^{2+}$ influx and is called "long-term potentiation." This could last from hours to days (Kandel 1981). Similar mechanisms which also involve the free $Ca^{2+}$ concentration in the presynaptic terminal govern the plastic capabilities of the neuron (Dunlap et al. 1995; Klein et al. 1980).

Essentially the calcium ions ($Ca^{2+}$) are intracellular messengers which translate the electrical activity of depolarization into all the non-electrical activities inside the neuron. Thus these ions serve the output of the system, and any delay in the initiation of these non-electrical activities reflects the time it takes for $Ca^{2+}$ channels to open and for $Ca^{2+}$ to trigger the process.

### 1.2.4 Neurotransmitters

The term "neurotransmitter" refers to a group of substances with diverse chemical structure but with the common function to serve the synaptic transmission. The term was introduced for the first time by Henry Dale (1875–1968) and George Barger (1878–1939), ironically in an article attacking the concept (Barger and Dale 1910). At that time and for many decades to come, the electrophysiology was considered to be the dominant function of nerve cells and the brain. However, notions of a receptive substance were first outlined by John Newport Langley (1852–1925) in 1878 (Maehle 2004). These ideas were picked up by Alexander Crum Brown (1838–1922) and Sir Thomas Richard Fraser (1841–1920) in Edinburgh, who drew attention to the differences between L-hyoscine and D-hyoscine, the isomers of atropine. However an even more important development came from an unexpected field: The Nobel Laureate Paul Ehrlich (1854–1915) used a variety of dyes to stain different bacteria and tissues. Out of this work came the notion that agents related to the dyes might chemically bind selectively and specifically, and thus Ehrlich conceived the notion of the "magic bullet." This was to become the dominant therapeutic metaphor for the second half of the twentieth century, and it gave early currency to the idea of a receptor. In the same line of thinking, another Nobel Laureate, Hermann Emil Louis Fischer (1852–1919), created the metaphor of the "lock and key" concerning the reaction between messenger substances and receptors, in 1890 (Lemieux and Spohr 1994).

However, the concept that receptors were behind neurotransmission and the effects of medication on the human body was still a matter of debate. At the root of this debate was a resistance to accept a materialistic view of the human body since electrophysiology was leaving space for spirituality, but this was not the case with chemistry. There are authors suggesting that the biological aspect of psychiatry was finally been accepted in part because of the "spiritual" and cultural effects of psychedelic drugs (Gerard 1949, 1955a, b; Gordon 1948).

The concept became popular in the 1930s, after the Nobel Laureate Otto Loewi (1873–1961) demonstrated the release of acetylcholine from vagus terminals in the frog heart and Henry Dale published his work on cholinergic and adrenergic transmission.

The essential function and characteristic of a neurotransmitter is that it is released in the synaptic cleft by the presynaptic neuron and affects the condition of the postsynaptic neuron. In contrast to hormones, neurotransmitters are never released in the bloodstream (to act as neurotransmitters), but instead their target neuron is in contact or very close to the secreting neuron. While their direct effects are short-lived and last from milliseconds to minutes, they might result in long-term changes in the postsynaptic neuron.

Although an important characteristic of neurotransmitters is that their effects are transient, lasting from milliseconds to minutes, neurotransmitter action can result in long-term changes in target cells lasting hours or days.

The modern definition of a neurotransmitter demands the following four criteria to be met:

1. It is synthesized in the presynaptic neuron.
2. It is located in the presynaptic terminal and is released in amounts sufficient to exert a specific action on the postsynaptic neuron.
3. When administered exogenously it mimics the action of the endogenously released transmitter exactly.
4. A specific mechanism exists for removing it from its site of action.

All neurotransmitters are synthesized in the cell body and are subsequently stored in areas called synaptic vesicles, which are located in the presynaptic terminal. Each vesicle contains several thousand molecules of a single specific neurotransmitter (Kelly 1993). The synaptic vesicles tend to cluster at regions of the membrane which are specialized for releasing the neurotransmitter, and they are called active zones (Unwin and Zampighi 1980).

The release of the neurotransmitter into the synaptic cleft is followed by a complex cascade of events, but the principal role is played by $Ca^{2+}$, which during the discharge of a presynaptic action potential enters the presynaptic terminal through voltage-gated $Ca^{2+}$ channels located at the active zone. This abrupt rise in the concentration of intracellular $Ca^{2+}$ causes the vesicles to fuse with the cell membrane (Bahler and Greengard 1987; Hanson et al. 1997). In this way a process called "exocytosis" permits the release of the neurotransmitter molecules into the synaptic cleft (Lawson et al. 1977). After exocytosis, the vesicle membrane which had been fused with the cellular membrane is retrieved rapidly and is recycled so that its material is used to generate new synaptic vesicles (Schweizer et al. 1995; von Gersdorff and Matthews 1994).

After their release into the synaptic cleft, the neurotransmitter molecules bind to their specific receptors located on the membrane of the postsynaptic neuron. This activates the receptors and causes a cascade of procedures in the postsynaptic neuron. All these steps take time, varying from 0.3 ms to several milliseconds or longer, and this is why chemical synapses are not as fast as electrical synapses. However,

chemical transmission has the important property of amplification, since a small presynaptic electrical current can result in the release of thousands of neurotransmitter molecules in the cleft and in turn to the activation of a large number of postsynaptic receptors with a profound effect even on a large postsynaptic neuron. Also, the action of a neurotransmitter in the postsynaptic neuron depends on the properties of the postsynaptic receptors that recognize and bind the specific neurotransmitter rather than on the chemical properties of the transmitter itself.

It is important to note that the storage and subsequently the release of neurotransmitters are done in standardized and fixed amounts (quanta) which are specific for each neurotransmitter and correspond to several thousand molecules. Following this, each vesicle affords to store only one quantum of the specific neurotransmitter and releases its entire contents into the synaptic cleft during exocytosis (Lindau and Almers 1995; Matthews 1996). The only exception identified so far to the quantal mode of neurotransmitter release is the retina. Each action potential in the brain releases only 1–10 quanta in comparison to an average of 150 quanta released at the neuromuscular synapse. Each quantum of transmitter produces a postsynaptic potential of fixed size, called the "quantal synaptic potential" (Liley 1956).

The neurotransmitters can be roughly classified into two big groups:

1. *Small-molecule neurotransmitters or biogenic amines*. This second term is rather imprecise in chemical terms but is being used for decades to label a group of neurotransmitters, including the catecholamines (dopamine, epinephrine, and norepinephrine) and serotonin but often also histamine which is chemically remote from both the catecholamines and the indolamines.

   The catecholamines are synthesized from the essential amino acid tyrosine in a common biosynthetic pathway. During the first step of this pathway, tyrosine hydroxylase converts tyrosine to L-dihydroxy-phenylalanine (L-DOPA). At the next step, L-DOPA is decarboxylated by a decarboxylase giving dopamine and $CO_2$. Then at the third step, dopamine β-hydroxylase converts dopamine to norepinephrine.

   Serotonin (5-hydroxytryptamine or 5-HT) is synthesized from the essential amino acid tryptophan. They both are indoles with an aromatic structure. Histamine has been identified as important during inflammatory reactions in the body. It is synthesized from histidine by decarboxylation.
2. *Excitatory amino acids and neuroactive peptides.*

   All types of neurotransmitters and neuroactive molecules can coexist in the same neuron. The combination usually consists of one of the small-molecule transmitters and one or more peptides derived from one kind of polyprotein (Kupfermann 1991).

### 1.2.4.1 Small-Molecule Neurotransmitters

#### Acetylcholine

Acetylcholine (Ach) is not an amino acid or its direct derivative, but still it is the only low-molecular-weight amine substance considered to be a neurotransmitter. It

is synthesized from choline (which derives from diet) in a reaction which includes a single step, catalyzed by choline acetyltransferase with acetyl-coenzyme A (acetyl CoA) as co-substrate. Acetylcholine is catabolized by acetylcholinesterase (AchE) and butyrylcholinesterase (BCHE).

Ach is widely distributed in the mammalian brain, and it is produced in the cell bodies of neurons located mainly in the Meynert nucleus (nucleus basalis magnocellularis). According to the literature (Mesulam 1994; Mesulam et al. 1983), there are eight regions where the cell bodies of cholinergic neurons are located (Ch1–Ch8). The Ch1 group concerns those cholinergic neurons located in the medial septal nucleus (Fujishiro et al. 2006), the Ch2 those in the nucleus of the vertical limb of the diagonal band (Fujishiro et al. 2006), the Ch3 in the lateral portion of the horizontal limb nucleus of the diagonal band (Mesulam et al. 1983), the Ch4 in the Meynert nucleus (Liu et al. 2015), the Ch5 in the pars compacta and pars dissipata of the pedunculopontine nucleus (Manaye et al. 1999), the Ch6 centered around the laterodorsal tegmental nucleus and spreads into the central gray and medial longitudinal fasciculus (Mesulam et al. 1989), the Ch7 in the medial habenula (Dautan et al. 2016), and the Ch8 in the parabigeminal nucleus (Mufson et al. 1986). The Ch1 and Ch2 groups provide the main cholinergic innervation to the hippocampus, the Ch3 to the olfactory bulb, the Ch4 to the hemisphere cortex and the amygdala, the Ch5 and Ch6 to the thalamus, the Ch7 to the interpeduncular nucleus, and the Ch8 to the superior colliculus. There are also projections of lesser importance from the Ch1–Ch4 and Ch8 to the thalamus and from the Ch5–Ch6 to the cortex (Geula and Mesulam 2011).

The main function of cholinergic system is to turn non-cholinergic neurons more sensitive to other excitatory stimuli. There is a bulk of pharmacological data suggesting that the central cholinergic system plays an important role in the acquisition as well as the expression of learned behaviors since it seems that scopolamine and atropine exert a negative effect on this kind of behaviors (Reiner and Fibiger 1994).

### Serotonin

Serotonin (5-hydroxytryptamine, 5-HT) (Marsden 1996) is an indoleamine which can be found not only in humans but also in most animals and even in plants. In mammals it can be found in the platelets, the mast cells, and the chromaffin cells of the intestine. In the brain, 5-HT acts as a neurotransmitter and regulates a number of functions including sleep, food intake, thermoregulation, emotions, and psychotic experiences. However its main role is to inhibit behaviors and to reduce impulsivity. Additionally, it seems that the mission of the serotonergic system of the forebrain is to attenuate the impact on human behavior stressful and adverse life events have. In other words its mission is prevention and adjustment to stress (Deakin 2013; Deakin and Graeff 1991).

Serotonin is synthesized in the raphe nucleus of the brain stem. It is divided in the dorsal raphe nucleus (DRN) and median raphe nucleus (MRN). The cells in the DRN project into the same regions of the brain in which the dopaminergic neurons of the ventral tegmental area (VTA) project and especially to the basal ganglia, the amygdala, and the nucleus accumbens. They are implicated mainly

in the regulation of locomotor and incentive-motivation activity. On the contrary, the cells of the MRN project to the cortex, the thalamus, and the hippocampus, and they contribute to the process of sensory stimuli. Thus, the first group of neurons is related to the motor part of the response mechanisms and acts mainly through the 5-$HT_2$, 5-$HT_{2A}$, and 5-$HT_{2D}$ receptors, while the second group is related to the sensory part and acts possibly through the 5-$HT_{1A}$ receptors (Blue et al. 1988; Mamounas et al. 1991). It is widely accepted that these pathways also regulate the approach-avoidance behaviors (Graeff et al. 1993; Hodges et al. 1987; LeDoux et al. 1990). Particularly high concentrations of 5-HT can be found in the limbic system and imply its relationship with emotions. However all the projections of serotonergic neurons, which are abundant and concern all brain areas, stem from the dorsal and median raphe nuclei. The median provides with thick fibers while the dorsal with more thin, which are probably more sensitive to toxic agents.

### Norepinephrine

Norepinephrine is the main catecholamine in the brain and one of the most important neurotransmitters. Its name comes from the Greek name of the adrenal glands which is *επινεφρίδια* (epinefridia, meaning "on top of the kidney"). It is synthesized via the catecholamine synthesis pathway from phenylalanine and tyrosine.

It is abundant in the brain stem and the dorsal nucleus of vagus nerve and plays an important role in the regulation of blood pressure. However the main norepinephrine pathway originates from the cells of the locus coeruleus and projects to the thalamus, the dorsal hypothalamus, the hippocampus, and the cortex. The ventral norepinephric bundle emerges ventral/rostral to the locus coeruleus and reaches the hypothalamus and the subcortical parts of the limbic system. The dorsal norepinephric bundle emerges from the locus coeruleus and projects to the cortex. Both bundles seem to relate with volition, drive, and motivation as well as with reward mechanisms and REM sleep.

### Dopamine

The dopaminergic system is significantly more complex in comparison to the norepinephric. Below its classical structure is described, which is considered to be important for educational purposes, although it is currently disputed due to the accumulation of more data. Traditionally, four main dopaminergic pathways are mentioned:

- The nigrostriatal pathway whose fibers originate from nucleus A9 and project to the nucleus caudatus and the putamen of the lentiform nucleus.
- The mesolimbic pathway whose fibers originate from the ventral tegmental area (VTA) and project to the amygdaloid nucleus, the dorsolateral septal nucleus, and the nucleus accumbens. The experience of stress activates this pathway.
- The mesocortical pathway whose fibers originate from the VTA and project to the frontal cortex and areas of the septum and the hippocampus. Again the experience of stress by the person activates this pathway.

- The tuberoinfundibular pathway (A12 region) (Moore and Lookingland 1994), whose fibers originate from the arcuate nucleus in the hypothalamus and project to the median eminence. Essentially they constitute a small minority of dopaminergic neurons; however they release dopamine in the stream of the hypophyseal portal veins, which eventually reaches the anterior pituitary gland where it inhibits the secretion of prolactin. Experiencing stress by the individual could lead to the inhibition of this pathway resulting in an increase in prolactin secretion and subsequently in sexual disorders in males and abnormal lactation and amenorrhea in females.

The dopaminergic neurons of mesolimbic and mesocortical pathways receive regulatory influence from serotonergic and norepinephric neurons located in the brain stem. Some VTA dopaminergic neurons are especially sensitive to input from excitatory amino acids.

The overall conclusion from the study of the dopaminergic system suggests that it does not serve any specific function, but instead it regulates and permits the synthesis of the functions which are hosted in the structures where this system projects (Le Moal 1994). Probably one of the rare but most important specific dopaminergic effects is a dopaminergic involvement in reward systems (dopaminergic theory of reward) (Jacques 1979; Wise 2008).

It is important to note that although low dopaminergic activity seems to relate to low ability to concentrate and reduced performance, also excessive increase is related to deficits in attention and stereotypical behaviors. It has been reported that intrapsychic conflict as a result of ambiguous situations with unclear solution leads to an increase in dopaminergic activity, and in this way they trigger displacement activities which reduce the level of arousal and stabilize the system (Tazi et al. 1986, 1988).

### Histamine

Histamine is derived from the decarboxylation of the amino acid histidine by L-histidine decarboxylase. In the brain it is catabolized by histamine-*N*-methyltransferase. The cell bodies of histamine neurons are located in the tuberomammillary nuclei of the thalamus, and they project throughout the brain, including to the cortex, through the medial forebrain bundle. Interestingly, they have a firing pattern which is closely related to wakefulness. During wakefulness the fire frequency is high, while during periods of relaxation or tiredness, the frequency is significantly lower. It seems they completely stop firing during REM and non-REM sleep. When antihistamines (i.e., older-type H1 receptor antagonists) cross the blood-brain barrier, they produce drowsiness. Similarly, destruction of histamine-releasing neurons or inhibition of histamine synthesis leads to an inability to maintain vigilance. On the contrary, H3 receptor antagonists increase wakefulness. Therefore it is believed that histamine increases wakefulness and prevents sleep (Brown et al. 2001). It is also involved in local immune responses and in the function of the gut. During immune responses, histamine is secreted by basophils and mast cells. It increases the permeability of the capillaries to white blood cells and some proteins.

Additionally to its arousing and stimulatory effects, histaminergic activity also protects against the susceptibility to convulsion, drug sensitization, denervation supersensitivity, ischemic lesions, and stress, probably through a suppressive type of effect (Yanai and Tashiro 2007). It has also been suggested that histamine controls the mechanisms by which memories and learning are forgotten (Alvarez 2009).

### 1.2.4.2 Excitatory Amino Acids and Neuroactive Peptides

#### Glutamate (Glu)

Glu is the most important and frequently used excitatory amino acid throughout the brain. It is also a major part of a wide variety of proteins, and therefore it is one of the most abundant amino acids in the human body (Meldrum 2000). Normally it is obtained from the diet and there is no need to be synthesized. However it can also be synthesized from alpha-ketoglutaric acid (part of the citric acid cycle which has citrate as starting point). Glu is actively transported through the blood-brain barrier (Shigeri et al. 2004; Vandenberg 1998). As a neurotransmitter it is dominant throughout the cortex and in most subcortical pathways (Stahl 2008). It plays a role in the mechanisms concerning brain plasticity and higher neurocognitive function. It could be said that the most important function of all other neurotransmitters is to regulate Glu activity.

#### Gamma-Aminobutyric Acid (GABA)

GABA is produced from Glu via the action of the enzyme glutamic acid decarboxylase. It is present at high concentrations throughout the brain and can also be found in other tissues (e.g., the pancreas and the adrenal gland). In the brain it is the major inhibitory neurotransmitter (Paul 1994).

#### Glycine (Gly)

Gly is the major transmitter in inhibitory interneurons of the spinal cord. It is synthesized from serine, and it is the smallest of the 20 amino acids commonly found in proteins. It bounds to ionotropic receptors, and it is a required co-agonist along with glutamate for NMDA receptors.

#### Neuroactive Peptides

More than 50 short peptides are active as messengers in the brain. Some of them had been previously identified as hormones (e.g., angiotensin and gastrin) or as products of neuroendocrine secretion (e.g., oxytocin, vasopressin, somatostatin, and thyrotropin-releasing hormone). (A decade of neuropeptides: past, present, and future. Tenth Annual Winter Neuropeptide Conference. Breckenridge, Colorado, January 16–20, 1989.) Most of them play an important role in mechanisms including thermoregulation, food and liquid intake, memory, learning, and reaction to stress and pain.

Most of them do not satisfy all criteria to be considered a neurotransmitter, but several do (Myers 1994). Neurons could contain and release several peptides which come from the same polyprotein, and their release leads to potentially different postsynaptic actions (Fisher et al. 1988).

ATP and its degradation products (e.g., adenosine) act as transmitters at some synapses. Adenine and guanine and their derivatives are called purines.

### 1.2.5 Neurotransmitter Reuptake

The neurotransmitter effect in the synaptic cleft lasts only for short periods of time, and after this the neurotransmitter molecules should be removed in time. Failure to do so could result in "noise" or even in total inhibition of new signal transmission, in the diffusion to neighboring synapsis resulting in signal contamination, while the signal itself these molecules carry will tend to degrade. Therefore the timely removal of transmitters from the synaptic cleft is critical for the quality of synaptic transmission. Transmitter molecules are removed from the cleft by three mechanisms:

- Diffusion.
- Enzymatic degradation.
- Reuptake.

While diffusion removes some fraction of all chemical messengers, it cannot remove the complete quantity. Enzymatic degradation of transmitter molecules is used primarily by the cholinergic synapses.

Neuropeptides are removed more slowly than small-molecule transmitters, and this probably contributes to their more lasting effects.

The most important mechanism of removal is reuptake, and it is important also because it "salvages" the neurotransmitter and its fragments for recycling. It is mediated by transporter molecules which are classically proteins which use transmembrane ion gradients and electrical potential to transport neurotransmitter across the membrane. There are several transporters for each transmitter (Nelson and Lill 1994; Amara and Arriza 1993).

Fast reuptake and fast recycling of secreted neurotransmitters contribute also to a fast overall information flow and quick reaction to environmental stimuli.

### 1.2.6 The Synapses

The point where two neurons communicate is called the synapse (Jessell and Kandel 1993). The word "synapse" comes from the Greek verb *συνάπτω* (bring together, join), and it was introduced in 1897 by Michael Foster (1836–1907) at the suggestion of Arthur Woollgar Verrall (1851–1912) which was an English classical scholar (Tansey 1997) (Fig. 1.5).

The neuron which transmits the signal is called "presynaptic," and the neuron which receives it is "postsynaptic." The physiologists, led by John Eccles (1903–1997), argued that all synaptic transmissions are electrical and that the action potential in the presynaptic neuron generates a current that flows passively into the postsynaptic cell. The pharmacologists, led by Henry Dale (1875–1968), argued

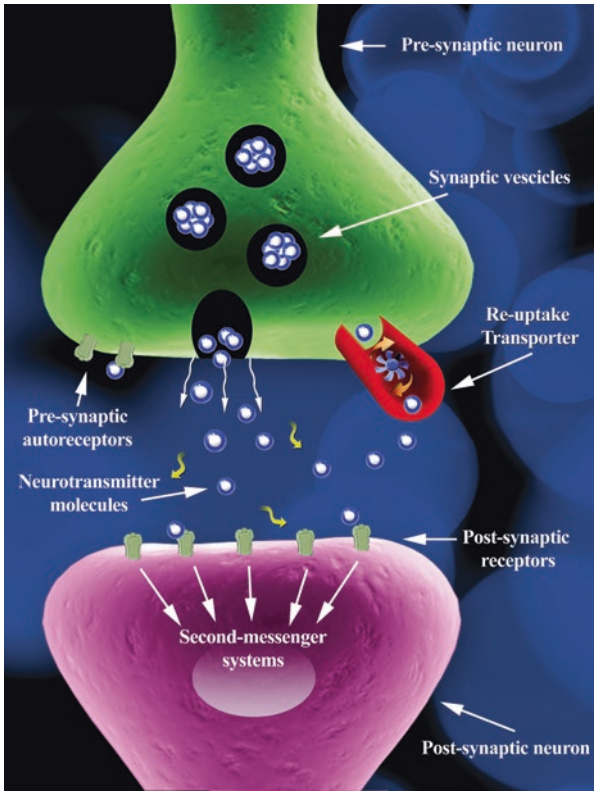


**Fig. 1.5** The synapse and its components

that transmission is chemical and that the action potential in the presynaptic neuron leads to the release of a chemical substance that in turn initiates current flow in the postsynaptic cell. When physiological techniques improved in the 1950s and 1960s, it became clear that both forms of transmission exist. Although most synapses use a chemical transmitter, some operate purely by electrical means (Eccles 1976).

So today we know that there are two kinds of synapses:

- Chemical synapses, where the electrical activity in the presynaptic neuron is converted into the release of a neurotransmitter.
- Electrical synapses, where the presynaptic and postsynaptic cell membranes are connected by channels called gap junctions or are in touch through a synaptic cleft that is capable of passing electric current.

It is to be noted that synaptic communication is distinct from ephaptic coupling (from Greek *εφάπτομαι* meaning being in touch), which refers to the exchange of ions between the cells or to the effect of local electric fields. In this way it influences the synchronization and timing of the firing of action potentials in neighboring neurons. It is exactly the phenomenon of ephaptic interactions that myelination prohibits (Arvanitaki 1942).

In chemical synapses, the two neurons are not in physical contact; instead there is an empty space between them, called the "synaptic cleft." The end of the presynaptic neuron is called "presynaptic terminal," and it can end almost anywhere on the postsynaptic neuron but preferentially on dendrites.

In the brain, electrical synaptic transmission is very rapid and rather stereotyped, and it is triggered explosively in an all-or-none manner. In contrast, chemical synapses are capable of more variable signaling and thus can produce more complex behaviors. They can mediate either excitatory or inhibitory actions in postsynaptic cells and produce electrical changes in the postsynaptic cell that last from milliseconds to many minutes. This comes at the price of longer latency, that is, longer time between the presynaptic spike and the postsynaptic potential, because chemical transmission demands several biochemical steps. On the contrary, at electrical synapses the gap-junction channels connect the cytoplasm of the two cells, and in this way they allow a direct ion flow between them. One important characteristic of the communication between neurons is that its strength can be enhanced or diminished by cellular activity, a phenomenon which is called plasticity, and it is crucial to memory and other higher brain functions.

One important principle in the function of neurons and synapses is that they transmit a signal always in one direction (principle of dynamic polarization) from the receiving site to the presynaptic terminal. A second principle is that neurons connect to each other in a way which leads to the formation of neuronal networks which serve some specific function (principle of connectional specificity). However, the complexity of these networks is extremely high. On average, a spinal motor neuron receives 10,000 contacts from other neurons, of which 2000 on the cell body and the rest on its dendrites, while a Purkinje neuron in the cerebellum could receive up to 150,000 contacts.

In chemical synapses and in the membrane of the postsynaptic neuron oriented toward the synaptic cleft, there are molecules called receptors. These receptors serve as docking sites for neurotransmitters. They are a sort of "receivers" of the signal which is transmitted by the presynaptic neuron. One important characteristic of transmission is that it is the receptor that determines whether a particular synapse is excitatory or inhibitory and whether an ion channel will be activated directly by the transmitter or indirectly through a second messenger.

The notion of a receptor was introduced in the late nineteenth century by the German bacteriologist Paul Ehrlich (1854–1915) to explain the selective action of toxins and other pharmacological agents and the great specificity of immunological reactions (lock and key). Chemical neurotransmitters act either directly or indirectly in controlling the opening of ion channels in the postsynaptic cell.

There are two main types of receptors:

- Ionotropic receptors: They include an ion channel in their structure, which opens as a response to the binding of the neurotransmitter (Unwin 1993).
- Metabotropic receptors: They act by stimulation of the production of second messengers, which are small freely diffusible intracellular metabolites such as c-AMP and diacylglycerol. Subsequently these second messengers activate protein

kinases that phosphorylate a variety of proteins, or they mobilize $Ca^{2+}$ ions from intracellular stores (Tanaka and Nishizuka 1994). Often metabotropic receptors gate ion channels, but this happens only indirectly through second messengers. There are two types of metabotropic receptors: the G-protein-coupled receptors and the receptor tyrosine kinases. The G-protein family contains the α- and β-adrenergic receptors, the muscarinic ACh receptors, the $GABA_B$, and others (Gilman 1989, 1990, 1995). Receptor tyrosine kinases are activated by hormones, growth factors, and neuropeptides.

Ionotropic and metabotropic receptors have different functions. The ionotropic receptors produce relatively fast synaptic actions lasting only milliseconds. These are commonly found in neural circuits that mediate rapid behaviors, such as the muscle stretch receptor reflex. The metabotropic receptors produce slower synaptic actions lasting seconds to minutes. These slower actions can modulate behavior by altering the excitability of neurons and the strength of the synaptic connections of the neural circuitry mediating behavior. Such modulatory synaptic pathways often act as crucial reinforcing pathways in the process of learning. Additionally ligand-gated channels function as simple on-off switches triggering an all-or-nothing effect, while on the contrary the metabotropic receptors manifest a complex function with the ability to vary in space and time as well as in the number of intracellular systems affected. While ionotropic excitation can only increase the ion flux through the channel, metabotropic activity can either increase or decrease (Hille 1994).

Essentially metabotropic receptors exert a modulatory effect on the postsynaptic neuron since they are normally not capable of firing an action potential. Their role is mainly to regulate the electrophysiological properties of a cell (e.g., resting potential, action potential duration, repetitive firing characteristics, etc.).

The main receptors for each neurotransmitter are as follows:

#### 1.2.6.1 Acetylcholine

Cholinergic receptors are classified into two main families, the muscarinic and the nicotinic, on the basis of muscarine and nicotine to mimic the effects of Ach.

Nicotinic receptors (Arneric et al. 1994) consist of one alpha (α1–α7) and one beta (β1–β4) subunits. Different combinations of these subunits result in different properties of the receptor. The only documented nicotinic neurotransmission in the brain concerns the communication between the motor neuron and a Renshaw cell in the spinal cord. However a nicotinic type of activity has been recorded in the retina, the hippocampus, the respiratory center in the brain stem, the cortex, the thalamus, the hypothalamus, the substantia nigra, the striatum, and the locus coeruleus. Nicotine interacts with nicotinic receptors and increases the secretion of various neurotransmitters, while the cholinergic system, in general, regulates and governs a number of important functions including attention and concentration, brain regional blood flow, glucose consumption, and the electrical activity of the cortex. Each one of these functions is enhanced by nicotine and attenuated by its antagonists. Additionally nicotine could improve memory and learning, and it has an anxiolytic effect probably through the release of endogenous substances acting on GABA

receptors. Nicotine-related disorders are related to depression, but the nature of this relationship is unknown (Edwards et al. 2011; Lyons et al. 2008; Fu et al. 2007; Killen et al. 2003; Cardenas et al. 2002; Breslau et al. 1993).

On the other hand, muscarinic receptors (Ehlert et al. 1994) are widely distributed in the human body. Their activation in the periphery causes drop of heart frequency, vasodilation, constriction of airways, increase of gastric tube mobility, and miosis in the eye pupil, among others. In the brain they are implicated in function including memory, learning, and control of posture.

There have been identified four types of muscarinic receptors with the use of pharmacological methods and five (M1–M5) with molecular biology methods. There is almost complete correspondence between the types identified with these two methods, and all receptors seem to act through their coupling with a second messenger system of a G-protein.

- The M1 type is abundant in the forebrain and the sympathetic ganglia, while its density is lower in the hindbrain. Its highest concentration is in the hippocampus, followed by the cortex, the striatum, the olfactory bulb, and the thalamus, while the concentration is far lower in the hypothalamus. This receptor is denser in the limbic system and the association cortices. Its activation results in an increase in the hydrolysis of phosphoinositol.
- The M2 type is widespread in the body, including the brain, but its density is rather low. It is the only muscarinic receptor located in the myocardium. It is the main muscarinic receptor of smooth muscles, excluding the intestine ones. Its density in the brain is low but the distribution is rather homogenous. It is relatively denser in the cerebellum, the medulla oblongata, and the mesencephalon, followed by the hypothalamus and the thalamus. Its highest density is in the primary sensory and motor areas. Its activation leads to the inhibition of adenylcyclase.
- The M3 type is the main muscarinic receptor of exocrine glands. It also triggers the constriction of smooth muscle fibers in spite of the fact it constitutes a minority among the muscarinic receptors in these fibers. Probably it constitutes the main receptor governing the intestine mobility. It exists in low density throughout the brain, and it is slightly denser in the forebrain. Its activation results in an increase in the hydrolysis of phosphoinositol.
- The M4 type is abundant in the telencephalon, the striatum, and the olfactory bulb. It is denser in the forebrain, and its activation leads to the inhibition of adenylcyclase.
- The M5 type constitutes less than 2% of total muscarinic receptors, and it is found exclusively in the brain. Its activation results in an increase in the hydrolysis of phosphoinositol.

#### 1.2.6.2 Serotonin

A significant number of 5-HT receptors (most recent number mounts to 14) have been identified so far, but for the role of most of them, we know little. The main are the following:

- 5-$HT_1$ (A, B, D, E, and F): They are negatively linked to the adenylcyclase system. They inhibit the transformation of ATP into c-AMP (in the hippocampus, substantia nigra, gray matter around the Sylvius aqueduct). An increase in the 5-$HT_1$ activity in the raphe nucleus leads to increased appetite as it reduces serotonergic activity. An increase of the activity of the rest of the 5-$HT_1$ receptors leads to reduced appetite (Montgomery and Fineberg 1989).
- 5-$HT_2$ (A, B, and C): They are positively linked to the phosphoinositol system and lead to an increase of intracellular Ca or to protein kinase activation. Animal research has shown that social isolation causes hypersensitivity of 5-$HT_{2C}$. These same receptors of the amygdala-hippocampus circuit probably lead to the manifestation of aggressive behaviors when danger is confronted, by overcoming the inhibitory effects of 5-$HT_1$ and 5-$HT_{2A}$ located in the gray matter around the aqueduct. An increase in the activity of these receptors again could lead to a reduction in appetite, especially in bulimic patients which also manifest affective disorders and disordered saturation feeling mediated by cholecystokinin (CCK). In general, 5-$HT_2$ exert a tonic inhibition on noradrenalin in the hippocampus.
- 5-$HT_3$: They have a positive link with fast ion channels and increase their permeability. They inhibit Ach activity in the cortex but augment dopaminergic in the corpus striatum and the limbic system.
- 5-$HT_4$: They have a positive link with the adenylcyclase system. They increase the transformation of ATP into c-AMP. Their relationship to behavior is unknown.
- 5-$HT_5$ (A and B): It is unknown the exact second messenger system they relate to, and equally unknown is their relationship to behavior.
- 5-$HT_6$: They have a positive link with the adenylcyclase system. They increase the transformation of ATP into c-AMP. Their relationship to behavior is unknown.
- 5-$HT_7$: They have positive link with the adenylcyclase system. They increase the transformation of ATP into c-AMP. Their relationship to behavior is unknown. Recently it has been suggested that they mediate the antidepressant effect of lurasidone (Cates et al. 2013).

#### 1.2.6.3 Norepinephrine

Norepinephrine (adrenergic) receptors belong to the G-protein-coupled superfamily. They can be found pre- and postsynaptically on neurons but also on glial cells (Salm and McCarthy 1992; Stone and Ariano 1989).

- Alpha-1 (α1; a, b, c, and d): Postsynaptic excitatory receptors linked to the phosphatidylinositol system (Hieble et al. 1995; Bylund et al. 1994). They can also be found in the muscles of the vessel wall and the smooth muscles of the intestine and the heart.
- Alpha-2 (α2; a, b, c, and d): They can be found presynaptically, and they are inhibitory receptors linked to the adenylcyclase system (Patel et al. 1981; Langer 1974; Aghajanian and VanderMaelen 1982; Anden et al. 1970; Cedarbaum and Aghajanian 1977; Langer and Arbilla 1990; Starke 1971; Svensson et al. 1975; Bylund et al. 1994). Apart from the brain, they can be found in the muscle of the vessel wall, the smooth muscles of the intestine, and the platelet membrane.

Subtypes are unevenly distributed in the brain, with high densities of α2a and α2c in the LC, amygdala, and hippocampus, while α2b is found mainly in the thalamus (Scheinin et al. 1994; Rosin et al. 1996; Talley et al. 1996; Wamsley et al. 1992; Nicholas et al. 1993a).

- Beta-1 (β1): They are excitatory receptors linked to the adenylcyclase system (Frielle et al. 1987; Shorr et al. 1982; Nicoll et al. 1990). They predominate in the cerebral cortex, the dentate gyrus, the CA1, and the medial dorsal hypothalamic nuclei (Nicholas et al. 1993b; Palacios and Kuhar 1982; Rainbow et al. 1984). Apart from the brain, they can be found in the heart.
- Beta-2 (β2): They are excitatory receptors linked to the adenylcyclase system (Tholanikunnel et al. 1999; Ostrowski et al. 1992; O'Dowd et al. 1988; Nicoll et al. 1990). They are more abundant in the cerebellum and reticular, paraventricular, and central thalamic nuclei (Nicholas et al. 1993b; Palacios and Kuhar 1982; Rainbow et al. 1984), but they can also be found both in the smooth and skeletal muscles and the liver. They are also present in the membrane of the lymphocytes where their function is unknown.
- Beta-3 (β3): They can be found in the adipose tissue, and little is known for them (Emorine et al. 1989).

#### 1.2.6.4 Dopamine

The following dopaminergic receptors have been identified so far (Civelli 1994; Mansur and Watson 1994). They can be grossly classified into D1-like (D1 and D5) and D2-like (D2, D3, and D4):

- D1: It is a postsynaptic excitatory receptor linked to the adenylcyclase system through a G-protein. It is abundant in the anterior cingulate gyrus, the cortex of the frontal pole, the insular (Reil cortex) and the olfactory cortex, the nucleus caudatus, the putamen, the nucleus accumbens, and the olfactory bulb and to lower density in the septum, the hypothalamus, and the rest of the cortex. It is absent from the substantia nigra, the VTA, and the hippocampus. It is dominant in the amygdaloid nucleus where D2 is absent. D1 is present solely in the brain and not in the rest of the body.
- D2: It is a presynaptic autoreceptor and inhibits the adenylcyclase system through a G-protein; however there is evidence that at least a subgroup of these receptors acts independently of this second messenger system (Roth and Elsworth 1994). It is the dominant dopamine receptor in the substantia nigra, the VTA, the globus pallidus, and the hippocampus where D1 is absent. It is also abundant in the olfactory cortex, the nucleus caudatus and the putamen, the nucleus accumbens, the olfactory bulb, and the hypothalamus and in lower density in the septum and the rest of the cortex. It is absent from the amygdaloid nucleus where D1 is dominant. Outside the brain it can be found in the cortex of the adrenal glands, the pituitary, and the retina. Possibly it plays a role in the regulation of pain through receptors located in the reticular nucleus of the thalamus and the gigantocellular reticular nucleus (magnocellularis) in the hindbrain.

- D3: It is a presynaptic autoreceptor, and probably it is linked to the same G-protein D2 is linked, but this is not solidly proven. It is located in the same areas with D1 and D2 but with a much lower density. It manifests some selectivity for the limbic system. It is not found outside the brain.
- D4: Probably it is linked to the same G-protein D2 is linked, but this is not solidly proven. It is located in the same areas with D1 and D2 but with a much lower density. It also manifests some selectivity for the limbic system. Probably it is also located in the kidneys and the heart.
- D5: It is an excitatory receptor linked to the adenylcyclase system through a G-protein. It is located solely in the hippocampus, the hypothalamus, and the parafascicular nucleus in the thalamus, and it is implicated in functions concerning affect, pain, and neuroendocrine secretion. It is probably located also in the kidneys and the heart.

#### 1.2.6.5 Histamine

Histamine receptors are classified as H1–H4 and are all bound to a G-protein. It is also believed that histamine activates ligand-gated chloride channels in the brain. These are located in the thalamus and hypothalamus and produce fast inhibitory postsynaptic potentials (Panula et al. 2015).

- H1: It is produced in the tuberomammillary nucleus, and fibers project to the dorsal raphe and the locus coeruleus, among other areas. Activation of this receptor increases wakefulness, while other roles include the regulation of temperature, endocrine function, appetite, and neurocognition (Panula et al. 2015; Blandina et al. 2012).
- H2: Their receptors are located exclusively in the gastrointestinal system and in vascular smooth muscle cells (Wouters et al. 2016; Panula et al. 2015).
- H3: It manifests both autoreceptor and heteroceptor functions and exerts an inhibitory effect on the secretion of histamine, Ach, norepinephrine, and 5-HT (Gilman 1990).
- H4: Found primarily in the basophils, the bone marrow, the thymus, the small intestine, the spleen, and the colon. It plays a role in various mechanisms of inflammation, etc. Its role on cognition is unclear (Panula et al. 2015).

#### 1.2.6.6 Glutamate (Glu)

Glu is excitatory at ionotropic receptors and modulatory at metabotropic receptors.

The *ionotropic receptors* of Glu are classified on the basis of the agonist they bind to, into the following types:

- *N*-methyl-D-aspartate (NMDA): These receptors are essentially a ligand-gated rapidly transmitting calcium ion channel. Glutamate binding causes the channel to open and be excited. NMDA receptors possess unique characteristics that allow them to be part of large macromolecular synaptic signaling complexes. In addition to glutamate, NMDA receptors also require the simultaneous binding of glycine as a co-agonist (Monaghan and Jane 2009; Asztely and Gustafsson

1996; Mayer et al. 1984; Monaghan et al. 1989). They are composed of multiple subunits which may belong to three related families: NR1, NR2, and NR3 (Nakanishi 1992). NMDA receptors with different subunit compositions show distinct distributions in the brain and different properties and regulation (Yamakura and Shimoji 1999). NR1 subunits contain a glycine-binding site, while NR2 subunit a glutamate-binding site (Hirai et al. 1996; Laube et al. 1997). It is important to note that NR1 receptor subunits are distributed ubiquitously in the brain and NR1 subunit mRNA is expressed throughout the different stages of neurodevelopment (Mony et al. 2009; Yamakura and Shimoji 1999; Laurie et al. 1997).

NMDA receptors are located in synaptic, presynaptic, and extrasynaptic sites, but in most neurons NMDA receptor density is higher in dendritic spines within the postsynaptic density (Mony et al. 2009). They are often found co-localized with AMPA receptors and are not activated by single synaptic events like the Glu binding alone (Huang and Bergles 2004). Two simultaneously occurring events are necessary for their activation: presynaptic release and binding of glutamate to NMDA receptors and sufficiently strong postsynaptic membrane depolarization leading to the removal of $Mg^{++}$ blockade which is normally present (Wu and Zhuo 2009). NMDA receptors become fully activated upon extensive stimulation of the synapse, because the repetitive activation of AMPA receptors results in sufficient depolarization of the postsynaptic membrane and thus the lifting of the $Mg^{++}$ block, during a process called use-dependent calcium influx (Monaghan and Jane 2009).

The role of the NMDA receptors includes synaptic plasticity, synaptic development, and function- and experience-related refinement of synaptic connections; thus these receptors play a crucial role in learning and memory formation and consolidation, general cognition, and attention but also in mood and anxiety (VanDongen 2009). However they also mediate a phenomenon called excitotoxicity which leads to neurodegeneration. Excitotoxicity is a pathological process that eventually triggers reckless glutamate activity causing a dangerous opening of the calcium channel allowing too much $Ca^{++}$ to enter and by the activation of intracellular enzymes leading to the formation of free radicals, which exert a toxic action on cellular organelles and membranes killing the cell (Stahl 2008).

- α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor: They are composed of combinations of four subunits (GluA1–GluA4) which combine to form heterotetrameric blocks consisting of two sub-blocks of GluA2 and either GluR1, GluR3, or GluR4 (Mayer 2005; Greger et al. 2007). Their distribution in the brain is similar to that of the NMDA.
- Kainate (KA): They are composed of heteromeric combinations of two related subfamilies of proteins which comprise the receptor subunits, GluR 5–7 and KA1 and KA2, and their variants (Bettler et al. 1990, 1992; Egebjerg et al. 1991; Herb et al. 1992; Sakimura et al. 1992; Werner et al. 1991). They have both presynaptic and postsynaptic actions, they are fewer in comparison to the other ionotropic receptors, and their function is not well understood (Contractor et al. 2011).

The *metabotropic Glu receptors* are coupled with a G-protein system and are divided into three groups and eight subtypes, mGluR1–8 (Pin and Acher 2002). They are causing a wide range of physiological effects on the postsynaptic neuron.

#### 1.2.6.7 Gamma-Aminobutyric Acid (GABA)

There are two main GABA receptors, named A and B (Zorumski and Isenberg 1991):

- $GABA_A$ is a fast ionotropic receptor linked to an ion channel (Cossart et al. 2005). It is made of at least five subunits which are transmembrane and are arranged in a ring creating a pore in the center, which constitutes the ion channel. There are three major types of subunits named α, β, and γ, but also the existence of δ, ε, π, and θ has been reported. The usual combination is two α subunits, two β subunits, and one γ subunit. These three subunits are allosterically connected, which means that binding to any of them modifies the binding ability of the others (Olsen and Sieghart 2009). The presence of a distinct type of subunit, named ρ, determines a subgroup of $GABA_A$ receptors named $GABA_C$ which do not manifest allosteric properties (Enz and Cutting 1998).
- $GABA_B$ is a metabotropic receptor and is linked to a G-protein. It is located presynaptically in the neurons containing GABA or Glu.

Most areas of the brain contain both A and B GABA receptors.

### 1.2.7 Second Messenger Systems

There are only a few second messengers which are well characterized and studied, in comparison to almost 100 neurotransmitters. Second messenger systems are classified into two broad categories: nongaseous and gaseous.

- The nongaseous second messengers include hydrophobic (water-insoluble) molecules like diacylglycerol and phosphatidylinositols and hydrophilic (water-soluble) molecules like c-AMP, cGMP, IP3, and intracellular $Ca^{2+}$. Hydrophobic messengers are membrane-associated and diffuse from the plasma membrane into the intermembrane space, while hydrophilic messengers are located within the cytosol (Majerus 1992; Arachidonate related lipid mediators 1990; Needleman et al. 1986). The most studied nongaseous second messenger systems are those of c-AMP, phosphoinositol, arachidonic acid, cGMP, and tyrosine kinase systems. The first three are coupled with the neurotransmitter signal through a G-protein. One interesting property of arachidonic acid and its metabolites is that they are highly lipid soluble, and thus they diffuse through membranes. In this way they can act also in neighboring cells, acting as a type of transcellular synaptic messengers.
- The gaseous second messengers (Mustafa et al. 2009) are highly diffusible and include nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H2S).

They are extremely short-lived. All of them can diffuse both through cytosol and across cellular membranes. The criteria of "gasotransmitter" are the following (Wang 2002, 2004):

- Small molecule of a gas.
- Freely permeable to membranes and its effects do not rely on membrane receptors.
- It is endogenously and enzymatically generated and its production is regulated.
- It has well-defined and specific functions at physiologically relevant concentrations.
- Functions of this endogenous gas can be mimicked by its exogenously applied counterpart.
- Its cellular effects may or may not be mediated by second messengers but should have specific cellular and molecular targets.

Eventually, all second messenger systems produce changes in specific target proteins within the cell, and the phosphorylation mediated by protein kinases and the action of phospholipases are central in the whole process (Tanaka and Nishizuka 1994). Protein kinases can also induce the synthesis of new proteins by altering gene expression. This leads to long-term changes which are important for neuronal development and for long-term memory. To make things more complex, the effects of second messenger systems are broadened through interaction between them with parallel, convergent, and antagonistic actions.

## 1.3 Functional Organization of the Brain

The human brain has a complex but highly efficient organization (Gazzaniga 1989, 1995). Throughout the brain, neuronal cells are more or less the same both morphologically and also in terms of function. It is their interconnections and the networks that arise which produce the differences in function between brain areas, and they give birth to behavior itself (Mishkin 1993; Changeux and Dehaene 1993; Lewis and Oeth 1995). Thus, this fundamental simplicity of structure supports a great complexity through astronomical numbers and exponential power. The end result is currently beyond our comprehension, even at its middle levels (e.g., coding and storing of external stimuli) not to mention the higher levels (e.g., consciousness).

The basic operationalized conceptualization of the human brain is that of a helmet with spheres at its basis. Both the helmet and the spheres are made of gray matter, while the space between them, that is, the internal space of the helmet, is full of white matter. The helmet corresponds to the cortex and the spheres to the thalamus, the hypothalamus, the amygdala, the hippocampus, and the basal ganglia (nucleus caudatus, putamen, and globus pallidus). Gray matter consists of the cell bodies of neurons, which are the processors where the information is being analyzed and processed, while the white matter corresponds to the axons, which are

the cables connecting the various processors. The spheres/basal ganglia deal with more primitive and primary processes (basic emotions, instincts, vital functions, and motor coordination), while the helmet/cortex deals with higher cognitive function especially in the frontal areas (detailed process and analysis, abstract thinking and planning). This whole design is extremely ergonomic; it permits the circulation of information in the fastest, most efficient, and economical way possible. The ventricles serve as the cooling system, and they also assist in the removal of toxic and metabolic waste (Fig. 1.2).

An important feature of the brain organization is that most inputs cross over to the opposite (contralateral) side of the brain or spinal cord. Subsequently the sensory and motor activities are mediated by the opposite-side brain hemisphere. The reason for this is not yet understood. What is however also known is that this asymmetry is accentuated in humans in comparison to primates because of the presence of complex and symbolic thought and behavior. While this is true, it is also a fact that most activities engage both hemispheres but with a different contribution. Classically, the dominant hemisphere is more concerned with detailed thought, abstract thinking, and speech and subsequently with intentional behavior, while the non-dominant hemisphere is more concerned with emotional aspects of behavior and spatial analysis. In some way it could be said that the dominant hemisphere is the "digital," while the non-dominant is the "analog" or better the "fuzzy." In the normal brain, there is communication between the two hemispheres, and there is now evidence that the capacity of one hemisphere to perform a particular task may deteriorate after commissurotomy.

The first component of behavior is the sense of the environment, external but also internal. The human brain utilizes five main senses: sight, hearing, smell, taste, and touch plus pain and the sensation of body movements, which give information both for the external and the internal environments. A number of other senses also provide information concerning the internal environment, which is of course the human body.

Concerning the external environment, specialized apparatus and receptor cells on the body surface receive stimuli and encode information. Essentially they transform external natural phenomena (e.g., sound, light, pressure, etc.) into neuronal phenomena, and in this way they register their intensity and their temporal and spatial characteristics. An important characteristic of these "sensors" is that they tend to focus on and prioritize specific characteristics of the stimuli. For example, sight has high resolution only in a small fraction of the visual field (spatial focus, priority to vision directly in front), while the visual color spectrum is limited (other species have different visual spectra probably as a result of natural selection pressure). Also the senses from the face or the fingers are much more detailed in terms of information in comparison to trunk or legs. As a result, the receptor cells in the sensor organs are arranged in a "topographical" way, reflecting this focus and prioritization, and this topographical arrangement is kept through the successive stages of processing; in this way an orderly neural map of information from the receptive surface is

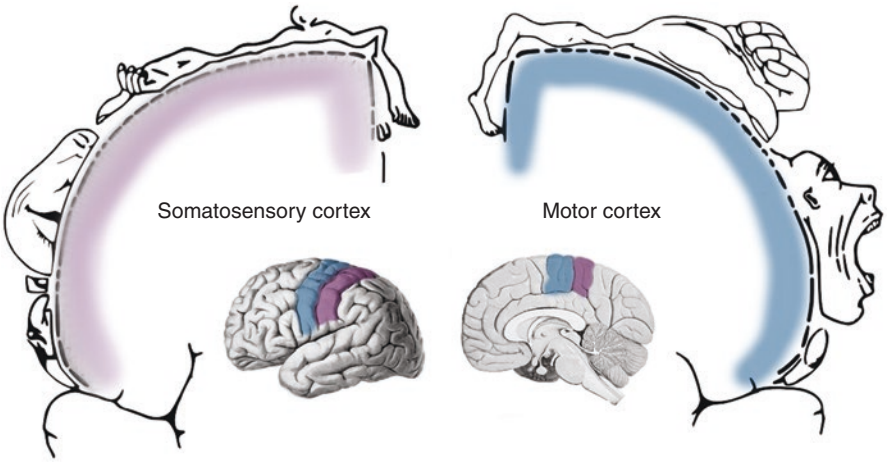


**Fig. 1.6** Topographic maps in the somatosensory and motor cortices

retained at each successive level in the brain (Fig. 1.6) (Penfield and Rasmussen 1950).

Sensory information is processed in several parallel pathways each of which handles a different set of information concerning the specific sense. This increases computational power. Central to this processing is the involvement of a number of neuronal circuits which contribute to the coding and processing of the information. There are three such major neural systems.

- The first is the thalamus which is the biggest structure in the diencephalon (Fig. 1.1). Its name comes from the Greek *θάλαμος* meaning "chamber." It is comprised by a number of nuclei. These nuclei are classified into the relay, the specific relay, the association relay, and the diffuse-projection nuclei. One of them, the reticular nucleus, regulates the functional relationship between the thalamic nuclei. The thalamus receives input from the spinal cord with the lateral spinothalamic tract, which carries pain and temperature information, and the anterior (or ventral) spinothalamic tract, which carries crude touch and pressure information. Every sensory system (with the exception of the olfactory system) includes a thalamic nucleus that receives sensory signals and sends them to the associated primary cortical area. The thalamus is manifoldly connected to the hippocampus via the mammillothalamic tract (Carlesimo et al. 2011; Stein et al. 2000), and this connection serves the link between memory mechanisms and new stimuli. The projection to the cerebral cortex is carried via the thalamocortical radiations (Briggs and Usrey 2008). These pathways provide information input to the cortex from the senses, but also the thalamus relays input from the basal ganglia and cerebellum to the cortical motor areas

(Asanuma et al. 1983; Evarts and Thach 1969). To summarize, the thalamus filters and processes both the sensory input to the cortex during the first steps of the process of information coming from the environment, but also it filters and processes the motor responses from the basal ganglia before their entering into the motor cortex during the early stages of response, after the process of the sensory information is completed. With its link to the hippocampus, it allows the brain to keep record of these processes in the form of a type of memory.

- Depending on the author, the limbic system includes the cingulate gyrus, the olfactory bulbs, the hippocampus, the hypothalamus, the amygdala, the fornix, the mammillary body, the septum pellucidum, the habenular commissure, the parahippocampal gyrus, and the limbic midbrain areas (Morgane et al. 2005). Essentially it includes the structures where the production of mood (amygdala), emotion (cingulate gyrus), and memory (hippocampus) is seated. There are a number of connections, many of them reciprocal, between these structures and the thalamus and the frontal association cortex. Information concerning sensory information are projected to the amygdala which adds an emotional component which is essentially a primitive kind of assessment and decision (e.g., fear in the sight of a snake) and the hippocampus, which stores aspects of perception in long-term memory and also provides with feedback from previous experiences and memories. In this way a comprehensive internal representation of the external environment is formulated. The hippocampus is responsible for the formation of long-term memories, but it is not the permanent storage site of memories. If damaged the subject loses the ability to form new memories but keeps old ones. Overall, the role of these connections is to input affect on the information process and the decision-making and to develop and store memories and to selectively retrieve them on the basis of current sensory input and emotional state (Van Hoesen 1993). Because of this complex emotional-mnemonic function, it has been proposed as the seat of the "social brain" (Brotehrs 1990).
- The basal ganglia (Lanciego et al. 2012; Ward et al. 2013; O'Connor 1998) include the nucleus caudatus, the putamen, the globus pallidus, the subthalamic nucleus, and the substantia nigra (Fig. 1.2). The term "striatum" refers to the nucleus caudatus, the putamen, and the globus pallidus, while the term "lentiform" or "lenticular" nucleus refers to the putamen and the globus pallidus. The basal ganglia take part mainly in the motor response, and their function will be described below.

Information is processed and transformed at every step, and at each stage every postsynaptic neuron typically receives inputs from thousands of presynaptic neurons. Eventually the sensory information are projected onto the cortex at areas specific for each sense. As said, most of this information comes through the thalamus which acts as a gatekeeper for information to the cerebral cortex and together with the limbic system prevents or enhances the passage of specific information and the retrieval of relevant memories and storage of new, depending on the behavioral state of the animal. These areas in the cortex are called "primary association areas," and their main characteristic is that they receive input from a single sense, and because

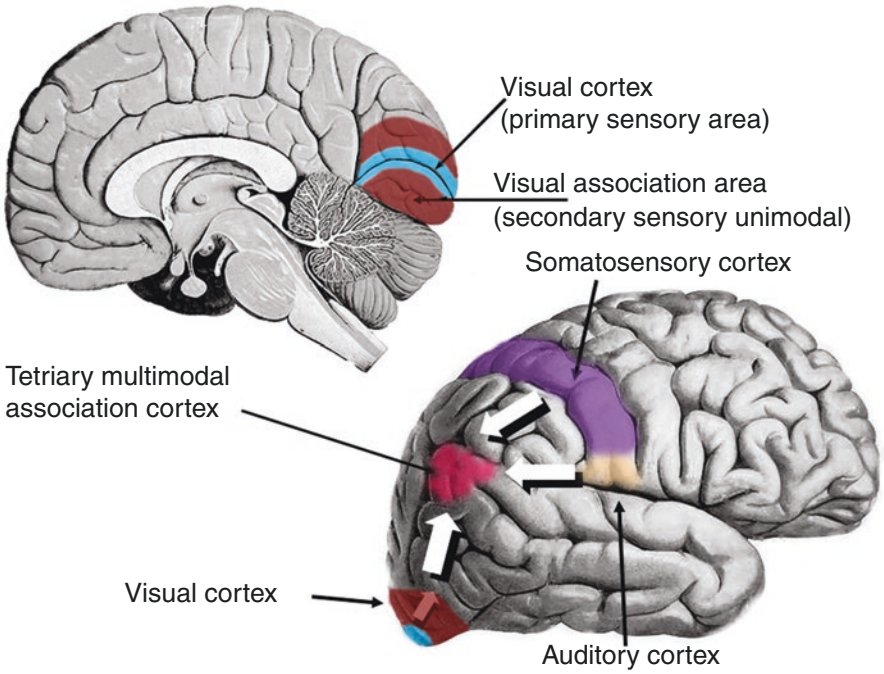


**Fig. 1.7** Association areas and the flow of information

of this they are called "unimodal." The areas where each of the five senses projects are well known, and it is the pole of the occipital lobe (calcarine sulcus) for sight and the Heschl's gyri in the temporal lobe for hearing and the posterior central gyrus in the parietal lobe for somatosensory senses. Next to or surrounding the primary association cortex, an adjacent, higher-order area, the secondary association cortex which is also unimodal is located (Fig. 1.7). The concept of "association areas" was introduced by John Hughlings Jackson (1835–1911).

An important characteristic is that the projection into the cortex is done in an orderly manner, thus creating a sort of a topographical map. This map corresponds to the characteristics of the specific sense (e.g., light touch vs. pain on the same area of skin), and it is spatial for sight and somatic senses and oriented toward the analysis of frequency and similar features for sounds whose source is also able to locate (Clark et al. 1988; Kaas et al. 1979; Jenkins et al. 1990; Meldrum 2000). It also corresponds to the differential resolution (and subsequently importance) given to each part of the sensory stimulus by the external sensors. Thus, the topographical map is not an accurate representation of the physical stimulus but rather a distorted one, according to the weight given by the senses. It reflects both the physical topography and the density of the perceived information. For example, in the somatosensory cortex, the face, tongue, and fingers occupy a much larger surface and neurons and subsequently more focus in processing, in comparison to the trunk or legs (Fig. 1.6). In the visual field, the center of vision (the fovea) occupies a much larger

area in comparison to the peripheral parts of the visual field (Fox et al. 1987; Penfield and Rasmussen 1950). These maps change with experience (Mogilner et al. 1993; Jenkins et al. 1990; Ramachandran 1993).

All secondary association areas project to one of the three tertiary major multimodal association areas. In these areas the integration of two or more sensory modalities takes place, and a more comprehensive internal neuronal representation of the external environment is developed (Van Hoesen 1993).

Three multimodal association areas are particularly important:

- The posterior association area, at the margin of the parietal, temporal, and occipital lobes. It receives information from several sensory modalities (Fig. 1.7).
- The limbic association area, which includes the anterior pole of the temporal lobe and the medial edge of the cerebral hemisphere. It is concerned with emotion and memory storage.
- The anterior association area (prefrontal cortex) which is located anterior to the postcentral gyrus. It is concerned with the executive functions, judgment, planning for the future, and holding and organizing events from memory for prospective action (working memory) as well as with the planning of movement (Goldman-Rakic 1992, 1996).

A simplistic functional description of the frontal lobe could consider it as a trilateral pyramid with the base toward the parietal lobe and with its top corresponding to the frontal pole. One of its lateral surfaces is horizontal and corresponds to the orbital cortex, while the other two correspond to the outer and the medial surfaces of the lobe. The two lateral surfaces corresponding to the orbital and the medial surfaces are joined in a 90° angle (Fig. 1.8). The outer surface (dorsal prefrontal association area) corresponds to what is closer to RAM in modern computers and hosts working memory. The medial surface (medial prefrontal cortex) concerns the production of affect, while the orbital surface (ventral orbitofrontal cortex) hosts the decision circuits.

After the decision is made, projections to the premotor cortex are triggered. Every decision implies the initiation of a behavior which almost always has a motor part, either to act or to stand still. A topographical map exists also in the

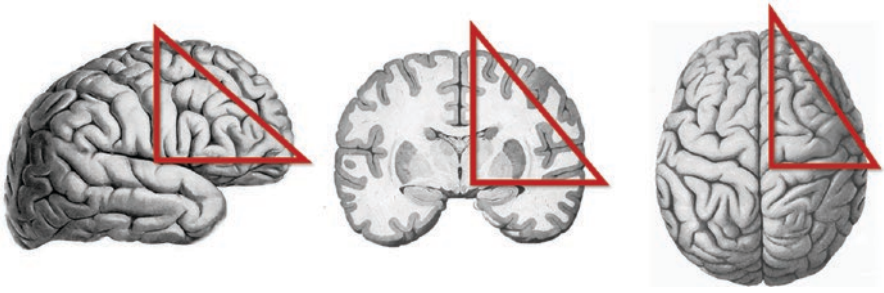

**Fig. 1.8** The simplified pyramidal shape of the frontal lobe

motor cortex (Fig. 1.6). This map, like the sensory maps, does not represent every part of the body equally, but it puts specific emphasis on individual body parts reflecting the fineness of control required for the motor function of these particular body parts.

The primary motor cortex probably contains the "software" of movement and is located rostral to the central sulcus and is associated with the motor systems of the spinal cord. The human corticospinal tract consists of about one million axons, and about 40% of them originate in the motor cortex, and the entire projection is also called the "pyramidal tract."

In this process, there is input to the motor cortex from the basal ganglia which constitute key structures for motor planning. There are two major pathways with projections from and to the basal ganglia:

- The "direct" pathway, which carries projections from cortical cells to the striatum via the SNr-GPi complex, which in turn projects to the thalamus through the inhibitory ansa lenticularis pathway, and eventually the thalamus projects to the motor cortex which in turn projects to the brain stem and ultimately mobilizes muscle fibers via the lateral corticospinal tract.
- The "indirect" pathway also originates from the striatum, and after stimulation by the cortex, it projects to the globus pallidus externa, which in turn projects to the subthalamic nucleus which also in turn projects to the SNr-GPi complex which inhibits the thalamus. This indirect pathway regulates the inhibition of the motor cortex by the thalamus. Both pathways are based on a serial sequence of inhibitory and excitatory projections which produce a fine-tuned end output. Overall, the direct and the indirect pathways are antagonistic in their functions, and this antagonism is modulated by the substantia nigra pars compacta. The antagonism serves balance and fine-tuning of motor movement.

It is important for the long-term adaptation and survival that those decisions, choices, and responses with a positive outcome for the individual be ranked higher in the consideration of future resolutions and given more weight and speed in situations of ambiguity. In other words, behaviors which are successful are also rewarding, and this is registered not only in terms of essential mnemonic registrations but also at a lower unconscious level. In general, dopaminergic neurons in the midbrain mediate these rewarding aspects of behavior.

The basal ganglia circuit probably serves the selection and enforcement of behaviors that lead to reward by using past experience to predict which patterns of input from the neocortex and the thalamus will lead to reward. In order to execute this function, the cells in the globus pallidus and the substantia nigra fire tonically producing a constant inhibition of neurons in the thalamus and superior colliculus. In case this inhibition pauses, then the neurons in these areas are released and respond to excitatory inputs that would otherwise be subthreshold. The central location of the globus pallidus in the basal ganglia formation implies also a central role in the functioning. It constitutes the inner component of the

lentiform nucleus, and with the putamen it forms a cone-like structure, with its tip directed medially. The majority of projections from the neostriatum (which receives input from the neocortex, the thalamus, and the substantia nigra) are to the globus pallidus which serves as an intermediate processing center (Wilson 2004). A role for the nucleus accumbens and the VTA is particularly well established. Numerous things that people find rewarding, including addictive drugs, good-tasting food, and sex, have been shown to elicit activation of the ventral tegmental area dopamine system.

This above network probably tests a variety of input concerning both the interpretation and also the response options on the basis of templates and maybe error memories provided by the prefrontal cortex to choose those that systematically and reliably elicit reward reactions in the brain. The prefrontal cortex provides the templates to test against but on the other hand also inhibits or modifies the "resolutions" of the basal ganglia. This is why although mood, affect, and initial tendencies to act are not under volitional control and cannot be influenced, the final output (externalized behavior) is under volitional control through effortful regulation.

A comprehensive but simplistic representation of the complete process from sensory input to the manifestation of motor response is shown in Fig. 1.9.

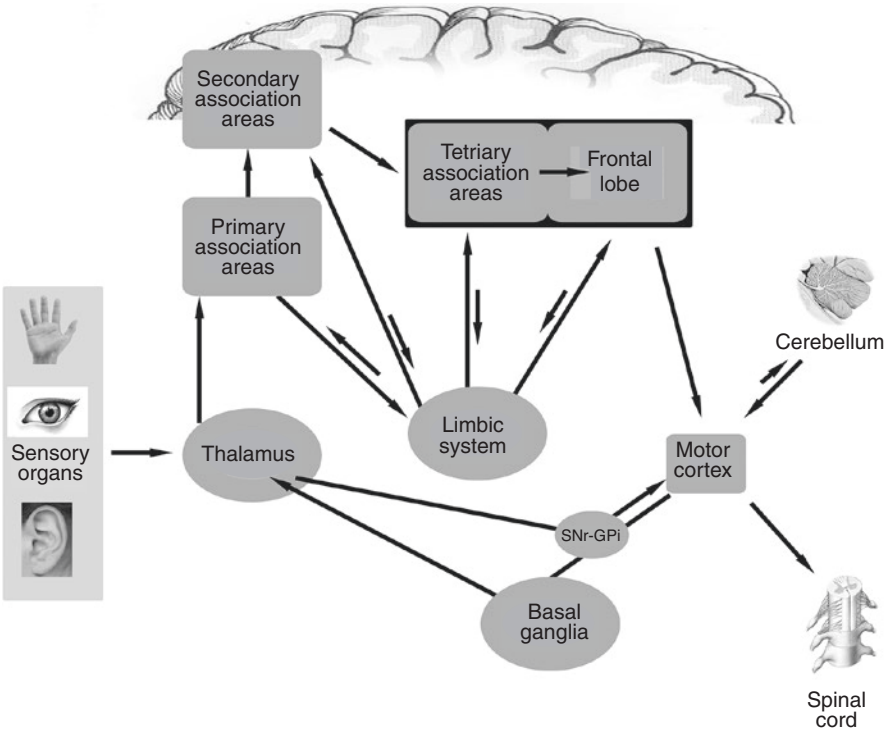


**Fig. 1.9** Abstract representation of the flow of information and its process through different brain areas

## 1.4 Thought and Intelligence

Thought is the end result of brain function and constitutes what is conceptualized with the term "mind." Philosophical and analytical approaches of this issue are beyond the scope of the current book chapter.

What is important to consider as an extension of all that has been mentioned and described so far in this book chapter are some basic macroscopic characteristics of the thought process and the concept of intelligence.

One astonishing characteristic of the human brain is that it is capable of performing complex process of information in extremely short time but is incapable of performing much less demanding process of information. It is as if it is calibrated to perform on high demands. For example, the human brain, apart from its ability to comprehend and analyze abstract concepts and meanings, in everyday life is able, e.g., to perform the complex visuospatial and motor calculations necessary to throw a spear to hit a moving target at a distance or to perform complex body acrobatics, in which modern engineering and computing find it difficult if not impossible to fully simulate, while on the contrary the human brain is unable, e.g., to perform a multiplication between two five-digit numbers, which is one of the easiest tasks for electronic-based calculators even at credit card size. This is because the essential architecture and the basic principles on which the brain function is based are completely different from that of electronic computers and specifically of what is called "Turing machines." Again this topic is beyond the scope of the current chapter; however it is useful to note that only recently we have started understanding the principles of the so-called non-Turing machines whose main characteristic is that their functions are not deterministic and of quantum computers which utilize a probabilistic system instead of a binary code.

One probable characteristic of some of these non-deterministic and non-binary computational systems is their complex coding at input and that they are extremely relying on templates and pre-acquired information in order to process novel input. This is also a characteristic of the brain, and at least some of these pre-acquired templates emerge in the form of archetypical thoughts and impulses as well as in the form of cognitive biases.

The concept of cognitive biases was introduced by Amos Tversky and Daniel Kahneman in 1972 (Kahneman and Shane 2002). Kahneman received the Nobel Prize in Economic Sciences in 2002, and his overall work challenges the assumption of human rationality prevailing in modern economic theory and decision-making.

Cognitive biases refer to a systematic pattern of deviation from norm or rationality in judgment. This leads to inferences about the environment and to events in an illogical fashion (Haselton et al. 2005). This way of thinking leads individuals to create their own subjective version of the world and especially of the social reality, and very often the pre-existing biases rather than the objective information input are what determines the response and overall behavior (Morewedge and Kahneman 2010; Kahneman and Klein 2009; Kahneman and Frederick 2007; Kahneman 2003; Kahneman and Tversky 1996, 1982; Tversky and Kahneman 1981; Gigerenzer and Goldstein 1996). Although some of these biases are the unwanted result of

limitations in the process capacity of the brain, in principle the role of biases is profoundly adaptive since they enable faster decisions when timeliness are more valuable than accuracy, as illustrated in heuristics (information-processing shortcuts which are simple for the brain to compute but sometimes introduce severe and systematic errors; comes from the Greek word *ευρίσκω*, that is, "to find"). The problem is that for most of biases, their basic principles were embedded in the human brain when humans were living in a much different environment than today, with different everyday needs, and therefore today in modern human society, they might not be always able to play an adaptive role since they can activate stereotypes and inaccurate judgments of others. It is important to note that cognitive biases can be controlled and are influenced by training and education, but often it seems that intelligent and educated persons use their knowledge and skills only to further strengthen and support their biases.

On the other hand, there is a concept which refers to the "objective" capacity to solve specific problems. This is called "intelligence" and has been defined in many different ways, including the capacity for logic, understanding, self-awareness, learning, emotional knowledge, planning, creativity, and problem-solving. Various approaches to human intelligence have been adopted, and its definition is controversial. The word derives from the Latin *intelligere* (to comprehend or perceive). As a scientific topic, it is the result of research on anthropological differences between humans which started in the late eighteenth and early nineteenth centuries. Further elaboration of the matter is beyond the scope of the current chapter.

## 1.5 Mood, Affect, and Emotions

The modern approach distinguishes between:

- "Mood" which is the long-lasting internal emotional tone and largely characteristic of the individual
- "Affect" which is the general emotional status during the last few days or weeks and is observable through the individual's behavior
- "Emotion" which corresponds to the transient emotional state which also manifests itself through motor behaviors (face mimics, body movements, complex behaviors, etc.)

Mood has an enduring nature, tends to be unfocused and diffused, involves expectation of the future, and is manifested in subtle ways, while, in contrast, emotions tend to be short-lived and to have a clear focus.

In terms of etymology, the word "mood" comes from Proto-Germanic "modaz" and is related to the old high German "muot" (in German: Mut) and the old Saxon mod (in Dutch: moed). Similar words exist in Scandinavian languages, and they mean "anger" and "emotion." The ancient Greek word *μῶθαι* (mothai) and the Latin *mos* (= mores) come for the same Indo-European root. The word "affect" comes from the middle French word "affecter" which is in turn derived from the Latin

*afficere* (*ad* + *facere* which means "to act upon," "influence," "attack with disease"). It seems that it had entered the English language in the fourteenth century, and it is first recorded in Geoffrey Chaucer's "Troilus and Cressida." "Emotion" comes from the French word "émouvoir" which is based on the Latin *emovere* (e-movere means "without move"). Thus the original meanings of these terms relate to anger and to the tendency to act or remain still.

Aristotle's concept of affect is "that which leads one's condition to become so transformed that his judgment is affected, and which is accompanied by pleasure and pain" (Aristotle, "Rhetoric" 6). While he was the first to elaborate on human affective states and various terms can be found in his works, in Greek the word for mood is *διάθεση* (diathesi = disposition, tendency, availability), for affect is *συναίσθημα* (synaesthima = complex or combined feelings, sentiment), and for emotion is *συγκίνηση* (synkinisi = complex set of movements as a response).

Affects and emotions serve two main aims.

- The first concerns the internal functioning of the individual and provides the individual with fast decisions which serve the survival of the individual but also of the species. Some of these decisions are easy to understand (e.g., fear of animals), but others are incomprehensible in principle (aesthetics and attraction to the opposite sex). In the same frame, emotions provide feedback concerning the behavior of the individual, and in this way they enhance the expression of the specific behavior or preclude its future manifestations. For example, sadness constitutes the emotional response to loss, defeat, disappointment, or other adversities. Its adaptive function includes permitting withdrawal to conserve resources and asking for support from significant others, and the autonomic arousal which might be present facilitates the search for the lost object or an appropriate substitute.
- The second aim is to communicate the internal emotional state of the individual to others, and this is achieved with facial expressions, gestures, bodily moves and posture, and voice verbal and nonverbal elements. These ways of communicating emotions vary between cultures, but most of the repertoire is universal for human beings. They constitute a main source for the interaction with others, since the emotions of an individual influence the emotions, thoughts, and behaviors of others, produce positive or negative feedback, and give birth to circles of future interactions and reciprocal influence.

The first modern neurobiological theory of emotions was independently developed in the 1880s by William James (1842–1910) and Carl Lange (1834–1900). That theory proposed that emotions are the result of changes in the physiology of the body caused by a stimulus and not the result of the stimulus directly.

A modern approach to the issue goes through a basic approach to brain function which could suggest that there are two distinct mental processes: logical thinking and emotions. While emotions are present also in animals, logical thinking is present primarily in humans, while some elements are also evident in the behavior of primates.

Traditionally, the left hemisphere is considered to be the site of logical thinking, while the right hemisphere serves the creation of emotions. Although this assumption is supported by some neuropsychological data, especially in neurosurgical patients and head injury, it is almost certain that complete and opposite lateralization of logic and emotions does not exist. A consequence of the above assumption is that the dysfunctions leading to schizophrenia are supposed to be localized in the left hemisphere, while those leading to depression are localized in the right.

A very simplified neurobiological model may propose that "mood" derives probably from processes largely taking part in the amygdala and the insula, while "emotion" is generated mainly in the anterior cingulate cortex (ACC) and more specifically in area 25. However, its effortful regulation is likely to implicate area 24 and the dorsolateral prefrontal cortex (DLPFC). In the middle between "mood" and "emotion" lies the "affect" which is at least partially generated in the ACC and partially in other brain areas including the prefrontal cortex (PFC) (Phillips et al. 2003; Fountoulakis et al. 2008).

Emotional processes are evolutionary older and are characterized by speed and dominance. They lead to fast decision-making, on the basis of predetermined strong assumptions concerning the gross characteristics of the situation. For example, fear is triggered immediately and almost before conscious recognition of the stimuli, and it leads to the fast manifestation of adaptive behavior (fight or flight). A snake will always trigger fear, no matter whether it is poisonous or not. On the contrary, logical thinking is slow, requires the conscious elaboration on the stimuli, demands concentration and effort, and is not as strong as emotion concerning the effect on behavior. Emotion is biased toward the triggering of those behaviors that serve the survival of the individual and the species, while logical thinking aims toward an "objective" assessment of the situation. In the language of artificial intelligence, the closest description which can be made today is that of a "fuzzy" vs. "digital" systems.

The database of assumptions emotions use is of unknown origin, probably partially inherited and partially acquired through experience, and possibly it is characteristic of the species. Logical thinking is based mainly on training. Decisions based on emotions are stronger than those based on logical thinking, and when they collide, the person faces a difficult dilemma, since it is very difficult for logical thinking to override emotional pressure.

The two processes, although independent in principle, interact and influence each other. The emotional status causes bias in logical thinking, and logical analysis triggers emotions depending on the positive or negative outcome. This interaction is likely to happen at multiple levels (e.g., selective memory recall, reinforcement through new analysis, biased selection of possible solutions, etc.).

Interest in emotions from an evolutionary perspective was triggered by the publication of the book *The Expression of the Emotions in Man and Animals* by Charles Darwin (1809–1882) in 1872. In that book, Darwin stresses the universal nature of emotions and the connection of mental states to the neurological organization of movement. Central to his understanding was a shared human and animal ancestry in

sharp contrast to the contemporary claims that there were divinely created human muscles to express uniquely human feelings. Darwin's original suggestion was that emotions evolved via natural selection and therefore have cross-culturally universal counterparts, a proposal confirmed almost a century later by the works of Paul Ekman (Ekman 1965, 1980, 1992a, b, 1993, 1994, 2003, 2009, 2016; Ekman and Friesen 1967, 1971; Ekman et al. 1969, 1987). Furthermore, animals undergo emotions comparable to those of humans.

## 1.6 Sleep

The old and lay understanding concerning sleep suggested that the awake state is actively maintained by sensory stimulation, and when fatigue along with a relative lack of sensory stimulation appears, sleep starts as a phase of recovery from the labor of the daytime.

There is a circadian periodicity of a little more than 24 h (close to 25 h) for sleep and wakefulness. A major role in this wake-sleep cycle is played by the reticular formation whose rostral portion contributes to wakefulness, but it is inhibited by the ventral portion which thus induces sleep. External timing cues called zeitgebers (time givers) serve as anchors to adapt the rhythm to the environment. The major external cue is sunlight, which acts through the retino-hypothalamic tract on the major internal clock of the suprachiasmatic nucleus in the anterior hypothalamus.

In terms of description, sleep has two distinct phases; the first is characterized by rapid eye movements (REM sleep), while in the second there are no rapid eye movements (non-REM sleep). During sleep, the two phases alternate cyclically in a highly structured pattern (Aserinsky and Kleitman 1953, 2003).

While its precise function and the reason all animals including humans need sleep (although exceptions and important variations do exist) are unknown, its universal presence in animals suggest an underlying importance. This importance is also shown by the fact that there is a rebound of sleep after sleep deprivation and a rebound of slow-wave or REM sleep after selective deprivation of these stages. Even more impressive is the functional impairments after sleep loss which might lead to death in extreme cases.

It is interesting that total sleep time seems to remain fairly stable from day to day even under widely varying conditions. While the lay belief is that fatigue (both mental and physical) causes a need for prolonged sleep, this has not been supported by data. The only factor that beyond doubt increases sleep is prior sleep loss (sleep deficit).

Although during sleep deprivation, food intake is increased and adipose tissue formation increases, there is no data suggesting that energy conservation is a function of sleep since the metabolism during sleep is only around 15% lower in comparison to wakefulness, but again winter hibernation in some mammals suggests otherwise. On the other hand, increased food intake and adipose tissue formation could be explained as a consequence of the co-occurring significant

stress in periods of sleep deprivation. There are some data regarding sleep having thermoregulatory and cooling functions especially in mammals, but this cannot explain the fact that such functions (including somatic rest) could be performed without leaving the animal vulnerable in a state of defense failure. It is essential to note that rest without sleep leaves the individual sleepy. After several days of sleep deprivation, there are no significant physiological changes in the human body, but interestingly there is an intellectual impairment. Even more interesting is the fact that this impairment can be reversed by drugs or motivation. This points to the possibility that the impairment could be due to a pressure to sleep rather than because of a physiological deficit in mental functioning because of prolonged lack of "housekeeping," but again there are no convincing data.

Dreams are another mental function during sleep which has an unknown usefulness for the brain. They are organized thematically and perceptually as separate short stories. They are far more likely to be recalled when subjects were awakened from REM sleep (3/4 or more of awakenings) than from non-REM sleep (less than 10% of awakenings). Non-REM dreams might be shorter, but otherwise there seems to be no difference between dreams in relationship to sleep phase (Rechtschaffen 1978, 1998; Frank 2006; Dement and Wolpert 1958).

Sleep and dreams will be the specific focus of another chapter in this book.

## 1.7 Consciousness and Human Experience

The word "consciousness" comes from the Latin conscious, meaning "knowing, being aware" which in turn comes from conscire (con meaning "together" + scire meaning "know"). Probably this is a loan translation of the Greek word *συνείδηση* (sinidisi) which comes from the verb *σύνοιδα* (meaning "I know well"). From the Latin scire also come the words "sense" and "science."

While consciousness has been the focus of philosophy in the frame of mind, self, and morality, and most philosophers had adopted the dualistic approach (brain vs. soul/mind) which was suggested for the first time by Rene Descartes (1596–1650) in his books *The Description of the Human Body* (1647) and *Passions of the Soul* (1649) (Descartes et al. 1984), modern advances in neuroscience point to the conclusion that it is fundamentally a function of the brain. However so far there was no success in the efforts to identify neural mechanisms that give rise to consciousness (De Sousa 2013).

A basic approach to consciousness is its conceptualization as a state of awareness. Modern philosophers of mind such as John Searle (1932–) and Thomas Nagel (1937–) ascribe three main features to awareness: subjectivity, unity, and intentionality.

- Subjectivity poses the greatest scientific challenge since it could be in direct conflict with the principles of conducting research and conceptualizing in a scientific way.

- Unity refers to the fact that experiences surface into consciousness as a unified whole and all the various senses are merged into a single conscious experience of reality.
- Intentionality refers to the attribution of meaning beyond the moment of experience.

There is a debate whether the human brain can completely understand itself and subsequently whether consciousness could be scientifically studied. While some philosophers, e.g., Colin McGinn (1950–), believe that there are limits to human cognitive capacities which preclude the comprehension of what consciousness really is, Searle and Nagel disagree. A third approach suggested by the Nobel Laureate Gerald Maurice Edelman (1929–2014) is that consciousness is simply the outcome of the computational workings of the association areas of the brain, and in this frame it could be the focus of scientific research (Edelman 1978, 1989, 1992; Edelman and Changeux 2001).

The great practical problem is the astronomical complexity of the brain's functional anatomy and physiology. A measure of this complexity can be shown with the following example. Let's take not the whole human brain but only one of the two optic nerves. This part of the nervous system contains between 770,000 and 1.7 million nerve fibers (Jonas et al. 1992), and to make calculations easy, let's assume it is one million. Now if each of these neurons can take only two distinct states (e.g., yes/no, fire/silent, etc.) which is a very simplistic approach if one takes into consideration the neuronal function as described earlier, then the total number of states the optic nerve can take is $2^{1,000,000}$. This number, if transformed in power of 10, is larger than $10^{250,000}$ which should be compared with $10^{80}$–$10^{97}$ which correspond to estimations of the number of all elementary particles of the visible universe.

This scale of complexity, considered together with the limited number of experimental trials we can conduct and the limited number of subjects and observations we can gather, makes impossible the study of these phenomena with the standard reductionist approach to events, which science normally follows.

Currently we lack the tools both theoretical and also operational to dig deeper into these mechanisms and to understand them, far less to extrapolate subjective properties (consciousness) from the properties of objects (interconnected nerve cells).

While eventually we have a general idea of how the brain works, from the atom and molecule level to the level of social behavior and abstract expression of ideas, we lack the precise knowledge that bridges different steps and levels in this system. We lack the knowledge of precisely how the incoming sensory information is broken, coded, and stored and how a non-deterministic process leads to a decision. We lack the knowledge of how electric currents and chemical reactions through a highly organized super-complexity give rise to consciousness, to sense of individuality, and even more important, in humans, to the realization of the inevitable future death. This realization and subsequent fear are, according to many philosophers, the driving force of creativity.

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# Learning and Memory

# 2

Stavroula I. Bargiota, Vasilis P. Bozikas, and Ioannis Nimatoudis

## 2.1 Introduction

According to the ancient Greek mythology, Mnemosyne was the goddess of memory and the mother of the nine Muses of the arts and science (Dudai and Carruthers 2005). Learning and memory are closely related fundamental higher brain processes that allow individuals to adapt to the environment, create, and widen not only their personal history but also the population culture (Benfenati 2007).

Learning helps people to enquire and encode information making them able to adopt new behaviors. Learning is a whole lifetime process that intervenes in almost all occasions of people's social living. As a result the acquired experiences can alter an individual's behavior (Mazur 2015).

Memory is connected with learning. The initial information is encoded, preserved over time, and used when any need occurs. Any damage in the encoding, the storage, and the retrieval of the information disturbs the process of memory. In fact, memory is the result of learning, but these two procedures are intermingled and essential for the survival of not only humans but also all living creatures (Engel 1999).

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## 2.2 Learning

Learning is the possession of knowledge and skill through systemic study or through experience and error. There are two types of learning under the interest of psychobiology: associative learning and nonassociative learning. The associative learning is the procedure by which an individual finds out the connection between two stimuli or between an action and an event. The nonassociative learning is a simple form of learning that describes a relatively stable alteration in the power of response to a single stimulus due to repeated exposure to this same type of stimulus (Mazur 2015; Rescorla 2014).

### 2.2.1 Associative Learning

Some typical forms of associative learning are complex enough, and they are presented as classical conditioning, operant conditioning, and observational learning.

#### 2.2.1.1 Classical Conditioning

In classical conditioning subjects learn to form an association between two events happening in sequence. In particular, a neutral stimulus produces a certain response to another stimulus. In the beginning of the twentieth century, the Russian physiologist Ivan P. Pavlov discovered the classical conditioning accidentally during experiments upon digestion. Pavlov gave food to a dog, and he watched the secretion of saliva, while the dog was consuming the food. In particular, he presented a stimulus like the sound of a metronome (conditioned stimuli), and afterward he supplied the food (unconditioned stimuli). He repeated this procedure a few times, and as a result he noticed that the dog started to salivate in response to the sound of the metronome. Pavlov came up with the conclusion that if a specific stimulus was present while the dog was given food, then that particular stimulus could be connected with food and could provoke salivation on its own. He made the dog to repeat this procedure, and as a result he realized that the dog was able to begin salivating before eating. This particular type of learning was named Pavlovian conditioning or classical conditioning (Pavlov et al. 1929).

Later, Pavlov and his colleagues introduced the terms acquisition, extinction, generalization, and discrimination in an attempt to clarify classical conditioning. They also introduced the rules of temporal contiguity and contingency. According to their studies, acquisition is the initial phase when a dog is trained, for example, to salivate at the sound of a bell. A conditioned stimulus should precede the unconditioned stimulus by several seconds interval (temporal contiguity). Then, a certain behavioral response, the conditioned response is produced. Conditioned stimulus must forecast the unconditioned stimulus (contingency). Extinction is a phenomenon that describes the gradual weakness and fading of conditioned response after the repetitive appliance of conditioned stimulus when the unconditioned stimulus is absent. For example, in extinction when salivation of the dog is the conditioned response, it will gradually decline if the bell is ringing repeatedly without supplying

any food (unconditioned event). Generalization is the procedure that an individual already conditioned to a specific event will probably respond to a similar event without the occurrence of training to the new event. For example, if a particular tone makes a dog to salivate, tones of higher and lower frequency will also lead to salivation. On the other hand, during discrimination the dog is taught to salivate in a different way to two different stimuli tones.

Classical conditioning was postulated to be related with some clinical presentations like phobias, but it was also used to treat some certain pathological behaviors like addiction (Mackintosh 1983).

#### 2.2.1.2 Operant Conditioning

Edward L. Thorndike and B. F. Skinner are two American psychologists who researched operant conditioning, another form of associative learning which is also called instrumental conditioning. Operant conditioning is a process which includes certain behaviors that a subject needs to perform in order to receive a reward or a punishment. The subject not only answers to the stimuli but also by its behavior causes changes to the environment (Mackintosh 1983).

In the 1890s, Edward L. Thorndike studied operant conditioning on different species of animals like dogs, cats, and chickens (Thorndike 1898). In particular, he placed the animal in a box called the operant box. In case the animal acted according to the right way, the box would open, and the animal would be able to get out and find food that was left outside the box. In the beginning, it was a difficult and long-lasting procedure for the animal to open the box and earn the reward. However, after placing the same animal in the box repeatedly, it started to learn and act correctly in a shorter period of time. After these observations, Thorndike formulated the first formal theory of learning, called law of effect. According to this principle, any behavior connected with pleasant results is likely to be repeated, and any response that produces an unpleasant effect is less likely to occur again (Thorndike 1927).

Later, during the 1930s, B. F. Skinner investigated and stated some significant principles of operant conditioning. He used rats and pigeons to create a way of learning based on reward and punishment. He experimented by training animals inside the known Skinner boxes. Inside the box, the animals were able to get food by using a small lever or by pecking at a food well. He observed the responses of the animal with a device designed to record the impact of food delivery on a subject's response. As a result, a positive reinforcement or a reward increases a behavior by adding a pleasant stimulus, while on the other hand, negative reinforcement or punishment decreases the probability of a certain behavior to happen again. There are a lot of rules that control the frequency and the timing of the reinforcers, like continuous or fixed-ratio schedule, called reinforcement schedules (Skinner 1990).

According to Skinner, punishments reduce the chance of the occurrence of a response and are divided to positive and negative punishments. A positive punishment is the decline of a behavior applying an unpleasant stimulus in case the behavior occurs, while negative punishment means the decline of a behavior by taking away a pleasant stimulus the time the behavior occurs. Shaping is a method of

learning animal and human behaviors that they have never met before, by reinforcing the behavior. Extinction is a process of eliminating a trained response by diminishing the reinforcer. For example, if the reward of food is not delivered by pressing a lever in rats, then the behavior will be eliminated. It is noticeable that if individuals are taught to perform a behavior in one occasion, then they are able to behave in the same way and in other similar occasions. For example, the greeting "congratulations" is used to others' happy events. Discrimination refers to the ability to learn when a response is possible to be followed by a reward or not in different circumstances. In the previous example, humans learn not to say "congratulations" to someone in a bad situation since it may lead to negative results (Skinner 1953).

#### 2.2.1.3 Observational Learning

In the early 1960s, Albert Bandura, a Canadian-American psychologist, introduced his social learning theory. It is an unquestionable fact that living organisms can also learn through observation. Bandura conducted several studies to investigate how observational/imitation learning impacts children's behavior (Bandura 1969). According to his theory, observational learning is composed of attention, retention, reproduction, and motivation. At the beginning an individual pays attention to the behavior of others; then the learner retains the information he observed. Afterward, he should mimic to perform the same behavior (reproduction), and finally he should have the motivation to mimic the behavior (Bandura and Walters 1977).

To sum up, learning by observation means that the subject should observe and then imitate the behavior of others. People are able to contact other people by using different languages. These languages have not only been officially taught to them, but they have also been learned through observation. In addition, they develop their personality and their social habits and abilities through experience they gain by observing other people. The mirror neurons that can be found in the ventral premotor cortex and inferior parietal lobe are considered to contribute to imitation. It has been suggested that mirror neurons explain many sides of social cognition, like the ability to realize the actions of others, to "read their mind," and to communicate by gestures and speech (Ramachandran 2000).

Although the precise substrate mechanism of action is still unspecified, observational learning plays an important role in social behaviors and communication through media and educational process.

### 2.2.2 Nonassociative Learning

The other simpler type of learning is the nonassociative learning, and it consists of several types like habituation and sensitization.

#### 2.2.2.1 Habituation

Habituation is a process that decreases the behavioral response to a repeated and innocent stimulus. Several examples of habituation exist in everyday life. When someone hears a very loud sound for the first time, he may be annoyed and even

frightened. But if the sound continues for a certain period of time, his annoyance and shock get reduced which is a typical case of habituation (Pinsker et al. 1970).

The Austrian-American neuropsychiatrist Eric Richard Kandel investigated the neural mechanisms of habituation examining the sea hare *Aplysia californica* because of its simplicity and its relatively large size of the underlying neural circuitry. *Aplysia californica* is a large shell-less sea snail or sea slug. The experiment was to apply a gentle touch to the siphon of *Aplysia* leading to a gill-withdrawal reflex. *Aplysia* hides inside the mantle shelf. Nevertheless, if the siphon is disturbed repeatedly, then the withdrawal reflex shows a gradual decrease. At the end, no response is observed. This steadily diminishment of the reflex after applying repeatedly a mechanical stimulus is called habituation. Kandel and his colleagues proved that habituation in *Aplysia* gill-withdrawal reflex (GWR) was due to a reduction on the synaptic transmission between sensory neurons of the siphon and motor neurons of the gill. The magnitude of the excitatory postsynaptic potential in motor neurons was reduced progressively after stimulating repeatedly the siphon (Kandel et al. 1976).

Habituation exists in short- and long-term form. In *Aplysia*, habituation can last for several weeks and is called long-term habituation (LTH) (Carew et al. 1972). It has been found that by this form of habituation, the sensorimotor pathway is suppressed and the presynaptic terminals and branches of the sensory neurons of the siphon are being retracted (Castellucci et al. 1970). However, the exact signaling pathways which after activation trigger long-term cellular changes are still unclear. Some recent studies suggested that LTH of the GWR relies on protein synthesis and activation of protein phosphatases 1 and 2A and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) receptors. The role of RNA synthesis, calcineurin activity, and l-type $Ca^{2+}$ channel activation in LTH in *Aplysia* has also been tested (Esdin et al. 2010; Ezzeddine and Glanzman 2003).

To conclude, despite the fact that habituation is one of the simplest types of learning, its neurobiological basis remains obscure.

#### 2.2.2.2 Sensitization

Sensitization is the opposite of habituation. The term refers to a nonassociative learning type that increases the behavioral response to repeated and innocent stimuli. Sensitization contributes to the learning of noxious and threatening stimuli in animals. If the animal comes across a threatening and fearful event, then it is able to respond more robustly to other stimuli even if they are not harmful or frightening (Landsteiner and Jacobs 1935).

Except for habituation, other mechanisms of learning were also investigated using *Aplysia californica* (Castellucci and Kandel 1976; Pinsker et al. 1973). As observed in habituation, repeated disturbance of the siphon leads to no GWR in *Aplysia*. However, after a period of rest, the response showed quick recovery. The scientists applied an electric shock one time to the tail of the slug, and the gill-withdrawal reflex was restored. This process of the facilitation of a habituated response after the presentation of a strong tactile stimulus to another part of the animal is also called dishabituation (Pinsker et al. 1970).

Eric Kandel and his group studied the neural mechanisms underlying sensitization by experimenting upon *Aplysia californica*. According to their studies, the appliance of electric shock to the tail generates a strong gill withdrawal. The gill withdrawal exhibits a form of plasticity called sensitization (Kandel et al. 1976). Sensitization like habituation is a result of changes in synaptic transmission of only a few different types of neurons. These neurons are the sensory neurons that innervate the tail and the siphon, motor neurons that stimulate muscles in the gill and interneurons that receive information from various sensory neurons. The electric shock to the tail triggers the sensory neurons that innervate the tail. Afterward, these neurons stimulate modulatory interneurons that secrete serotonin on the presynaptic terminals of siphons' sensory neurons. The synaptic excitation of the motor neurons increases, and a receptor, called stimulatory G protein-coupled, is stimulated by the binding serotonin. This stimulatory receptor binds to a transmembrane protein which once activated is going to stimulate a G protein. Afterward, the enzyme adenylyl cyclase is activated and converts ATP into cyclic AMP (cAMP). Cyclic AMP (cAMP) plays the role of the second messenger and triggers cAMP-dependent protein kinase (PKA). Protein kinase phosphorylates K+ channels, and the action potentials increase as a consequence to the ceasing of K+ channels. Then, the influx of $Ca^{2+}$ raises, and as a result the glutamate release from the presynaptic siphon's neuron to gill's motor neuron is increased. This augmentation of glutamate release is the mechanism that turns *Aplysia*'s gill-withdrawal reflex back to normal and ends habituation. Apart from *Aplysia* sensitization occurs also in other animals, and a similar procedure takes place (Bristol et al. 2004; Squire and Kandel 2000).

### 2.2.3 Features of Learning

Since learning is a composite process, learning ability differs due to reasons like experience, age, and mental state. Learning can happen in all ages of a living organism, but the process is not the same. For example, aged people find it more difficult than children to learn a new language. Some people are able to speak fluently two languages because they are exposed to them naturally from their infant age. In addition, experience helps people to learn easily new things relevant to already known information. Adults are also more capable to understand abstract thinking related to adolescents.

Learning ability is influenced by developmental disorders. People with attention deficit hyperactivity disorder (ADHD) or with the diagnosis of autism find it difficult to learn and develop social skills. On the other hand, degenerative diseases like Alzheimer's disease can affect the ability of learning as well as memory.

Different levels of intelligence result to different academic achievements, or there are talented people with flair to music or mathematics. Learning differs among individuals because of differences in motivation and emotion. Additionally, motivation can enhance the ability of people, in particular students, to learn (Mazur 2015).

## 2.3 Memory

Memory is the process according to which information is initially encoded, then retained, stored, and finally retrieved and recalled in the brain. All the living organisms need memory to exist. In particular, memory gives people the ability to remember the past, to acquire experience, and finally to learn (Arnold 2013). A lot of scientists, thinkers, and philosophers have talked and written about memory. "Our memory is a more perfect world than the universe: it gives back life to those who no longer exist" are some words of the French writer Guy de Maupassant (1903).

Memory consists of three distinct systems: the sensory memory, the short-term memory, and the long-term memory. Each one of these categories includes subcategories (Squire 2004).

### 2.3.1 Sensory Memory

Sensory memory refers to the representation of the stimulation of human sense organs for a brief period of time. Iconic memory means a brief recording of visual information, while echoic memory stands for the representation of auditory stimulation. Sensory memory is also represented in other sensory modalities and shows modality specificity (Anderson 2000).

#### 2.3.1.1 Iconic Memory

The American cognitive psychologist George Sperling was the first to document the iconic memory, using the partial-report model. Specifically, his experiment was to present briefly a 3 × 3 or 3 × 4 array of letters to some observers. He saw that people were able to report all the letters in any indicated row (partial report) if this happened directly after the visual presentation. Moreover, if the individuals were asked to recall all the letters (whole report), they were found able to report only four to five. The probability of the presentation of each row was equal, which means that the observer had access to all the letters at the end of the display. The fact that partial-report shows an advantage compared to whole-report phenomenon led the scientists to conclude that there is a rapid-decaying iconic memory that holds at least 9–12 items (Sperling 1960). The exact duration of iconic memory has been calculated to be about 300–500 ms for young adults (Coltheart 1980; di Lollo 1977; Dick 1974; Mewhort et al. 1981; Neisser 1967).

#### 2.3.1.2 Echoic Memory

Guttman and Julesz (1963) designed a creative experiment in order to measure echoic memory. A computer was used to create repeating patterns of white noise. White noise sounds like "shhh," cannot be memorized or described, and consists of all frequencies mixed together at random. The computer was putting together a repeating segment of white noise with no gap between them. The subjects were instructed by the

investigators to wear headphones, listen carefully to the noise, and write down what they heard. The subjects did not know that a sound was being repeated. In case the repeating part of white noise endured longer than a few seconds, the subjects were not able to recognize the repetition. They could only hear a whooshing sound with no pattern. On the other hand, if the segment lasted shorter than 2 s, the subjects could realize that they heard a repeated sound even if they were not able to describe it.

Echoic memory is the system used to preserve the exact copy of sound for a few seconds by giving individuals the capacity to detect a repeating pattern of frequencies.

### 2.3.2 Short-Term Memory

Short-term memory refers to the system that holds essential information in mind temporarily, in an available and active state for further cognitive activities (James 1950).

Short-term memory has the feature to decay rapidly. In case no practice of the information is conducted, it is preserved for a limited time, no longer than 30 s. The retaining of information for longer periods requires periodical rehearsal. During this process, the information is kept for greater time through reentrance to the short-term store.

Another feature of short-term memory is its limited amount of capacity which when talking about humans is around seven items plus or minus two. These seven items are called "magical number seven." The term "word length effect" refers to the fact that fewer words are recalled when their pronunciation is longer. According to the "phonological similarity effect," fewer words can be recalled when they have similar pronunciation, while a greater number of phonologically dissimilar words can be recalled. On the other side, if the words are familiar or belong to the same category, they can be retrieved more easily (Miller 1956).

Chunking is a property that increases short-term memory capacity and especially the amount of recalled items. The ability of a person to remember information can be improved if every unit is placed in a meaningful word or phrase. For example, it is easier for someone to keep in mind a telephone number if the digits are chunked into groups rather than try to recall ten digits in a row (Gobet et al. 2001).

The cerebral cortex seems to be responsible for the most types of memory and short-term memory as well. Different parts of the body, like the eyes or ears, send sensory information to the cerebral cortex where they are stored for a few seconds. The non-attended information are thrown away, while the attended ones will be stored in the sensory areas of the cortex or will be moved to the hippocampus and will be kept into the long-term memory (Jonides et al. 2008).

### 2.3.3 Working Memory

Working memory was introduced by Baddeley and Hitch in 1974 (Baddeley and Hitch 1974) and is related to short-term memory although it refers to a distinct

procedure. This memory system is used to plan and carry out behavior and is based to the dorsolateral prefrontal cortex. Some individual uses working memory when trying to recall the partial results during the solution of a mathematic problem without paper or to prepare a cake without using the same ingredient twice. Thus, working memory is a mental workbench which not only keeps but also processes information. Opposite to the passive nature of short-term memory, working memory is an active procedure. Working memory is also linked by some scientists with intelligence (Baddeley 2003).

### 2.3.4 Long-Term Memory

Long-term memory is a brain system that deals with information from the past and stores it for a great period of time. Long-term memory appears capable to keep countless information, from something learned recently to long-lasting memories.

There are different aspects describing the engagement of information in long-term memory. According to one aspect, in the beginning information is stored in short-term memory, and afterward it is processed and transmitted to long-term memory. On the other side, there is the belief that information is processed separately and enters short-term and long-term memory at the same time (Goelet et al. 1986).

Long-term memory is divided in psychobiology into declarative and non-declarative memory.

#### 2.3.4.1 Declarative Memory

Declarative memory is linked with the hippocampus and related structures and gives individuals the ability of conscious recall and declaration of the information. Endel Tulving divided the declarative memory into episodic and semantic memory, in 1972 (Tulving 1972).

Episodic memory refers to the process involved in recalling specific experiences throughout a person's life. In this type of autobiographical memory, an event is related to a context during a specific time in a specific place, answering the questions "where" and "when." For example, episodic memory is used to remember a holiday in a beautiful island (where) with family 2 years ago (when). People are not only able to remember these events, but they talk about them, declaring them. As a result, episodic memory belongs to the category of declarative memory (Tulving 2002).

Semantic memory refers to general knowledge, like information about things that we know or about the world in general. The fact that someone knows that the Big Ben is in London and the Parthenon is in Athens represents an example of semantic memory. This memory system, unlike episodic memory, is not linked with the specific time and place that a memory was created. An individual does not have to keep in mind when and where he learned about Big Ben and Parthenon (Squire and Zola 1998).

#### 2.3.4.2 Non-declarative Memory

Non-declarative memory can be recalled unconsciously without effort, is not declared, and is expressed through performance. Non-declarative memory system includes procedural memory, priming, habits (conditioning), and nonassociative learning (Squire and Zola-Morgan 1988).

Procedural memory, which involves visuomotor learning, includes all the skills that some individuals hold, for instance, playing a guitar, driving a car, or writing. The difference between procedural and declarative memory systems relies on the difference between procedural and declarative learning. Procedural learning refers to how to learn something, whereas declarative learning refers to what someone learns. Procedural memory is expressed through behaviors and can be easily influenced by practice. For example, driving ameliorates over time, and a guitarist can improve his skills by practicing repeatedly.

Priming is a well-studied phenomenon of non-declarative memory that refers to perceptual detection of words and objects. During priming, exposure to one stimulus affects the response to another stimulus by the activation of certain representations or associations in memory, just before executing an action or task. Priming reveals the underlying mechanism of perceptual tasks that is formed without awareness and has been implicitly memorized. For example, if a subject sees the word "red," it will be easier to find the word "heart," since red and heart are closely connected in memory. Priming is assessed through perceptual and conceptual techniques like word-stem completion and word association, respectively. The first task is the ability of representation of words such as medication with the three letters med. The second task incorporates, for example, the free association of the word ship with the related words sea and port (Squire and Zola 1996).

Habits, which occur in conditioning, as well as nonassociative learning, have been already described in this chapter.

#### 2.3.4.3 Explicit and Implicit Memory

The American psychologist William McDougal divided long-term memory into explicit and implicit memory.

Explicit memory is the process that facilitates the recall of past experiences and corresponds to declarative memory. Explicit memory is needed for someone to remember his holiday in a mountain.

In contrast to explicit memory, implicit memory retrieves stored information without any conscious awareness and is supposed to correspond to non-declarative memory. The fact that people are imitating the behaviors of people they have met or unconsciously sing a song that they heard before is attributed to implicit memory. This category of memory also includes priming effect (McDougall 1924).

#### 2.3.4.4 Neural, Regional, Synaptic, and Molecular Mechanisms of Long-Term Memory

##### Neural

One of the basic aims of neuroscience is to find out how memories are encoded and stored in the brain. Richard Semon was the first to introduce the term

"engram"—a memory trace, which consists of neurons that represent memory physically (Semon 1921). Later, the American psychologist Karl Lashley conducted his famous search by training rats. Specifically, he made them traverse a maze to gain a food reward, and after the experiment or before, he surgically removed various lesions of different cortical regions. His investigations were published to his famous "search of the engram" 30 years later (Lashley 1950).

### Regional

Nowadays, a lot of brain regions are supposed to interact in order to encode, store, and retrieve distinct information for each separate memory process. Brenda Milner and her colleagues studied the role of the *hippocampus* in episodic memory through the observation of the case of their famous patient H.M. In 1953, an operation was performed to the 27-year-old young man H.M. with the aim of treating his intractable epileptic seizures. A bilateral mesial temporal lobectomy has been conducted including the hippocampus, amygdala, and surrounding cortices, leading to the decrease of the frequency and the severity of the seizures. However, a new amnesic syndrome occurred, and the patient was unable to remember anything that happened to him following his operation, whereas his perceptual and intellectual skills remained intact, as he carried out normally a wide range of tasks. He was able to achieve some retention of simple visual and tactual mazes, tasks that were not long enough for his short-term memory capacity though the rate of acquisition was extremely slow. After investigating the case of H.M. almost for 40 years, the scientists concluded that bilateral lesions of the hippocampus and parahippocampal gyrus cause a severe and enduring disorder in episodic memory, a memory system that relates events with specific places and specific time, and they shed light to the realization that the components of the limbic system are bottleneck structures through which information needs to pass in order to be kept long-term (Milner et al. 1968, 1998; Smith and Milner 1981). The left (dominant) hemisphere has been found to control verbal memory, while a specialization has been found for the right hemisphere for spatial processing, a phenomenon called hemispheric asymmetry of memory (De Renzi et al. 1977; Habib et al. 2003; Ojemann and Dodrill 1985).

Except for the hippocampus, other brain regions are also involved in the function of memory. In 1937, when Papez proposed his well-known emotional circuit, the Papez circuit (hippocampal formation (subiculum) → fornix → mammillary bodies → mammillothalamic tract → anterior thalamic nucleus → cingulum → entorhinal cortex → hippocampal formation) for controlling the emotional expression, he also showed that this circuit plays an important role in the transfer of information into long-term memory (Markowitsch 2005; Papez 1937). Modern brain imaging procedures provided information about the participation of brain regions like the cerebellum, striatum, amygdala, and other motor or sensory systems in non-declarative memory (Markowitsch 2005).

### Synaptic Molecular

The distinctive property of the nervous system which is called plasticity was first proposed by Santiago Ramon y Cajal (1852–1934) as the potential of the brain to adapt to the environment, in a congress in Rome in 1894 (DeFelipe 2006). Donald

Hebb introduced a theory to explain the associative learning in his book in 1949. The Hebbian learning refers to the simultaneous activation of neurons which increases the synaptic strength between those neurons in a way that activity in one results to an activity in the other (Hebb 2005). Later in 1966, the Norwegian Terje Lomo was working with the hippocampus of anesthetized rabbits, studying the consequences of triggering the perforant path to dentate granule cells when he observed that high-frequency tetanic stimuli could lead to an enduring increase in efficiency of transmission at the perforant path-granule cell synapses (Lømo 2003).

In 1968, Terje Lomo and Tim Bliss followed up the preliminary results from 1966 and did the experiments that resulted in the discovery and fully description of long-term potentiation (LTP)—a cellular model of memory and learning in 1973 (Bliss and Lømo 1973). LTP represents an artificial form of plasticity and is measured both as an increase in the efficiency of synaptic transmission at the perforant path synapses and as the increase in the postsynaptic cell population spike (Bliss and Lømo 1973). LTP occurs in both excitatory and inhibitory neural synapses, and aside from the hippocampus, it has been investigated in the cerebral cortex, the amygdala, the cerebellum, and the spinal cord. However, since the hippocampus controls declarative memory, and LTP was induced in the hippocampus, it was concluded that LTP is a cellular model of the memory function (Lynch 2004).

Nowadays, it is widely known that several structural changes lie behind synaptic plasticity and memory formation. In a few milliseconds, glutamate is released from presynaptic neurons and activates the AMPA receptors and depolarizes the postsynaptic neuron. As a result, $Mg^{2+}$ induces the removal of the NMDA receptor inhibition leading to the influx $Ca^{2+}$ through the ion channel of the NMDA receptor. Moreover, voltage-gated calcium channels are also activated by the aforementioned depolarization, leading to further increase of $Ca^{2+}$ supply. A few minutes since the beginning of the process, the influx of the calcium into the synapse leads to the activation of kinases able to modulate their substrates' activity. The substrates are responsible for local alterations at the synapse, like morphological change through cytoskeletal regulation. They also regulate transcription factors and lead to the induction of the transcription of RNA. Finally, in a few hours, the translation of the transcribed RNA into proteins will have taken place. Activated synapses capture these proteins contributing to the stabilization of synaptic changes (Lamprecht and LeDoux 2004).

### 2.3.5 Forgetting and Other Phenomena Related to Memory

#### 2.3.5.1 Forgetting

Forgetting is a term described by Hermann Ebbinghaus, defined as the loss or modification of information already stored in long-term memory. During his experiments, he created lists of three-syllable meaningless words, consisting of a vowel between two consonants, like KET or SIP. He practiced a lot, and he was able to remember the list incorruptly by heart. He was aware of the duration and the times

that he tried in order to learn the list. Afterward, he checked his remembering of the list intermittently. He observed that rapid forgetting took place initially and then a steady increase in forgetting followed. Forgetting is believed to occur because new information interferes as time passes. Although it could cause some trouble, it is considered to naturally clean and exclude outdated and useless data (Ebbinghaus 2013; Murdock 1985).

#### 2.3.5.2 Other Memory Phenomena

*Flashbulb memory* is a category of memory linked with significant emotional incidents in an individual's lifetime. For example, someone is able to remember where and when he/she heard the bad news of the death of one's beloved person, since a flashbulb memory has been formed (Winograd and Neisser 2006).

*Déjà vu* describes the feeling of the physical presence in a place that the person has never been before or the feeling of the experience of an event that the person has not experienced before. Déjà vu creates an implicit familiarity of an unrecognized stimuli, as it unconsciously evokes a former situation and as a result provokes a familiar sense (Brown 2003).

*Jamais vu* is the opposite of déjà vu, as individuals have the feeling that they have never experienced a situation before, even though they know that they did (Cleary 2008).

*Tip-of-the-tongue state* is a state when a well-known or familiar word cannot be immediately recalled (Brown 2012).

*The method of loci*, also known as *the memory palace* or *mind palace technique*, is an ancient mnemonic device adopted in Roman and Greek rhetorical essays. Through spatial memory, it helps a person to enhance serial remembering. The trained individuals imagine themselves to walk through in a well-known environment, and they place what they need to remember in specific locations. In order to retrieve specific memories, the person reimagines navigating the environment "searching" for the placed items in order. A lot of mnemonists use this method to recall faces, digits, and lists of words (Legge et al. 2012).

#### 2.3.5.3 Memory and Sleep

Sleep has been found to play a significant role in memory processes. The sleep-related mechanisms of neural plasticity contribute to the consolidation of memory and learning. Rapid eye movement and non-rapid eye movement sleep are important for learning and memory, and a sleep cycle controls memory consolidation through multiple ways, but the actual processes remain unknown (Born and Wilhelm 2012; Maquet et al. 2003).

The relationship between sleep and academic performance is of a great interest. It is widely known that sleep enhances learning and memory processes, while sleep deprivation worsens these functions influencing academic performance. Students with more regular sleep-wake patterns, such as fewer night awakenings, shorter sleep latency, and earlier rise times on weekends, have been found to gain higher grades compared to students that were sleepy during the day due to disturbed night sleep (Vatthauer 2009).

#### 2.3.5.4 Memory Distortion

In 1932, Frederick Bartlett revealed the existence of a phenomenon called memory distortion. Memory distortion means that a memory report is different from the real experience. Bartlett investigated the course of memory, and he came up with the idea that memory transforms over time including omissions, deletions, and distortions. In particular, during his experiments, he asked the subjects to read a folktale the "War of Ghosts." According to the plot, there is a battle between two enemy tribes. He used the method of serial reproduction known to people by the game "telephone," when children sit in a queue and each one tries to reproduce the same initial story, having been heard by each previous player. Likewise, he asked the subjects to remember the tale they heard from their immediate predecessor with the most possible details and try to narrate it to the next one. He revealed that memory of the original story undergoes huge distortion after only a small number of repetitions (Bartlett 1932).

Since then, a lot of work has been done by scientist trying to identify the brain regions that are responsible for true and false memories. The medial temporal lobe has been suspected for false recognition. The prefrontal cortex plays a role in memory monitoring errors. Other studies suggest that true and false memories activate the same brain regions (Schacter and Slotnick 2004).

## 2.4 Disorders of Learning and Memory

### 2.4.1 Age-Associated Memory Impairment

It is well known among scientists that aging leads to a decline in the function of memory among healthy individuals. Kral, in 1958, was the first to use the term "benign senescent forgetfulness" (BSF) to separate adults with mild memory impairment from those with severe changes or normal memory systems (Kral 1958). Later, the term age-associated memory impairment was constructed, and criteria were presented with the aim of facilitating the communication among scientists about the memory loss that may occur in healthy elderly individuals in the later decades of life (Crook et al. 1986). In the mid-1990s, the term mild cognitive impairment was introduced by Peterson and his colleagues (Petersen et al. 1999). It refers to a transitional stage between age-associated impairment and dementia presenting with subjective memory complaints, lower scores on memory tasks, absence of dementia, and good levels of quality in activities.

During aging a lot of changes take place in the brain. Recent MRI studies have shown that atrophy of the medial temporal lobe and the hippocampus is a usual phenomenon in elderly persons and might lead to memory decline (episodic) (Golomb et al. 1993). Frontal lobes present with the greatest reduction in brain volume during aging (Hänninen and Soininen 1997); they have been found to underlie in several memory systems such as the working memory, the retrieval process which needs conscious mental effort, the temporal organization of memory, and source memory.

## 2.4.2 Amnesias

### 2.4.2.1 Introduction

The term amnesia refers to a situation characterized by the impaired ability of a person to learn new details and recall information from the past. Common reasons for amnesia not only include brain injuries, neurological deficits, and vascular incidents like a stroke but neurodegenerative and psychological disorders as well (Snodgrass and Corwin 1988). Amnesia can happen with or without the existence of other cognitive deficits.

Memory consists of multiple different systems, but not all of them are impaired in amnesia. While amnesic humans are not able to acquire information about facts and events (explicit memory), they keep the ability for several types of learning like conditioning and habit learning and skill learning. Explicit—declarative—memory relies on the structures of the medial temporal lobe and diencephalon unlikely implicit memory that depends on brain structures that remain intact in amnesia (Kopelman 2002).

### 2.4.2.2 Anterograde and Retrograde Amnesias and Memory Consolidation

Anterograde amnesia is called the failure to learn new information. The patient finds it difficult to remember new persons, situations, and words following the onset of amnesia. Anterograde amnesia is more severe when more locations of the medial temporal lobe are defected. On the other hand, retrograde amnesia refers to the damaged ability of an individual to recall events that took place soon before amnesia occurred. Thus, memories estimated in the time period before amnesia are lost, while old memories, like childhood events, remain. Retrograde amnesia is met alone or in combination with anterograde amnesia (Winocur 1990).

During the process of memory consolidation, after the initial encoding of the information, cortical and neural processes and reformation take place, leading to the permanent storage of memory. Retrograde amnesia supports the idea of memory consolidation proving that what has been learned is not immediately made stable. Memory consolidation starts after information which has been encoded in the neocortex are linked with a memory trace in the hippocampus and related structures in the medial temporal lobes as well as the diencephalon, i.e., the posterior part of the forebrain that includes the thalamus, hypothalamus, and ventral thalamus. This initial procedure engages a short-term consolidation process, which ends within seconds or minutes. Afterward, long-term consolidation begins. Even though the hippocampus and related structures store and retrieve the information in the beginning, as consolidation proceeds, the neocortex alone becomes capable of keeping the permanent memory trace and mediating its retrieval (Nadel and Moscovitch 1997).

### 2.4.2.3 Amnesias of Dementias

Dementias are disorders that have taken their name from their profound symptoms characterized of deficits in mentation. The pathophysiological reasons for

dementias are considered to be cortical and subcortical. For example, Alzheimer's disease is a cortical disorder but includes decline of cholinergic neurons in subcortical regions, as well. On the other hand, vascular dementia is a subcortical disease presented also with atrophy of the frontal cortex. The predominating impairment in most dementias is amnesia which depends on the stage of the pathology as well as the participating brain locations (Economou et al. 2006).

### Alzheimer's Disease

Alzheimer's disease refers to a chronic neurodegenerative illness that usually starts gradually and deteriorates over time and leads to the majority of cases of dementia. The cause of Alzheimer's disease is believed to be 70% genetic with many genes involved. The disease process is associated with plaques and tangles in the brain. In particular, the neurodegeneration in Alzheimer's disease (AD) may be attributed to the deposition of amyloid β (Aβ) peptide in plaques in brain tissue (Hardy and Selkoe 2002). It most often affects people over 65 years of age, although 4–5% of cases are early-onset Alzheimer's disease (Hardy and Higgins 1992).

Episodic memory impairment is the first and main deficit in Alzheimer's disease, while deficits in semantic memory follow (Perry et al. 2000). In fact, patients in the early stages of the disorder indicate a decline in retaining new information. They are not able to remember the names of other persons, appointments, conversations, and where they have left their bag or keys. This episodic memory decline does not regard only verbal context, but the known information about visuospatial context is restricted (Barbeau et al. 2004).

Patients with Alzheimer's disease also suffer from semantic memory impairment which is proven from their impairment on various tasks like basic word retrieval, naming objects, and recalling examples of a semantic category (Nebes 1989). They also find it difficult to define concepts and separate them from one another (Alathari et al. 2004). Alzheimer's disease is not related with perceptual implicit memory decline though there are some scientists that support the opposite. Habit learning is preserved in Alzheimer's disease, while fear conditioning is often impaired.

Medications for Alzheimer's disease improve cognitive deficits and the affective and behavioral presentations. Donepezil, rivastigmine, and galantamine have been proved to ameliorate cognition in patients with Alzheimer's disease. The mechanism of action of acetylcholinesterase inhibitors relies on the inhibition of acetylcholinesterase, leading to an increase in the available acetylcholine, stimulating postsynaptic cholinergic receptors, and reducing the deficit in cholinergic transmission attributed to the degeneration of basal forebrain nuclei (Birks 2006).

### Vascular Dementias

There are several types of vascular dementias with different clinical symptoms depending on the etiology of damage and the region of the brain that is affected. Vascular dementias include stroke-related dementias (single-infract and multi-infract dementia), subcortical dementia, and mixed dementia (along with Alzheimer's disease). Single-infract dementia, caused by a single infract, is capable

of leading to amnesia, affecting cortical or subcortical areas responsible for memory functions (Szirmai et al. 2002). The most prevalent subcategory of vascular dementias is the subcortical ischemic dementia, characterized by impairment in the procedural memory system due to deficits in subcortical nuclei such as the caudate, putamen, and substantia nigra (Cummings 1994).

The treatment of vascular dementias depends on the understanding and management of the cause. Manipulating risk factors such like hypertension, diabetes, and smoking could help to prevent the illness. The techniques of carotid endarterectomy and atrial fibrillation using anticoagulant therapy are secondary preventive methods. Cholinesterase inhibitors have been found to improve the cognitive symptoms of the disease (Román 2003).

#### Frontotemporal Dementia

Frontotemporal dementia describes subjects with dementia associated with focal atrophy of the orbitomedial frontal and anterior temporal lobes. As a result, it is divided into temporal and frontal variant. The temporal variant leads to semantic amnesia, whereas the frontal variant is connected with behavioral disorders as well as deficits in working memory and retrieval of information (Englund et al. 1994).

The frontal variant of frontotemporal dementia is also called behavioral variant. Patients with behavioral variant frontotemporal dementia are characterized by insidious changes in personality, interpersonal behavior, and emotional variety. These changes show progressive collapse of the neural circuits that take part in social cognition, emotion regulation, motivation, and decision-making. In addition, apathy characterized by reduced interest in previous activities and social isolation coexists with disinhibition that leads to impulsive actions along with socially embarrassing behavior (Piguet et al. 2011; Rascovsky et al. 2007).

The temporal variant of frontotemporal dementia is also represented by the term semantic amnesia. It was introduced in 1975 by Warrington and refers to the loss or the inaccessibility of events and ideas that have been pieces of an individual's personal knowledge. Recent memories are spared, and episodic memories along with the possession of new information are not noticeably affected (Warrington 1975). Taking into account that the most semantic memory are verbally coded, semantic amnesia occurs as difficulties in finding specific words, naming objects, recalling and linking facts, and understanding the meaning of already known words and concepts. The syndrome of semantic amnesia is caused by bilateral temporal lobe lesions located posteriorly, inferiorly, and laterally but not medially from the poles. As a result, the hippocampus and neighbor limbic structures stay intact (Squire and Zola 1998).

#### Lewy Body-Related Dementias

This category includes two dementia syndromes: the synonymous dementia in which Lewy bodies are cortical in location and Parkinson's disease, in which the pathology is primarily in the basal ganglia. The clinical presentation of both syndromes deteriorates over time, and the patients tend to present with identical cognitive impairments.

#### Parkinson's Disease

In patients with dementia due to Parkinson's disease, attentional problems are more severe than memory deficits. The cognitive decline must follow established Parkinson's disease, and there must be a gradual development. Working memory and visual-perceptual process are impaired. Decline in procedural learning also occurs, making these patients unable to perform mainly motor learning tasks. As a result, patients with Parkinson's disease become dependent on their caregivers, since not only their motor dysfunction but also working memory deficits prevent them from performing daily living activities.

#### Dementia with Lewy Bodies

Patients with dementia with Lewy bodies present with fluctuating cognition and pronounced variations in attention and alertness. In particular, this disorder includes early changes in complex attention and executive function.

Treatment of Lewy body-related dementias involves dopamine replacement by L-dopa and dopaminergic agonists in order to improve cognitive function rising psychomotor speed. Acetylcholinesterase inhibitors are also effective because they reduce visual hallucinations, apathy, anxiety, and sleep disturbances caused by cholinergic deficits of these patients (Papanicolaou 2005).

#### Huntington's Disease

Huntington's disease is an illness that presents with unequivocal, extrapyramidal motor abnormalities (choreoathetosis) along with progressive cognitive impairment. It is diagnosed either in family members with a history of the disease or in individuals that show an expansion in the HTT gene on chromosome 4 and atrophy in the caudate nucleus. Impairment in psychomotor skills, speed of processing information, and initial memory functions like procedural memory are the main deficits in the early stages of Huntington's disease, due to its frontostriatal etiology, characterized by a progressive nature. Deficits in visuospatial and semantic memory show no progressive decline.

Pharmacological treatments help to manage the symptoms as well as the social, physical, and occupational deficits of this progressive disease. First-generation antipsychotics are used to improve choreoathetosis and psychiatric symptomatology, but due to their implications, they have been replaced by the newer second-generation antipsychotic agents (Butters et al. 1985).

### 2.4.2.4 Traumatic Amnesia

A traumatic brain injury refers to any insult to the brain caused by a physical external force leading to alteration in consciousness and affecting cognitive function.

The cognitive impairments in people who survive after a serious traumatic brain injury are divided into four stages according to the time of occurrence related to the injury. The first two phases last some days and a post-traumatic delirium is included. The first stage is the period of an altered state of consciousness or coma. The second stage consists of different abnormalities in cognition and behavior, psychomotor activity as well as an inability to recall events and/or acquire new information, which is also called post-traumatic amnesia. Cognitive functions rehabilitate

rapidly after 6–12 months (third stage). The fourth phase may include permanent damages in processes like attention and vigilance, memory and new learning, verbal skills, self-regulation of mood, executive functions, emotional reactions, and awareness of one's limitations (Kosmidis et al. 2006).

#### 2.4.2.5 Transient Global Amnesia

Transient global amnesia was initially introduced by Fisher and Adam in the 1950s, and it describes an unknown pathophysiology well-recognized clinical syndrome. Patients present with a sudden onset of both anterograde and retrograde amnesia, without any other cognitive and neurological abnormalities. Transient global amnesia has a total duration of a few hours until 1 day and is observed mainly in middle-age to elderly persons (Fisher and Adams 1964).

Patients who develop transient global amnesia have memory deficits, but they retain their full consciousness and awareness. As a result their ability to carry on normal activities remains intact. Disorientation to time and place is the basic clinical feature of this entity. Memory for events during the acute phase is permanently damaged. The inner world of the patients remains to a specific point of time in the past, while the outer world occurs in the present time. The pathogenesis of transient global amnesia remains unclear. Some scientists support that focal ischemic lesions, migraine headaches, and brain tumors can be some causes. The medial temporal lobe is suspected (Szabo 2014). Other studies have suspected ischemic dysfunction in the medial temporal lobe, especially the hippocampus, to underlay in transient global amnesia (Webb and Rothwell 2013).

No semantic or procedural memory impairments occur during the episode of transient global amnesia (Papanicolaou 2005).

#### 2.4.2.6 Amnesic Syndrome

The amnesic syndrome is defined as permanent and total disorder of memory attributed to organic brain dysfunction. The amnesic syndrome presents alone, without any other perceptual or cognitive disturbance. It is a mental disorder that affects short- and long-term memory with anterograde and sometimes retrograde amnesia. This decline occurs in a normal state of consciousness. The amnesic syndrome is associated with different causes that lead to damage to certain structures in the median temporal lobe and the diencephalon. It may result from close-head injury, penetrating head injury, subarachnoid hemorrhage, cerebral infraction, hypoglycemia, hypoxia, tumor, and thiamine deficiency as the result of heavy alcoholism (Wernicke's disease-Korsakoff's syndrome), carbon monoxide poisoning, and herpes simplex encephalitis (Parkin and Leng 1993).

The clinical manifestations of the amnesic syndrome involve disorientation, confabulation, and a lack of insight into the memory deficit. The term confabulation was introduced by Whitlock in 1981 and refers to "false statements that are not made to deceive, are typically more coherent than thoughts produced during delirium, and do not reflect underlying psychopathology" (Johnson et al. 1997). These manifestations are related to frontal lobe dysfunction produced by damage to neural links in a thalamo-frontal network (Johnson et al. 1997).

#### 2.4.2.7 Psychogenic Amnesia

Psychogenic amnesias or functional amnesias are retrograde and present with reversible amnesia of autobiographical events. This type of memory loss is supposed to have psychological reasons since no obvious structural abnormalities are involved. Nevertheless, there are functional deficits in frontotemporal region that reverse after amnesia resolves (Savvidou et al. 2006).

Dissociative amnesia is subsequent to a traumatic experience, and according to DSM-5, it is defined as the inability of the individual to recall important autobiographical information of a traumatic or stressful nature, inconsistent with ordinary forgetting. The specifier for dissociative fugue refers to an apparently purposeful travel or bewildered wandering that is associated with amnesia for identity or for other important autobiographical information (APA 2013).

## 2.5 Conclusion

Learning and memory are closely connected brain processes. The application of the underlying biological mechanisms to the observation of the behavior is the aim of the field of psychobiology. Describing this aspect of memory and learning functions can be a useful tool for every scientist, leading to a deeper and more complete understanding of daily tasks and events. Memory is considered to be a big, rich, and awesome phenomenon, and it must be studied as such (Cahill et al. 2001).

A lot of light has been shed into understanding how the brain learns, forms, preserves, or loses memory. Conclusions should be derived from carefully investigating behaviors, taking under consideration the previous findings in the history of science. Actually, forgetting past lessons and experiences can be nothing more than a memory disorder.

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# Basic Vital Functions and Instincts

3

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## 3.1 Basic Vital Functions

Basic vital functions are supposed to be what is common in all living organisms and what distinguishes them from nonliving things. However, there is no unequivocal definition of the phenomenon of life, which represents a challenge for biologists and philosophers (Cleland and Chyba 2002). Therefore, a variable number of basic vital functions have been proposed in the literature, including nutrition, metabolism, respiration, excretion, homeostasis, growth and development, organization and compartmentalization, adaptability, sensitivity to environmental stimuli, locomotion, reproduction, and evolution (Koshland 2002; Chodasewicz 2014). We focus on three core vital functions recognized by many authors as the defining features of life: *nutrition (feeding)*, *interaction with the environment (social interaction)*, and *reproduction*. Here follows an overview from a psychobiological perspective of the first two core vital functions, with a specific emphasis on humans, while the third is discussed in Chap. 6.

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### 3.1.1 Nutrition (Feeding)

Feeding provides the energy that is essential for survival and therefore is subject to intense regulation by the human brain. Adequate nutrition is ensured by a complex brain system regulating the levels of various nutrients in the blood and in the body stores. The hypothalamus is the center of the network of control on food intake and metabolism in response to peripheral signals that reflect the feeding state and energy reserve, i.e., homeostatic control.

Hunger is associated with discomfort providing a strong drive for feeding and satiety and is accompanied with satisfaction preventing further consumption of food. However, the rewarding nature of food goes beyond the feelings of hunger and satiety. Modern humans often eat without being hungry, and nowadays obesity is a serious public health problem. Hedonic eating, i.e., eating based on pleasure rather than energy needs, is controlled by complex neural mechanisms associated with reward. The insular cortex, orbitofrontal cortex, nucleus accumbens (NAc), amygdala, and ventral tegmental area (VTA) have a key role in the control of feeding behavior in response to the hedonic aspects of food.

Over the last two decades, our knowledge of neural circuits and molecules involved in *homeostatic* and *hedonic control* of food intake has improved substantially, in large part due to the findings of research in experimental animals and functional neuroimaging in humans. These findings also provide insight into the mechanisms underlying obesity and abnormal feeding behavior in neuropsychiatric disorders. Only the main aspects of the current knowledge on mechanisms controlling feeding behavior can be emphasized here.

#### 3.1.1.1 Homeostatic Control of Food Intake

The hypothalamic network that regulates food intake and energy balance consists of interconnected neurons located in the arcuate (infundibular in humans) nucleus (ARC), ventromedial nucleus (VMH), paraventricular nucleus (PVN), dorsomedial nucleus (DMH), and lateral hypothalamic area (LHA). Peripheral signals that stimulate (orexigenic) or inhibit (anorexigenic) food intake are received by neurons in the medial zones of the hypothalamus, including signals from circulating nutrients (glucose, fatty acids), hormones (insulin, leptin, ghrelin), and gastrointestinal peptides (cholecystokinin and peptide $YY_{3–36}$) (Adan et al. 2008; Chaudhri et al. 2006; Benarroch 2010). The dorsomedial and lateral hypothalamic neurons receive circadian influences and interact with neural circuits for thermoregulation and arousal (Saper et al. 2002; Benarroch 2010). The integration between orexigenic and anorexigenic signals is accomplished via complex interactions between the hypothalamic nuclei mediated by a variety of neurotransmitters (Meister 2007). The hypothalamic network exerts control on food intake and peripheral metabolism acting via projections to sympathetic and parasympathetic nuclei (nucleus of the solitary tract, area postrema, dorsal motor nucleus of the vagus, and locus coeruleus) on the endocrine glands and the gastrointestinal system (Williams et al. 2001; Gao and Horvath 2007). Cognitive and emotional aspects of food intake relay on reciprocal connections of the hypothalamus with cortical and mesolimbic circuits and the hippocampus (Gao and Horvath 2007; Kampe et al. 2009).

In the following we present the main peripheral and central signals and hypothalamic pathways related to feeding behavior, which are also briefly displayed in Table 3.1.

**Table 3.1** Main signals and mechanisms for homeostatic control of food intake

| Signal | Source | Target (receptors) | Effect | Mechanisms of action |
|---|---|---|---|---|
| *Peripheral (hormones)* | | | | |
| Insulin | Pancreas | Hypothalamus (insulin receptors, IR) | ↓ Food intake | Activation of POMC neurons in ARC<br>Activation of BDNF neurons in VMH<br>Inhibition of LHA neurons |
| Cholecystokinin<br>Peptide $YY_{3–36}$ | Gut | Hypothalamus via vagus nerve (CCK-1, Y2) | ↓ Food intake | Stimulation of vagus nerve—signals via NTS and PBN projections to POMC neurons in ARC |
| Leptin | Adipose tissue | Hypothalamus (leptin receptors, OB-R) | ↓ Food intake<br>↑ Metabolism | Activation of POMC neurons in ARC<br>Activation of BDNF neurons in VMH<br>Inhibition of LHA neurons |
| Ghrelin | Stomach | Hypothalamus (GHR1) | ↑ Food intake | Activation of neuropeptide Y, Agouti-related peptide, and GABA neurons in ARC |
| *Central* | | | | |
| α- and β-MSH | ARC | Hypothalamus (MC4R) | ↓ Food intake | Agonists of MC4R in PVN and VMH |
| Agouti-related peptide | ARC | Hypothalamus (MC4R) | ↑ Food intake<br>↓ Metabolism | Inverse agonist of MC4R in PVN |
| Neuropeptide Y | ARC | Hypothalamus (Y1, Y2, Y5) | ↑ Food intake<br>↓ Metabolism | Direct activation of PVN<br>Inhibition of POMC neurons in ARC |
| BDNF | VMH | Hypothalamus (Tropomyosin receptor kinase B, TrkB) | ↓ Food intake | Agonist of TrkB and MC4R in PVN and VMH |
| Melanin-concentrating hormone | LHA | Hypothalamus, VTA (MCH1 and MCH2) | ↑ Food intake<br>↓ Metabolism | Agonist of MCH receptors in hypothalamus and VTA |
| Orexin/hypocretin | LHA | Hypothalamus (OX1 and OX2) | ↑ Food intake | Agonist of OX1 and OX2 in PVN (short-term regulation of energy balance) |
| Endocannabinoids | LHA | Hypothalamus (cannabinoid-1 receptors, CB1) | ↑ Food intake<br>↓ Metabolism | Inhibition of anorexigenic signals via CB1 |

*ARC* arcuate (infundibular in humans) nucleus, *BDNF* brain-derived neurotrophic factor, *GABA* γ-aminobutyric acid, *LHA* lateral hypothalamic area, MC4R melanocortin 4 receptor, *MSH* melanocyte-stimulating hormone, *NTS* nucleus of the solitary tract, *PBN* parabrachial nucleus, *POMC* pro-opiomelanocortin, *PVN* paraventricular nucleus, *VMH* ventromedial nucleus, *VTA* ventral tegmental area

### Central Regulation of Feeding and Energy Balance

The ARC is a key regulator of food intake and energy balance containing a group of neurons that synthesize two neuropeptides, *α-* and *β-melanocyte-stimulating hormone (MSH)*, derived from *pro-opiomelanocortin (POMC)*, and another group of neurons synthesizing *neuropeptide Y (NPY)*, *Agouti-related protein (AgRP)*, and *γ-aminobutyric acid (GABA)*. α- and β-MSH decrease food intake and increase energy expenditure acting on melanocortin 4 receptors (MC4R) in the PVN and VMH (Hillebrand et al. 2006). By contrast, NPY via Y1, Y2, and Y5 receptors and AgRP acting as an inverse agonist of MC4R in the PVN increase food intake and reduce energy expenditure (Meister 2007). Moreover, the same group of neurons can inhibit POMC neurons in the ARC via GABA and NPY projections (Benarroch 2010). Thus, the ARC mediates both orexigenic and anorexigenic signals from periphery and regulates feeding and energy metabolism integrating these mutually opposing influences.

Neurons in the VMH that synthesize *brain-derived neurotrophic factor (BDNF)* receive signals from POMC neurons of the ARC, and they also respond to glucose and leptin reducing food intake and increasing energy metabolism (King 2006). Groups of neurons in the PVN receiving signals from the ARC synthesize hormones with anorexigenic effects—corticotropin-releasing hormone (CRH), thyrotropin-releasing hormone (TRH), and oxytocin (Benarroch 2010).

The LHA has also a key role in the regulation of feeding and metabolism, integrating signals from the periphery (i.e., glucose, leptin, ghrelin) and interacting with other hypothalamic areas and the mesolimbic system (Williams et al. 2001; Dietrich and Horvath 2009; Berridge 2009). A group of neurons in the LHA synthesizing *orexin* (or *hypocretin*) plays a significant role in the short-term regulation of energy balance. Orexin neurons are inhibited by glucose and stimulated during fasting, and they promote food intake acting on specific receptors (OX1 and OX2) in the PVN (Tsujino and Sakurai 2009). Moreover, they are involved in food reward as we will present below. Another group of LHA neurons synthesizes *melanin-concentrating hormone (MCH)*, and they act on specific receptors (MCH1 and MCH2) increasing food intake and decreasing energy metabolism (Guyon et al. 2009). The function of LHA on food intake is related to sleep-wake cycle: the MCH neurons are active during slow-wave sleep, while the orexin neurons are activated in wakefulness (Benarroch 2010).

### Peripheral Factors Regulating Food Intake and Metabolism

*Gut peptides (cholecystokinin, peptide* $YY_{3–36}$*)* are released after a meal and suppress food intake and meal size activating via vagal afferents the nucleus of the solitary tract, which signals fullness to the hypothalamus and other brain regions, initiating satiety and resulting in meal termination (Chaudhri et al. 2006; Dietrich and Horvath 2009). Another gut peptide under investigation with similar effects on food intake and a significant role in the control of glucose and energy homeostasis is *glucagon-like peptide-1* (Williams and Elmquist 2012). On the other hand, *ghrelin* is the hormone that is released from the stomach during fasting and provokes hunger and meal initiation. Ghrelin, acting on the growth hormone secretagogue receptor

(GHSR) in the ARC, stimulates NPY, AgRP, and GABA neurons (Kageyama et al. 2010). *Leptin* is a hormone synthesized in the adipose tissue that circulates at levels proportional to the amount of fat. Leptin, acting on specific receptors in the ARC, stimulates POMC neurons and inhibits the release of NPY and AgRP, thus contributing in long-term weight and glucose homeostasis (Farooqi and O'Rahilly 2008; Williams and Elmquist 2012). It also produces anorexigenic effect stimulating BDNF neurons in VMH while inhibiting LHA neurons (Farooqi and O'Rahilly 2008; Benarroch 2010). *Insulin*, the hormone released by beta cells in the pancreas and regulating glucose homeostasis, has also anorexigenic effects possibly through similar mechanisms of action as those of leptin (Konner et al. 2009; Williams and Elmquist 2012).

#### 3.1.1.2 Hedonic Control of Feeding Behavior

Many aspects of human behavior, like seeking for pleasant food, cooking, or obesity, indicate that feeding is not controlled solely by homeostatic mechanisms but is also influenced by the rewarding nature of food.

##### Gustatory Regulation of Feeding

Food reward is associated with palatability qualities, particularly taste and smell. Animals consume sweet and salty food beyond their homeostatic needs and avoid sour or bitter food even if they are hungry. In the human brain, taste information passes via the nucleus of the solitary tract and parabrachial nucleus to the thalamus, the lateral frontal cerebral cortex, the central nucleus of amygdala, and several hypothalamic areas, including LHA. Although gustatory thalamus is critical for hedonic aspects of taste, other subcortical areas also mediate the motivational qualities of palatable food cues (Saper et al. 2002).

##### Reward System for Feeding

The pleasure of palatable food is associated with activation of many areas of the brain reward system, including the VTA dopaminergic system, NAc, ventral pallidum, and amygdala (Berridge 2009; Kampe et al. 2009). Dopamine release in the NAc mediates the motivational aspects of food intake, especially the drive to eat food that is hedonically desirable ("wanting") (Lutter and Nestler 2009). As yet, the mechanisms by which food stimulates dopamine release are not well understood. It has been found that food can stimulate dopamine signalling independent of the processing of taste information (de Araujo et al. 2008).

Release of *orexin* during feeding directly stimulates dopamine neurons in the VTA increasing dopamine release in the NAc (Harris and Aston-Jones 2006). Other hypothalamic neuropeptides may also play a role in hedonic regulation of feeding influencing dopamine release. The *cocaine- and amphetamine-regulated transcript (CART)* which is found in several hypothalamic areas decreases food intake possibly inhibiting dopaminergic neurons in VTA. However, the anorexigenic effect of CART is associated with its multiple actions in hedonic and homeostatic regulating systems, which are not clear yet (Rogge et al. 2008). By contrast, *galanin* stimulates food intake, in particular the intake of fat, possibly acting on specific receptors in

the PVN. However, it still remains unknown which of the multiple central and peripheral effects of galanin might be related with this effect (Fang et al. 2011).

The hedonic reaction per se to the pleasure of food reward ("liking") is regulated by *endogenous opioids* and *endocannabinoids* acting via μ-type opioid receptors and CB1 receptors, respectively, within the shell of the NAc and possibly within the ventral pallidum (Berridge 2009). Although "liking" and "wanting" are needed together for complete food reward, they are mediated by interacting but partially independent neural substrates.

#### 3.1.1.3 Interactions of Homeostatic and Hedonic Regulatory Mechanisms

The stability of body weight over adult life in spite of the availability of highly palatable and energy dense food, as well as the discrepancies from normal eating, e.g., overweight, obesity, and eating disorders, indicates an interface between the metabolic and hedonic drives of eating. Therefore, the possible neural circuits and mechanisms that underlie interactions between homeostatic and hedonic regulation of feeding have been a focus of research during the last two decades.

The NAc plays a key role in the integration of homeostatic, hedonic, and cognitive aspects of food intake via its connections with the prefrontal cortex, amygdala, and lateral hypothalamus (Berridge 2009; Kelley et al. 2005). There are also multiple functional connections between hypothalamic, cortical, and mesolimbic circuits mediated by POMC, orexin, and MCH that may play a role in homeostatic–hedonic control interactions (Kampe et al. 2009). Hormones involved in homeostatic regulation of feeding, such as leptin, insulin, and ghrelin, also exert effects on motivation to obtain food through their influence on mesolimbic dopamine signalling, especially on the dopaminergic neurons in the VTA (Murray et al. 2014). Leptin decreases the firing rate of the VTA dopaminergic neurons. Insulin increases dopamine release and the firing rate of dopaminergic neurons but reduces dopamine levels in the VTA probably by upregulation of the dopamine active transporter (DAT). Ghrelin enhances signalling from the VTA to the NAc increasing the activation of dopamine $D_1$ and $D_2$ receptors and dopamine levels.

Like ghrelin, other factors involved in meal-to-meal regulation of feeding may also affect food reward in a way that even highly palatable food may be unpleasant after satiation. There is evidence that the rewarding effects of food are potently modulated by indicators of satiety, such as peptide $YY_{3–36}$ that was found to elicit a switch of activation from the hypothalamus to the orbitofrontal cortex and diminished orbitofrontal activation in response to the rewarding aspects of food (Batterham et al. 2007). The main pathways related to hedonic control of feeding behavior are briefly displayed in Table 3.2.

#### 3.1.1.4 Cognitive and Emotional Control of Feeding Behavior

Homeostatic and hedonic mechanisms controlling feeding behavior described above only partially operate outside awareness. However, there is also a "top-down" control of human feeding behavior: interactions between cognitive and emotional processes could lead to different responses to food cues and changes in food intake

**Table 3.2** Main signals and mechanisms for hedonic control of eating behavior

| Signal | Source | Target (receptors) | Effect | Mechanisms of action |
|---|---|---|---|---|
| *Peripheral (hormones)* | | | | |
| Leptin | Adipose tissue | VTA (leptin receptors, OB-R) | ↓ Food intake<br>↑ Metabolism | Inhibition of dopaminergic neurons in VTA |
| Insulin | Pancreas | VTA (insulin receptors, IR) | ↓ Food intake | Reduction of dopamine levels in VTA probably by upregulation of DAT |
| *Central* | | | | |
| Ghrelin | ARC | VTA (GHR1) | ↑ Food intake | Activation of dopaminergic neurons in VTA<br>Increase of the activation of dopamine D1 and D2 receptors and dopamine levels in NAc |
| Orexin/hypocretin | LHA | VTA (OX1 and OX2) | ↑ Food intake | Activation of dopaminergic neurons in VTA |
| Endocannabinoids | Local | Nucleus accumbens (cannabinoid-1 receptors, CB1) | ↑ Food intake<br>↓ Metabolism | Enhancement of dopamine effect on nucleus accumbens |
| Endogenous opioids | Local | Nucleus accumbens (μ-opioid receptors) | ↑ Food intake | Increase of dopamine release in nucleus accumbens |
| CART | ARC, LHA | Hypothalamus, Mesolimbic system | ↓ Food intake | Unknown |
| Galanin | ARC | Hypothalamus, especially PVN (GALR) | ↑ Food intake | Unknown |

*ARC* arcuate (infundibular in humans) nucleus, *CART* cocaine- and amphetamine-regulated transcript, *DAT* dopamine active transporter, *LHA* lateral hypothalamic area, *NAc* nucleus accumbens, *PVN* paraventricular nucleus, *VTA* ventral tegmental area

(Berthoud 2011). Thus, humans can voluntarily inhibit their drive to eat or develop involuntary changes in their appetite and body weight related to emotional states.

Cognitive control of feeding behavior involves integration of peripheral signals related to energy status of the body, food-related signals in the form of sensory and environmental cues, and memory of past feeding experiences (Benarroch 2010). The insular, orbitofrontal, and anterior cingulate cortical areas have a key role in the processing of interoceptive and food-related information and participate in motivational aspects of feeding behavior (Craig 2009; Shin et al. 2009; Saper et al. 2002).

There is now evidence from preclinical studies that emotional factors influence both hedonic and homeostatic aspects of food intake, altering the activation of many mediators such as ghrelin, orexin, and leptin. For example, chronic stress may influence feeding and body weight independent of palatability of food or energy status

of the individual (Lutter and Nestler 2009). This is more obvious in human behavior, since changes in appetite and body weight are frequent symptoms and one of the core diagnostic features of major depressive disorder. Furthermore, the association rate between mood disorders and obesity is about 25% (Simon et al. 2006). Influences of mood on hedonic and homeostatic control of feeding may be partially mediated by the serotonergic system, e.g., action of serotonin on POMC neurons in ARC via $5HT_{2C}$ receptors (Heisler et al. 2002). Aside from depression, serotonergic system dysfunction is also implicated in the pathophysiology of eating disorders, i.e., anorexia nervosa and bulimia nervosa (von Hausswolff-Juhlin et al. 2015).

### 3.1.2 Interaction with the Environment (Social Interaction)

Humans form organized groups of conspecifics and live within societies. To properly function in such context, we display instinctive social behaviors aimed at facilitating the formation of social networks of support, competing for resources, avoiding or facing conflicts, assessing social interactions and intentions of others, conveying and exchanging emotional and social cues, bonding and creating romantic relationships, nurturing and teaching offspring, etc. Such complex behaviors have their basis in evolutionary preserved neurobiological mechanisms, which can be studied in humans or in other social animal species. For several years, our understanding of this neurobiology was based on neuro-structural and neurochemical-related parameters. Indeed, for example the *superior temporal sulcus* and the *fusiform gyrus* are known to be involved in the processing of perceived social stimuli. Then, the *amygdala* and the *prefrontal cortex* designate an emotional value to this perception (Ordonana et al. 2013). However, over the last decade, there was a significant progress on the role of the pro-social peptides, such as *oxytocin* and *arginine vasopressin* (AVP), which also appear remarkably conserved across species. Overall, the modulation of social behavior by these peptides has been confirmed by several experimental and clinical studies and in various contexts of social behavior (Keverne and Curley 2004; Heinrichs and Domes 2008; Meyer-Lindenberg et al. 2011; Insel 2010). In this chapter, we focus mainly on findings from human studies. However, it should be noted that such studies are sometimes limited by the fact that studying central oxytocin and AVP systems would ideally require direct access to the brain, which can only be done easily when using experimental rodents. In vivo imaging in humans remains impractical for studying the neurobiology of social instincts, as human subjects are constrained by the limitations of imaging techniques (Crockford et al. 2014). Although some would wrongly argue about the ability of rodents and other experimental animals to experience emotions in social contexts, such research has led to significant advances into our understanding of social instincts and emotional behavior (Panksepp 2016). Additionally, much of our understanding about how pro-social peptides act is by studying not the systems themselves but the effects of the exogenous administration of peptides, as it will be discussed further on. Thus, oxytocin is involved in fear response, anxiety, and generally in the stress response. It is thought that oxytocin is involved in processes that attenuate stress related to

social interaction and therefore facilitates interaction between humans. Moreover, several studies have shown that oxytocin can decrease activity in the amygdala, a brain region responsible for fear regulation. In addition, oxytocin further modulates human emotional, social, and affiliative behaviors, such as adult bonding, mother-infant relation, and generally social attachments. On the other hand, AVP is known to play an important role in fluid homeostasis and in the regulation of cardiovascular and autonomic systems. Therefore, by regulating those systems and functions, AVP may also play an important role in attention, arousal, competition, and aggression. It is therefore believed that oxytocin and AVP may have opposing actions. Oxytocin is more involved in regulating pro-social behaviors, such as social bonding, romantic relationships, and parenthood. Moreover, it is thought that oxytocin may even inhibit actions of AVP, during certain periods, such as pregnancy and lactation (Galbally et al. 2011). Finally, it should be noted that both AVP and oxytocin present significant sex differences, as evidenced by experimental and human studies and discussed in this chapter (Kokras et al. 2011; Carter 2007).

#### 3.1.2.1 Facial Expression and Impressions

As humans are social beings, we continuously form impressions of conspecifics, based on prior learning, appearance, and behavioral cues of people that we interact with. This human instinctive behavior does not follow objective criteria but instead may present significant bias. A well-studied example is that people experiencing fear or stress tend to assign hostile characteristics to neutral facial expressions that are presented to them. Recognition of faces and extrapolation of useful social and emotional cues from the facial expression are of paramount importance for humans, perhaps in contrast to other mammalian species, which rely on other systems and cues, such as odor and pheromones, for recognition of conspecifics. Several studies have demonstrated that in this process the *dorsomedial prefrontal cortex (DMPFC)* is crucially involved. Interestingly, whereas the hippocampus is thought to be involved in learning and memory functions, specifically for social cues and impressions, it appears that the dorsomedial prefrontal cortex plays a key role. In fact, individuals with hippocampal lesions apparently preserve their ability to form impressions of other people based on facial expressions (Lass-Hennemann et al. 2011). On the other hand, the *amygdala* is a key brain region involved in complex social behaviors. The amygdala activates in the presence of perceived threats but also activates while experiencing emotions, when processing faces, and interestingly, while making social judgments. Decreased activation of the amygdala in humans is linked to decreased social fear and thus resulting into more pro-social behaviors. On the contrary, it is well-known that increased amygdala activity relates to phobias and social avoidance (Ordonana et al. 2013). As humans have to continuously interact socially, the ability to exchange information on emotions is critical. Bonding between members of a social group depends on mutual recognition, for which most mammals rely on odor and pheromones. In humans, however, recognition of conspecifics and bonding relies heavily on vision and facial recognition. Moreover, the communication of our feelings, such as joy or sadness, facilitates others to understand our needs, and inversely by extrapolating the emotional status

of people around us, we can obtain valuable information, such as linking fear in others with the notion that we might as well be in danger. Women are generally more capable than men in decoding emotional cues, and aside verbal communication, emotions can be conveyed through facial expressions. The amygdala is the brain region heavily involved in this process, as persons with lesions in that brain structure are incapable of correctly interpreting facial expressions (Somerville et al. 2011). Several brain imaging studies support this finding as activation of the amygdala happens during both positive and negative emotional cues, facial expressions included (Costafreda et al. 2008). It has been demonstrated that oxytocin can attenuate the activation of the amygdala, which is rich in oxytocin receptors, thus reducing fear responses when confronted with facial expressions (Kis et al. 2013). AVP plays an important role in recognizing each other's emotions, as administration of exogenous AVP facilitates men's pro-social behavior and processing of social information. However other studies showed that in men but not in women AVP deteriorated recognition of facial emotions and promoted aggressive responses (Thompson et al. 2006). It appears that AVP increases attention generally to social stimuli with the potential of facilitating either a pro-social or an aggressive response depending on the context. Moreover, AVP mediates many of its behavioral effects through the AVP receptor 1a. It appears that genetic variations of AVP1a affect the behavioral response and bonding of men, but not women, as evidenced by decreased probability of being married, and increased chance of marital problems and divorcing. More sex differences have been observed after intranasal administration of oxytocin. Women display increased brain activity when seeing angry or fearful facial expressions after exogenous oxytocin administration. On the contrary, men show decreased activity in the involved brain regions, such as the amygdala and the temporal lobe (Zink and Meyer-Lindenberg 2012). In this context, it has been proposed that oxytocin and AVP act toward a divergent stress response in men and women. Certainly, a significant overlap exists in the typical "fight or flight" stress response. However, under certain situations and due to the influence of sex-dependent actions of oxytocin and AVP, women tend to adopt an affiliative ("tend-and-befriend") response significantly more often than men (Taylor et al. 2000; Kokras et al. 2011).

#### 3.1.2.2 Competition and Aggression

Competition plays an important role in human societies, as individuals confront each other for primary resources, such as food, and secondary resources, such as employment, money, etc., which in turn improve access to primary resources. Such confrontation is dependent on the characteristics of each social group and accepted social norms and can have many forms, from pure aggression to elaborate political maneuvers in order to successfully compete and prevail. A common characteristic, however, is that such competition obeys rules of social order, whose purpose is to finally resolve and settle competitive confrontation. Several lines of evidence have linked modulation, usually reduction, of *testosterone* levels to those processes that control the evolvement and then mitigation of social competition. However, the complexity of human behavior while competing with conspecifics, together with methodological problems, creates a challenge for testosterone-related research in

this field, given that testosterone levels have been found increased, decreased, or unaffected, depending on the involved competitive task, effort invested in obtaining the resources, coping styles, and many other confounding factors. Furthermore, it is now known that women are no less competitive than men, particularly in modern societies that engage women at many levels. However, research in the psychobiology of female competition is dragging behind, and the role of testosterone in modulating aspects of female social competition is still unclear. In any case, social competition, whether it results in dominant and subordinate individuals in experimental studies or more elaborate outcomes in human societies (such as socioeconomic status), is long known to affect the biology of individuals. Parameters that have been studied and found affected by outcomes of social competition are cardiovascular indices, body/organ weight and size, sperm quality, autonomic and endocrine function, as well as brain function as expressed by neurotransmitters, receptors, and neurogenesis (Salvador and Costa 2009). Social competition may also lead to aggression. It has been long known that testosterone levels relate to aggressive behavior; however, this relation is apparently true only for social expressions of violence and not for aggressive behavior in general. Moreover, it seems that only high testosterone levels, or at best considerable increases, induce such effect. Testosterone rather primes males for anger, feeling threatened and challenged and thus more reactive to responding aggressively (Goetz et al. 2014). High testosterone levels also impede the amygdala-prefrontal cortex connectivity, reducing the conscious control over unconstrained social behavior in males (Gettler 2014). Such testosterone-primed aggressive behavioral response may be adaptive or not, depending on the social context. Moreover, in experimental studies, other steroids, such as *estrogen* and of course peptides, such as *AVP*, have been found to fluctuate in conjunction with testosterone, depending on whether confronting a male or a female conspecific and also depending on social context (mating, territorial behavior, social status, etc.) (Bos et al. 2012b). Experiments with intranasal AVP administration in healthy volunteers showed that AVP may facilitate aggression by predisposing persons to respond aggressively to ambiguous social cues, which by a presumed AVP-mediated action are perceived as threatening. Such actions however are sexually dimorphic. Indeed, whereas in men AVP apparently decreases a perception of friendly social cues, in women AVP administration seems to facilitate a friendly, non-threatening perception of ambiguous social cues, such as unfamiliar faces. Genetic studies also support the involvement of AVP receptors, specifically subtype 1A. Polymorphisms in this receptor modulate social bonding in men but not in women. Thus, it seems that centrally acting AVP modulates social human communication in a sex-dependent manner (Heinrichs et al. 2009). Without doubt, many simultaneous physiological systems, neurotransmitters, hormones, and centrally acting peptides are activated, as many researchers have argued (Neumann and Landgraf 2012; Taylor 2006). In addition, AVP and testosterone actions that prime humans for competition and eventually aggression also interact with *oxytocin's* actions that promote social bonding, as it will be discussed further on. Thus, it appears that high oxytocin and low testosterone levels promote nurturing behavior and gentle affiliations, whereas high oxytocin and high testosterone promote loyal

comradeship, risky and dangerous group actions that individuals would not undertake alone (such as warfare) (Van Anders et al. 2011; De Dreu 2012). Finally, it should be noted that those neuroendocrinological mechanisms are also thought to be involved in the termination and settlement of aggressive and competitive behaviors. A remarkable example is face blushing. Blushing and gaze aversion are considered, from an evolutionary point of view, as displays of conciliation, thus facilitating the resolution of conflict and aggression between humans (Stein 2015).

#### 3.1.2.3 Social Bonding and Support

Despite humans forming complex and sophisticated social bonds, those functions are based on brain circuits that apparently are conserved through most mammalian species. Thus, substantial research has been devoted into decoding the involvement of specific neuronal circuits affecting social bonding and close relationships. Romantic love between partners and parental love were successfully linked by imaging studies to the *anterior cingulate gyrus (ACG)*, *medial insula*, *caudate nucleus* of the striatum, and *ventral tegmental area* (VTA). Whereas those brain areas are seemingly activated, others such as frontal, parietal, and temporal cortical brain areas, including the amygdala, appear to deactivate. Deactivation of cortical areas in close relationships (which also appears to happen in sexual arousal) would justify common saying that during love, sex, and other highly rewarding conditions, lapses in judgment frequently arise. Moreover, it is now supported with reasonable certainty that the dopaminergic projections coming from the VTA and crucially involved in reward in general are also involved in attachment and social bonding. Furthermore, pro-social neuropeptides (oxytocin and AVP) facilitate this dopaminergic neurotransmission, as in the case of breast feeding, thus enhancing the subjective rewarding feeling and in turn strengthening social bonding and close relationships (Stein and Vythilingum 2009). Specifically for oxytocin, its involvement in the formation of a romantic relationship and more generally in the expression of affectionate behavior is now well documented. However, several studies now support the notion that oxytocin's actions are not universal but instead context-specific and with considerable interactions with other factors, such as whether expression of affectionate behavior is directed toward next of kin individuals or other more distantly familiar individuals (Gettler 2014). Similarly to what was mentioned previously, peptide actions with regard to bonding present significant sex differences. In humans, plasma oxytocin correlated with romantic relationship-related perceived distress in women but not men, while plasma AVP correlated with such distress in men but not women (Taylor et al. 2010). But seeking rewarding interpersonal interactions is not limited to the formation of close romantic relationships only. Forming a social network and perceiving social support are other social instinctive behaviors aimed at improving human health and chances of survival. In fact, the degree of perceived social support by an individual has been linked to reduced stress and autonomic activation, such as reduced blood pressure, heart rate, reduced cortisol and adrenaline levels, etc. Remarkably, similar effects in stress reactivity are observed independently of whether social support is offered or received by an individual, and therefore, the dampening of the HPA axis response

is now considered a key mechanism in promoting pro-social behavior (Ditzen and Heinrichs 2014). Several brain regions are implicated in this process in the ACG and the prefrontal cortex. Specifically, the *ventromedial prefrontal cortex (VMPFC)* appears to activate in the presence of a familiar social supporter, providing reassurance and safety and ultimately increasing pain threshold. Interestingly, there are sex differences in the effects and benefits of social support. Men seem to benefit most from verbal forms of support, including practical advice and instructions, whereas women benefit more from nonverbal expressions of support, such as touching, holding hands, smiling, etc. (Eisenberger et al. 2011). Moreover, differences also appear not only due to sex but also because of different coping styles of individuals. Indeed, subjects who have as a primary coping mechanism their reliance on social support display higher levels of salivary cortisol in response to conflict than those who rely on other coping styles. Finally, oxytocin is also considered a key peptide in regulating pro-social behavior, and several studies with intranasal administration of exogenous oxytocin evidenced its role in attachment during adulthood, ability to trust, generosity, altruism, pro-social motivation, empathy, and positive communication between couples (Hostinar et al. 2014). Whereas no mechanism acts independently, the combined action of all those presented neurobiological mechanisms increases the chances of social contact, facilitates repetitive social interactions, and promotes reward when socializing, and this ultimately results in the formation and maintenance of stable social bonds between members of a group (Crockford et al. 2014).

#### 3.1.2.4 Parental Behavior

Parental behavior extends to a varied repertoire of instinctive behaviors aimed at securing the survival of the offspring. Human infants are born more immature, have significantly more needs, and require more attention compared to other mammals. Therefore, a close bond between human parents and offspring is paramount to their survival, and several mechanisms are involved to secure this bonding. Early in the postpartum, levels of hormones such as *estradiol*, *progesterone*, and *cortisol* correlate with maternal feelings of nurturing, which are enhanced. Young mothers are vigilant for sounds of distress from infants (such as crying), displaying accelerated heart rate and cortisol increases. Learned maternal behavioral responses and the reward from successful nurturing in that period appear linked to such fluctuations of cortisol levels (Olazabal et al. 2013). Moreover, genetic polymorphisms in the dopaminergic neurotransmission system, such as in the DRD1/2, DRD4, and the DAT1 genes (Kaitz et al. 2010; Mileva-Seitz et al. 2012), appear to influence how the mother responds and interacts with the infant but with significant gene by environment (or more specifically gene by social context) interactions. Such complex interactions highlight the difficulties encountered in genetic research of social instincts but also difficulties in genetic research in general (Duncan and Keller 2011; Hewitt 2012). In addition to genetic polymorphisms, the mesolimbic dopamine reward circuit of the nurturing mother is also strongly modulated by prolactin and oxytocin, thus ensuring that the young mother experiences reward by nurturing her offspring. *Oxytocin* has been

consistently associated with delivery, lactation, nurturing, and other complex parenting behaviors. Increased oxytocin during pregnancy promotes instinctive maternal behavior and facilitates mother-infant bonding. During pregnancy, both mother and fetus produce oxytocin, which is thought to influence antenatal bonding. Oxytocin has a significant role postnatally as well, as it can moderate amygdala activity, dampen hypothalamic-pituitary-adrenal (HPA) axis activity, reduce the stress and anxiety associated with caring of an infant, and, in addition, promote rewarding feelings. Indeed, less anxious mothers are more efficient in recognizing and responding to nonverbal infant cues. During the postpartum, oxytocin levels remain high by stimuli received during lactation but also by other infant-derived stimuli, such as vocal calls, infant facial expressions, and mother-infant physical contacts. Oxytocin is released rapidly in response to such stimuli and thus promotes maternal caregiving behavior and attachment (Galbally et al. 2011). In the human species, usually mothers and fathers cooperatively raise offspring, although the degree of cooperation may differ across cultures and social situations. The neurobiology of paternal behavior is relatively less studied, but fathers with higher oxytocin levels engage more often in playing with their children, and inversely playing with children resulted in more pronounced spikes of oxytocin. Like mothers, fathers with higher oxytocin displayed closer attachment to their infants. However, there have been other conflicting results; hence it is still not clear whether peripheral oxytocin levels accurately depict the parenting behavior or whether there are context-specific parenting situations and related emotional and behavioral responses that are facilitated by oxytocin. *Testosterone* is also involved in expression of paternal behavior. Fathers involved in raising offspring were found with attenuated levels of testosterone. It is hypothesized that from an evolutionary point of view, human fathers displaying reduced testosterone levels would be primed to less aggressive behavior and would be more attentive and more prone to display cooperative behaviors. However this phenomenon appears linked to the degree of paternal investment and commitment; hence cultural differences in the levels of father involvement and cooperation with the mother are expected to influence the degree of testosterone attenuation (Gettler 2014). Moreover, several lines of evidence support the involvement of *prolactin* not only in the well-studied mechanism of lactation in women but generally into shaping the maternal behavior in close interaction with oxytocin, AVP, and importantly the dopaminergic neurotransmission (Rilling and Young 2014). Interestingly, prolactin also seems to play an important role in influencing father behavior. Experimental studies in rodents and other species show that increased prolactin correlates well with paternal behavior, this correlation is absent from species that do not exhibit significant paternal care, and pharmacological suppression of prolactin in specific periods may inhibit the appearance of paternal behavior (Wynne-Edwards 2001). Although human research in this field is not conclusive, prolactin was also shown in human males to increase just before birth, higher prolactin levels associated with stronger paternal emotional responses, and a link with prolactin was found in expectant fathers' sympathetic pregnancy ("couvade") (Storey et al. 2000).

### 3.1.2.5 Conclusion

Humans possess but also develop complex social instinctive behaviors, which are destined to support social accession and continuous adaptation to varying social stimuli, thus ultimately ensuring survival and promoting personal well-being. Such complex social behaviors rely on appropriate and equally complex neurobiological mechanisms, involving several brain regions, major neurotransmitter systems, stress, and sex hormones, as well as peptides such as oxytocin and AVP, all forming coordinated networks in our brain and body (Skuse and Gallagher 2009). A simplified representation of these systems is shown in Fig. 3.1 (Baribeau and Anagnostou 2015; Meyer-Lindenberg et al. 2011; Boccia et al. 2013). Genetic polymorphisms and epigenetic mechanisms during several critical periods, such as the neonatal, early childhood, and adolescence further carve the neurobiology of social behavior and contribute to high individual variability. Moreover, it should be noted that observing, understanding, predicting, and responding appropriately in the social context may be innate but also learned behavior. In fact, important aspects of the psychobiology of social behavior are not simply hardwired but prone and receptive to social learning. Indeed, innate but untrained

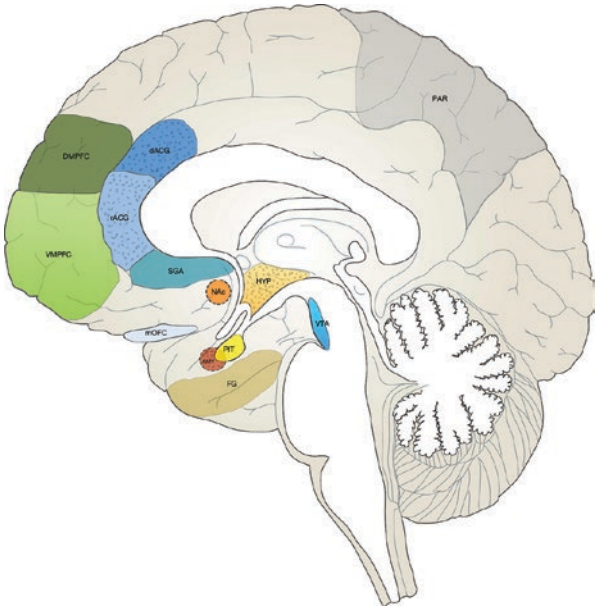


**Fig. 3.1** Brain areas significantly involved in social behavior. *DMPFC* dorsomedial prefrontal cortex, *VMPFC* ventromedial prefrontal cortex, *dACG* dorsal anterior cingulate gyrus, *rACG* rostral anterior cingulate gyrus, *SGA* subgenual anterior cingulate cortex, *mOFC* medial orbitofrontal cortex, *NAc* nucleus accumbens, *AMY* amygdala, *PIT* pituitary gland, *HYP* hypothalamus, *FG* fusiform gyrus, *VTA* ventral tegmental area, *PAR* parietal lobe. Of those areas, AMY, HYP and ACG are thought to be particularly rich in oxytocin receptors (shaded areas); however, despite numerous experimental studies, there is inconclusive evidence about the distribution in the human brain of vasopressin 1a and 1b receptors (Baribeau and Anagnostou 2015; Meyer-Lindenberg et al. 2011; Boccia et al. 2013)

neural networks at the time of birth provide later in infancy and childhood the neurobiological basis of learned social skills such as language and imitated behavior. Finally, at the cornerstone of social psychobiology is the understanding of several and important sex differences, as it is clearly the case in aggression, social support, bonding, and parenting.

## 3.2 Instincts

An instinct is the inherent tendency of a living organism to exhibit a particular complex pattern of behavior. Instinctive behaviors are therefore the manifestation of innate biological factors, are not based on learning or prior experience, and do not implicate consciousness or cognition. Instincts are displayed by most members of the species and can be thought of as the ability possessed by a living organism to perform, without anticipating their benefits, acts which secure the development and preservation of the individual or the species. However, the extent to which instincts determine the behavior of animals varies across species. The higher a species stands on the evolutionary ladder, the more developed its nervous system is, and education/learning plays a greater role than instinct in shaping behavior. Instinctive behaviors escape the individual's volitional control (i.e., they are automatic) although their expression can be modifiable by social learning. Instincts are by definition complex patterns of behavior and should be distinguished from *reflexes*, which are simple behaviors in response to specific stimuli (e.g., deep tendon reflexes) as well as *taxis* (locomotion of organism or cell toward or away from a specific external stimulus, e.g., negative phototropism) and *kinesis* (rate of movement is determined by some feature of the environment).

The term instinct was introduced into the field of psychology by W. Wundt in the 1870s (Wundt 1874), and by the end of the nineteenth century, almost all stereotyped animal behavior was considered as instinctive. Freud (1920, 1923) further elaborated on the notion of instinctive drives ("Trieb") and incorporated them into his topographical model. He described two kinds of unconscious instincts, the life instinct (libido, "eros") and the death instinct (aggression, "thanatos"), which are the major sources of psychic energy and are stored in the id. Both of these are in continuous need of satisfaction, leading to a buildup of tension/excitation; their fulfillment results in discharge of psychic energy and the alleviation of tension (see also Chap. 11 for further details). Instinct as a concept came out of fashion with the advent of behaviorism in the 1920s; most behaviors were then considered as the result of learning, conditioning, and reinforcement.

Interest in innate behaviors was revived again in the 1950s with the work of ethologists Lorenz (1952) and Tinbergen (1951). According to their theory, instinctive behaviors consist of one or more *fixed action patterns* (FAPs), stereotyped behavior sequences exhibited invariantly by all members of the species, which are elicited in response to a specific external sensory stimulus (called the

*sign stimulus* or *releaser*) and almost inevitably run to completion once started. FAPs are supposed to be "hardwired" and produced by a neural network (called the *innate releasing mechanism*) described schematically in Lorenz's (1950) *psychohydraulic model* (Fig. 3.2). The model incorporates a reservoir within which action-*specific energy* gradually accumulates over time (representing the individual's state of internal motivation); energy flow is regulated/impeded by a valve on which two very different forces act additively (*law of heterogeneous summation*), i.e., the pressure of the energy building up within the reservoir and the weight exerted by external stimuli (releasers). When the sum of these two forces overcomes the restraining capacity of the valve, energy is discharged to produce a FAP. A period of time follows when a stimulus is less likely to produce a FAP (*behavioral quiescence*). A notable implication of the model is that a FAP can occur even in the absence of external stimuli (*vacuum activity*) following an excessive buildup of energy within the reservoir.

Despite its attractive simplicity, the major limitation of Lorenz's hydraulic model is that it did not include any mechanism for learning, i.e., there was no way that the consequences of the animal's behavior feedback into the system to modify subsequent behaviors. Yet, Lorenz highlighted the effect of developmental phase-sensitive learning (called *imprinting*, first described in geese learning their mother's identity during a critical period). However, he believed that the mechanisms producing instinctive behaviors (FAPs) were largely innate, i.e., solely determined by the effect of genes, and subsequently triggered by environmental stimuli. More recent

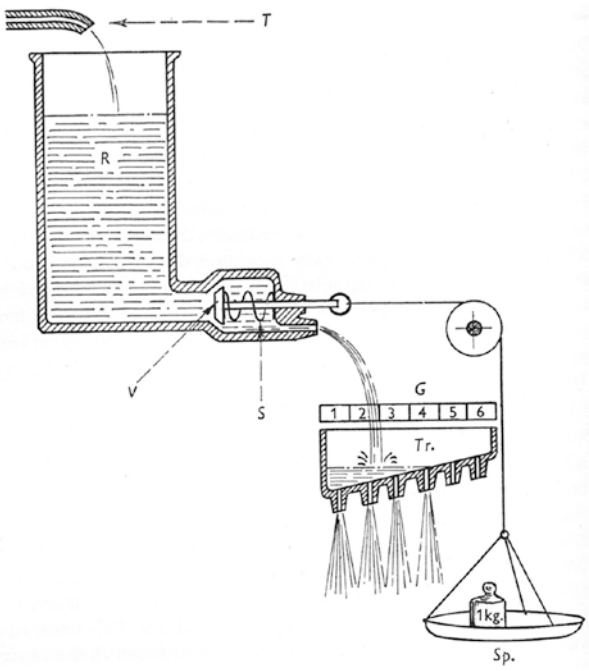


**Fig. 3.2** Lorenz's psychohydraulic model of instinctive behavior. *T* tap, *R* reservoir, *V* valve, *S* spring, *Sp* scale-pan with weight, *Tr.* trough, *G* graded scale. Reproduced with permission from Lorenz (1950), courtesy of the Society for Experimental Biology

evidence calls for a revision of Lorenz's model. We now know that since the beginning of ontogenesis environmental stimuli are in constant interplay with genes at several developmental stages to shape the neural substrate in a process called *epigenesis* (Fuller 1954; Sokolowski and Corbin 2012).

Here follows a psychobiological overview of the instinct of aggression, while Chap. 6 covers aspects related to sexuality.

### 3.2.1 Aggression

Aggression is defined as overt behavior that involves threat or physical damage to another individual in the context of competition/conflicting interests, defense, or emotional arousal. Human aggression is associated with a considerable toll on society. More than one million people die each year as a result of violent acts (homicide, wars); males and young people are particularly overrepresented among the victims of violence (WHO 2010). Patients with neuropsychiatric disorders (psychotic, mood and anxiety disorders, personality disorders, impulse control and substance use disorders, dementia, organic brain damage) are at increased risk of manifesting aggression.

#### 3.2.1.1 Classifications of Aggression

Various classifications of aggression have been proposed, e.g., by the nature of the aggressor (individual or collective), context (defensive or predatory, maternal, territorial, sex-related, dominance, or intermale), the target of aggressive acts (self-directed or other-directed), the mode of its expression (physical or verbal, direct or indirect), or its causes (psychiatric, medical, etc.). Aggression might also be classified according to social acceptability, depending on cultural context. Socially accepted aggression might comprise sports, hunting, corporal punishment, or warfare; socially prohibited aggression includes homicide, rape, child abuse, torture, and terrorism. Normative levels of aggression can facilitate survival, self-defense, or competition; however, when aggression is exaggerated in intensity, persistent, disproportionate to its eliciting stimuli, or out of social context, it is considered as pathological or maladaptive.

However, the most widely used and neurobiologically founded taxonomy of aggression in humans is that of *reactive* (or impulsive or affective or defensive or "hotheaded") versus *proactive* (or premeditated or instrumental or predatory or controlled or "cold-blooded") aggression (Gelles 1994; Barratt et al. 1999). Reactive aggression is considered to be an impulsive response to a perceived threat, associated with anger and autonomic arousal and probably underlies most incidents of aggression encountered in our society; proactive aggression is considered to be more purposeful, often not associated with emotional or autonomic arousal and accounting for higher profile crimes (genocides, mass assassinations). A phenomenological comparison of these two subtypes of aggression is presented in Table 3.3. On the basis of this classification, two quite distinct populations of aggressive individuals can be recognized: those who exhibit mostly reactive aggression and those

**Table 3.3** Phenomenological side-by-side comparison of reactive and proactive aggression

| Reactive aggression | Proactive aggression |
|---|---|
| Impulsive, unplanned ("hotheaded") | Planned, premeditated ("cold-blooded") |
| Responding to perceived threat, provocation, or frustration | Started by the offender, not provoked |
| Associated with high levels of emotional excitement (frustration, rage, fear) and autonomic arousal | Not associated with emotional or autonomic arousal |
| Not aiming at self-benefit (only defensive or reactive to rage) | Aiming at self-benefit or gain |
| Exposure to risk of physical self-harm or damage of own property | Protection against self-harm during aggression |
| Loss of control of aggressive behavior | Ability to control aggressive behavior |
| Public display of aggressive behavior | Hidden expression of aggression |
| May be followed by remorse | Feeling proud to be aggressive |
| Associated with neuropsychiatric disorders (psychotic, mood, personality and substance use disorders, IED, PTSD, organic brain damage) | Associated with psychopathy and violent offenses |

*IED* intermittent explosive disorder, *PTSD* post-traumatic stress disorder

who exhibit mostly proactive and some reactive aggression; it follows, therefore, that the two subtypes are partly correlated (Poulin and Boivin 2000).

The two subtypes also have distinct pathophysiological underpinnings and neurobiological signatures. Reactive aggression seems to be a conserved pattern of behavior across all mammalian species; it is part of a graded response to increasingly threatening stimuli, starting from freezing toward low-level threats and culminating in flight/escape and reactive aggression toward medium- and high-level threats, respectively (Blanchard et al. 1977). Reactive aggression is largely mediated by hyperresponsiveness in a subcortical (hypothalamic and limbic) network or hyporesponsiveness in higher cortical regulatory areas or both. Proactive aggression in humans has been suggested to parallel predatory aggression in omnivorous/carnivorous animals and is thought to be much more dependent on higher cortical circuits. Much more data is available on reactive aggression, which will be the main focus of the remaining chapter.

### 3.2.1.2 Functional Neuroanatomy of Aggression

#### Reactive Aggression

Lesion (ablation) and electrical or, more recently, optogenetic stimulation studies in experimental rodents have highlighted the significance of the so-called subcortical rage circuit in the manifestation of reactive aggression (Falkner et al. 2016; Lin et al. 2011). This circuit relays perceived threatening sensory stimuli either directly via the thalamus (thalamoamygdalar pathway) or indirectly via the cortex (primary and secondary association cortices) to the *medial amygdaloid areas*, then to the *anterior* and *ventromedial hypothalamus (VMH)*, the *bed nucleus of the stria terminalis* and *lateral septal areas*, and from there to the *dorsal half of the periaqueductal gray* (Panksepp 1998; Nelson and Trainor 2007). As expected, lesions of all

components of this circuit reduce aggression. However, a hierarchical organization is evident, since, for example, stimulation of the periaqueductal gray elicits a rage response even in the absence of an intact amygdala but not vice versa. Moreover, depending on the social context, different subnuclei of the aforementioned structures may be activated.

Brain lesion and brain imaging studies have in large part provided evidence (although less conclusive) that the subcortical rage circuit is important in mediating reactive aggressive expressions in humans and nonhuman primates, as well (Gregg and Siegel 2001; Davidson et al. 2000). However, in primates (as well as in other mammals but to a much lesser extent) prefrontal cortical areas exert central regulatory surveillance on the subcortical network by evaluating the salience of the threatening stimuli, planning actions, adjusting them to environmental feedback, anticipating their consequences, and assessing their potential reward value (Bachevalier et al. 2011; Anderson et al. 1999; Coccaro et al. 2011). Lesions of the *orbitofrontal cortex (OFC)* are generally associated with increased aggression (de Bruin et al. 1983; Machado and Bachevalier 2008), exemplified in the classic case of Phineas Gage (Damasio et al. 1994). The medial division of the OFC receives feedback on endogenous parameters (e.g., arousal, muscle readiness), while its lateral division receives sensory input about exogenous parameters of the perceived threat (e.g., its size or its proximity); both divisions are reciprocally connected with the amygdala (Ghashghaei and Barbas 2002). It seems, therefore, that the OFC is involved in the interpretation of interpersonal cues and the inhibition of inappropriate behavioral responses. The *anterior cingulate gyrus (ACG)* has been the focus of intensive research in recent years; it receives input both from the limbic system and the prefrontal cortex and serves as a conflict processor by assessing the social appropriateness of emotionally laden aggressive impulses. The infracallosal part of the ACG (often called subgenual ACG) may be more linked to predatory aggression, while the supracallosal part of the ACG is possibly involved in restraining inappropriate social behaviors and reactive aggressive impulses. The *ventromedial prefrontal cortex (VMPFC)*, in concert with the *dorsomedial (DMPFC)* and *ventrolateral (VLPFC) prefrontal cortices*, is involved in the detection of contingency changes of motor plans (i.e., of whether planned actions continue achieving their goals) and in the implementation of alternative plans according to social cues of conspecifics ("social response reversal") (Budhani et al. 2007). Failure to do so results in a buildup of frustration thought to underlie reactive aggression in individuals with psychopathic tendencies (Budhani and Blair 2005; Gorrindo et al. 2005; Dickstein et al. 2010). The *dorsolateral prefrontal cortex (DLPFC)* acts in synergy with the VMPFC and the ACG to consciously plan motor actions and anticipate their consequences before they are executed in the supplementary motor area and premotor and motor cortices. Lastly, the *temporal lobe* is also implicated in reactive aggression responses, especially in patients with organic temporal lesions or temporal lobe epilepsy (Ito et al. 2007). Concludingly, in primates the *medial amygdala* lies at the intersection of subcortical (unconscious) and cortical (partly conscious) circuits mediating reactive aggression; it is, therefore, actively

involved in the assessment of the necessity of an aggressive response on the basis of sensory input and social cues and not just a releaser of a stereotyped aggressive behavior (Coccaro et al. 2007).

Interestingly, the hypothalamus, amygdala, septal areas, and prefrontal cortex provide sites of monoaminergic modulation of aggressive responses via their connections with mesolimbic dopaminergic projections stemming from the ventral tegmental area and serotonergic projections from the raphe nuclei, which result in disinhibiting and dampening, respectively, of aggressive behaviors (Seo et al. 2008; Siever 2008). Moreover, oxytocin and AVP exert opposing effects on the amygdala, hypothalamus, and possibly prefrontal cortical areas (Huber et al. 2005).

#### Proactive Aggression

Predatory aggression in animals is mediated by a circuit including the *dorsolateral hypothalamus* and the *ventral half of the periaqueductal gray* (Gregg and Siegel 2001). However, the suggested association of human proactive aggression with animal predatory aggression has been criticized mainly because the latter is not displayed toward conspecifics and is little influenced by learning, unlike the former.

Proactive aggression is probably dependent on the same cortical circuits involved in any purposeful behavior. A maladaptive proactive aggressive behavior will be selected by the individual when the neural systems involved in moral socialization and current decision-making are dysfunctional. Recent literature suggests that the core deficit in individuals exhibiting mainly proactive aggression is a decrease in the responsiveness of the *amygdala* to fearful and sad facial expressions of others, which is necessary for developing empathy through reinforcement learning and a prerequisite for moral socialization by parents and peers (Dadds et al. 2006; Dolan and Fullam 2006; Marsh and Blair 2008). As reinforcement information is normally represented in the medial OFC, it is no surprise that psychopathic individuals display reduced amygdala responses but also reduced *rostral ACG/medial OFC* activation in response to emotional tasks (Kiehl et al. 2001), while youths with psychopathic/callous-unemotional traits display reduced amygdala-OFC/*VMPFC* functional connectivity when processing fearful expressions (Marsh et al. 2008) or moral dilemmas (Marsh et al. 2011).

### 3.2.1.3 Neurochemistry of Aggression

There is gross evidence from both animal and human studies about the involvement of several neurotransmitters, neuropeptides, and steroid hormones in the modulation of aggressive behaviors (Table 3.4).

#### Neurotransmitters and Neuropeptides

*Serotonin (5-HT)* innervates both subcortical (hypothalamus, amygdala, septal areas, periaqueductal gray, hippocampus) and prefrontal cortical areas implicated in aggression (Frankle et al. 2005). Several lines of evidence point to 5-HT's role in modulating aggressive responses. In specific, low 5-HT levels are associated with higher levels of impulsivity and aggression as suggested by reduced cerebrospinal fluid (CSF) concentrations of the 5-HT metabolite 5-HIAA (5-hydroxyindoleacetic

**Table 3.4** Major neurotransmitters, neuropeptides, and steroid hormones modulating aggression

| Biological effector molecule | Effect on aggression |
|---|---|
| (a) *Neurotransmitters and neuropeptides* | |
| Serotonin (5-HT) | |
| SSRIs<br>Tryptophan loading<br>5-$HT_{1A}$ or 5-$HT_{1B}$ agonists<br>5-$HT_{2A}$ antagonists (atypical antipsychotics)<br>5$HTT^{-/-}$ knockout mice | ↓ |
| Reduced 5-HT levels, reduced 5-HIAA<br>Tryptophan depletion<br>5-$HT_{1B}^{-/-}$ knockout mice | ↑ |
| Dopamine (DA) | |
| $D_2$ blockers (antipsychotics)<br>$D_2^{-/-}$ knockout mice | ↓ |
| $D_2$ agonists (ropinirole, pramipexole)<br>$DAT^{-/-}$ knockout mice | ↑ |
| Norepinephrine (NE) | |
| β-Blockers (propranolol)<br>DA β-hydroxylase $(DBH)^{-/-}$ knockout mice | ↓ |
| $\alpha_2$ agonists (clonidine) | ↑↓ (Dose-dependent) |
| γ-aminobutyric acid (GABA) | |
| GABA reuptake inhibitors (tiagabine)<br>$GABA_A$ agonists (muscimol) | ↓ |
| $GABA_A$ allosteric modulators (benzodiazepines, barbiturates) | ↑↓ (Dose-dependent) |
| $GABA_A$ antagonists (flumazenil) | ↑ |
| Arginine vasopressin (AVP) | |
| AVP microinjection in mice<br>Increased AVP levels | ↑ |
| Intranasal AVP | ↑↓ (Sex-specific) |
| AVP receptor antagonists<br>$AVP1b^{-/-}$ knockout mice | ↓ |
| Oxytocin (OXT) | |
| Intranasal OXT<br>OXT microinjection in mice<br>Increased OXT levels | ↓ |
| OXT receptor antagonists<br>$OXT^{-/-}$ knockout mice | ↑ |
| (b) *Steroid hormones* | |
| Testosterone | |
| Increased testosterone levels<br>Exogenous testosterone | ↑ |
| Castration, androgen replacement<br>AR mutant mice | ↓ |
| Cortisol | |
| Reduced basal cortisol levels<br>Adrenalectomy in mice<br>Increased acute HPA axis activity<br>Increased HPA axis reactivity | ↑ |
| Exogenous cortisol | ↑ (Females) |

*AR* androgen receptor, *DAT* DA transporter, *GAD* glutamic acid decarboxylase, *SSRI* selective serotonin reuptake inhibitor, *5-HIAA* 5-hydroxyindoleacetic acid, *5HTT* 5-HT transporter

acid) (Brown et al. 1982), reduced 5-HT transporter binding sites both in platelets and in cortical areas (ACG, OFC) (Coccaro et al. 1996; Frankle et al. 2005), increased 5-$HT_{2A}$ receptor binding sites in platelets and in the hippocampus (Coccaro et al. 1997b; Soloff et al. 2007), as well as blunted prolactin responses (Coccaro et al. 1997a) and reduced OFC, ACG, and VMPFC activation (Siever et al. 1999; Soloff et al. 2000) following challenge with serotonergic probes (d,l-fenfluramine) in aggressive individuals or violent suicide attempters. Furthermore, lowering 5-HT neurotransmission through depletion of tryptophan (a 5-HT precursor) increases impulsivity and aggression (Wood et al. 2006). Conversely, increasing 5-HT neurotransmission with tryptophan loading, selective serotonin reuptake inhibitors (SSRIs) or 5-$HT_{1A}$, and 5-$HT_{1B}$ receptor agonists (termed "serenics") reduces aggression (Marsh et al. 2002; Miczek et al. 2001; Knutson et al. 1998); interestingly, 5-$HT_{2A}$ antagonists (including various atypical antipsychotics) also produce the same aggression-dampening effect (Krakowski et al. 2006). Genetic manipulation of experimental rodents has also been extensively used to study 5-HT's role in aggression; knockout mice for the gene encoding the 5-HT transporter display reduced aggression (Holmes et al. 2002), while mice lacking the gene for the 5-$HT_{1B}$ receptor are more impulsive and aggressive (Saudou et al. 1994). Further studies are warranted to clarify the specific role of various 5-HT receptors and their interactions in modulating impulsive aggression.

*Dopamine (DA)* is considered necessary for the manifestation of all kinds of aggressive behaviors via its mesocorticolimbic projections, although its specific role in modulating aggression is unclear. $D_2$ agonists increase aggression (Siegel et al. 1999), while $D_2$ blockers (antipsychotics) have antiaggressive effects, especially in psychotic patients, although these could also be attributed to non-specific sedative, motor and overall antipsychotic effects, as well as concomitant 5-$HT_{2A}$ antagonism. $D_2$ receptor knockout mice display reduced aggression (Vukhac et al. 2001), while DA transporter (DAT) knockout mice have increased extracellular DA concentrations and exhibit increased levels of aggression (Rodriguiz et al. 2004).

*Norepinephrine (NE)* is crucially involved in both central and peripheral functions that subserve the individual's adaptive response to threat, by promoting vigilance, cardiovascular, and muscle adaptation. However, evidence for NE's role in aggression is mostly indirect through pharmacological studies. Propranolol, a β-receptor blocker, reduces aggression in both rodents and humans (Silver et al. 1999). Clonidine, an α2-receptor agonist, increases irritability and aggression at low doses but may have useful antiaggressive effects in hyperactive or autistic children (Hazell and Stuart 2003). Finally, knockout mice for DA β-hydroxylase, the enzyme involved in NE synthesis, cannot produce NE and display reduced aggression (Marino et al. 2005).

Pharmacological interventions on *γ-aminobutyric acid (GABA)*, a ubiquitous inhibitory neurotransmitter in the brain, have various effects on aggression. Tiagabine, a GABA reuptake inhibitor, has been shown to mitigate aggressive behaviors (Lieving et al. 2008). $GABA_A$ receptor agonists (e.g., muscimol) reduce aggression, while antagonists (e.g., flumazenil) have the opposite effect (Siegel et al. 1999). However, allosteric modulators of $GABA_A$ receptors, such as benzodiazepines, barbiturates, and alcohol, evoke paradoxical aggression in some patients at low-moderate doses and only reduce aggression at high doses (Miczek et al. 2002), suggesting that individual patient traits also contribute to variability of responses.

Various neuropeptides have also been implicated in aggression, the most important of which are the pro-social nonapeptides *AVP* and *oxytocin*, both key regulators of social interaction. Knockout mice for AVP1b receptors display less aggression between conspecifics (Wersinger et al. 2007), and microinjection of an AVP receptor antagonist into the anterior hypothalamus of male mice has the same effect (Ferris and Potegal 1988). Conversely, oxytocin gene knockout mice show exaggerated aggression (Ragnauth et al. 2005), and microinjection of an oxytocin antagonist increases aggression in female rats (Lubin et al. 2003). CSF AVP concentrations correlated with lifetime aggression in subjects with personality disorders (Coccaro et al. 1998), while CSF oxytocin concentrations correlated inversely with lifetime aggression and suicidality (Lee et al. 2009; Jokinen et al. 2012). Therefore, AVP and oxytocin have opposing complementary effects on aggression; more details about their actions, interactions, and underlying mechanisms can be found in Sect. 3.1.2.

**Steroid Hormones**

*Androgens* have both perinatal organizational and pubertal activational effects on the brain and its preparation for aggression. Androgen receptors are abundant within the basic threat system (Hamson et al. 2004); therefore, unsurprisingly, higher testosterone levels are associated with increased reactive aggression in several animals, exogenous testosterone increases aggression, and male castration and androgen replacement reduce aggressive behaviors, while androgen receptor mutant mice are less aggressive (Siegel et al. 1999; Archer 1991). Interestingly, however, the well-established effect of testosterone on aggression in nonhuman animals depends on genetic background, is context-specific (applying more clearly to social aggression), and modulated by interactions with pro-social peptides (AVP, oxytocin), monoamine neurotransmitter systems, and other steroids (estradiol, cortisol). Evidence in humans about the effect of testosterone on aggression is less compelling, with only a weak positive relationship recorded in a meta-analysis of 45 studies (Book et al. 2001). Apart from the aforementioned reasons, inconsistencies in the human literature may be explained by the fact that testosterone levels display age-related and situational variation and circadian and seasonal fluctuations and are affected by past experience and social rank. Furthermore, methodological discrepancies in published studies (self-report aggression measures or task-based design, testosterone sampling method) may be important. In fact, studies using a provocation methodology (rather than relying on self-reported aggression measures) record most often a positive relationship between testosterone and human reactive aggression (Pope et al. 2000; Hermans et al. 2008; Bos et al. 2012a).

Basal *cortisol* concentrations are generally lower in both animals and humans (especially prepubertal children) with higher levels of aggression (McBurnett et al. 2000; van Goozen et al. 2007), and experimentally induced adrenalectomy in mice increases aggression (Haller et al. 2001). Conversely, acute HPA axis activity and reactivity correlate positively (although less consistently) with aggressive responses in both animals and humans (Lopez-Duran et al. 2009). Furthermore, exogenous glucocorticoid administration enhances aggression in human females (Bohnke et al. 2010). Cortisol has, additionally, been shown to moderate testosterone's effect on

aggression; testosterone was positively correlated with aggression and activation of subcortical (amygdala and hypothalamic) areas in response to angry faces only in subjects with low serum cortisol (Popma et al. 2007; Hermans et al. 2008), giving rise to the "high testosterone/cortisol ratio" hypothesis of aggression (Terburg et al. 2009). However, the interplay of testosterone and cortisol is actually complex and likely depends on additional factors, such as gender, age, trait aggression, and psychopathy.

#### 3.2.1.4 Genetics of Aggression

Family, adoption, and twin studies suggest genetic effects on aggression; a meta-analysis of 24 twin and adoption studies using dimensional measures of aggression calculated a mean heritability estimate of 50%, which increased with age (Miles and Carey 1997). Of note, no distinction between reactive and proactive aggression is unfortunately made in earlier studies. However, more recent twin studies have shown that psychopathy, and associated callous/unemotional traits are highly heritable (67% heritability) in 7-year-olds (Viding et al. 2005).

More recently, candidate gene association studies in general population or patient samples have reported links of aggressive behavior to several common single nucleotide polymorphisms (SNPs) in various genes, selected on the basis of neurochemistry data (Table 3.5). A recent meta-analysis of 132 association studies of 225 independent SNPs in 11 genes with categorical or continuous outcomes of aggression with at least two replications (i.e., at least three separate samples per SNP) found no significant findings (Vassos et al. 2014). No genome-wide association study (GWAS) has been published yet. Here follows a synopsis of associations for the two most interesting candidate genes, importantly also involved in gene by environment interactions (GxE), accompanied by supporting preclinical and translational data.

The X-linked gene encoding monoamine oxidase A (*MAOA*), an enzyme catabolizing 5-HT, NE, and DA, was one of the first to be implicated in the genetic regulation of aggression, as a missense point mutation (resulting in no MAOA expression) was identified in several males of a Dutch pedigree with mild mental retardation and high levels of impulsive aggression, including arson, attempted rape, and exhibitionism (Brunner et al. 1993). Although very rare and, therefore, unlikely to explain much of the variation in human aggression, this mutation moved the focus of aggression-related genetic research to *MAOA*. Curiously, *MAOA* knockout mice were subsequently shown to have increased brain levels of 5-HT, NE, and DA and displayed increased aggression (Cases et al. 1995). A more common variable number tandem repeat (VNTR) polymorphism in *MAOA* promoter region has four common alleles with 3–5 repeats of a 30-bp sequence; alleles 2 and 3 are associated with increased MAOA expression (MAOA-H) while alleles 1 and 4 with lower (MAOA-L) (Sabol et al. 1998). Although MAOA-VNTR has inconsistently been associated with human aggression (MAOA-L genotypes most often associated with increased lifetime aggression), it has more robustly been shown to interact with the severity of early life stress (child maltreatment) in predicting adult antisocial behavior (Kim-Cohen et al. 2006; Caspi et al. 2002), in one of the most

**Table 3.5** Major candidate genes associated with human aggression

| Gene (chromosome) | Polymorphism | Risk allele → effect on expression/activity | Associated behavioral phenotype |
|---|---|---|---|
| *Catecholaminergic neurotransmission genes* | | | |
| *MAOA* (Xp) | VNTR (3–5 30-bp repeats) in promoter region | Alleles 1 (3R) and 4 (5R) → lower MAOA expression (MAOA-L) | – Impulsive aggression, conduct disorder, adult antisocial behavior (males only)<br>– MAOA-L∗ (child maltreatment) → adult antisocial behavior (males only) |
| | Rare point mutation in exon 8 | C936T → premature stop codon (missense) → no MAOA expression | Cross-generational violence (impulsive aggression, arson, rape) and borderline IQ in several males of Dutch kindred |
| *COMT* (22q) | SNP in exon 3 | G1947A (Val158Met) → lower COMT expression | Inconsistent association with aggression in different populations |
| *DRD4* (11p) | VNTR (2–11 48-bp repeats) in exon 3 | 7R allele → lower DRD4 affinity for DA | – Physical other-directed aggression in schizophrenia patients<br>– DRD4-7R∗ (prenatal stress) → trait aggression in adulthood |
| *DAT1 (SLC6A3)* (5p) | VNTR (3–13 40-bp repeats) in 3′-UTR | 10R allele → lower DAT expression | Impulsive aggression, violent delinquencies, conduct disorder, poor inhibitory control |
| *Serotonergic neurotransmission genes* | | | |
| *SLC6A4* (17q) | 5HTTLPR (s,l alleles with 14 or 16 22-bp repeats) in promoter region | Short (s) allele → lower 5HTT expression | − Inconsistent association with aggression and impulsivity in different populations<br>− 5HTTLPR∗ (child maltreatment) → adult antisocial behavior |
| *TPH1* (11p) | SNPs in intron 7 | A779C/ A218C → reduced TPH activity | Impulsive aggression, unprovoked anger |
| *HTR1B* (6q) | SNP in single gene exon | G861C (synonymous) → lower HTR1B expression | Impulsive aggression |
| *HTR2A* (13q) | SNP in promoter region | A1438G → higher HTR2A expression (?) | Aggression, impulse control disorders |

*bp* base pair, *COMT* catecholamine-*O*-methyltransferase gene, *DA* dopamine, *DAT* DA transporter, *HTR1B* 5-HT receptor 1B type, *HTR2A* 5-HT receptor 2A type, *MAOA* monoamine oxidase A, *R* repeat, *SNP* single nucleotide polymorphism, *TPH* tryptophan hydroxylase, *UTR* untranslated region, *VNTR* variable number tandem repeat, *5HTT* 5-HT transporter

cited gene by environment (GxE) interaction paradigms. Finally, functional imaging studies show that MAOA-L carriers exhibit increased amygdalar reactivity to angry and fearful faces and negatively valenced memories retrieval as well as decreased prefrontal reactivity in inhibitory control tasks (Meyer-Lindenberg et al. 2006; Passamonti et al. 2006), thereby being more prone to aggressive behaviors than MAOA-H individuals.

The gene for the 5-HT transporter (5HTT or SERT), named *SLC6A4*, harbors an insertion/deletion polymorphism in its promoter region (5HTTLPR), which has been extensively studied in various internalizing psychiatric phenotypes and in aggression. The polymorphism consists of two common variants, the short (s) and long (l) alleles, containing 14 or 16 copies of a 20- to 23-bp sequence and associated with decreased and increased 5HTT expression, respectively (Lesch et al. 1996; Heils et al. 1996). 5HTTLPR has been inconsistently associated with human aggression, with studies most often reporting higher aggression in s allele carriers. However, 5HTTLPR was shown to interact with acute stress to produce laboratory-assessed aggressive expressions (Verona et al. 2006) as well as with child maltreatment (GxE) in predicting adult antisocial behavior (Cicchetti et al. 2012; Reif et al. 2007). Finally, functional imaging studies have shown that s allele carriers have increased amygdala reactivity to fear-inducing stimuli (Hariri et al. 2002, 2005) and reduced functional connectivity of amygdala to perigenual ACG compared to l/l homozygotes (Pezawas et al. 2005).

#### 3.2.1.5 Integration and Conclusions

Neurobiological evidence seems to substantiate the distinction between reactive and proactive aggression, which manifest in different psychopathological contexts. In reactive aggression, sensory (e.g., hearing or vision) deficits or distortions (caused by drugs, alcohol, or metabolic disturbances) can initially affect sensory processing of the provocative stimulus, increasing the likelihood that it is perceived as threatening; cognitive appraisal of the stimulus in limbic or higher cortical areas can then be modulated by coexisting cognitive impairment or disordered reality testing (e.g., in dementia or psychosis), current mood or anxiety disorders, past emotional conditioning, and affective dysregulation induced by early trauma (e.g., in personality disorders) as well as by cultural and social factors (Siever 2008). In any of these contexts, susceptibility to aggression can be understood as an imbalance between "bottom-up" proaggressive drives arising in limbic subcortical areas (amygdala, hypothalamus) and "top-down" regulatory/suppressing control circuits nested in limbic (OFC, ACG) or higher (VMPFC, DMPFC, VLPFC) cortical areas, which evaluate the salience of the threatening stimuli, adjust planned actions to social cues and environmental feedback, and anticipate their consequences or potential reward value. Connectivity between these subcortical and cortical circuits seems to be developmentally modulated by interactions between genetic susceptibility (e.g., MAOA or 5HTT gene polymorphisms) and early trauma. Finally, aggressive diathesis is further moderated by a continuous complex interplay of catecholaminergic neurotransmitter systems with pro-social neuropeptides (AVP,

oxytocin) and steroid hormones (testosterone, cortisol), which is gender-, context-, and developmental stage-specific.

On the other hand, less well-studied proactive aggression manifests mainly in the context of psychopathy. Recent evidence suggests that the core deficit in individuals exhibiting mainly proactive aggression is a hyporesponsiveness of the amygdala to fearful and sad facial expressions of others, which is necessary for developing empathy and a prerequisite for moral socialization by parents and peers. Psychopathy and youths' callous/unemotional traits are actually associated with a reduced responsiveness of both amygdala and limbic cortical (ACG, OFC) centers and a reduced connectivity between amygdala and VMPFC in emotional or moral tasks.

Concludingly, substantial progress has been achieved in understanding the neurobiological underpinnings of aggression, especially the reactive subtype. Further exploring the neurobiological signature of aggression will hopefully contribute to the development of clinically useful biomarkers and effective treatment strategies.

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# Temperament-Personality-Character and Evolutionary Biology

4

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## 4.1 Introduction

One peculiarity of humans is the marked differences observable in personality and behaviour. While most characteristics of living organisms converge from differences to similarity and a single optimum which is the most efficient and adequate in the given environmental circumstances leading to maximum adaptation and fitness, human personality traits and temperaments show several remarkably distinct manifestation levels considering each trait, temperament or characteristic leading to a multimodal distribution along these dimensions. Research has also revealed that such differences in personality traits are heritable, based to a large extent on genetic variability, and are also associated and interact with environmental influences. Thus the question emerges: unlike other genetically and biologically based characteristics of living organisms which through evolution aim towards manifesting in a single optimal phenotype with maximal fitness underpinned by a universal, invariant and species-typical genome, why are there such significant heritable differences observable in human personality (Penke and Jokela 2016)? If evolution generally aims at eliminating variation of less adaptive forms and thus at zero variance around the most fitness-increasing optimal level of a given characteristic, then why does genetic and phenotypic variation persist in such adaptive systems as personality and temperament? The answer to this question is hidden under understanding the genetic architecture and interactions shaping the manifestation of personality traits and temperaments.

Personality and temperamental traits are the most basic systems which underlie and govern how humans interact with their environment; therefore such systems are

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designed to be aimed at survival and reproduction. Evolutionary psychology is built on the adaptations theory, guiding the identification of such particular ancestral problems which favoured psychological adaptations through natural selection (Penke and Jokela 2016), and the evolutionary perspective on personality focuses on consequential life-related outcomes in the variation of personality, encompassing its effect on health, relationships and reproductive efficiency and life expectancy which are the most basic components and indicators of biological fitness (Nettle 2011). Thus personality evolution and psychological adaptation proceeds by mechanisms which have been designed by natural selection through evolution to solve specific adaptive problems (MacDonald 2012).

Very highly specific emotional and motivational structural neural systems underlie human behaviour, with important variation among people in the function of these systems (MacDonald 2012). In our current understanding, personality traits and temperaments have biological bases and are therefore heritable to a substantial, possibly differing degree (Penke and Jokela 2016), yet we still do not sufficiently understand their genetic background. Temperament definitions build on the centrality of biology (Buss and Plomin 1984; Rothbart 2016) in determining emotional reactions to stimuli. In contrast, personality, in addition to biologically based characteristics, also includes such components as beliefs, skills, morals, social cognition, which are more determined by social influences (MacDonald 2012).

Individual differences in personality and temperament which manifest in the normal range are variations in the evolved systems (MacDonald 2012), but what is the reason for the existence of a persisting variation in personality traits temperaments, which develop based on substantial polymorphic genetic components contributing to differences in neurobiology (Nettle 2005)? Differences in health, mating, social and sexual behaviour influence reproductive success, and as the marked personality variation contributing to interindividual differences significantly influences related processes, personality variation may be subject to natural selection (Nettle 2005).

There are several theoretical frameworks aiming to understand how the genetic variation underpinning personality differences is maintained. Each personality trait and temperament is polygenic and multifactorial, which means that a given trait develops based on a large number of genes, interaction between these genes and interaction between the genes and the environment. Most of the heritable individual differences are not adaptations themselves, but rather reflect dimensions which tolerate some degree of genetic variability (Penke and Jokela 2016). Adaptive individual differences are in fact conditional strategies which are implemented in universal adaptations, and which are elicited by specific cues in the environment (Penke and Jokela 2016).

One possible answer to the question of personality differences is the presence of substantial environmental heterogeneity in space and time which must be confronted by individuals (MacDonald 1995). Phenotypic variation in the population is likely the effect of a regime of fluctuating selective pressures arising from these divergent environments, each of which favours specific phenotypic values under certain conditions while disfavours them under others (Nettle 2011). This approach argues for the role and importance of environmental heterogeneity in maintaining

variation in personality and temperament, postulating that a personality profile which may be adaptive when an environment is rich in resources may be highly inadaptive in environments where resources are scarce and thus different personality traits and temperaments and constellations will be adaptive in different environments creating the basis for sustained personality and temperamental differences in humans (MacDonald 2012). Furthermore, as there is a correlation and covariation between facets and components of personality traits, the pattern of covariation may also provide clues about the synergistic relationship between behaviours in common situations (Nettle 2011).

## 4.2 Turning Points in the History of Evolutionary Psychology

Along with fashions in science, there has been a long history of increasing and decreasing interest evolutionary psychology, which saw a pike in attention in recent years. As evolutionary psychology aims at delineating how natural selection eventually locks the optimum of complex psychological adaptation in humans (Penke and Jokela 2016), it has been challenging to adapt evolutionary mechanisms to explain the differences observable in human personality traits and temperaments. Thus evolutionary psychology for a long time focused on the 'psychic unity of mankind' (Tooby and Cosmides 1990) rather than its individual differences, that is, on universally shared psychological mechanisms which contribute to limited phenotypic plasticity due to varying environmental input, but without much attention to genetic variability underlying observable personality differences or heritable traits (Figueredo et al. 2009).

This initial perspective meant that in the beginning evolutionary psychology aimed at uncovering species-typical mechanisms by focusing on situation-typical behaviours (Nettle 2005) and postulating that variability in behaviour is determined by the situation rather than underlied by genetic differences. Cosmides and Tooby (1995) stated that human genetic variation is largely reduced into functionally superficial biochemical differences, contributing to a universal and species-typical complex functional design in humans and observable individual differences arise mainly from noise (Tooby and Cosmides 1990). However, highly prevalent genetic polymorphisms described in the background of neurochemical and neuroanatomical systems giving rise to human behaviour indicate that between-human variation is far from superficial (Nettle 2005), but is rather strongly rooted in the genome and is the result of evolutionary processes and natural selection rather than accidental noise. This contributed to a shift of focus from species-typical mechanisms to inter-individual variations through the works of Buss (1991, 1999) and MacDonald (1995) as series of accumulating observations demanded attention and explanation for individual differences from an evolutionary psychology aspect. One such observation was that most early environment-induced phenotypic polymorphism showing lifelong stability observable in wild populations could have evolved only if there is not one universally optimal phenotype independent of context, but rather a series

of contexts acting throughout evolution each selecting for a different optimal phenotype (Nettle 2011). Another observation reasoning for genetically based interindividual variation was that heritable variation in crucial characteristics is ubiquitous and significantly exceeds what can be expected from and predicted by population genetic models, which also demanded explanation (Nettle 2011). Thus evolutionary psychology refocused from conceptualising human nature as a unity built from universally shared psychological mechanisms to understand interindividual differences in such universal characteristics. While universally shared mechanisms may indeed lead to some degree of phenotypic plasticity due to varying environmental effects and influences, it was also increasingly accepted that the between-individual genetic variability of traits should no longer be neglected (Figueredo et al. 2009). However, there is still very little research targeting this important question.

While Tooby and Cosmides (1990) claimed that personality traits which are variable and heritable cannot result from adaptation, most evolutionary psychologists suggest that individual differences in the manifestation level of personality traits and temperaments, though differing in their effectiveness in adapting to different strategies in complex social groups, are indeed adaptive in their nature (Figueredo et al. 2005; Buss and Greiling 1999), and besides personality differences leading to increased adaptation in social interactions, personality variation allows different individuals to be better suited to particular niches in both social ecological and physical environments (MacDonald 1995). However, the adaptationist view of evolutionary personality psychology would predict that eventually there would be no heritable genetic variation, which is contradicted by research supporting the heritable variance of human personality (Penke and Jokela 2016).

## 4.3 Human Personality and Personality Genetics from an Evolutionary Aspect

Personality traits and temperaments are theoretical constructs which exist functionally and predict typical behavioural reactions and tendencies evoked in given situations or settings but giving space for diverse adaptive reactions. Appearing randomly, behavioural tendencies and underlying psychological mechanisms can be fixated and become prevalent if they enhance adapting and fitness, thus leading to little variation, at least according to classical evolutionary theory, since in case of varying manifestation levels of a trait, one would contribute to higher fitness than the other; therefore natural selection would remove the variant with the lower fitness. From this aspect any psychological trait with a history of evolution and selection would not show a significant variation but rather be universal and species-typical (Nettle 2006).

It seems, however, that human nature cannot reach a global optimum (Workman and Reader 2014). Personality traits and temperaments being multigenic, there are a large number of genes encoding for complex adaptation mechanisms, and variation in any of those genes would disrupt the complex pattern of function (Nettle 2006). To overcome this problem, it was postulated that if there is variation in a trait,

it indicates that the given trait is not under natural selection, or, in other words, if there is heritable variation in a trait, then it indicates that it has no significance from an adaptive aspect (Nettle 2006).

From the 1930s, evolutionary genetics has been studying the origins and maintenance as well as the implications of genetic variations underlying personality traits, focused both on between-species and between-individual differences and on understanding the role of such evolutionary processes as mutation, selection, migration and drift in shaping personality besides providing information on its genetic background (Penke and Jokela 2016). While due to universal genomic identity there is a 99.9% overlap in the DNA base sequence in humans, with this shared genome giving rise to species-specific phenotypes in the focus of adaptationist evolutionary study, there is also significant phenotypic variation in one part due to phenotypic plasticity and in another part due to genotypic variation which is in the focus of evolutionary personality genetics (Penke and Jokela 2016). While inherited, this universal genome is never inert with a range of processes causing its physical alterations. Cell replication cycles inherently give rise to multiple copying errors and mutations leading to variation in the base sequence and contributing to the emergence of single nucleotide polymorphisms (SNPs), copy number variations (CNVs) or inversion and translocation of larger regions. Currently the 1000 Genomes Project reported more than 88 million variants including 84.7 million SNPs, 3.6 million insertion/deletions and 60,000 structural variants (1000 Genomes Project Consortium et al. 2015). The effect of mutation and polymorphism may or may not leave their marks in the expressed phenotype, with many not contributing to structural differences or not even impacting gene expression, while others severely disrupt either gene expression or regulation contributing to deleterious effects, and in rare cases improve function of the organism and its adaptation to the environment. While larger genomic rearrangements more severely disrupt expression and function contributing to prenatal death or birth defects, SNPs and CNVs, which are the most common sources of between-individual genetically based variations, can have a range of magnitude of effects on the resulting phenotype (Penke and Jokela 2016).

Personality differences are not governed by one or a few genetic variations but are built from quantitative traits with a multigenic or even omnigenic background, based on quantitative trait loci (Plomin et al. 1994) with possible additive effects or interactions between different alleles as well as with the environment contributing to different phenotypic manifestations which can be studied by comparing them across individuals in a given populations (Penke and Jokela 2016). Twin and adoption studies suggest that 30–60% of personality trait variation is accounted for by genetic factors, with the parents' level of a given personality trait being the strongest predictor of the level of that trait in the offspring (Polderman et al. 2015; Keller and Miller 2006). However, effect of individual genes and variants appears to be minute at most, and identified candidate gene effects can generally neither be replicated nor confirmed in genome-wide association studies (Genetics of Personality Consortium et al. 2015). In the background of personality traits thus a very large number of genes each with only a very small individual effect play a role. According to genome-wide complex trait analyses, common genetic variants explain 0–21% of

variance in personality (Power and Pluess 2015). The heritable psychological differences are underpinned by gene sets encoding neurophysiological functions which can be studied as more discrete and better characterisable endophenotypes. Several of these endophenotypes contribute to reaction types and behavioural tendencies, which together and in correlation give rise to observable traits influencing and determining behavioural output in given situations, and through the adaptiveness of a given reaction in a given situation influence fitness (Penke and Jokela 2016).

What is the reason behind the persistence of mutation and variation introduced by mistakes in DNA copying during the cell cycle? The primary source of variation is the appearance of mutations, and the level of variation in a population reflects a balance between the introduction of variance by mutations and selection aimed at eliminating them. As mutations are infrequent, in case of any trait based on a single gene, no strong selection would be needed to keep the variation near zero; however, if a number of genes are involved in encoding for a given trait, which is the case for personality and temperamental traits, then there is a large number of possible mutations, and selection would not be able to remove these as efficiently. Therefore in case of polygenic traits, there would be a significant amount of variation in the genome giving rise to observable variations in reactions, behaviours, personality traits and temperaments (Nettle 2006; Houle 1998).

## 4.4 Evolutionary Processes in the Background of Personality Variation

Evolution is an adaptive process underlied by constant interaction between multiple genetic and environmental factors directed towards increased reproductive fitness resulting in a great number of gene × gene and gene × environment interactions in the background of personality. Thus the best way to conceive evolutional processes in the background of personality is by understanding the process of evolution in response to stressors, events, influences and complex ecological surroundings (Cloninger 2009).

### 4.4.1 The Role of the Environment in the Appearance of Personality Variation

The aforementioned 30–60% genetic determination and heritability of personality traits leave 50–70% to non-genetic factors provided by environmental influences (Workman and Reader 2014). One asset of humans is selecting such an environment which suits both their capabilities and their needs and preferences which is covered under the term gene-environment correlation or niche picking. This also means that individuals with a given personality are most likely to put themselves in such environments where their particular personality profiles would yield the best possible results. There are varied environments, so each individual is able to pick a niche corresponding best to their personality (Penke and Jokela 2016).

Evolutionary theory is environmentalistic in that it is about the extent an organism adaptively fits its environment. Animal studies suggest that environmental heterogeneity imposes varying selection pressures on traits (Dingemanse and Kalkman 2008). Thus observable characteristic are the results of gene × environment interactions (G × E). However, while selection acts at the level of the phenotype, G × E interactions take place at molecular genomic levels contributing to a double role of the environment in evolutionary genetics by interacting with the genotype in producing the phenotype and then as a selection force determining its fitness and also its destiny (Penke and Jokela 2016).

Environment has a profound role in determining adaptiveness of a given phenotype and behaviour. In case of humans, the social environment with its social niches exerts heterogeneous effects, contributing to the diversification of personality traits in order to fit different social niches (Figueredo et al. 2009). Environments show high variation both in time and in space, and during the 3.5 million years of human evolution, there have been significant fluctuations in the environment. Adapting to such heterogeneous environments has three possible solutions, including developmental plasticity, genetic diversity and spatial migration. If a variable occurs over time, then developmental phenotypic plasticity is adaptive as long as there are reliable cues available to signal the optimal alternative phenotype under the particular conditions. In case of spatial environmental heterogeneity, the emergence of genetically distinct individuals showing variation along locally optimal trait levels will be advantageous. Those individuals who cannot adapt to the stress of ecological variability can migrate to environments which are more ecologically supportive. A mixture of these three distinct processes play a role in the background of human personality trait variability, and they likely contribute to the partial heritability and partial environmentality observable in case of personality traits (Figueredo et al. 2009). The currently prevailing theory postulates that humans originated in Africa and from there progressed towards the current global distribution of the human species which means significant climate differences which, coupled with development, contributed to different self-sustaining practices (Figueredo et al. 2009). Altogether, early ancestral humans had to face three basic types of selective environmental pressures including climatic, ecological and social (Geary 2005), with most major ones being social, but also the other types of selective pressures may have enhanced social competition over the limited resources. Thus sociality is likely the most important cause for personality variations in humans (Figueredo et al. 2009).

### 4.4.2 Putative Processes Governing Evolution of Individual Differences

Adaptive evolution proceeds by the accidental appearance of rare but fitness-increasing mutations and elimination of the less adaptive ones by natural selection, towards one most optimal and most adaptive design without any variation in the population (Nettle 2005). Human personality traits, however, exhibit both a highly complex design and a high degree of continuous interindividual variation which

indicate that they are underlied by a significant number of genetic polymorphisms at a large number of genetic loci (Penke and Jokela 2016). There are three possible approaches to explain the persisting genetic variation in the background of human personality traits, including selective neutrality, mutation-selection balance and balancing selection, which are not mutually exclusive but may rather operate in some combination (Verweij et al. 2012).

#### 4.4.2.1 Selective Neutrality

Selective neutrality postulates that variation in personality traits does not contribute to differences in adaptation or fitness; therefore these would drift randomly in frequency unaffected by selection, and while some variants are lost to genetic drift, variation will be maintained by the appearance of new mutations through a process called mutation-drift balance (Verweij et al. 2012). Tooby and Cosmides (1990) hypothesised that in the background of personality differences, accumulating fitness-neutral and consequentially selectively neutral mutations play a role, which have no impact on survival or reproductive success. Other authors, however, find the role of selective neutrality in the background of variation of personality highly implausible (Penke and Jokela 2016), as a given variation could be selectively neutral only if there are no costs and benefits associated with it in any of the relevant environments, that is, no G × E interaction can be observed, meaning that a given level of a trait in question cannot be more adaptive in one environment compared to another. Personality traits are well-reported to influence performance and outcome in various domains of life (Penke and Jokela 2016) and are related to various well-established components or proxy variables of fitness including mortality (Mosing et al. 2012), physical and mental health (Lahey 2009), physical attractiveness (Lukaszewski and Roney 2011), mating behaviour (Zietsch et al. 2010) and number of offspring (Verweij et al. 2012; Jokela et al. 2009). However, a zero net effect may also result from positive correlations and negative correlations with different fitness components counterbalancing one another (Nettle 2005), or it is also possible that as personality trait dimensions are in fact a spectrum of fitness-maximising alternative strategies, in the normal personality range, average fitness will be uniform (MacDonald 1995; Verweij et al. 2012). Also, genetic polymorphisms which have an impact on several traits could be neutral to selection when multivariate genetic constraints yield little variation in fitness effects, such as when individual personality traits have a significant genetic polymorphism and correlate with fitness (Verweij et al. 2012).

#### 4.4.2.2 Mutation-Selection Balance

The basic idea of mutation-selection balance is that genetic variance in personality traits would be maintained in a mechanism where any deviation from the optimal personality trait level is corrected through selection by the elimination of those alleles which predispose to trait levels outside the range of this optimum. This process also reduces genetic variation in the background of the trait but is complemented by the emergence of new mutations (Verweij et al. 2012). As human personality traits are multigenic, each of them is determined by a large number of

genes, all of them are subjected to random, although rare and mildly harmful mutation effects, continuously counterbalanced by selection maintaining fitness-increasing ones. Mutation-selection balance is likely to influence components of cognitive fitness (Penke and Jokela 2016) or traits underpinned by a large number of rare variants each contributing a very small effect (Verweij et al. 2010).

From the aspect of mutation-selection balance, explanations postulate that fitness-maximising selection would contribute to the emergence of one optimal adaptive design. However, random mutations disrupting this design and therefore decreasing fitness should also arise. Most of such nonneutral dominant mutations with a strong effect will randomly disrupt the function of sophisticated systems and are thus harmful and are therefore easy selection targets shortly removed; so recessive mutations or ones with a weak effect are the ones which are likely to persist and spread to become common (Penke and Jokela 2016; Eyre-Walker 2010). With the constant appearance of new mutations, all individuals carry an individual pattern of the accumulated mutation load consisting of rare, partly recessive and mildly deleterious alleles (Verweij et al. 2012). In addition, everyone carries about 500 harmful mutations which is also likely to contribute greatly to the variance in fitness-related traits (Penke and Jokela 2016). More than half of the human genome is expressed in the brain (Sandberg et al. 2000), and personality traits arising from a large number of loci have a large mutational target size so have the potential to be more exposed to the effect of mutations (Verweij et al. 2012).

There are several characteristics of personality traits which cannot be explained by mutation-selection balance, including the various candidate genes associated with personality traits, the intermediate prevalence rates, and the fact that nonadditive variance is in many cases as high as additive variance which makes it unlikely for mutation-selection balance to account for variation in personality traits. Mutation-selection balance is rather a plausible mechanism to account for the genetic variation in the background of characteristics which affect overall functionality, such as intellectual function, than an explanation for the variation in personality traits and temperaments (Penke and Jokela 2016).

#### 4.4.2.3 Balancing Selection

While in the previous cases mutations are either invisible to selection, or selection depletes but cannot eliminate all variation, in the process of balancing selection, selection actually maintains variation by fluctuating selection pressures. Environmental conditions show a significant spatiotemporal variation thus contributing to a spatiotemporal fluctuation of selection pressures for different alleles (Penke and Jokela 2016). Balancing selection by environmental heterogeneity thus means that the same personality trait in different places or at different times may be influenced by selection pressures acting in different directions; thus in general and on average, no genetic variant could consistently be favoured over the other variants, contributing to the persistence of variation in personality traits with environment-contingent fitness consequences (Penke and Jokela 2016). Personality traits are likely to be influenced by balancing selection underlied by a limited number of medium-effect common genetic variants as opposed to mental disorders

which may arise as a consequence of a large number of mildly deleterious rare variants and mutations (Penke et al. 2007). As human beings show a tendency to actively search for and construct their environments and adapt to these, personality traits are plausible to be under balancing selection rather than either being neutral to selection or being under stabilising selection (Penke and Jokela 2016). While selective neutrality and mutation-selection balance maintained genetic variation because it couldn't be depleted by selection, if selective forces are balanced, it is selection itself which would maintain variation, for example, in cases where, due to both extremes of a personality trait being adaptive in the same magnitude but under different conditions, both extremes are favoured by selection (Penke and Jokela 2016).

Balancing selection has various types including environmental heterogeneity or negative frequency-dependent selection which latter favours traits occurring at a low frequency (Penke and Jokela 2016). In case of balancing selection, there should be several varying selection pressures which under different conditions favour different phenotypes and should be stronger than that unidirectional selection pressure which favours a single optimal trait level in a given environment. The consequence would be either a whole continuum of phenotypes or the appearance of multiple distinct phenotypes with identical average fitness averaged across all environments which cannot be optimised further (Penke and Jokela 2016).

As during evolutionary history humans were exposed to significantly varied and changing social and physical environments, the genetic variation underpinning personality traits is likely to have been maintained by balancing selection by environmental heterogeneity mediated by negative frequency-dependent selection on life history strategies (Penke et al. 2007; Penke and Jokela 2016).

## 4.5 Individual Differences from an Evolutionary Aspect

There are consistent differences in the behaviour between individuals belonging to the same species even under the same ecological conditions, contributing to a previously ignored but in fact substantial amount of within-species interindividual differences in reactions in a given environment, commonly referred to as personality differences (Nettle and Penke 2010). While personality differences are likely adaptive, and impact and determine suitability to different ecological and social niches, they also put a constraint on the behavioural repertoire and flexibility which is a function of the constellation of personality characteristics arising from an interaction between genetic and environmental factors during early development (MacDonald 2012). This constraint may appear maladaptive since as a consequence individuals would not be able to exploit the full range of possibilities within different situational contexts. However, the biological preparedness for certain behaviours and the developmental plasticity of these behaviours may vary independently (Figueredo et al. 2009). Individuals are prepared to pick environments where their prepared behaviours would be suitable, and individuals manifesting different personality and temperamental traits orient towards different niches best suiting their personality, and benefits of selecting suitable social niches allowing for the best

performance overcome the constraints imposed by personality differences (Figueredo et al. 2005).

As investment in one component of fitness usually takes place at the cost of other components, it is hard to establish an obvious and clear advantage or disadvantage. However, at a given point in space and time, there could generally be an optimum value for a trait from the aspect of fitness, and this optimum shows variation across space and time. This means that there would be a complex interaction between spatiotemporal variation in selective optima and tradeoffs in different fitness components, also applying to personality traits. However, as there is a gene flow between populations, if all populations are taken together, a normal distribution of genetic polymorphism-based traits can be observed, while in different subpopulations at different times and in different spaces, the optimal levels of that given trait may differ (Nettle 2006). Due to the polygenic or even multigenic nature of personality traits and behavioural phenotypes coupled with the fluctuating nature of selection, variation is both normal and ubiquitous. Behavioural alternatives can be considered as tradeoffs with any level of a trait giving rise to a mixture of costs and benefits rather than an obvious advantage, so the optimal value of a trait would be a function of the given circumstances (Nettle 2006), contributing to several different optimal values in the manifestation of a given trait.

## 4.6 Evolutionary Aspects of Personality Trait and Temperament Dimensions

Personality as a constellation of behaviours and reactions has an obvious impact on fitness. In humans most of the between-individual behavioural variation can be accounted for by 3–7 basic personality dimensions or traits, and about 30–60% of between-individual variation of personality traits is due to genetic variation according to twin family and adoption studies (Verweij et al. 2012; Johnson et al. 2008). In spite of this high heritability, it is not fully understood how heritable variation in genetic background is maintained. There have been no common genetic variants consistently and replicably identified associated with personality factors and differences. This missing heritability observable in case of the majority of complex traits has been partially explained by the fact that the majority of variants with a small effect have not been identified as yet, or that available genotyping methods have a low capacity to detect rare variants, or that structural variants including CNVs cannot be sufficiently captured by current methods, or have been attributed to the low power of current methods to detect gene-gene (G × G) interactions. Lack of common genetic variants associated with personality traits even in GWAS-s suggest that other mechanisms should account for personality variation (Verweij et al. 2010). During development personality shows a genotype-determined and early environment-influenced canalization of the manifested behaviours, followed by stability after the developmental phase in spite of changes in environment and circumstances (Verweij et al. 2012). While personality is highly stable, between individuals it clearly varies along quantitative dimensions with continuity (Nettle and Penke 2010).

The most comprehensive and acceptable explanation of evolution of personality differences as discussed above postulates that selection effects on personality show variation in space and time and by condition; thus personality variation is adaptive. Payoffs may vary based on the frequency of personalities in the population leading to frequency dependence influencing fitness. Adaptive value of personality variation considering costs and benefits of specific dispositions and how it maintains multiple phenotypic equilibria can be conceptualised in case of individual personality and trait dimensions.

Personality traits and temperaments are defined as relatively stable dimensions of describing individual differences related to behaviour, affect and cognition, conceived as major reflections of causal agency embedded in humans by evolutionary processes (Bouchard Jr. and Loehlin 2001). While personality traits have distal causes, they are influenced, triggered and moderated by proximal internal and external stimuli (Bouchard Jr. and Loehlin 2001). Several personality models exist describing personality at the intersection of a varying number of traits starting from three in the Eysenck model and going up to 16 in Cattell's model just to name a few better known ones. The Big Five or five-factor personality models describing personality variation along five trait dimensions are the most prevalent in studies with several lines of evidence supporting their validity. Thus several researchers hypothesised selection regimes for personality traits at this hierarchical level, although some Big Five personality trait dimensions share common mechanisms and therefore are not entirely orthogonal. Furthermore each of the traits in the five-factor personality model consists of a number of facets expressing motivational and behavioural tendencies which often belong to different life domains, and it is not straightforward why they cluster together in their trait which is purely a result of factor analytic studies with little information on why the given facets are related (Nettle 2011).

### 4.6.1 Evolutionary Aspects of the Five-Factor Model of Personality

The axes of the five-factor model of personality capture the major dimensions in human dispositional variation by describing stable individual differences in people's reactions to circumscribed classes of environmental events, defining characteristic ways of thinking, feeling and behaving clustered in five independent traits. Descriptive work related to the five-factor models in personality research captures about 50% of dispositional variation reflected in a variety of languages concerning the most robust dimensions of personality. Twin studies suggested a 40–50% role of genetic variation in determining each of the five traits (South et al. 2018), while genome-wide complex trait analyses estimated that contribution of common genetic variants explains 0–21% of variance of the individual traits, with the highest heritability reported for neuroticism and openness and the smallest for conscientiousness and agreeableness (Power and Pluess 2015; Genetics of Personality Consortium et al. 2015). These latter figures are much lower than those reported in previous quantitative genetic

studies reflecting a significant missing heritability possible explained either by rare mutations or substantial and widespread epistatic or gene × environment interaction effects (Penke and Jokela 2016; Johnson et al. 2008).

In case of the five-factor model traits, several lines of evidence were previously presented for balancing selection maintaining variance in the individual traits, specifying fitness costs and benefits for each dimensions (Nettle 2005, 2006, 2011). As discussed above, given the temporospatial fluctuation of selection pressures, differing environmental contexts in a given time favour different optimum trait manifestations with distinct cost-benefit curves, contributing to the maintenance of a range of distinct personality trait levels with separate costs and benefits. The large amount of evidence available for the effect of personality traits in the five-factor model on such fitness-relevant outcomes as life expectancy, relationships, mating success or health (Roberts et al. 2007) clearly indicates that personality traits are not neutral from an evolutionary and fitness-related perspective; thus there are both possible fitness benefits and costs of being high or low on each personality trait dimension. The key is to identify in case of each personality trait the costs and benefits corresponding to different phenotypes in different environmental contexts (Nettle 2006, 2011). Putting it very simply, the five higher-order traits in the five-factor personality model represent basic dimensions of social adaptation: who is good company (extraversion), who is kind and supportive (agreeableness), who puts in sustained effort (conscientiousness), who is emotionally undependable (neuroticism) and who has ideas that pan out (openness) (Bouchard Jr. and Loehlin 2001).

#### 4.6.1.1 Evolutionary Aspects in Differences in Extraversion

Extraversion, part of both Eysenck's three-factor and all five-factor models of personality is one of the most researched and best described personality traits from various aspects. There are three types of conceptualisations of extraversion. The first type includes models associating extraversion with activation vs. inhibition of impulses, contributing to differences in behavioural approach or the sensitivity of the reward system. The second cluster of conceptualisations contains models which focus on the involvement of extraversion in hierarchical and leadership potential disposition to wield power as well as dominance and submission, while the third type of models conceptualises extraversion in terms of a motivational predisposition to experience social interactions as rewarding, expressed also in terms of assertiveness vs. passivity in initiating social contacts (Denissen and Penke 2008a). These various aspects of the single trait of extraversion also reflect that costs and benefits of distinct and varying manifestations along the extraversion dimension will also be manifold and complex.

From the aspect of activation and inhibition of impulses, extraverted behaviour may be a consequence of the strength of response to such naturally rewarding stimuli as sex, food, physical excitement and joy; thus these cues will be more salient for extraverted persons who consequentially invest more energy in them (Denissen and Penke 2008a). On a psychological level, extraversion is related to positive emotionality, exploration, and reward, and is thought to be underlied by the reward circuitry with dopamine as the chief neurochemical determinant. Extraversion shows a strong

positive relationship with several evolutionally relevant behaviours such as the number of sexual partners which has an obviously positive impact on fitness at least in men (Nettle 2006), and is also related to the chance of partnering with higher quality partners. Beyond mating, high extraversion also correlates with higher sensation seeking, through more social behaviour initiation consequentially yielding more social support, higher physical activity and more exploration. The evolutionarily positive aspect of these behaviours is easy to grab. This all, however, is also associated with increased risk of exposure to dangerous and harmful situations, as evidenced by such contemporary consequences as higher hospitalisation risk for traumatic injury, accidents, and illnesses, higher chances of migrating, committing criminal acts or antisocial behaviour and being arrested, which in the ancestral environment probably meant ostracism or death (Nettle 2005, 2011). Contemporary consequences of behaviours related to higher extraversion also include an increased risk that children will be exposed to step parents which in turn is a risk for their well-being. So while the high side and benefits of extraversion include increased mating opportunities and exploration of novelties in the environment and thus increased access to possible novel resources, it also has risks for personal survival and welfare of offspring; thus this tradeoff curve probably has no universal optimum but is rather determined by such local conditions which cause a constant fluctuation of optimal value due to changes in density and behavioural strategies which contribute to the retainment of its genetic polymorphism (Nettle 2006).

Considering the second aspect of extraversion related to hierarchy and leadership, a cost-benefit analysis of tradeoffs along the continuum suggests that extraversion represents a variability in phenotypic strategies related to social exchange and hierarchy negotiation. High extroversion means more superficial participation in social exchange with a lot of people, while low extraversion means a smaller number of deep engagements and solitary activities. Thus the benefit of high extroversion will include large cooperative networks increasing potential gains in trade through dyadic exchange and collective action. Costs on the other hand arise from socialising with non-relatives which consumes time, energy and other resources which could be invested in close relationships or other fitness-relevant tasks, risks potential exploitation or increases exposure to pathogens. Optimal level of extroversion among ancestors varied with circumstances buffering either against potential costs or increased potential benefits of participating in social exchange with a large network of cooperative partners. So for anyone who is unlikely to be exploited, able to easily attract quality associates and unlikely to contract communicable illnesses, there would be a higher optimal level of extraversion (Lukaszewski and von Rueden 2015). Another facet of extraversion is motivation to attract social attention and compete for high social status and leadership positions. Extraversion aspects pertaining to individual differences in status motivation such as assertiveness, social boldness or desire for attention can be conceptualised as a leadership-followership gradient. Cost related to leadership orientation mostly arise from the costs of acquiring and maintaining influence, while benefits arise from the advantages related to high status and respect. On the other hand, followers unlike leaders benefit from participation in collective actions and without paying the costs of competing for and

implementing leadership. Optimal level of status motivation for ancestors varied with circumstances altering potential benefit of leadership and followership, such as possession of characteristics determining leadership ability or the ratio of leadership-oriented individuals to followers in the local social world (Lukaszewski and von Rueden 2015). Phenotypic strategies related to cooperation and hierarchy are also relevant for mating (Lukaszewski and von Rueden 2015) as far as extraversion means proactively approaching and getting attention of others which facilitates mating, while females prefer resourceful and high status mates. Competing for access, however, also increases risk for conflicts with rivals, while mating with multiple partners increases risk of STD exposure and the burden of multiple offspring (Lukaszewski and von Rueden 2015).

Taken together, from the aspect of cost-benefit tradeoffs of the extraversion continuum, high extraversion means several benefits including a larger cooperative network, more success on the mating market, increased likelihood to attain positions of higher social status and leadership, a higher likelihood of increased social alliance formation, increased exploration, as well as access to resources, but it is also more likely that as costs those high on extraversion experience antagonistic conflict, spend limited time and energy in socialising, are exposed to multiple increased physical risks, are more likely to contract illnesses and sustain injuries and in general have a lower life expectancy (Lukaszewski and Roney 2011; Lukaszewski and von Rueden 2015; Friedman et al. 1995; Nettle 2005; Samuels et al. 2004). Weighing costs and benefits, high extraversion still positively predicts reproductive success, especially in males. A complete theory of the origins of extraversion would explain whether and how distinct personality strategies manifested by individuals are adaptively patterned in relation to variable circumstances and why natural selection maintained differences in extraversion despite the consistent positive association of its high levels with reproductive success (Lukaszewski and von Rueden 2015).

Considering also the environmental context, high extraversion carries a net fitness cost in adverse environments, while in safe environments a net benefit, environmental variability and fluctuation thus maintain genetic variation in extraversion (Nettle 2011). The end results of net increase or decrease in fitness arising from extraversion varies in two ways. First, there may be individual characteristics determining the optimal level of extraversion. Individuals with increased physical strength, attractiveness and an immune function are better suited to face the risks associated with extraversion; thus their optimal levels of extraversion are higher. Second, considering beyond-individual levels, there are ecological contexts, such as fluid social structures or novel habitats which specifically favour risk-taking attitudes, where the optimal level of extraversion will also be higher. On the other hand, in social structures with already saturated habitats and stable hierarchies increased cautiousness would be more optimal (Nettle 2011). In general, nomadism and new environments favour sociability, assertiveness, sexual motivation and high physical activity, whereas in ecologies with established social structures, none of these are favoured (Nettle 2011). Altogether, the optimal level of extraversion will vary across individuals sharing a given habitat, within one habitat over time, and will also vary across habitats which leads to the maintenance of the full range of phenotypic variation (Nettle 2011).

There is only little evidence supporting common alleles explaining personality traits or other aspects of personality including extraversion, as generally candidate gene studies either provide contradictory results or fail replication, and there are generally no SNPs with genome-wide significance identified for personality traits. Common variants collectively explain only about 10% of variance in extraversion which is a small percentage of heritable variance, leaving the remaining variance to be explained by very rare alleles due to recent mutations (Verweij et al. 2012). The distinction between adaptiveness of different levels of extraversion in different circumstances, however, is evident also at the genetic level. The long alleles of the *DRD4* gene which encodes the D4 dopamine receptor and have been associated with extraversion-related traits and behaviours are significantly more common in nomadic populations or in populations having completed long migrations historically, as compared to sedentary populations (Chen et al. 1999; Ebstein 2006), which we will discuss under novelty seeking, a construct related to one aspect of extraversion. This association, however, only informs about the association between nomadism and extraversion on a genetic level, but does not indicate whether nomadism selects for increasing extraversion or extraverted populations have an increased propensity for migrating lifestyles (Chen et al. 1999).

#### 4.6.1.2 Evolutionary Aspects of the Neuroticism Trait

Neuroticism or emotional stability/lability is related to differences in affect regulation and intensity, handling of stress and facilitation of performance under pressure, and in general reflects sensitivity of a domain-general system to respond to environmental threats, and vigilance to environmental hazards as well as increased risk aversion (Denissen and Penke 2008a). Neuroticism reflects variability of the levels of negative emotions including fear, anxiety, guilt or sadness and is a strong predictor of psychiatric morbidity, especially anxious and depressive manifestations, besides showing an overall negative impact on physical health due to the overactivation of stress-related processes (Gurven et al. 2014; Nettle 2006).

While these associations of high neuroticism generally grab the negative and maladaptive side of the trait, there also have to be benefits as indicated by the globally normal distribution of this trait. In ancestral environments the adaptive aspect of neuroticism may have been the avoidance of acute dangers by enhanced detection of potentially threatening stimuli as reflected in the constant apprehension and increased startle response, as well as anxiety and also increasing reaction and its decreasing latency to these stimuli. From this aspect negatively interpreting ambiguous stimuli and fixing attention on such stimuli is also adaptive (Nettle 2006). In environments where threats are more prevalent, more sensitive threat detection mechanisms are needed and are advantageous even at the expense of false positives and the negative physiological consequences of these (Haselton and Nettle 2006). On a neuropsychological level, neuroticism is associated with increased performance on psychomotor tasks related to detecting predators. Animal studies also support the advantage of vigilance and wariness to avoid predators and dangers. However, in the absence of predation risk those benefits also disappear. Environments with high actual threats or where individuals are poorly able to deal with undetected

threats favour high neuroticism, while selection reduces it in more benign environments. Furthermore, in modern life actual physical threats are less, while the negative psychophysiological and health consequences of increased neuroticism are more apparent. Nevertheless, those seeking highly risky environments such as alpinists show low neuroticism, and as these occupations show an increased lethality, avoiding them through neuroticism is indeed adaptive.

Also, there is a positive correlation between neuroticism and competitiveness and thus academic success and working on to bettering one's own position. Low neuroticism has further disadvantages like lack of striving, while high neuroticism is an achievement and competition motivator which is adaptive if you can succeed (Nettle 2006).

High neuroticism, as briefly touched upon above, is associated with serious drawbacks including increased risk of stress-related physical and mental illness and, due to increased negative affect and anxiety, difficulties in relationships (Neeleman et al. 2002). Neuroticism-related diseases are more common in women (Costa et al. 2001) even though the environment they experience is the same; thus it appears this is because the impact of undetected threats differ in genders, as succumbing to physical hazard or social ostracism has more serious effects on reproductive success in women because of greater effect on offspring survival (Nettle 2011). Neuroticism also predicts social isolation and failure (Gurven et al. 2014; Nettle 2006).

In summary, neuroticism is composed of vigilance to physical and social threats, perceived vulnerability to disease, and angry hostility, and has benefits related to increased vigilance to threats, while its costs include related mental and physical illnesses as well as its consequences on relationships (Nettle 2011; Denissen and Penke 2008b). Optimal level of neuroticism depends on actual conditions and other characteristics and traits of the subject (Nettle 2006).

#### 4.6.1.3 Evolutionary Aspects of the Openness Trait

There are several approaches to conceptualise the trait of openness, but all of them involve a high level of cognitive activity and a broad, deep and permeable consciousness, a high capacity for innovation, advanced problem-solving skills, engagement in the intellectual and creative domain, capacity to process incomplete information as well as intrinsically motivated curiosity enhancing cognitive competence (Denissen and Penke 2008a).

Openness is related to artistic creativity which attracts mates as it is associated with increased sexual attractiveness. However, openness, as a cognitive style associated with seeking novelty and complexity, and making associations between apparently unconnected domains, correlates with unusual experiences; increases inclination to paranormal beliefs, schizotypy, a break with reality, and eventually delusions and psychosis; and is also elevated in schizophrenia patients. Thus individuals on the high end of the openness dimension can be both socially successful through creativity or become socioculturally marginalised through bizarre beliefs and related behaviour (Nettle and Clegg 2006). The emergence of disorganised psychotic or psychotic-like beliefs is a clear cost of high openness.

Schizotypy and similar conditions also significantly diminish mating chances that are otherwise associated with increased openness. It is hard to determine when openness leads to positive and when to negative consequences, and whether this outcome is determined by the level of the trait or rather by an interaction with life events; thus the outcome is highly context-dependent (Nettle 2006). In case of the openness dimension, not so much different ecologies select for different levels, but different levels of openness are optimal depending on other characteristics (Nettle 2011).

#### 4.6.1.4 Evolutionary Aspects of the Conscientiousness Trait

Conscientiousness is involved in task-related behaviours including intensity of engagement, monitoring nonattainment of goals, executive regulation in the performance domain, capacity for reliable work and enduring commitment, as well as trustworthiness and dependability (Buss 1991). Conscientiousness involves self-control in pursuit of goals and orderliness, delaying immediate gratification for a long-term good manifested in and associated with goal-orientedness, being hard-working and cautious about health with such components as industriousness, and orderliness which lead to such benefits as planfulness and care in premediated tasks (Nettle 2011).

Both ends of the conscientiousness dimension have positive aspects related to promotion of immediate vs. distant goal striving (Denissen and Penke 2008a). While conscientiousness is associated with longer life expectancy through engaging in healthy behaviours and avoiding unhygienic risks, in extremely high levels conscientiousness-related traits such as perfectionism and self-control have been related to obsessive-compulsive personality disorder and eating disorders. In ancestral and also contemporary environments, being obsessional may be adaptive through increased safety as well as its relation to high achievement, but rigidly sticking to sometimes pathological routines and missing spontaneous opportunities which would enhance reproductive fitness are damaging. This latter is exemplified by the association of conscientiousness and missing short-term mating episodes, which means that in case of increased conscientiousness, by emphasising long-term payoffs, the opportunistic grabbing of middle payoffs would be decreased (Nettle 2006).

Higher levels of conscientiousness are associated with making plans and sticking to them which leads to high office and school attainment in the modern world, and being able to stick to internally generated plans and goals in the face of distraction may have been advantageous in ancestral contexts which involved repeating tasks when outcomes and optimal schedules were predictable (Nettle 2011). Other situations, however, like those including a sudden attack or opportunistic hunting can't be planned and thus require spontaneous reaction without the chance for extensive reflection. Costs associated with conscientiousness thus include rigidity, inflexibility, difficulty in adapting to changing circumstances as well as the likelihood to miss short-term mating and resource opportunities (Nettle 2011; Schmitt 2004). Those towards the high end of the conscientiousness dimension also tend to perform worse when spontaneous response is needed to changes in the environment because they

stick to previously defined goals. Thus while both of the two major aspects of conscientiousness including industriousness and orderliness (DeYoung et al. 2007) can be useful in scenarios which involve recurrent maintainment, management and exploitation of the same resources in a predictable manner, neither of them is advantageous in case of opportunistic or unpredictable exploitation of resources which explains why variation in the level of conscientiousness with varying environmental contexts is adaptive (Nettle 2011). Optimal balance between planfulness and spontaneity depends on local ecology and personal role and the nature of resource extraction tasks (Nettle 2011).

#### 4.6.1.5 Evolutionary Aspects of the Agreeableness Trait

Agreeableness is related to differences in motivation to cooperate versus acting selfishly in resource conflicts, and also reflects individual differences in the tenacity of goal pursuit under distracting circumstances (Denissen and Penke 2008a). Agreeableness can be interpreted in two major ways: on the one hand, from the aspect of fostering intimate family relationships and parental investment, and from a dispositional aspect, with a role in human cooperative behaviour, willingness to cooperate, acting cooperatively vs. acting competitively, trust vs. self-interest, and coordination vs. opposition of joint interests, with high scorers more likely to avoid interpersonal conflicts but also to be stuck in prisoners' dilemma games (Denissen and Penke 2008a). It shows correlation with empathy, which is in turn correlated with theory of mind and awareness of the mental states of others, and trust, while its absence is associated with antisocial traits and antisocial personality disorder. In highly social species ability to understand others' mental states is highly advantageous, as it facilitates interactions and cooperation, thus leading to the avoidance of violence and interpersonal hostility. However, excessive or unconditional trust also isn't adaptive. Furthermore, high agreeableness may lead to excessive attention to needs and interests of others in expense of one's own well-being and needs. Agreeableness is also negatively related to creativity and achieving higher status. Thus investing positively in others does not maximise fitness, and while empathic cognitive style is adaptive in social species, its costs are exploitation or inattention to personal material or fitness needs and gains. Also, a population where cooperativeness and agreeableness are widespread, offers large advantages for less agreeable cheaters or sociopaths for exploitation, so frequency-dependent advantages to agreeableness would maintain a mixture of phenotypes at an equilibrium (Nettle 2006, 2011).

Thus while benefits of high agreeableness include increased likelihood of cooperative ventures and engaging in harmonious alliances, its risks include failure to maximise personal returns and falling victim to cheaters (Nettle 2011). While high agreeableness is associated with investment in cooperative joint ventures and harmony in interpersonal relationships which is beneficial in human societies, and selection favours coordination with others, in certain contexts this can be counterprofitable with increased benefit for individuals fending themselves off. Whether increased or decreased level of agreeableness is adaptive depends on the available resources as well on the local social structure (Nettle 2007).

### 4.6.2 Evolutional Aspects of the Traits and Temperaments of the Psychobiological Model of Personality

Unlike the five-factor personality models which were developed exclusively based on a lexical approach, the Cloninger taxonomy of personality was developed to reflect the psychobiological aetiology of personality components, incorporating results of genetic, longitudinal developmental as well as neuroanatomical and pharmacological studies on behaviour and behaviour conditioning, and human and animal learning studies with psychometric research. The original four temperamental dimensions, novelty seeking, harm avoidance, reward dependence and persistence were theoretically associated with independent neurobiological systems developing on nonoverlapping genetic backgrounds, and each temperamental dimension has initially been associated with activity of specific neurotransmitter circuits (Verweij et al. 2010; Cloninger et al. 1993). The revised biopsychosocial model includes four temperamental and three character domains where temperaments are conceptualised as heritable biases in memory processes involving presemantic perceptual processing and encoding of visuospatial structural information and affective valence, processes functionally organised as independently varying brain systems aligned to monoaminergic systems for autonomic responses involved in activation, maintenance and inhibition of behaviour (Gillespie et al. 2003). Character traits on the other hand are conceptual memory biases involved in processing or conversion of sensory input into abstract symbols which translate into concepts of personal, social and universal identity (Gillespie et al. 2003). So while temperaments are involved in behavioural conditioning, character traits are in conceptual learning. Both temperaments and character traits are heritable, and they are likely to involve different brain systems evolving in different stages of evolution of learning in animals (Gillespie et al. 2003).

Heritability estimates for the temperamental traits measured by the Tridimensional Character Inventory (TCI) and the Tridimensional Personality Questionnaire (TPQ) are estimated between 30 and 60% (Gillespie et al. 2001, 2003; Keller et al. 2005) which magnitude corresponds to heritability of other personality traits. In spite of this, no specific genetic variants surviving replications have been identified, although meta-analyses indicated an association between *DRD4* encoding the D4 dopamine receptor and novelty seeking explaining a 3% variance (Munafo et al. 2008), while there are conflicting results concerning the association between harm avoidance and *5-HTTLPR* (Munafo et al. 2009; Minelli et al. 2011).

Temperamental dimensions in the biopsychosocial model carry a high likelihood of being related to fitness. More recently a genome-wide association study with SNP data from 8000 subjects indicated little, on average 7.2% variation in temperamental dimensions due to the combined effect of common, additive genetic variants across the genome, and concluded that common genetic variants do not contribute significantly to temperamental variation suggesting other mechanisms in its background, and that most heritable personality variation is due to rare variants and/or a combination of dominance and epistasis (Verweij et al. 2010). These findings are consistent with genetic variation in personality traits having been maintained by mutation-selection balance (Verweij et al. 2012).

While the current psychobiological model contains four temperamental and three character dimensions, only the temperament dimension of novelty seeking has been extensively examined from an evolutionary point of view.

#### 4.6.2.1 Evolutionary Aspects of Novelty Seeking

Novelty seeking, linked to dopaminergic activity in the original psychobiological model (Cloninger et al. 1993), is associated with behaviour activation and initiation as well as with a tendency to react to novelty, cues of reward and cues of relief from punishment, and shows overlap with extraversion to a certain extent. In several studies genetic variation in the *DRD4* gene encoding the D4 dopamine receptor have been associated with both extraversion and novelty seeking, although the majority of studies focused on this latter (Golimbet et al. 2007).

Studies clearly indicate evolutionary drivers in the background of between-population variations observable in case of the *DRD4* exon III locus associated with novelty seeking. *DRD4* exon III allele frequency has been shown to exhibit significant geographical variation with striking differences described in studies comparing several populations (Chen et al. 1999; Gören 2016; Matthews and Butler 2011), and an association has been reported between this global distribution of variants and variation in novelty-seeking levels, which also provides insight on the evolutionary advantages of differing levels of novelty seeking and adaptiveness of between-individual personality variation as opposed to a single optimal level in general.

Adaptive nature of *DRD4* variants in migratory societies appears important in geographic areas and environmental conditions unsuitable for sedentary practice. Hyperactivity, inattention, impulsiveness, response-ready traits and explorative behaviour associated with novelty seeking may be adaptive in rapidly changing, hostile and resource-depleted environments, and in societies and populations constantly on the move through unfamiliar environments (Chen et al. 1999). Greater distance from East Africa was associated with higher *DRD4* exon III heterozygosity, explaining 21% of variance, while the remaining nonexplained variation in heterozygosity is due to other factors including genetic drift, population-specific histories, and environmental conditions (Gören 2016). There is a clear geographic pattern of *DRD4* exon III allele frequencies, with a clear shift from the 4-repeat to the 7-repeat allele since the exodus from Africa (Gören 2016). The 4-repeat allele is observed in every population suggesting that it is the ancestral variant (Wang et al. 2004). The 7-repeat allele is the second most observed predominantly in American and also European populations, and nearly absent in Asian populations, while the 2-repeat variant is frequent in Asian and Oceanic populations and uncommon in Africa, suggesting that the observable polymorphism in the *DRD4* gene may be the result of a recent mutational event of positive selection after the exodus from East Africa 40–50,000 years ago (Matthews and Butler 2011). That is, migratory distance increases the frequency of long allele variants with 6- and 7-repeats; however, frequency of an 8-repeat variant is not correlated with distance from Africa but rather with local biogeographic conditions. Altogether, research on the worldwide distribution of *DRD4* exon III allele frequencies in a large sample of indigenous populations clearly indicated that migratory distance from the east of Africa, considered as the origin of the

development of humankind, and population-specific biogeographic factors including latitude, suitability of land for agriculture, pasture land and terrain ruggedness all contribute to between-population variance in *DRD4* polymorphisms and are most likely to be the key selective forces defining the appearance and distributions of its variants (Gören 2016). In harsh environments or where resources are scarce which are characteristic of hunter-gatherer societies, cooperation, strong pair bonds and family ties, and investment from both parents are necessary for survival and to secure effective reproduction which contributes to the retainment and maintenance of more ancestral and risk-averse *DRD4* variants (Harpending and Cochran 2002). On the other hand, the relatively evolutionarily newer 7-repeat allele of *DRD4* which has been associated with response-ready and extraverted novelty seeking shows a higher frequency in the western hemisphere including Europe and America compared to Asia (Chang et al. 1996). Specific circumstances, where this type of novelty-seeking behaviour is advantageous, such as migrating to new environments versus settling down in less harsh and more luxurious and resource-rich conditions as in agricultural and more modern societies, appear to have favoured selection of this novel and more risk-seeking allele, which also contributes to increased sexual promiscuity as well as intrasexual competition (Penke and Jokela 2016). Also in present day nutritionally stressed Ariaal population living in Kenya, DRD4 long alleles related to increased novelty seeking have been associated with increased body mass in those leading a nomadic lifestyle as this trait is advantageous under such conditions; however, in the settled Ariaal populations, where such traits are disadvantageous, long DRD4 alleles showed a significant association with lower body mass (Eisenberg et al. 2008). Human behaviour including inattention, impulsivity and risk-taking advantageous in hostile or unfamiliar environments during constant migration is less suitable in modern societies which require a minimum of hierarchical organisation and predictability in individual social outcomes (Williams and Taylor 2006), so focus on *DRD4* exon III variation also gained importance as possibly playing a role in ADHD and impulsiveness. It must also be noted that the hypothesis on natural selection operating on DRD4 is not supported by population genetic evidence yet.

#### 4.6.2.2 Evolutionary Aspects of Other Temperamental Dimensions in the Psychobiological Model of Temperament and Character: Harm Avoidance, Reward Dependence and Persistence

Harm avoidance, linked to serotonergic activity and associated with acquired behavioural inhibition, expresses a tendency to react to aversive stimuli (Cloninger et al. 1993). There appears to be a straightforward association between harm avoidance and survival and reproduction, with extremely low levels leading to high risk of injury and death, whereas extremely high levels leading to extreme shyness and withdrawal severely impairing chances of survival and reproduction through diminished exploration and exploitation of resources and decreased success in mate acquisition, suggesting that different environmental conditions, depending on their inherent risk-advantage constellations, favour different manifestations along the harm avoidance spectrum.

Reward dependence, linked to noradrenergic activity, plays a role in behavioural maintenance and is associated with continuation of behaviour previously associated either with reward or with relief from punishment. Those showing high reward dependence are ambitious, sociable, and sympathetic, and are also more likely to recognise socially relevant cues, and are therefore effective communicators, show genuine care for others, and have warm social relations which increases fitness in social species. However, those with high reward dependence, as a cost are also more socially dependent and also have an increased capacity for dependence towards behaviours, which involve rewarding cues, and are characterised by behaviours that are easily influenced by such cues independently of their advantage with respect to survival and reproduction. Those who show low reward dependence, on the other hand, are more nonconformist and independent and reserved with respect to revealing their feelings and are consequentially socially detached and more insensitive to social cues and unmotivated to please others and respond to cues for immediate gratification, leading to social withdrawal and dissocial or antisocial behaviour, detachment and coldness in interpersonal relationships. Persistence reflects the nature and strength of responses to frustration and partial reinforcement in abandoning on maintaining behaviours in spite of these. Frustration and consequential cessation of behaviour may be adaptive and advantageous as a reduction in effort that is disproportionate for the current reward and thus is likely to be beneficial in rapidly changing environments making it possible to alternate behaviours more rapidly until finding the one most fruitful in case of the given environmental conditions (Cloninger 1994).

#### 4.6.2.3 Character Traits in the Psychobiological Model of Personality

Even less attention was paid from an evolutionary or genetic aspect to the character traits of the biopsychosocial model of personality, in part because it is postulated that learning and social influences play a relatively larger part in their development compared to genetic or biological ones, and there is evidence of common environmental influence from recent research in their development. The self-directedness dimension spans between being responsible, purposeful, resourceful, self-accepting and disciplined at the high end of the trait vs. being blaming, aimless, inept, vain and undisciplined. In case of cooperativeness, high levels are manifested in being empathic, tender-hearted, compassionate, helpful, whereas those with low levels are intolerant, insensitive, hostile, revengeful and opportunistic. In case of self-transcendence, high levels are associated with self-forgetfulness, transpersonality, spirituality, enlightedness and being idealistic vs. low manifestations including being unimaginative, materialistic, possessive, controlling and practical (Cloninger 1994). A previous large sample study in Australian twins indicated that familial aggregation for the character dimensions could be explained by additive genetic action alone in spite of the hypotheses that shared environmental effects would account for a large proportion of character trait variance attributed at least partly to social learning. Heritability explained 26%, 37% and 10% of additive genetic variance in self-directedness, cooperativeness and self-transcendence, respectively, and almost all non-shared environmental variance was unique to each character dimension (Gillespie et al. 2003). A twin study involving monozygotic and dizygotic pairs

(Lester et al. 2016) found varying proportion of a shared environmental component in case of self-directedness and cooperativeness subscale components, while the shared environmental component was relatively stable in case of self-transcendence. In a subsequent twin study, however, support for environmental effects was reported in the character variability in case of adolescents reflecting initial concepts and subsequent reports on the effect of cultural and rearing influences in character development (Lester et al. 2016). The proportion of shared environmental components showed variation in case of the subscales within self-directedness and cooperativeness higher-order traits, while it was stable in case of self-transcendence (Lester et al. 2016).

## 4.7 Conclusion

There has recently been increased interest in the evolutionary aspects of personality and especially interindividual personality differences. It appears that in spite of the obvious disadvantages of the extreme ends of personality and temperamental trait dimensions encountered in clinical practice, there is not one mid-range optimum manifestation but several optimal levels carrying advantages especially in interaction with specific environmental settings. The appearance of such multiple optima is likely to be the result of fluctuating selection pressures.

There are several advantages of considering evolutionary aspects of personality. Integration with evolutionary theory may help to enhance and advance personality models by fostering prediction concerning the mechanisms which govern personality, and widen our understanding of the function of personality traits, and how these traits provide means of adaptation and how they lead to the development of pathology. When it comes to personality, we understand how it works but not why it works, why the architecture of personality is structured in the way it is, and what mechanisms and forces gave rise to the basic sets of personality traits and temperaments that operate in humans today (Figueredo et al. 2009). Evolutionary theory could also help to disentangle the effects of environmental influences both in shaping the evolution of personality and in determining its reactions today, and why and how they are responsive to the environment, and how epigenetic mechanisms may have an influence on them. In summary, evolutionary psychology may bring us closer to delineating the adaptive function of human personality.

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# Psychobiology of Sexuality

5

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## 5.1 Introduction

Sexuality is widely seen as an intrinsic component of human experience and psychological function and a major aspect of human behavior. It includes biological, psychological-interpersonal, and sociocultural aspects and serves reproduction (biological target) but also other aims (including pleasure, communication, etc.) and develops through the various stages of human psychosexual development. Sexual attitudes and the approach to sexual issues such as female sexuality and sexual orientation (classified as a psychiatric disorder in the past) are dependent on religious and sociocultural factors; they change through centuries; however, this does not always happen toward a more tolerant direction. Gender identity, gender role, and sexual orientation are important aspects of one's identity. Sex refers to the biological characteristics.

There are still significant gaps in our knowledge, and since research on sexuality has been mainly male-oriented, these gaps exist especially regarding female sexuality. Sexuality is shaped in a multifactorial way; however, the psychological and biological components seem to play a major role. Therefore the study of the psychobiology of sexuality can be a very interesting and productive approach to the field.

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## 5.2 Sexual Differentiation of the Brain

There are both similarities and different aspects when human sexuality is compared to the sexual behavior of various nonhuman primates. In humans sexual activity may occur at any time during the menstrual cycle and regardless of age. Central neural control of sexual behavior involves brain regions, which are linked to motivation, consummation, and reward and are similar to those brain regions involved in the majority of primates. Many observational and experimental studies on the basic cellular mechanisms involved in sexuality come from animals. However, when such comparisons are made, the different epigenetic, cognitive, and sociocultural factors should be taken into account since they may also play an important role in humans (Martin 2007; Salonia et al. 2010).

The presence—or absence—of the Sry gene on the Y chromosome codifies the testis-determining factor (TDF) and initiates gene expression and protein products toward the development of testis, or accordingly the ovaries, from the bipotential gonads (Salonia et al. 2010). During the "sensitive period"—a restricted developmental period in male and female animals—the brain is sexually differentiated. The critical hormone for masculinization of the brain is estradiol (E2) which derives from testicular testosterone and leads to the male differentiation of the rodent brain, while male differentiation of the body tissues occurs due to dihydrotestosterone (DHT), through the effect of 5a-reductase on testosterone. In primates, including humans, this procedure begins during the second trimester of gestation and is largely prenatal, while the critical masculinizing hormone is testosterone (T). The "organizational/activational hypothesis" supports the early action of gonadal steroids which organize the main neural architecture which regulates sexual behavior (Phoenix et al. 1959). This behavior will be activated in adulthood after the secretion of steroids in response to appropriate stimuli. Therefore, shortly after birth and the formulation of brain differentiation during the sensitive period, the testis ceases androgen production. Only during puberty will these circuits be activated and hormones will permit sex-specific sexual behavior. It is hypothesized, but not proven, that male and female neuronal circuits are largely the same, but critical nodes are weighted differently (Salonia et al. 2010).

*There seems to exist greater connectivity* between the cerebral hemispheres in females, and this has been indicated since the anterior commissure, which connects anteriorly two-thirds of the right and left temporal neocortices and the posterior part of the orbital aspect of the frontal lobes (Demeter et al. 1988), was found to be 12% larger in women than in men (Swaab 2002).

In all animals, including humans, the hypothalamus is the main brain structure involved in sexual behavior, exerting an effect on the anterior lobe of the pituitary gland (hypophysis). The hormones that are secreted from the pituitary gland act upon the genitalia and specifically on the ovaries and on the testes, secreting estrogen and testosterone, respectively. Finally, these hormones affect the hypothalamus controlling sexual behavior.

The sexually dimorphic nucleus of the preoptic area (SDN-POA) has first been described in the rat brain (Gorski et al. 1978) and is located between the dorsolateral

supraoptic nucleus (SON) and the mediorostral pole of the paraventricular nucleus (PVN) in the hypothalamus. Interestingly enough, it seems to be three to eight times larger in the male than in the female rat, due to different perinatal steroid levels. Sexual differentiation of the SDN-POA in humans occurs after 4 years of age according to sex, due to a decrease in both cell number and volume in women, while in men both cell number and volume remain the same until the fifth decade, where the number of cells also decreases. The SDN-POA in the young adult human brain is twice as large in men than in women on one side and contains twice as many cells (Swaab 2002). Although unclear, there are indications that the SDN-POA area is involved in sexual behavior since lesion experiments in rats in this area demonstrate its involvement in aspects of male sexual behavior, i.e., recognition of sensory stimulus as appropriate sexual targets, mounting, intromission, and ejaculation (Swaab 2002).

The median preoptic area (mPOA) is a critical hormonally sensitive region, sharing connections with the ventromedial nucleus (VMN) and other brain regions relevant to mating, and seems to be important regarding motive and completion of sexual encounter, based on lesions of the area in animal studies (Vaidakis 2005). The POA is considered the critical area for male and female sexual behavior, mainly through inhibitory mechanisms in its expression (Pfaff et al. 2009; Salonia et al. 2010). Interestingly enough, sexual intercourse seems to increase intrinsic opioids, and especially beta-endorphin, in the mPOA of the male rat. There are indications that beta-endorphin in the mPOA inhibits sexual activity, probably through the feeling of saturation (Vaidakis 2005).

The VMN of the hypothalamus is quite an essential brain region for receptive sexual behavior in female rodents, since its estrogen receptor-expressing neurons project to the estrogen-sensitive neurons of the midbrain and then to the spinal cord activating important back muscle groups. The sensory information is then transferred back to the brain-activating regions that are linked to reward, such as the ventral tegmental area and the nucleus accumbens. Additionally, the amygdala, receiving important olfactory information, also sends signals to the VMN (Pfaff et al. 2009; Salonia et al. 2010). Sexual dimorphism exists also in the VMN, since males have two to three more dendritic spine synapses that are also longer and branch more frequently than in the female brain, maybe due to higher steroid levels in male rodents during the critical period of brain development (Salonia et al. 2010; Schwarz et al. 2008).

The interstitial nucleus of the anterior hypothalamus-2 and interstitial nucleus of the anterior hypothalamus-3 (*INAH-2* and *INAH-3*) seem to have differentiations in males and females regarding its size and its secretions. More specifically they were found larger in the male than in the female brain, and they seem to have a continuous secretory pattern in men and a more "cyclic" one in women (Swaab 2002). Moreover, regarding hypothalamic peptides, oxytocin seems to be more representative of the female circuitry and vasopressin of the male one (Cuzin 2015).

*The bed nucleus of the stria terminalis* (*BNST*), situated at the junction of the hypothalamus, septum, and amygdala, contains nuclear androgen receptors and seems to play an important role in rodent sexual behavior (Fernandez-Guasti et al.

2000; Swaab 2002). Sexual dimorphism of this nucleus has not been detected so far, except for the volume of a region of the BNST called "the darkly staining posteromedial BST" (BNST-dspm) which is 2.5 times larger in men than in women (Allen and Gorski 1990).

The sexual differentiation of the hypothalamus (especially of the SDN-POA and the BNST) becomes apparent between 2 years of age and puberty, following earlier developmental periods (mid-pregnancy or neonatal period). Testosterone—deriving from estrogens through aromatization—is a major mechanism for androgenization, but the development of human male gender identity and male heterosexuality needs also the direct action of androgens on the brain, while other factors other than hormones (e.g., compounds that influence hormone or neurotransmitter metabolism such as alcohol and some drugs, kinases, enzymes, receptors) may affect sexual differentiation. Finally, continuous expression of critical genes (such as the Sry and the ZFY) may be necessary in order to maintain sex-specific structural or functional properties of differentiated male neurons (Swaab 2002).

Central nervous system dimorphisms are a biological basis for the differences and disparities in sexual desire, expression, content, and intensity of sexual thoughts and fantasies, erotic dreams, and daydreams, as well as differences in the perception and expression of arousal and orgasm (Cuzin 2015). Perhaps indicative of the human brain might be a spectrum of various degrees of masculinization and feminization and the potential for any individual to be divergent, following the variety of the steroid hormone action toward cellular mechanisms in the developing brain (Salonia et al. 2010).

## 5.3 Sexual Orientation

Sexual orientation may be described as a person's pattern of romantic, emotional, and sexual attraction as well as the gender/genders of the people the person is attracted to. Evidence suggests a genetic influence on sexual orientation, although environmental factors seem also to explain variation in orientation (Dean 2012b). There seems to be a linkage between DNA markers on the X chromosome and male sexual orientation, while sex hormones during development also seem to have an influence on sexual orientation, as shown on the increased percentage of bisexual or homosexual orientation in girls with congenital adrenal hyperplasia (Hamer et al. 1993). Maternal stress, as well as other gestational and perinatal factors, has been connected to increased occurrence of homosexuality in boys and girls. Finally, some authors suggested that postnatal social or environmental factors may play a role in the development of sexual orientation, but to date there are no solid evidence in support of this (Swaab 2002).

Regarding brain morphology studies, minor differences have been found between heterosexual and homosexual men, specifically in the interstitial nuclei of the anterior hypothalamus (INAH), which is larger in heterosexual men, and in the anterior commissure, which is larger in homosexual men, although it is not clear if these findings are causal or consequential. More likely, the determinants of both sexual

orientation and identity are multifactorial and not the sole consequence of nature or nurture, while most authors seem to agree that they are probably not a matter of individual choice (Dean 2012b).

Other differences which were found most notably in the amygdala, the hippocampus, and the prefrontal cortex (PFC), as well as in parts of the hypothalamus (Allen et al. 2003; Salonia et al. 2010), might explain some of the differences between male and female sexual behavior and orientation (Salonia et al. 2010). Interestingly enough, there are studies showing similarities between homosexual women and heterosexual men regarding the activation of certain nuclei (the dorsomedial and the paraventricular nucleus of the hypothalamus) when smelling an estrogen-like odor (Savic et al. 2001; Berglund et al. 2006). Similar congruent activity is shown between homosexual men and heterosexual women when smelling androgen-like odor (the ventromedial hypothalamus and POA) (Salonia et al. 2010; Savic et al. 2001; Savic et al. 2005). Moreover, female sexual orientation has been connected to symmetrical cerebral volumes, while male sexual orientation has been connected to rightward cerebral asymmetry. Additionally, the amygdala has differences according to sexual orientation, showing specifically more connections from the left than from the right in heterosexual women and homosexual men (female sexual orientation) and the opposite for individuals who have a male sexual orientation (Savic and Lindstrom 2008; Salonia et al. 2010).

Regarding animals, the SDN-POA is presumed to be involved in sexual orientation, as lesions in this area seem to cause a significant shift from male-typical pattern of sexual behavior to a more female-typical pattern (Swaab 2002). Its possible involvement in human sexual orientation has been suggested (Swaab 2002), as well as theories that homosexual men have a "female hypothalamus," although studies did not reveal any differences in the size or the cell numbers of this nucleus in relation to sexual orientation. A study based on a small sample of homosexual men found that the INAH-3 nucleus in these subjects is closer to female size, while on the contrary it is two times bigger in heterosexual men (Levay 1991).

Regarding the suprachiasmatic nucleus (SCN), which seems to be involved in sexual behavior, orientation, and reproduction both in animals and in humans, morphometric analysis in a small study sample revealed that its volume was 1.7 times larger and it contained 2.1 times as many cells in homosexual than heterosexual men. Additionally, the number of vasopressin-expressing neurons was increased in homosexual men, reflecting perhaps a difference that is formed during the early stages of brain development. Regarding the BST-dspm which, as mentioned before, is found larger in men than in women, no relationship was observed between its volume or somatostatin cell number and sexual orientation (Swaab 2002).

## 5.4 Sexual Identity

Sexual or gender identity is the individual's personal sense, and subjective experience, of their own gender (Dean 2012a). Some individuals may be also self-referred as non-binary. Research on this filed is limited and often presents controversial

findings. Some evidence in the literature supports the involvement of multiple factors in its development, which may be biological (genes and their regulation, pre- and postnatal hormone levels), sociocultural (family upbringing, norms and expectations, sociocultural or religious requirements), as well as social learning factors (which assumes that gender identity is also developed through observing and copying gender-specific behaviors, which may then be rewarded or punished) (Dean 2012a). Interestingly enough, it has been recently proposed that gender identity disorders may be considered disorders of sexual differentiation limited to the central nervous system, without involvement of the reproductive tract (Meyer-Bahlburg 2010).

Regarding biological/genetic variables, only a few reports have found chromosomal abnormalities in transsexual people (Turan et al. 2000), while some indications exist that it is a disorder of the hypothalamic-pituitary-gonadal axis, considering the high frequency of polycystic ovary syndrome, oligomenorrhea, and amenorrhea in female-to-male transsexuals (Sadeghi and Fakhrai 2000; Swaab 2002). Congenital adrenal hyperplasia, characterized by high androgen levels during prenatal development, seems to be a risk factor for the development of gender identity disorders, as well as maternal use of some medicine (e.g., phenobarbital and diphantoin) during pregnancy which are assumed to alter steroid levels (Swaab 2002). These observations support the theory that intrauterine or perinatal factors, which influence sex hormone levels, may permanently affect gender identity, in interaction to the developing brain (Swaab 2002).

Interestingly enough, some evidence exist regarding brain morphology of transsexuals. Both male-to-female (MtF) and female-to-male (FtM) transsexuals have been reported to have sex reversal in terms of volume and cell number of sexdimorphic nuclei, such as the central portion of the BNST (BNSTc) (Kruijver et al. 2000), the gray matter in the right putamen (Luders et al. 2009), and the interstitial nuclei 3 and 4 of the anterior hypothalamus (INAH 3 and INAH 4) (Garcia-Falgueras and Swaab 2008). More specifically, the BNSTc was found to be smaller (40% of the male volume and neuron number) in a small sample of MtF transsexual persons, suggesting that this size, formed during psychosexual development, may be part of a network that is involved in gender (the feeling of being male or female) (Kruijver et al. 2000; Swaab 2002). Moreover, gender-atypical brain activation patterns regarding the process of steroid-based odors and erotic stimuli have been demonstrated (Berglund et al. 2008; Gizewski et al. 2009). Finally, genetically based systemic sex hormone abnormalities that do not cause abnormalities of the reproductive tract, but influence the brain and its functions have been proposed, e.g., androgen receptor gene polymorphisms (Hare et al. 2009; Meyer-Bahlburg 2010).

## 5.5 Normal Sexual Function and the Sexual Response Cycle

Biological, psychological, and sociocultural factors influence human sexual function, while sexual behavior involves several behaviors such as motivation to seek a partner, evaluation of the appropriate cues, execution of the appropriate behavior, as

well as processes which may include reward that derives from the experience and may reinforce the behavior to be repeated (Salonia et al. 2010). Many brain regions and neural nodes are activated in order to collect and process relevant information and organize the corresponding behavior. In general, high levels of steroid receptors are expressed in these critical brain regions, while a hormonally sensitive network is created (Salonia et al. 2010).

"Sexual response models" represent the interaction of the several factors that seem to be important during sexual response, explaining the emotional and physical changes that take place when a person participates in a sexually stimulating activity (Tripodi and Silvaggi 2013).

Masters and Johnson were the first to describe a human sexual response model which was analogous for men and women, involving excitement (arousal), plateau, orgasm, and resolution (known also as EPOR model, taken from the initials of the words) (Masters and Johnson 1966). In 1979, Kaplan added the concept of "desire" as a prerequisite and separate phase of the human sexual response cycle which now consisted of sexual desire, excitement (arousal), orgasm, and resolution (known also as DEOR model, taken from the initials of the words) (Kaplan 1979). Until recently this has been the main model in clinical practice, for the diagnosis of sexual dysfunctions and for research activities. Nevertheless, the presence of exact sequential sexual response phases in women (desire-arousal-orgasm-resolution) has been criticized and questioned (Basson et al. 2004). Women's conscious sexual motivation may be more related to a desire for emotional connection or the avoidance of negative consequences rather than by internal feelings of genital tension, or by sexual thoughts or fantasies, which seem to describe the meaning of sexual desire. On the other hand, sexual desire in men is more readily and more reliably accessed, is usually palpable, and has a direct association with the experience or sight of an erection and the feeling of subjective sexual arousal, while in women there isn't always an association between subjective arousal and genital vasocongestion (Leiblum 2007). Additionally, in females, the phases of sexual response (especially desire and arousal) are not always discreet since they may overlap (Kirana 2013a, b).

Research suggests that there are many differences in the arousal response between men and women. In many females, the sexual arousal precedes the conscious feelings of sexual desire, whereas in most men desire precedes arousal and is a prerequisite in order to achieve or maintain an erection (Leiblum 2007). Based on the above, a circular/dynamic sexual response model that depicts a different conceptualization of women's sexual function than the previous models was suggested (Basson et al. 2004). Spontaneous/intrinsic desire is not necessarily a prerequisite since their sexual response may begin for a number of other reasons, which may even not be sexual such as her willingness to be receptive (this has been termed responsive sexual desire). Motivation to be sexually active again is increased if the experienced sexual activity is physically or emotionally positive (Kirana 2013a, b).

Genital arousal in females does not necessarily reflect their stated sexual interest in the same way that it does for men and therefore is considered nonspecific. This is

supported by studies that show that non-preferred sexual partners, or even nonhuman stimuli, may provoke physiological changes of the genital system (e.g., vasocongestion) in women, but not in men (Leiblum 2007; Salonia et al. 2010). An evolutionally perspective may explain this finding, since females are vulnerable to several forms of aggressive sexuality, and therefore a rapid vasocongestive response and concurrent lubrication protect their genitals (Chivers 2005). Physiological genital response in females has also been proposed to be an automatic reflex that precedes conscious processing of sexual stimuli and cues and can occur in the absence of subjective experience of sexual arousal (Chivers 2005). Concluding, solely genital response may be inaccurate to reflect women's sexual desire and sexual attractions (Salonia et al. 2010). Female sexuality has evolved, highly influenced by cultural, social, and interpersonal variables, which also play an important role in the nature of female sexual problems. Nowadays, it seems quite differentiated from male sexuality, while among other things, the influence of biological, anatomical, and hormonal deficits is not the same (Leiblum 2007).

### 5.5.1 Sexual Desire

Mammals and other species respond to hormonal and neurochemical changes that signal sexual desire and arousal (Goldstein et al. 2004). In humans this appropriate "internal state" of arousability is often referred to as "sex drive." Besides that, instinct, learning, and feedback involve several neural structures in order for the interaction with the external environment to take place. Additionally, neural mechanisms that assess the feedback of a sexual act as positive and rewarding may reinforce or not a similar behavior in the future (Goldstein et al. 2004).

Sexual desire is part of the reproduction instinct, including both biological and cognitive parameters. More specifically, it may be divided into three separate components: sexual drive, sexual motives, and sexual expectations. *Sexual drive* includes all the neuroendocrinological pathways that are involved and are mainly controlled by androgens. *Sexual motives* describe the individual reasons for which somebody wishes to engage in a sexual activity. This parameter is quite complex, since sexual motives are multiple, may be sexual or nonsexual (as mentioned before, especially regarding women's sexual behavior), and seem to differ between genders and individuals or throughout the lifespan. Sexual motive, as a component of sexual desire, is actually describing the reasons that partners approach each other for a sexual encounter. Finally, *sexual expectations* are supposed to be the cognitive dimension of sexual desire and refer to the needs that an individual is expecting to fulfill through sexual function.

The biological basis of human sexual desire seems to include, as mentioned before, cognitive (such as thoughts or fantasies) and affective parameters, as well as central neurophysiological mechanisms of arousal (Corona and Maggi 2012). It has been postulated that sexual excitation and sexual inhibition brain systems seem to be responsible for an individual's behavior related to sexual desire and arousal (two separate functions, which in the brain are often difficult to differentiate).

Hypothalamic and mesolimbic dopamine (DA) transmission is involved in sexual excitation, including three major systems (Corona and Maggi 2012):

- Diencephalic incertohypothalamic DA systems terminating in the medial preoptic area (mPOA) of the anterior hypothalamus.
- The mesolimbic and mesocortical DA system, which terminates in the nucleus accumbens and medial prefrontal cortex, respectively.
- The nigrostriatal system, which terminates in the striatum (caudate and putamen).

Initiation of sexual desire activates the limbic system both in males and in females, including sexual fantasies, sexual dreams, mental sexual arousal, as well as the neurovascular events responsible for body and genital reactions. Additionally, a problem at any level of the limbic system may cause sexual dysfunction in both sexes, affecting desire, central arousal, and socially appropriate sexual behavior (Cuzin 2015). The tuberoinfundibular DA system controlling hormone release from the anterior pituitary gland is also involved in the control of sexual desire. The mPOA is the central core of this pathway, projecting to the ventral tegmental area of the midbrain which contains DA cell bodies. These bodies project to various limbic and cortical regions, such as the prefrontal cortex, olfactory tubercle, nucleus accumbens, anterior cingulate cortex, lateral septum, and corticomedial amygdala (Corona and Maggi 2012).

Regarding the inhibition of desire and arousal, the prefrontal lobe seems to play an important role over the basic instinctual drives, while opioid, endocannabinoid, and serotonin systems are activated and block the normal excitatory pathway (Cuzin 2015). Hormones, particularly testosterone, are involved in the modulation of the proposed excitatory and inhibitory sexual desire systems. Testosterone (T) acts on androgen receptors (AR) which are present in several areas of the brain, such as the temporal and the preoptic areas, the hypothalamus, the amygdala, the midbrain, the frontal and prefrontal areas, and the cingulated gyrus (Corona and Maggi 2012).

Specifically regarding the male sexual desire, several cerebral areas that have been related to sexual drive are androgen related. For example, Brodmann area 24 (BA24) is a sexual dimorphic AR area, related to emotional behavior and arousal reaction, since it is activated during the demonstration of erotic films. Interestingly enough, when T is administered to hypogonadal men, it seems to increase blood perfusion in this area and in other areas (the midbrain, superior frontal gyrus, middle occipital gyrus) which are involved in the processing of visual stimuli (Corona and Maggi 2012). T is also modulating the strength of activation in the brain areas that are related to female sexual response (Levin et al. 2016). Regarding the role of other hormones on male sexual desire, data is unclear. For example, reduction of dihydrotestosterone (DHT) may or may not reduce sexual desire, while estrogens—although evidence is scarce—seem not to play an important role for normal male sexual behavior. Elevation of prolactin has a negative effect on sexual desire, since it induces a decrease in the secretion of luteinizing hormone (LH) and therefore a decrease in testosterone. Finally, elevation or reduction of cortisol levels may

negatively affect sexual desire, through the modification of the hypothalamic-pituitary-gonadal axis and testosterone production (Corona and Maggi 2012).

Neuroimaging studies using visual sexual stimulation (VSS), with erotic or sexually explicit photos or film excerpts, reveal interesting results regarding brain regions that are activated during sexual response, especially in women (Levin et al. 2016). It has been reported that women activate the following areas of the brain when they watch erotic material: occipitotemporal cortex, superior parietal lobule, orbitofrontal cortex, inferior frontal gyrus, anterior cingulate cortex, anterior insula, ventral striatum, amygdala, thalamus, and hypothalamus. Interestingly enough, similar brain areas are activated during the first phases of sexual response (detection of sexual stimuli, sexual interest, attraction, and expectancy), which has been demonstrated through pheromone stimulation (Levin et al. 2016). The same brain areas are also activated when watching more vivid type of VSS (video instead of photos), as well as during the experience of genital sexual arousal and consequent body responses or during objective sexual arousal without genital response (Levin et al. 2016). This is not the case in males, where different brain areas seem to be activated when exposure to VSS is longer or more vivid, and this exposure leads to different affective or behavioral consequences with the analogous body response (Levin et al. 2016). VSS in males produce greater activations than in females in the amygdala and the hypothalamus, and visual stimuli seem to have fast access to primordial systems. This may reflect the presence of a higher "sensitivity" to sexual cues and stimuli in males, through a system which includes mainly the hypothalamus and the amygdala, and is more phylogenetically tuned toward this direction. This supports the theory that females take a more thoughtful approach regarding sexual encounters, while males follow a more instinctive mechanism through a different brain system (Salonia et al. 2010). Finally low gray matter density in these areas or enhanced activity in the prefrontal cortex has been related to hypoactive sexual desire disorder in women (Levin et al. 2016).

### 5.5.2 Male Sexual Arousal and Ejaculation

#### 5.5.2.1 Arousal

Male sexual arousal resulting in penile erection takes place after central processing of several stimuli (tactile, visual, olfactory, and imaginative) (Gratzke et al. 2010). Neurotransmitters and specific CNS areas that are involved are not completely understood yet. Some brain anatomical areas that have a role in sexual function have been identified, including the medial amygdala, medial preoptic area (MPOA), paraventricular nucleus, periaqueductal gray, and ventral tegmentum (Gratzke et al. 2010). The spinal network consists of primary signals from the genitals, spinal interneurons, as well as sympathetic, parasympathetic, and somatic nuclei. Information from the periphery is gathered, eliciting erections, while it also receives supraspinal information (Gratzke et al. 2010; Giuliano and Rampin 2000).

The first level of reflex organization in sexual function is located in the lumbar spinal cord. Spinal reflexes can be regulated by descending signals from the

midbrain and higher centers. A cascade of parasympathetic activity, reduced sympathetic activity, and somatic muscular support is activated by both local sensors in the penis and descending spinal signals (Saenz de Tejada et al. 2004a, b). The thalamus seems to receive significant sensory inputs from the male genitalia relevant to sexual response. In particular, the nucleus paragigantocellularis (nPG) receiving sensory input has neurons that innervate the penis and appears to have a role in orgasm. Although maybe not crucial for erection, the paraventricular nucleus (PVN) sends neurons to the penis via the nPG. Additionally, the PVN has direct projections to pelvic and autonomic neurons and is connected to the medial preoptic area (mPOA). The mPOA seems to be important for the control of sexual behavior (especially regarding mate selection) and is connected to the nPG and the periaqueductal gray (PAG), an area connected to the hypothalamic site involved in sexual response (Saenz de Tejada et al. 2004a, b).

Regarding higher brain centers, studies in rats show that the medial amygdala has a role in recognizing the appropriate partner for sexual arousal, while mainly peptide neurotransmitters are associated with these mechanisms. Functional MRI (fMRI) studies have identified the activation of the dominant (L > R) brain hemisphere after imagery of sexual stimuli, while VSS seems to activate the occipital cortex, inferior frontal lobe, cingulate gyrus, insula gyrus, corpus callosum, thalamus, caudate nucleus, globus pallidus, and inferior temporal lobe. Penile erection has also shown activation in the right sub-insular region including the claustrum, left caudate and putamen, right middle occipital and middle temporal gyri, bilateral cingulate gyrus, right sensorimotor and premotor regions, and right hypothalamus (Saenz de Tejada et al. 2004a, b). Activation of the somatosensory thalamus and of the nucleus of the solitary tract—which is the brainstem nucleus to which the vagus nerves project—is shown in PET and MRI studies (Saenz de Tejada et al. 2004a, b).

Multiple neurotransmitters seem to have a role in sexual function, while for a few of them, evidence is more concrete. Dopamine (DA), for example, clearly has a role in the PVN and the mPOA, since central dopaminergic neurons project there (Saenz de Tejada et al. 2004a, b). In general terms, DA is supportive of copulation and is increased in the mPOA at the time of ejaculation. Changes in DA and 5-HT (serotonin) in different areas of the brain may promote copulation and sexual satiety, respectively (Saenz de Tejada et al. 2004a, b). Both the two major types of dopamine receptors (D1-like and D2-like) have been associated with central erectile functions, while D2-like receptors seem to have a predominating effect (Gratzke et al. 2010). Testosterone enhances DA release in the mPOA at rest and with sexual challenge possibly by upregulating NOS, which increases nitric oxide (NO), thereby increasing DA release (Saenz de Tejada et al. 2004a, b).

Serotonin (5-HT) and thyrotropin-releasing hormone (TRH), both seem to inhibit penile erection through common or parallel sets of neurons (Saenz de Tejada et al. 2004a, b). Also in animals, 5-HT seems to generally inhibit male sexual behavior. Nevertheless, its action may be inhibitory or facilitatory depending upon the different sites and receptors within the central nervous system, explaining conflicting reports regarding enhancing or depressing effects of 5-HT agonists in sexual function (Gratzke et al. 2010).

Oxytocin is supposed to induce erection when injected into the lateral cerebral ventricle, the paraventricular nucleus, or the hippocampus of laboratory animals, while intracavernous oxytocin is not effective (Gratzke et al. 2010; Saenz de Tejada et al. 2004a, b). Nitric oxide (NO) influences sexual behavior and penile erection, especially at the level of the paraventricular nucleus of the hypothalamus and at other levels of the neural pathway, supporting sexual response (Gratzke et al. 2010; Saenz de Tejada et al. 2004a, b). Gamma aminobutyric acid (GABA) activity in the PVN seems to balance (inhibit) pro-erectile signaling, since it is supposed to modulate autonomic and somatic reflex pathways that inhibit penile erection (Gratzke et al. 2010; Saenz de Tejada et al. 2004a, b). Prolactin is associated with changes in striatal dopaminergic activity, since it is supposed to inhibit the dopaminergic incertohypothalamic pathway to the mPOA. Therefore hyperprolactinemia in the long term may inhibit sexual behavior, diminish sexual potency in men, and suppress genital reflexes in rats. Nevertheless, it is still unclear if this effect is mediated centrally by reduction in sexual interest and drive or peripherally through the effect of prolactin on corpus cavernosum smooth muscle (Gratzke et al. 2010). Endogenous and exogenous cannabinoids have been associated with changes in erectile function and sexual activity, possibly by modulation of PVN oxytocinergic neurons, while opioid peptides, acting centrally, prevent penile erection affecting oxytocinergic neurotransmission (Gratzke et al. 2010). ACTH and α-melanocyte-stimulating hormones (α-MSH) are able to induce penile erection, probably via stimulation of melanocortin receptors (MC). Particularly MC4 receptor subtype seems to contribute to the pro-erectile effects observed with MC pan-receptor agonists (Gratzke et al. 2010).

Finally androgens, and testosterone in particular, are necessary—but not sufficient—for sexual function in men. They are essential for the maintenance of libido and for the regulation of erectile capacity. Circulating testosterone levels within normal limits do not correlate however with sexual interest, activity, or erectile function in men with normal gonadal function. Literature findings seem controversial, since castration in humans may result in complete loss of libido along with erectile and ejaculatory dysfunctions and may be restored with testosterone administration, although in other cases sexual function following castration may be normal. Thus, the role of androgens in erectile function is complex, and androgen deprivation may not always cause erectile dysfunction, either in man or in rats (Gratzke et al. 2010).

#### 5.5.2.2 Ejaculation

Orgasm seems to be a spinal reflex, since it may persist even after spinal cord injury, while reward deriving from orgasm is represented in higher brain centers (Saenz de Tejada et al. 2004a, b). Sensory receptors and areas, cerebral sensory and motor regions, spinal motor centers, and efferent and afferent pathways are also involved in this function (Rowland et al. 2010). In general, cerebral blood flow seems to decrease during orgasm, except for the right prefrontal cortex, where it increases (Saenz de Tejada et al. 2004a, b). Additionally, other limbic cortical areas are activated, the cerebellum and the ventral tegmental area of the meso-diencephalic

junction, where dopamine neural circuits in animal sexual arousal and psychostimulant reward are located (Deak and Panksepp 2004).

The ejaculatory process is typically divided into three phases, emission, ejection, and orgasm, and is a result of actions in the central as well as the peripheral nervous system. Sympathetic nerves (T10-L2) provoke emission, while ejection is mediated by somatic nerves (S2–S4) but also involves a sympathetic spinal reflex upon which little voluntary control exists (Rowland et al. 2010). Orgasm though is the result of CNS processing of pudendal nerve sensory stimuli resulting from sexual organs (e.g., pressure and muscle contraction) (Rowland et al. 2010).

The main CNS structures that are involved in ejaculation include the mPOA, the nucleus paragigantocellularis (nPGi), the posteromedial bed nucleus of the stria terminalis, the posterodorsal medial amygdala, and the magnocellular neurons of the PVN of the anterior hypothalamus (Rowland et al. 2010; McMahon et al. 2004). More specifically, the mPOA, situated rostral to the anterior hypothalamus, seems to elicit seminal emission or ejaculation in rats and monkeys, as well as the urethrogenital reflex in rats, similar to orgasm in humans (McMahon et al. 2004). MPOA seems to stimulate ejaculatory response, while the nPGi is inhibitory (Rowland et al. 2010). Descending serotoninergic signals from the nPGi to the lumbosacral motor nuclei inhibit ejaculation, while the mPOA inhibits the nPGi and provokes ejaculation (Rowland et al. 2010). Finally, the parvocellular neurons of the hypothalamic PVN mediates erectile function in rats, while oxytocinergic activation in the magnocellular neurons of the PVN mediate ejaculation (McMahon et al. 2004).

The neurotransmitters involved in ejaculation include dopamine, norepinephrine, serotonin, acetylcholine, oxytocin, GABA, and nitric oxide (NO) (Rowland et al. 2010). Dopamine and serotonin seem to play the major role. Specifically, dopamine via D2 receptors and mainly through the anterior hypothalamus seems to provoke ejaculation, since it is released in the mPOA of male rats in the presence of an estrous female and increases during copulation, triggering ejaculation (Rowland et al. 2010; Hull et al. 1995). Serotonin, on the other hand, seems to inhibit ejaculation, based mainly on the hypothesis of premature ejaculation that supports the hyposensitivity of the 5-HT2C and/or the hypersensitivity of the 5-HT1A receptor. More specifically, stimulation of the 5-HT2C receptor with 5-HT2C agonists results in delay of ejaculation in rats, while stimulation of postsynaptic 5-HT1A receptors results in shortening of ejaculation latency time (Rowland et al. 2010).

### 5.5.3 Female Sexual Arousal and Orgasm

#### 5.5.3.1 Arousal

Sexual arousal in females can be described by *subjective sexual arousal* and by *genital sexual arousal*.

**Subjective Sexual Arousal**

It includes the cognitive characteristics of arousal, such as the ease with which sexual stimuli arouse a woman. Most women express difficulties differentiating

sexual desire from subjective sexual arousal; thus, DSM-5 is describing sexual interest/arousal disorder as one clinical entity (American Psychiatric Association 2013; Kirana 2013a, b).

Subjective sexual arousal would probably be considered as a slower response involving brain circuits which consciously and subconsciously recognize and process the stimulus. Genital sexual arousal therefore may precede, since it includes an automated, reflexive response of the autonomic nervous system (Basson 2000). Emotional stimuli are probably processed in the sensory thalamus and the amygdala, while supraspinal centers organize genital autonomic nerve activity. Subjective sexual arousal which seems to pursue genital sexual arousal, apart from the sensory thalamus and the amygdala (for further information processing), also involves the hippocampus (important in relating present experience to memories of past experiences), as well as cortical centers (Basson 2000).

### Genital Sexual Arousal

It involves vaginal lubrication, swelling, and tingling and does not necessarily relate to subjective sexual arousal, which involves the sexual excitement component (Kirana 2013a, b).

Functional MRI (fMRI) studies have identified areas of the brain which are activated during sexual arousal, including areas subserving the genital vasocongestive response, such as the posterior hypothalamus, which correlate with subjective arousal response in men but not in women (Basson 2000; Karama et al. 2002). Interestingly enough, the location of the genitalia on the somatosensory brain area has not yet reached a consensus. Nevertheless, the primary somatosensory cortex, the operculum (secondary somatosensory cortex), and the posterior part of the insula have been proposed (Levin et al. 2016). These areas have emerged based mainly on studies of women with sexual disorders (vulvar vestibular pain and persistent genital arousal disorder) and seem to be important for processing the emotional meaning of the genital stimulation (Levin et al. 2016).

Visual sexual stimulation (VSS), as mentioned above, has been used to document, through PET and fMRI, the areas that are activated during sexual arousal (Salonia et al. 2010). Multiple cortical and subcortical areas are activated during VSS. More specifically, extrastriate visual areas in the occipitotemporal cortex, the lateral prefrontal cortex (PFC), the inferior parietal lobule, the orbitofrontal cortex (OFC), the ventral striatum, the amygdala, the insula, the cingulate cortex, the inferior temporal lobe, the thalamus, and basal ganglia seem to be activated both in women and in men, during the arousal phase (Salonia et al. 2010; Park et al. 2001). Interestingly enough, although an increase in sexual arousal presented in women while they were watching an erotic video, no correlations were found between perception of sexual arousal and brain activity (Park et al. 2001).

Other studies have demonstrated the activation of the amygdala and the hypothalamus, as well as decrease in the activation of bilateral temporal lobe. This is quite interesting, since sites in the latter area have been associated with moral (Salonia et al. 2010). Therefore, decreased activity of these sites would not inhibit the response to a sexual stimulus. Greater activation (especially of the entorhinal

cortex) has been reported in women with reduced sexual desire disorder (Salonia et al. 2010; Maravilla and Yang 2008; Arnow et al. 2009). Similarly to these findings, studies with partnered clitoral stimulation resulted in increased activity in mainly cortical somatosensory areas and decreased activity in prefrontal areas and medial temporal areas (including the amygdala) (Levin et al. 2016). Decreased brain activity of these areas could mediate the disinhibition in order for a woman to engage in intense sexual activity and feelings (Levin et al. 2016). On the other hand, arousal resulting from vaginal self-stimulation in women with spinal cord injury did not result in decreased activity of the aforementioned areas (although it resulted in activation of the similar cortical and subcortical areas) (Levin et al. 2016; Komisaruk et al. 2004). Activation of the amygdala and the hypothalamus in heterosexual women seems to need longer VSS periods with erotic videos, than the rest of the brain areas involved (e.g., extrastriate visual areas, the inferior parietal lobule, the anterior cingulated cortex, and the ventral striatum, all of which are also activated in men) (Salonia et al. 2010). Heterosexual and lesbian women's brain responses showed specificity in brain areas activated, with regard to woman's sexual orientation (Salonia et al. 2010). Hypothalamic response however did not show category-specific response for either group (heterosexual and lesbian women), while specificity in amygdala function was found for lesbian women only and was non-specific in heterosexual women (Salonia et al. 2010; Chivers 2005).

Although useful information emerges through the interpretation of VVS-induced brain responses, it is important to point out the epiphenomenal, "contaminating" effect of the general emotional arousal that is present in any neuroimaging experiment. If controlled for the general emotional effect, only a restricted amount of brain areas seem to be activated due only to sexual content processing (Salonia et al. 2010; Walter et al. 2008).

#### 5.5.3.2 Orgasm

Studying orgasm in women includes some difficulties, such as the lack of an objective measure to document that orgasm is occurring, as well as the lack of an agreed-upon definition of orgasm (Heiman 2007). The brain is undoubtedly an important source of sexual arousal and orgasm, since there is evidence of individuals who reach orgasm without direct genital stimulation. Phantom orgasm of paraplegics, orgasms induced through hypnosis, or orgasms induced from fantasy alone are only some paradigms suggesting that the brain is part of the anatomical requirements for orgasmic experience (Heiman 2007). On the other hand, persistent genital arousal and orgasm can occur not only in the absence of any genital or mental stimulation but even when both systems provide with negative feedback concerning orgasm (Fountoulakis et al. 2017).

Many brain areas, cortical and subcortical, show activation during orgasm. Orgasm resulting from vaginal self-stimulation in women with spinal cord injury reveals that the orgasm-related brain activity seems to be an expansion of that found in genital stimulation alone (Levin et al. 2016). In general, women's brain responses (brain areas that are activated) during orgasms seem to be similar to men's, suggesting that the main differentiations exist regarding the use of different cerebral

pathways in order to reach orgasms (Salonia et al. 2010). Clitoral stimulation and clitoral orgasm, compared to passive nonsexual resting state, seem to increase regional cerebral blood flow (rCBF) in the bilateral primary somatosensory cortex (SI), left secondary somatosensory cortex (SII), and left supplementary motor area (Georgiadis et al. 2006). Probably, SII activation is a reflection of the context of the sensory stimulus, "weighting" the salience of somatosensory stimuli before they become conscious (Salonia et al. 2010).

Interestingly enough, rCBF decreased during orgasm in some brain regions. The inferomedial temporal lobe—including the amygdala—showed decreased rCBF (Salonia et al. 2010). Temporal lobe probably inhibits sexual arousal, and release of this inhibition may be imperative for sexual opportunity (Salonia et al. 2010). The female amygdala, although activated during long periods of VSS, shows deactivation in response to sexual stimulation crucial for sexual encounters to take place (Georgiadis et al. 2006). Similarly, CBF seems to decrease in the prefrontal cortex (PFC) and the orbitofrontal cortex (OFC), with the largest blood flow decrease being measured between clitoral stimulation and orgasm in the OFC, and between the nonsexual resting state and orgasm for the ventromedial area of the PFC (vmPFC) (Georgiadis et al. 2006). The PFC is a crucial part of the brain network that has to do with social behavior and executive function, while the vmPFC is an important brain area for self-monitoring and self-referential thought (Salonia et al. 2010). The OFC consists of lateral, middle, and medial parts (Salonia et al. 2010). The middle OFC is activated with increasing satisfaction and subjective pleasantness and deactivated with feelings of satiety, playing a role in hedonic experience, while the lateral OFC is linked to urge suppression (Salonia et al. 2010; Beauregard et al. 2001; Rolls 2000). It is suggested that the activity level of OFC reflects conscious control over the sexual urge, with high rCBF during clitoral stimulation and low rCBF during orgasm, indicating the reduced conscious control that is necessary (Georgiadis et al. 2006). Failed orgasm attempts are also associated with increased rCBF in the OFC (since it is associated to sexual arousal), revealing that possibly the release of tension and the loss of conscious control that is experienced with orgasm are strongly related to decreased OFC activity (Salonia et al. 2010; Georgiadis et al. 2006).

Increased brain activity during orgasm seems to take place in the cerebellum, although its contribution is quite unclear. More specifically, the left anterior lobe of the cerebellar vermis and adjacent deep cerebellar nuclei activate during orgasm in both sexes (Salonia et al. 2010; Georgiadis et al. 2006). Additionally, a strong positive association was found between activity of the left vermis of the cerebellum and rectal pressure (van Netten et al. 2008). The vermis takes part in axial motor control, but also in autonomic regulation and effect, explaining its activation during orgasm, since substantial cardiovascular and respiratory arousals take place (Salonia et al. 2010).

Cholinergic and adrenergic nerves, as well as a number of peptides, have been found to play a crucial role in the arousal of the female genitalia (Heiman 2007). Orgasm is correlated with increased secretion of prolactin and oxytocin—which is reflected by the elevated activation of the pituitary gland (Huynh et al. 2013)—and vasopressin and

**Table 5.1** Major brain sites activated and deactivated during orgasm and clitoral stimulation in women

| Brain region | Orgasm vs. rest | Orgasm vs. clitoris stimulation |
|---|---|---|
| *Frontal lobe* | | |
| Primary motor cortex (pelvic floor) | Activation | Activation |
| Lateral orbitofrontal cortex | Activation | Deactivation |
| Ventromedial prefrontal cortex | Deactivation | Deactivation |
| Dorsomedial prefrontal cortex | Deactivation | Deactivation |
| *Temporal lobe* | | |
| Inferior temporal gyrus | Deactivation | Deactivation |
| Middle temporal gyrus | Deactivation | Deactivation |
| Fusiform gyrus | Deactivation | Deactivation |
| Temporal pole | Deactivation | Deactivation |
| *Parietal lobe* | | |
| Primary somatosensory cortex (SI) (genital) | Activation | Deactivation |
| Secondary somatosensory cortex (SII) | Activation | Deactivation |
| Superior parietal lobule | Activation | Deactivation |
| Precuneus | Activation | Deactivation |
| *Occipital lobe* | | |
| Lingual gyrus | Deactivation | Activation |
| *Limbic system* | | |
| Posterior insula | Activation | Activation |
| Amygdala | Deactivation | Activation |
| *Cerebellum* | | |
| Deep cerebellar nuclei | Activation | Activation |
| Anterior vermis | Activation | Activation |
| Cerebellar hemisphere | Activation | Activation |

Courtesy of Georgiadis JR. Reprinted from Journal of Sexual Medicine, volume 7, Salonia A, Giraldi A, Chivers ML, Georgiadis JR, Levin R, Maravilla KR, McCarthy MM, Physiology of Women's Sexual Function: Basic Knowledge and New Findings, 2637–2660, Copyright 2010, with the permission of Elsevier)

vasoactive intestinal peptide (VIP), while serotonergic and dopaminergic factors play an important role (Meston et al. 2004). More specifically, increased serotonin levels and decrease in dopamine seem to have a negative impact on sexual response, although the complete mechanism of this action is not clear (Heiman 2007). A list of brain regions activated and deactivated during orgasm in females is shown in Table 5.1.

## 5.6 Conclusions

Human sexuality and therefore human sexual behavior are influenced by factors that have to do with one's genitalia but also far from them, such as the central nervous system. Therefore, one's *sexual identity* and *normal sexual function* rely upon central and peripheral mechanisms and anatomic structures in the brain but are also strongly influenced by social morals, personality traits, religious values, moral beliefs, and

family upbringing, which all affect the way sexual issues are approached (Vaidakis 2013). The critical masculinization hormone of the brain is estradiol which derives from testicular testosterone. The main neural structure that regulates sexual behavior seems to be influenced mainly by gonadal steroids that act during sensitive periods of development. The hypothalamus and specific areas, such as the SDN-POA, the mPOA, the VMN, the INAH-2 and INAH-3, the BNST, and the SCN, seem to play a major role in sexual behavior including sexual orientation and sexual identity. Sexual responses of men and women seem to have similarities as well as differences and are linked to regions of the CNS that modulate sexual function. Hypothalamic structures (e.g., the mPOA) and limbic and cortical sites (e.g., the prefrontal lobe) activate and deactivate during sexual desire, arousal, orgasm, and ejaculation in both genders (Fig. 5.1). Visual sexual stimulation (VSS) using neuroimaging techniques have given interesting results, regarding specific brain regions that are involved during sexual response. Hormones (especially testosterone) and numerous neurotransmitters (especially dopamine and serotonin) with their receptors are all important contributors to the male and female neuronal network, mediating particular sexual functions. More research is needed in order to achieve a better understanding of the various aspects of the psychobiology of sexuality.

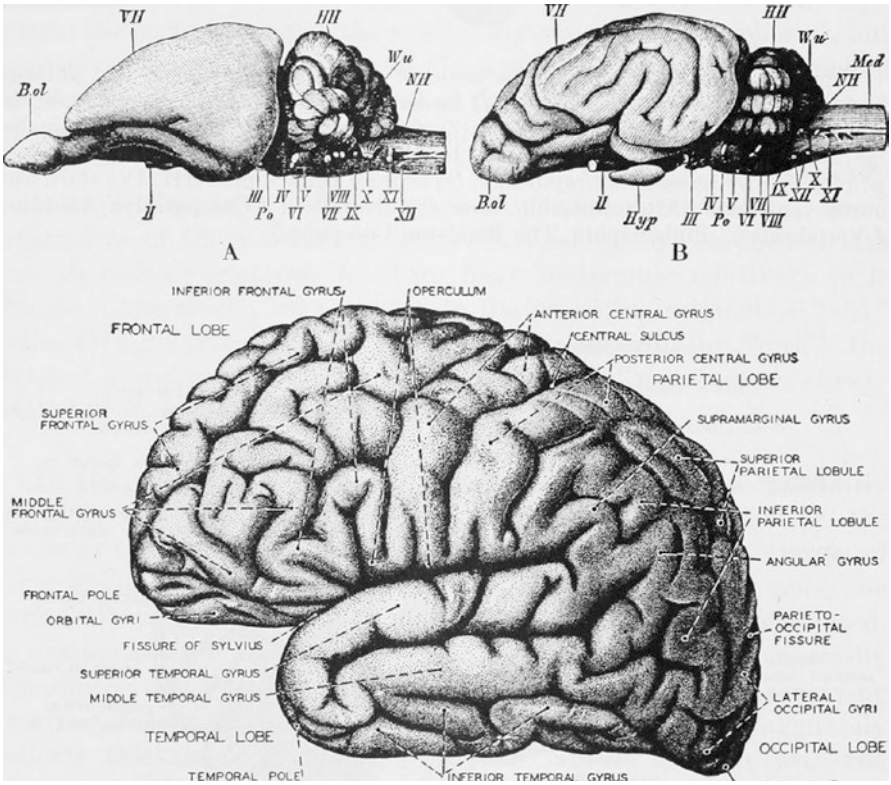


**Fig. 5.1** Morphology of the cerebral cortex. Various areas are involved in human sexual response

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# Neurobiology of Aging

6

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## 6.1 Aging in Our Developed Society

We evolve in a consumer society in which, every passing minute, the sellers of pleasures solicit our mind. Responding to these calls, we are constantly looking to have more and to win more, and we are launched into a performance race. However, this performance is measured by the results of our competitors, and the spirit of competition infuses.To succeed, the required standard appears to be beauty and youth, whose images are sent back continuously to us through all the media channels. Unfortunately beauty and youth are ephemeral and very subjective. To resist the stress caused by the difference between what we are and these images, we exhaust ourselves in a continuous struggle, of which depression can be the pathological consequence. Another mechanism for responding to this stress is avoidance. Among the images we refuse to see, that of old age is probably one of those carrying the strongest negative emotions. This association between old age and negative emotions is not new. Both in philosophy and the arts, there exists a multitude of examples of this bias referring to disgust, sadness, or nostalgia.

The image of our aging body refers to the painful feeling of no longer arousing the desire of the other. But the desire of the other nourishes us and gives us the impression of existing. It flatters our ego. It empowers us by giving us the possibility to use the other and to access our own desires more easily. Accessing our desires by using the other is also given to us by physical force or cognitive abilities, by subjecting him to our will. Nevertheless beauty/youth, physical strength, and cognitive abilities decline with age. These losses, therefore, lead to the fear of dependence and

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the seizure of our own power and self by the other. At least, the satisfaction of our most basic needs will also depend to a great extent on others. Old age will then be felt as a disease in the sense that dependence will be directly threatening for the survival of the individual.

## 6.2 Physical and Cognitive Weakening

### 6.2.1 Brain Aging

The mechanisms of aging are multifactorial and concern the rest of the body like the brain. One of these main changes is the alteration of DNA by intrinsic and external factors. The resulting modifications will modify gene expression and protein synthesis. Oxidative stress participates in this process. It also leads to alteration of membrane lipids or cytoskeletal proteins. Because of its high lipid content, the brain is particularly vulnerable to this phenomenon. Oxidative stress is also accompanied by inflammatory phenomena with multiple repercussions including modifications in cytoskeletal proteins that lead to changes in the transport of neurotransmitters or neurotrophins. Microcirculation is also affected by this phenomenon, which consequently affects oxygenation and glucose supply resulting in a cascade of self-sustained microdysfunctions. This condition promotes the appearance of pathology including neurodegenerative diseases.

The different major neurotransmission systems are affected to varying degrees by this set of processes. The alteration of the dopaminergic system is the earliest, the most constant, and the most important. It leads to a relative frontal deafferentation and the alteration of sensitivo-motor performances. Cholinergic involvement is more moderate and would be responsible for changes in memory capacity outside pathological processes such as that of Alzheimer's disease. In a more marginal way, serotonergic and noradrenergic transmission is impaired.

From a macroscopic point of view, these microscopic modifications lead to a change in the appearance of the brain. The loss of white matter is relatively greater than that of the gray matter. They are the result of processes such as the neuronal loss, the dendritic arborization decline, and the demyelination of neurons. Frontal and associative regions are those whose volume is the most affected compared to primary regions.

### 6.2.2 Cognitive Aging

Cognitive psychology bases its classical distinction of the two dimensions of intelligence on the evolution, with age, of the cognitive capacities that underlie them (Belsky 1990). Fluid intelligence is considered a form of intelligence very sensitive to the effects of age. On the contrary, crystallized intelligence is very robust to passing time. The fluid intelligence relies heavily on visual-motor and/or spatial capabilities and is required for tasks requiring instantaneous use of information to solve

a problem. The crystallized intelligence is mobilized during the resolution of verbal tasks and/or involving the knowledge and general culture that develops with experience. The nonverbal capacities would reach their maximum toward 30 years and decline afterward. This maximum is reached at about 60 years for the verbal capacities.

*The executive functions* are the elementary cognitive abilities that allow planning, organization, and synchronization of processes involved in controlling the execution of the action. Three of main cognitive processes that allow this task are inhibition of automatic responses, updating of relevant information in working memory, and flexibility which is the ability to alternate the multiple cognitive tasks required for execution of a planned global task. These three processes can be independently altered. However the disruption of one will tend to resonate on the other two. During aging, it is the inhibition and updating abilities that would be the most disturbed, the flexibility process being more spared. Higher-order executive functions such as planning and fluid intelligence require simultaneous use of such multiple basic executive functions. These higher-order processes are then also affected by aging.

One of the classic models of *memory* is that proposed by Tulving (1995) who organizes it into five major types of process. The first two, the *procedural memory* and *the system of perceptual representation*, are said to be implicit. They involve an unconscious treatment of information. Procedural memory is the process of learning perceptual motor skills or behavioral algorithms. The system of perceptual representations is involved in the maintenance and encoding of perceptual information allowing the perceptive identification of objects and words but without reference to their meaning. These two types of implicit memory would be little affected by age.

*Working memory* is a mnesic representation of a very recent, real or mental, event. It contains a limited number of information kept active for a short time. It allows the temporary storage and the mental manipulation of information relevant to the realization of a task. This memory is affected by aging, but for the more demanding tasks.

*Semantic memory* is the memory of general knowledge acquired on the world. This memory is an essential constitutive element of crystallized intelligence. It allows the connection between knowledge by ordering them in conceptual categories ("I know the distinction living/non-living; dog and cat are living objects"). This memory of knowledge is little affected by age; however certain categories of knowledge seem to be disturbed, such as proper names.

*Episodic memory*, which is the memory of personal events as a sensory event ("I remember seeing …"), is sensitive to the effects of age. The difficulty in rendering the information presented results from not only a weakening of the strategies allowing the encoding of this information for their storage but also difficulties growing in recovery strategies of already stored information.

As memory, *attention* is a cognitive function that is not unitary, and it can be defined as the ability to maintain cognitive processes directed toward a goal while filtering the continuous flow of the information. The changes that affect it during aging are therefore heterogeneous (Verhaeghen and Cerella 2002).

*Selective attention* is the ability to extract information relevant to the realization of the current cognitive task from the mass of information that constantly stimulates the nervous system. Aging alters this faculty incidentally by disrupting the ability to disengage from the cognitive processing of a first object when performing complex and multiple tasks.

*Sustained attention* is the ability to maintain a consistent behavioral response during continuous and repetitive activity. This corresponds to vigilance which is little changed by aging. However, elderly subjects are more vulnerable to alterations in alertness and especially to delirium. The physical or psychological stresses that trigger delirium in the elderly are much lower than those with the same consequences in younger subjects.

*Alternative attention or mental flexibility* is the ability to shift the focus of attention and move between tasks requiring different cognitive processes which decline with age.

*The divided attention* is the higher form of attention. It allows the distribution of attentional resources on several simultaneous stimuli according to the relative importance of each of them. All things being equal, older subjects are obliged to mobilize more cognitive resources than younger subjects have. When the task become particularly complex, they are therefore more penalized.

### 6.2.3 Affects in Aging: The Paradox of Aging and High Well-Being

Psychoanalysts have identified an existential crisis between the beginning of adulthood and the end of life which they called the "midlife crisis." This crisis would be part of the normal maturation of individuals. It will intervene as a transition in what Erickson (1963), the theoretician who proposed a development in eight stages, called the middle adulthood. During this period, individuals are particularly concerned about the meaning and purpose of their lives. This then allows them to achieve more stable personal satisfaction at the end of their lives, which he calls "late adulthood."

The idea that a lesser period exists around the age of 40 refers symmetrically to the idea that psychological well-being would be superior before and after this turning point in life. This is indeed what many studies show (Blanchflower and Oswald 2008; Stone et al. 2010).

The emotional well-being would follow a U-shaped curve with a low point around 45 years. The result would be that the well-being around 80 years would be equivalent to that of 20 years. Indeed, even with aging-related hardships, older adults are relatively satisfied with their emotional well-being, decreasing in negative effects (Grühn et al. 2005).

Some authors have argued that these results would mainly concern the populations of the most developed countries (Steptoe et al. 2015). However, there also seems to be a midlife crisis in apes (Weiss et al. 2012), suggesting this phenomenon could exist outside of any cultural context. A recent review of the literature found these results to be robust and the criticisms rather limited (Ulloa et al. 2013).

Much of our well-being and stress depends on our social relationships. Indeed, Almeida and Kessler (1998) demonstrated that interpersonal relationships are the main source of daily stress and can induce very strong emotional distress. However, older people are more satisfied with their social networks than younger (Carstensen 1992). Their relation with their family members is more a source of positive emotion than for younger adults(Charles and Piazza 2007), and they experience more positive than negative exchanges. The more positive emotions they generally report could thus reflect these social experiences.

The socioemotional selectivity theory (SST) (Carstensen et al. 1999) argues that two broad categories of life goals are evolving in relation to perceived time: the ones related to the acquisition of knowledge and the ones concerning the regulation of states of emotion. When the horizon of time to live appears as unlimited, the individuals prioritize their objectives around optimization of the collection of information, the exploration of the novelty, and the widening of the knowledge. When time seems limited, the priority objectives are those that can be achieved in the short term. From then on, emotional well-being becomes an objective in itself, depending on the affective experience and the regulation of emotional states. This emotion regulation aims to maximize positive experiences and minimize negative ones. In this view, older adults would thus be more focused on their emotional well-being and behave in accordance with this goal. They tend to reduce their exposure to negative situations and increase their exposure to positive events. They report fewer social conflicts in the social world they navigate in and are more effective in solving the interpersonal problems they encounter than younger adults (Birditt et al. 2005).

*Happiness* has long been neglected from the field of psychology and psychiatry. The main objectives of these disciplines were to understand the mechanisms of pathological states and to provide therapeutic solutions. But the researchers have found that positive psychosocial characteristics are associated with objectively better health outcomes and greater longevity. Moreover happiness predicts success in many areas and helps develop resilience to the difficult circumstances of existence (Cohn et al. 2009). In contradiction with the widespread idea that people become less happy as they age, in studies on well-being, happiness appears to be specifically higher when the age advances (Stone et al. 2010). If we easily imagine that the generation of baby boomers can say that they are happy because of the improvement of the quality of life and health for the 50- to 70-year-olds, it is difficult to imagine that the very old ones can keep the happiness. Diseases and griefs multiply. But above all the loss of autonomy can significantly alter the idea that one can have of one's dignity. However again contrary to the a priori, a study of German centenarians showed that they were as happy as their younger compatriots (Jopp and Rott 2006). Moreover in the context of highly controlled study, the happiness experience by ones seems to correlate with age (Gross et al. 1997).

The frequency of *anger* increases in the young adult but then decreases markedly with aging. In laboratory studies, elderly patients respond with less anger than younger subjects while maintaining an identical sensitivity to stimuli causing sadness (Charles and Carstensen 2008). Visual evoked potentials in response to angry faces are lower in elderly subjects, but this is not true for faces expressing sadness or happiness

(Mienaltowski et al. 2011). This tendency toward decreased reactivity to anger appears to be beneficial for health, as it is recognized that anger increases cardiovascular risk (Mostofsky et al. 2014). This mechanism would therefore be adaptive.

Moreover, as previously underline, the negative interactions with members of their social networks are scarcer than for youngers, and interpersonal tensions are less distressing for them (Birditt et al. 2005). Eventually, when these tensions exist, they lead to less anger, and older subjects regulate them by milder strategies (Kunzmann and Thomas 2014).

*Sadness* is triggered by loss and older adults are as sensitive as younger to sad stimuli (Charles and Carstensen 2008). Losses and deficits in personal abilities increase with age, and the contentment with performance should then decline with age; however it does not (Rothermund and Brandtstadter 2003).Older adults have relationships with older individuals, so they are confronted with more frequent mourning in their social relationships in general. Old age is also accompanied by more symbolic losses such as physical abilities or autonomy. Old age therefore refers to a greater probability of sadness. Yet when sadness is measured at a given point in time, elderly people are no more so than other parts of the population (Kunzmann and Thomas 2014). It seems even that the feeling of sadness shows a slight peak in the middle of life, to decline then (Stone et al. 2010).

*Regret* involves sadness or remorse over past acts. Having a longer life to look back on means that there are more things to regret and also potentially fewer opportunities to address the regret via new behaviors. But older adults are less likely than younger adults to report regrets (Timmer et al. 2005). There is a difference in how to look at situations that can generate regrets depending on age. In a game in which a choice is presented with several options that can generate different gains, older subjects do not use the same strategy to guide their decisions. Elderly subjects are more likely to focus on potential gains than avoid potential regrets in such situations (Mather et al. 2012). Regrets also influence the elderly subjects' choice behaviors much less than those of young or depressed elderly subjects (Brassen et al. 2012). It appears that the old age is associated with a greater emotion regulation, involving the medial prefrontal areas, during the choices inducing regrets. This regulatory strategy does not therefore seem to imply a cognitive strategy of the reappraisal type requiring significant executive resources but more probably a strategy of regulation by external attribution.

### 6.2.4 Positivity Effect

As we have already pointed out, aging is accompanied by physical decline and the likelihood of greater loss. However, aging is also accompanied by greater emotional stability and often a feeling of "successful aging," a term associated with both the physical and psychological dimensions. A possible explanation of this apparent paradox is that there is an age by valence interaction in cognitive processes. The older adults remember the smiling faces (Charles et al. 2003) or their happy stories but less vividly feel the financial losses (Samanez-Larkin et al.

2007). This bias is called "positivity effect" and would rely on a memory and attention bias (Mather and Carstensen 2005). The SST discussed above explains this psychological bias. The time available to live for the elders appears shorter which leads them to regulate emotional states in order to optimize psychological well-being.

### 6.2.5 Emotion Regulation

Emotion regulation involves all the processes aiming at modifying the nature and intensity, the duration, or the expression of emotions. It relies on various strategies and cognitive processes in order to be efficient. Both the paradox of aging and well-being and the positivity effect support the idea that emotion regulation is specifically efficient in older individuals. However in experimental conditions during which they are given emotion regulation tasks, older individuals don't have better emotion regulation skills than their younger counterparts (Mather 2012). How then could older subjects be more successful in eliminating negative emotions? One explanation would be that older adults are more focused on positive emotions and devote more daily resources to regulate their emotions. Younger subjects, who can change their future by modifying it, have less need to be positive, and their negative emotions can motivate them in this perspective. They have less need to eliminate negative emotions and therefore devote fewer cognitive resources (Mather and Johnson 2000). Another explanation is a difference in emotion regulation strategy. When SAs and young people are compared on specific tasks, SAs perform worst or not as good. Since SAs have a decreasing executive capacity relying on the lateral prefrontal areas, they must rely on strategies involving the more medial cerebral areas that favor distraction rather than reappraisal. In favor of this hypothesis, a study showed that in AS the distractibility by positive stimuli is parallel to the activity of the anterior cingulated cortex (ACC) and that this activity of the ACC is correlated with the emotional stability (Brassen et al. 2011).

### 6.2.6 Brain Connectivity and Aging

For a long time, the paradigm that allowed the study of the brain was a function/a brain area. It is now widely accepted that most cerebral functions are supported by the coordinated activity of a set of structures that make up a more or less complex network. Thus, one talks of cerebral connectivity. We talk about connectivity to translate the idea of links between brain areas. This link is reflected either by a direct connection by fibers or a synchronous activity over time. This method of connectivity has made it possible to identify networks of structures whose activity is intense when the brains are at rest. The DMN has been identified as a network of areas that activity typically decreases below baseline level during cognitive tasks requiring externally directed attention. It is a deactivation of this global network. In healthy older adults, this deactivation is however reduced (Damoiseaux et al. 2008). This

reduced deactivation would result from a decrease ability to suppress task-irrelevant processes, compared to young adults (Grady et al. 2006). An alternative view is that when cognitive tasks require important resources, older individuals rely more on processes mediated by the DMN (Maillet and Schacter 2016), in which the medial prefrontal cortex is a key hub. Interestingly, elderly subjects rely more on strategies involving the medial prefrontal areas for emotion regulation as cited above. Elderly better emotion regulation and well-being would then be linked to this DMN overuse.

## 6.3 Conclusion

The very reason why man has become a social animal is because his survival depends very much on his ability to integrate among his fellows and maintain himself in the social hierarchy. However, this capacity seems to diminish with age.

Yet every strength that gives us our place in society does not necessarily disappear with age, so emotion management and temperance are qualities that are attributed to older individuals. These abilities are becoming more important as people are confined in the immediacy of emotions aroused by our digital world.

Moreover, our social position lies not only in our ability to dominate the other but also in our ability to arouse sympathy. Compassion and empathy are motivational forces as powerful as envy in initiating behaviors. Vulnerability can thus also lead to a strengthening of the social bond. This shows that there exist reasons to not be pessimistic.

Ultimately, the relationship of the individual to himself and his regrets changes with age as we have explained. The frequency of regrets decreases. The feeling of having accomplished one's life according to one's abilities allows the disappearance of the anxiety of success, and the fear of the future decreases as the future shrinks.

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# Psychobiology of Addictions

7

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## 7.1 Overview

Investigation has been increasing into which function is closer to the core of the addictive neurobiology that we witness as a globally subverted ensemble of psychological parameters (Table 7.1).

First of all, one should take the pre-relapse status as the apparent normality following temporary detachment from the addictive cycle and compare it with the renewal dynamics of already initiated relapse.

Abnormality does not loom as an altered sensitivity to a substance, even if it also includes that; it mainly involves an altered appetitive drive, followed by a paradoxical project of pleasure and balance.

Along with the comparison that can be drawn with diabetes (the 'thrifty gene' hypothesis), we may say that human self-stimulation is a system built to be engaged in or else disengaged from external cues. Its evolutionary interpretation may be that of anticipating events that may otherwise take place in a state of need or of happening fortuitously. For instance, appetite should be seen as the dynamic that leads to eating food before the same behaviour is evoked as hunger, that is, in extremis, so complying with the need to avoid the running out of supplies. On the other hand, the instinctual drive towards reproduction leads to systematic intercourse by linking arousal to acting out, instead of waiting for the environment to put together a

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**Table 7.1** Structure of addiction psychobiology

| Components | Clinical aspects | Neurobiological substrate |
|---|---|---|
| Psychological and psychiatric precursors | Temperamental disposition, symptoms related to mood, anxiety, impulse-control dimensions | • Dysfunction in reward and stress system<br>• Hypo-activity of prefrontal brain region<br>• Other molecular changes (CREB, etc.) |
| Acute substance-induced effect | Symptoms related to mood, anxiety, impulse-control dimensions | • Activation/inhibition of specific receptors and neuronal circuits<br>• Activation of dopamine release in nucleus accumbens |
| Addictive processes | Repeated brain-substance interaction resulting in:<br>• Craving for and dyscontrol over substances<br>• Symptoms of mood, anxiety, impulse-control dimensions | • Dysfunction of limbic dopamine circuits and reward system<br>• Hypo-activity of prefrontal brain regions<br>• Changes in stress system<br>• Other molecular changes (CREB, etc.) |
| Interaction of addictive processes and psychological-psychiatric precursors | Worsening of craving, loss of control, symptoms of mood, anxiety, impulse-control dimensions | • Positive feedback between assets preceding substance use and those following addictive processes (reward system, impulsive-reflective system, stress system) |

Longitudinal perspective (from Pani et al. 2010, modified)

favourable environment. Appetite and sexual drive are structures, which anticipate and amplify the behavioural template, and answer to the environment by enabling the achievement of certain objectives.

These systems have a high threshold of overstimulation, with respect to an average baseline, so that an individual may handle a wide range of stimuli and increase stimulation in order to maintain high levels of performance, in a reverberating circuit. Once that threshold is exceeded, the system fails, but its failure does not take place as a loss of functionality but rather as a decoupling between stimulation seeking and performance. In other words, the systems suddenly go 'out of order' in conditions of irreversible overdrive, which may be intermittent or continuous.

## 7.2 Theories of Addiction

Theories about addiction should usually try to illustrate the mutual relationships between the three factors involved: the individual, the substance and the social or environmental function of consumption. Some of them actually fail to focus on the dynamics of basic factors, so providing only a possible explanation of what addiction may mean to others, rather than what addiction means intrinsically. Those portrayals do not deserve the status of theories of addiction.

Apart from descriptions of the intrinsic dynamics of addiction, other explanations actually present consumption and addiction as variants of a unique phenomenon, addiction being its extreme and excessive form, while seeming to recognize no qualitative threshold between habitual and heavy consumption and addiction itself. Such theories, although commonly accounted for as theories of addiction, should, more precisely, be referred to as theories of consumption.

We now come to real theories of addiction. In an attempt to summarize the theoretical views on addiction, we may distinguish between the genetically oriented theory, on one hand, and the environmentally oriented theory, on the other, where the substance itself functions as the environmental agent.

### 7.2.1 Genetic Theories of Addiction

Obviously, the development of addiction requires the individual to interact with an environmental element, which is the source of stimulation, so that no direct genetic determinism of the phenotype is possible in a stimulus-free environment. In this connection it might be argued that, given the presence of some addictive stimulus, a genetic array can influence those who are prone to engaging in self-stimulation (toxicophilia). Recent research has proven the high frequency of certain affective temperamental profiles among drug addicts, regardless of drug type (alcohol, heroin, cocaine polyabuse). Such a genetically based, early-onset disposition to addiction is quite a common phenotype, so that it is better classified as a risk factor rather than a specific substrate for the development of addictive ties.

In other words, a large number of individuals are theoretically predisposed to engage in addictive drug use. Curiously, the temperamental profile seems to vary according to the stage and type of drug: hyperthymia creates a risk of early-onset alcohol consumption, whereas cyclothymia is a correlate of addiction (to alcohol or other substances). Since addiction also looms as a later stage of consumption, this difference may be induced by chronic intoxication rather than by an originally different substrate (Maremmani et al. 2009; Pacini et al. 2009; Rovai et al. 2013).

In individuals who come into contact with psychoactive substances, some genetic variables are concentrated among addicts, though not to the point of allowing a definition of addiction as a genetic result of a ‘per se’ variable environmental factor (substance use) (Ouzir and Errami 2016). In other words, genetic factors may favour but are not necessary to the development of addiction. It is likely that a number of individuals lacking genetic proneness to addiction will never engage in substance use, so that we cannot state that the generic array is enough by itself to bring about a switch from consumption to addiction, though such a hypothesis remains plausible. All things considered, the psychopathological phenomenon known as addiction comes about either in the presence or in the absence of genetic determinants.

### 7.2.2 Addictogenic Potential

Exposure to the consumed substance is the only constant of drug addiction, as a premorbid common ground (Pani et al. 2010). On the other hand, cases share the same clinical features and have been described as having common neurobiological substrates. Reviewing these neurobiological findings, some may just mirror the effects chronic exposure has on the human brain, without there being any difference between heavy consumers and addicts. Others may be rather specific to addiction, such as those displaying the different receptorial arrays of detoxified alcoholics and the sensitivity to cueing in preconditioned human brains with respect to craving.

Also, some neuroendocrine features have been described as predictors of relapse, such as prolactin for cocaine users or the hypothalamus-hypophysis-surrenal axis for detoxified heroin addicts (Teoh et al. 1990).

According to the substance-centred hypothesis, exposure to certain addictogenic substances is enough by itself, given a variable period of time, to induce a stable change in the human brain, to be located as overlapping with the reward-motivational circuit. The stability of such a new array is enough to constitute a bridge across the symptom-free periods in between and reveal itself as long-term relapsing behaviour. Cueing, stressful life events and other factors may shorten the intervals of short- and medium-term latency before each relapse but would make no difference in a longer-term observation. On the whole, the diagnostic criteria show a good fit with this view of addiction, as long as the development of certain behaviours makes it automatic to formulate a prognosis of automatic relapsing (chronic-relapsing course).

The definition of addictogenic potential seems to correspond to a common pharmacological feature, shared by all addictive stimuli, that is, the time-to-peak (the shorter it is, the higher the non-medical use potential), regardless of other factors. Changes in time-to-peak that correspond to a different route of administration (i.e. oral instead of inhalation) do have an impact on the non-medical use potential of the same molecule, as also happens with any change in the kinetics of release.

Among benzodiazepines, for instance, the more lipophilic (sharper alpha phase) they are, the more they are welcomed by drug users and the more implicated they are in cases of sedative use, regardless of duration, chemical structure and potency (Lalive et al. 2011). The same goes for free base products, which are sometimes so highly addictive that they provide a perfect fit for the dead-end subpopulation of street addicts (from a pusher's point of view).

An addictogenic profile must, therefore, be conceived as a combination of a molecular target (receptor) and a pharmacokinetic profile characterized by a short time-to-peak, together with a high ratio of brain/blood distribution (partial distribution volume).

Highly addictive 'preparations' include snorted, inhaled and injected heroin, buprenorphine, morphine, cocaine and methamphetamine, while their slow-acting or oral variants show little or no problematic use liability. Such a radical difference makes it clear why certain substances may be employed for the treatment of an

addiction that was induced by other substances belonging to the same class (e.g. methadone treatment for heroin addiction). In some cases, the same molecule in a different preparation becomes the treatment agent for addiction to its fast-acting form (as happens with slow-release morphine and slow-release heroin for heroin addiction).

### 7.2.3 The Self-Medication and Self-Selection Hypothesis

This hypothesis bears the name of Khantzian, who originally described it as a possible explanation for two case reports concerning cocaine and heroin use (Khantzian 1980, 1985, 1997).

The theory assumes that consumers become addicts in an attempt to treat symptoms of discomfort, which is equivalent to granting them an average balance, from a homeostatic perspective. Once they learn that certain substances fit their discomfort, they are likely to use them on a regular basis, only to discover later on that the effect is transient and the risk/benefit ratio becomes inverted with respect to the initial phase. Unfortunately, they cannot detach themselves from their acquired use, due to the exacerbation of the original discomfort while tapering, let alone interrupting that use altogether, so that they find themselves hooked: in other words, they came to depend on a substance in order to avoid suffering, but at a later stage they no longer gain any benefit from it.

Although this theory is easy to understand and is intrinsically consistent, it actually fails to describe addiction as a relapsing phenomenon. Despite the spread of psychopharmacological treatment, reaching out to a variety of psychopathological areas (including depression, psychosis and anxiety), drug addiction has continued to spread. Moreover, substance-using trends among psychiatric patients fail to show a choice, which is consistent with a homeostatic link: depressed patients use sedatives and hypnotics, while overexcited patients use anything, with a special liking for stimulants (Maremmani et al. 2012). The majority of psychotic patients endure in psychotomimetic use, despite having experienced hospitalization (Maremmani et al. 2004).

Epidemiological findings following Khantzian's work have failed to confirm his hypothesis, either on grounds of personality profiles or of DSM axis I psychiatric disorders.

On conceptual grounds, detachment from the substance is far from being unlikely in the course of an addict's career. The feasibility of detoxification and the opportunity to have it tailored to one's personal needs make it implausible that addicts stay hooked on substances due to their incapability to handle withdrawal. Also, evidence of being tied to self-medication can no longer be found in the addictive phase, where all parameters of psychic well-being worsen. Lastly, the experience of the failure of addictive drugs as a valid means of long-term self-medication should immunize former users from relapse and make them likely to resort to psychiatric facilities for the management of their psychic discomfort. Neither of these happen to be true (Lovrecic et al. 2004).

### 7.2.4 Environmental Induction

This theoretical view assumes that the external objective conditions in which the individual meets the substance may play a crucial role in the development of addiction. The environment could make the difference in raising the utility of certain substance-induced effects or encouraging a substance-based lifestyle (Enoch 2012; Meyers and Dick 2010; Mayfield et al. 2008). Yet neither type of explanation is consistent with the diagnostic evidence of the disadaptive condition of drug addicts, which does not allow them to fit any environment, no matter how substance-based it may be. In other words, addicts are unhappy, disorganized and clumsy consumers, and they certainly have fewer resources at their disposal in handling environmental stress.

More recently, this theory has been revisited in epigenetic terms: environmental factors may change the brain's sensitivity to substances, thus playing an important role in the issue of how much addictive power substances express into the brain (Kalda and Zharkovsky 2015; Enoch 2011). The extent to which exposure to substances leads to addiction may be conditioned by an epigenetic effect that makes individuals prone to addiction. However, any such common epigenetic ground does not have yet to be defined, nor has any precise correspondence between epigenetic molecular changes and life events been ascertained so far.

### 7.2.5 Behavioural Addictions

Theories of behavioural addiction do not differ substantially. Gambling addiction has been investigated in some depth as far as addictogenic features are concerned. The short time gaps between game opening and betting and between betting and its outcome are powerful variables, as well as the time elapsing between repetitions of the betting cycle within the same prepaid game session.

Although expectations about winning chances and the overrating of the rational strategies for successful betting may play a role in getting involved in habitual gambling, the addictive phase is intrinsically independent of such factors. At this stage evidence of negative balance is there to prove how strongly addiction is distinguished by loss of sensitivity to losing and winning. In other words, no reward or negative reinforcement is enough to stop the overwhelming automacy of behavioural relapse (Wiehler and Peters 2014; Gaher et al. 2015).

## 7.3 The Reward and the Decision-Making System

Addiction is usually described as a disease of the reward system or the incentivizing, decision-making system, which is reinforced by rewarding stimuli and held back by drawbacks and negative reinforcement (Bjork et al. 2009).

Yet, it may not be clear whether we are referring to the impairment of liking, an abnormal intensity of reward seeking, a twist in the attribution of reward or a failure by regulatory areas in the brain to filter the development of craving.

### 7.3.1 Habit

Habit differs from addiction in the intentionality of use or the lack of any effort to refrain from a certain behaviour that is performed frequently or regularly. Although 'the habit' is a term often used as a synonym for the drug problem, or addiction, the issue of control is not involved: it may happen that people do not give up habits or stick to them simply because they actually feel better when exposed to some stimulus and suffer from its absence. It is, in fact, accurate to say that the revealing moment of addiction is the loss of control when the stimulus is widely available and exposure to it becomes frequent.

Habitual exposure to certain stimuli may also imply a homeostatic change known as 'tolerance', which implies a susceptibility to transient withdrawal discomfort as a consequence of abrupt interruption of such exposure. So too, habitual stimulation may imply toxic consequences that individuals may only become aware of much later—consequences that may lead them to quit or reduce their exposure.

As far as giving up the habit is concerned, addicts are probably the human category that is best at doing so, before any relapse takes place. It is relapsing, not the inability to detach, that is the crucial feature of addiction.

### 7.3.2 Reward

The central role of reward is sometimes made equal to craving, which is quite a serious conceptual mistake. Reward should never be thought of as 'pathological', not even in addiction. What ceases to work properly in the system of reward, once addiction has developed, is the capability to optimize reward. Although drug addicts worsen their chances of getting rewards from sources other than the drug, it is also true that their first failure is that of handling reward by the drug itself. Addiction develops in the place of physiological reward, so that the best way to grasp its meaning is to compare addictive use with use that is pre-addictive or is still under physiological control.

The presence of other sources of pleasure, interest into them and endurance in searching for pleasure from the same source may vary from individual to individual. On the other hand, all addicts share the same incapability to pursue reward by the substance they are dependent on.

Habitual use, far from meaning how frequently addicts need to be stimulated, is, rather, a proof of their inability to learn how to prevent the development of a state (tolerance) that is unfavourable to internal development. In fact, they find themselves striving again and again to overcome withdrawal, if possible very rapidly, in order to be able to sense the drug again. Addicts probably end up spending more time far from reward than occasional users are, regardless of the other harmful correlates of their condition.

### 7.3.3 Reinforcement

Addicts become insensitive to either kind of reinforcement. On one hand, individuals usually go through a refractory period after being exposed to rewarding

stimulation, so that some time passes before they engage in stimulation again. Although sessions of repetitive stimulation may be featured in physiological self-stimulation, spontaneous intervals take place, which are distinguished by enduring well-being. It also happens that repetitive stimulation ends up in saturation of reward, together with boredom and loss of interest in a specific source of stimulation (Rovai et al. 2013).

On physiological grounds, positive reinforcement is expected to work both to make the individual closer to, and more efficient in, self-stimulation and also to promote the completion of the stimulation cycle and the onset of boredom.

Negative reinforcement is usually rooted in the experience of negative consequences after drug-taking. Real-time negative reinforcement (e.g. vomiting after heroin use) may be a weaker kind of conditioning than positive reinforcement, but it is resorted to as a strategy of aversion from drug use, as in disulfiram treatment for alcohol and cocaine addiction. Later reinforcement consists of the negative consequences of addictive behaviours and a drug-related lifestyle. Such reinforcement, however, is more likely to be experienced once addiction has developed. Early negative reinforcements are likely to be effective in preventing drug use in a pre-addictive phase, although in that stage, they are powerfully counteracted by the increasing positive reward ('honeymoon') phase (Heinz et al. 2004).

A major source of negative reinforcement is the withdrawal syndrome (Heinz et al. 2004). Some users may be held back from enduring in drug use just because of the transition from a positive balance (prevailing positive reward) to a negative balance (emerging withdrawal, decreasing reward). As long as such a transition takes place in the not-yet-addicted individual, it may be perceived as a reason strong enough for breaking the habit. It may be hypothesized that such a balance soon becomes unsatisfactory for those drug users who start using drugs for environmental reasons or self-medication.

Negative reinforcement shows a different degree of influence on drug use according to the drug use stage. In nonaddicted individuals, negative reinforcement may lead to quitting, cutting down or temporarily detaching. Conversely, negative reinforcement during addiction may produce the opposite effect, especially when it is linked to drug deprivation. The experience of withdrawal, far from being a 'rock-bottom' experience that strengthens the individual's motivation to quit, may leave a memory similar to that of a panic attack. In the subsequent addictive cycle, the individual becomes more and more phobic about being on withdrawal, so that his/her phobia becomes a stronger and stronger path to craving, so bringing the individual closer to the essential appetitive stance. In other words, addicts are led to come to grips with withdrawal, or the fear of it, by enduring drug use rather than trying to detach from it. Eventually, they may experience spontaneous withdrawal or cue-elicited withdrawal starting in a drug-free condition and be led to relapse by the abrupt emergence of craving (Grace 2000; Maremmani and Pacini 2003)

On the whole, positive and negative reinforcement become neutral for the addicted individual and may even be subverted. A smaller reward becomes enough to maintain a heavier habit, whereas a worse trail of consequences becomes

ineffective in encouraging detachment from the drug, possibly ending up by working in the opposite direction, as auxiliary to craving.

The output behavioural array that appears in response to a rewarding stimulus (more simply indicated as 'wanting') is a variable dependent on other psychobiological variables and may be divided into two main subtypes: appetitive and avoidant (Weiss et al. 2001). Appetitive behaviour aims to achieve exposure to a certain stimulus, whether passively or actively, in order to reach the highest peak stimulation possible. Avoidant behaviour aims to prevent suffering, pain or discomfort. When the individual's array has been conditioned by a rewarding dynamic, the balance between appetite and avoidance shifts towards the former, as a result. Despite this, to a certain extent, the behavioural output stays sensitive to pro-avoidant inputs. When the lack of stimulation is followed by the onset of acute withdrawal, a special form of avoidance is strengthened, and it converges with appetite in aiming for the same objective. At this stage, the behavioural array may be redefined in terms of detachment from exposure to the addictive stimulus, which is the source of a vicious circle between reward impairment, appetite endurance and harm increase. However, appetitive drive may already have developed so far that it overwhelms any attempt by the individual to become detached or stay abstinent.

It should also be kept in mind that the appetitive subsystem mostly grows through a fast-acting subcortical mechanism, which is reward, whereas the avoidant subsystem mostly grows by a slow-acting, cortical mechanism (Milton et al. 2008). Once appetite has taken over in a stable mode, the behavioural array becomes rigidly oriented towards a certain output, which is hardly influenced by any other harm-avoidant drive, let alone intention. In other words, the array is not influenced by recurrent harm, nor is it discouraged by the lack of reward. In fact, appetite itself is set at an overdrive level, where no reward can further reinforce it and no frustration is able to decrease it.

Awareness of such a condition may vary across the different stages. Addicted people tend to lose their awareness of (insight into) the change they have gone through. The hierarchical position of the cortical 'inhibitory' areas seems to be subordinate to the subcortical, instinctual ones, so that the individual's attitude may change along with increasing appetite, so that he/she becomes self-unaware when addiction has set in. The expectancy that inhibitory areas will come to grips with increasing appetite and put a limit to it is true below a certain threshold. Over that threshold, the array is subverted: not only are inhibitory areas weaker and slower than antagonist instinctual drives, but they also tend to be obscured by them. As a result, the psychobiological state of the addicted individual becomes wholly consistent with the appetitive purpose, with no room left for a different outcome.

The reinforced appetite drives towards self-stimulation by the reinforcing objectives. Stressful experience leads to the instinctual activation of withdrawal-related harm avoidance and thus eventually to self-stimulation, though theoretically in a withdrawal-relieving perspective. Inhibitory areas fail to hold back appetite or alarm, while the thought about this dynamic is focused on the pursuit of stimulus optimization and control rather than detachment.

## 7.4 Factors Affecting Non-medical Use Potential

The psychobiology of risk dispositions includes genetic, epigenetic and environmental factors and is to be understood as a focus on the psychobiological dynamics corresponding to the different correlates of problematic use and addiction (Pani et al. 2010).

In other words, the question arises: at what level may different factors influence the circuit of drug-related decision-making, regardless of whether those factors are genetic, epigenetic or environmental?

Relying on these premises, we may now try to describe how addiction may be facilitated, or enhanced, at different levels, by pre-existing dispositions affecting drug-liking, impulsivity and behavioural inhibition vs. elation, reward and reinforcement.

Some of those factors may be psychologically 'silent', that is, have no cognitive translation, only a behavioural ground of expression. Others may contribute to psychological variants of addictive phenotypes. Furthermore, some factors seem to affect the severity of expression of core addictive features (expressivity) and the threshold of exposure to the substance at which addiction sets in (penetrance).

To date, several studies have indicated the concentration of genetic variants among populations of addicts, though without clarifying whether they indicate a genetic disposition to risk behaviours, substance use or a specific vulnerability to developing addiction with respect to nonaddicted users. In fact, control groups are often made up of non-users, and they often fail to produce evidence about the role of genetic features in determining the addictive potential of substances (Blum et al. 2012).

Clinical research into the dynamics of addiction has revealed how the feature of cyclothymia is maintained across different substance use groups (cocaine, heroin, alcohol) and stands out as a discriminant trait of addicts regardless of dual disorder, even of dimension-related psychiatric pictures (major mood disorders) (Maremmani et al. 2009; Pacini et al. 2009; Rovai et al. 2013). Heroin addicts, cocaine users/addicts and alcoholics are more cyclothymic than control subjects. Dual Disorder addicts are as cyclothymic as single-disorder ones, and both groups are more cyclothymic than controls. Looking deeper into the typology of dual disorder, some interesting data emerge. In a group of alcoholics, cyclothymia is higher in lifetime polyabusers (of heroin and alcohol), but the stronger link does not apply to the more deviant substance (heroin) but to the more common one (alcohol). In fact, when heroin addicts are compared with a control group composed of non-users and pure alcoholics, the level of cyclothymia shows no difference, whereas a difference is measurable when alcoholics are compared with non-users grouped together with heroin users.

It should also be noted that the same temperamental disposition may not play the same role at all stages of the pathophysiological process, leading from first exposure to addiction. In fact, adolescents with early-onset recreational alcohol use show a

higher raw score for hyperthymia and are more likely to have a dominant hyperthymic profile (Placidi et al. 1998). Hyperthymia, however, is not the most likely profile among addicts, as mentioned above. Otherwise, in the comparison between heroin addicts and controls, hyperthymia appears to be discriminant for nonaddicts, whereas cyclothymia, variably mixed up with other 'polar' features, is typical of addicts (Maremmani and Gerra 2010).

We may, therefore, hypothesize that hyperthymic traits play a role in favouring the first contact with either legal or illegal drugs, whereas it is the cyclothymic profile as a dominant structure that favours the transition from physiological to pathological use and addiction.

On psychiatric grounds, major psychiatric disorders seem to be neutral, although some may be underrated as to the presence of 'para-physiological phases' such as hypomania for bipolar disorder II and also due to the interpretation of substance-related mood disturbances as intoxication rather than as clinical variants of the psychiatric disorder (bipolar phenotype III) (Akiskal et al. 2003).

In order to avoid the classic overlap between an ambiguous diagnosis of depression (as an episode, syndrome or longitudinal unipolar disease) and minor bipolar disorders, we have compared the diagnoses received by alcoholics according to their substance use status, dedicating special attention to the recognition of hypomania. Our comparative analyses reveal that depression and bipolar disorders (which also include depressive phases) play opposite roles with respect to alcohol problematic use and addiction. First of all, the anamnesis of a major depressive episode is related to the absence of polyabuse (heroin-alcohol), whereas the presence of polyabuse, as anticipated above, was predicted by cyclothymia. At a later stage, we divided the sample into two subgroups (dual addiction or alcoholism coupled with a history of nonaddictive heroin use). The negative correlation was still evident between a history of depression and dual addiction, but not in cases of single drug use (Pacini et al. 2009).

On the whole, the pathway to addiction seems to start on the wings of hyperthymic traits, proceed along cyclothymia and be interrupted by the occurrence of major depression. Prominent hyperthymia, on one hand, and depressive phases loom as obstacles to the progression of substance use in moving towards the addictive stage.

The addictive potential of substances, in other words, may be enhanced by cyclothymia and minor bipolar syndromes ('less than manic') and diminished by a reward-refractory state, such as depression.

The course of polyabuse is also related to the dual disorder of bipolar disorders, so that bipolar heroin addicts or alcoholics are those who mostly tend to engage in use of cocaine as a secondary substance (Maremmani et al. 2008; Pacini et al. 2010).

A reduced latency to addiction is reported for aggressive patients. The meaning of such a link is not known, although we can hypothesize that it has to do with the opioid system, which is involved both in the modulation of aggressiveness and in the reception of opiates. The malignancy of addiction appears to run parallel with the loss of control over aggressiveness, which is weaker from the beginning, and is

later hampered by opiate intoxication. The fragility of the opiate system therefore seems to independently underlie aggressiveness and addiction proneness (Bacciardi et al. 2013; Maremmani et al. 2014; Bacciardi et al. 2012).

The self-medicating pathway may shorten the period of latency prior to regular use. It should, however, be remembered that self-medicating would-be addicts do not engage in regular use just as a consequence of the substance's medicating potential. A study on a group of social phobic patients clarified the differences between alcohol-abusing and non-alcohol-abusing ones (Perugi et al. 2002). Although a majority of socially phobic patients agreed on the medicating, anti-phobic potential of alcohol on the basis of personal experience, only one subgroup had chosen to use it wilfully to antagonize social anxiety on a regular basis. This latter subgroup was characterized by a higher prevalence both of individual and family diagnosis of bipolar disorder.

As regards alcohol use in depressed patients, available data for a group of atypically depressed patients show that dominant cyclothymic temperament is far more concentrated among alcohol-abusing than non-abusing depressed peers. Comorbidity with bulimia displays the same correlation with cyclothymia, whereas other anxious or somatic forms of comorbidity do not (Perugi et al. 2002).

It is difficult to establish whether cyclothymic patients feel the effects of substances as sharper, in terms of reward intensity. The self-reports of reward intensity do not allow any easy comparisons between different diagnostic groups, due to the different thresholds of satisfaction they may refer to. In any case, the professional literature is lacking in studies about the influence of psychiatric diagnosis on the salience and the reward correlates of non-medically used drugs, which should become a future field of clinical research.

Epigenetic research has shown that exposure to stress triggers biochemical cascades, which end up stably influencing DNA transcription rates (McGowan and Roth 2015). Persistent changes lead to a second genetic array, resulting from a modulation of the basic array, and may justify a stable change in function at a local level, involving single cells, circuitry or cell types (Bale 2015). It is known that chronic intoxication is related to abnormalities in stress-related endocrine circuits, such as the cerebral-surrenal axis, which accounts for the acquired difficulty of heroin addicts in handling normal or exceptional stress (Kreek et al. 2004). Endocrine abnormalities do persist after the accomplishment of detoxification and are linked with a chronic-relapsing course. Stressful events, although to a lower degree than drug cues, are effective in provoking relapses, by a sharp increase in craving levels. Beyond the subjective meaning that can be attributed to these events, the behavioural output either of negative emotions or a positive tickling of desire for the chosen drug ends up leading the individual to relapse.

Nevertheless, data are unable to clarify whether stressful stimulation has an influence and, if so, of what kind, on the liking for drugs, and the intensity of reinforcement after occasional or habitual drug use, before addiction has settled in. On the other hand, indirect or concurrent rewards may play a crucial role in enhancing the reinforcing power of drugs and accelerating the process of addictive binding, starting from equal levels of exposure.

## 7.5 Human Biological Correlates of Drug Using Behaviour: From Physiology to Pathophysiology

Non-medically used substances share a common acute effect, which connects up the subjective effects of euphoria, 'high' pleasure, with the increase occurring in dopamine release in certain subcortical areas, notably the ventral striatum, in particular in a smaller area known as the nucleus accumbens.

While both slow-onset and rapid-onset dopamine increases do correspond to a neuroimaging change, only fast-onset dopamine increases are real-time correlates of a subjective pleasurable change (Grace 2000; Volkow and Swanson 2003).

In comparable conditions of metabolic hyperstimulation, the reinforcing effect is thus due to a fast-acting dopamine high tide (peak) (Volkow et al. 1996). Non-medically used substances may differ as to their primary receptor, the quality of their effects and the duration of otherwise similar effects, but their use liability is rooted in their rapidity of dopamine-mediated action. In order to produce a rapid action, the route of administration is crucial, since oral administration is unlikely to produce a fast blood peak, as happens with intranasal absorption, inhalation or intravenous injection (Volkow et al. 2000; Chait 1994; Volkow et al. 2001).

An expectation of pleasant effects, which is automatically conditioned by previous experiences, corresponds to an amplification of the drug's effects (Kalivas and Volkow 2005). As a result, people who try a drug which matches the effects they expect experience a higher level of reward and are more strongly reinforced. Also, at an addictive stage, a heightened expectation running in an automatic way, regardless of any recent negative experiences, does increase the reinforcing power of even low doses or allows some effect to break through in a condition of theoretical tolerance.

During chronic intoxication, the common ground is represented by a downregulation of D2 receptors in the striatum, which is attributed to a competition with endogenous dopamine. Once dopamine release dwindles, due to the discontinuation of substance use, the D2 downregulation endures long after the end of acute withdrawal and corresponds to a subjective feeling of dysphoria, dullness, reduced sensitivity to and interest in previously pleasant stimulation. On the other hand, sensitivity to drug-related cues is amplified (Heinz et al. 2004; Volkow et al. 1993, 2001, 2007).

Consequently, symptoms of chronic intoxication, residual 'late-withdrawal' symptoms, as well as acute withdrawal increase the discrepancy between the indifference shown towards general stimulation and the exacerbation of drug-selective craving (Childress et al. 1988; Martinez et al. 2004; McClernon et al. 2009; Volkow et al. 1997).

The activity level of functionally antagonist systems seems to be enhanced in chronic drug users. For instance, acute cocaine withdrawal is distinguished by supersensitivity to GABAergic medications, as well as to opioidergic medication. From a chronic perspective, cocaine exposure may become less and less pleasant, and its side-effects more and more likely, so that people may resort to polyabuse in order to buffer cocaine toxicity or switch to substances they have become more sensitive to, such as benzodiazepines, alcohol or opiates (Volkow et al. 1998; Zubieta et al. 1996)

All of these phenomena that belong to a reversible pattern feature the sequence: hyperstimulation-desensitization, followed by functional impairment and hypersensitivity. Moreover, features of chronic intoxication emerge over time as signs of chronic, persistent (sometimes permanent) brain damage.

As to addiction, we have to map out a different pattern that underlies the features that are peculiar to addictive diseases, namely:

1. Chronic relapse, despite the intention to stay detached
2. Enduring use, despite the absence of expected effects and the presence of individual knowledge about the dynamics of tolerance
3. Loss of insight into the right perspective for handling substance use and becoming detached from it

Chronic cocaine users show an attenuated response to stimulants, which indicates that their capability to self-stimulate has been hampered. The hypothesis that repeated exposure results in sensitization is probably true in the medium term, but further changes take place later on, which account for the chronic-relapsing course, extending beyond each single cycle of non-medical use.

Repeated exposure to drugs induces a chain of reaction that starts from the ventral tegmental area, proceeds throughout the nucleus accumbens and is projected onto the dorsal striatum. The dorsal striatum shows dopamine increases which are rather specific to addiction, and correlate with subjective craving, as long as they correspond to spikes of dopamine (phasic), rather than a slow-onset tonic increase. Studies on cueing have also suggested that craving runs parallel with activation of the dorsal striatum and does not depend on exposure to substances: any such chain of reactivation would, in fact, be unlikely, due to the downregulation or desensitization of D2 receptors after chronic exposure to drugs.

It has been hypothesized that addicted individuals differ from nonaddicted ones due to the presence of an inner source of dorsal striatum dopamine increases, which is no longer related to reward from the outside but can be triggered by cueing (McClernon et al. 2009). This source may correspond to the anatomic area of the cingulate gyrus, orbitofrontal cortex and extended amygdala and its glutamatergic connection with the striatum (Franklin et al. 2007; Volkow et al. 2004, 2005, 2008).

The global brain change originating from outreach of the areas involved in the affective encoding of experience, and in long-term memory, is likely to correspond to the development of a strong incentivization and motivation ‘pole’, which hijacks the pre-existing moral array of the individual and prevents any other array from replacing the one that stays focused on drug availability and consumption.

## 7.6 Clinical Issues

On psychobiological grounds, we feel the need to overcome the clinical limitations and uncertainty resulting from the evolution of DSM layouts. Addiction had, in fact, been defined in a qualitative way in the DSM-IV era, with DSM-IV TR presenting

a set of criteria that first opened the way for a clinically based solution (APA 2000). Going now into greater detail, the patient's history was accounted for as diagnostic criteria with prognostic weight, and intoxication-related aspects were isolated so as not to weigh as core criteria. Later on, DSM-5 provided a completely different layout, with addiction and use aligned along a quantitative continuum (APA 2013). The failure to justify the distinction separating the putative 'non-medically used' category from vice, by reference to physiology, on one hand, and addiction, on the other (by considering it as a disease), was eventually overcome by dissolving all firm qualitative barriers between substance use disorders. The difficulty encountered in delineating the borders between pathology and physiology can be called something of a constant in this sequence of classification attempts.

We propose a three-stage clinical classification leading from physiological use to addiction, possibly through an intermediate problematic use stage (Table 7.2).

At stage I, the picture features a variable pattern of use, displaying global post hoc satisfaction after episodes of fulfilling acute consumption. People may develop a physiological habit and dislike the absence of the stimulus that rewards them. At this stage they do show interest and arousal when the stimulus is available.

At stage I-a the individual is engaged in an intensive way with self-stimulation and may experience negative consequences or implications arising from this behaviour, whether it is habitual or not. Nevertheless, this behaviour cannot be said to be out of control, as long as the reason for increasing commitment can be found in an increasing level of reward. This kind of picture corresponds to what is usually meant by 'problematic use' and can be assigned to the area of pathology, as far as intoxication symptoms are concerned, but it could also be assigned to the area of physiology, as far as control is concerned.

At stage II, a leap has taken place, and what is shown is a different kind of behavioural disarray. The person is dissatisfied, although he/she may not identify the problem as being due to the loss of control. The acute reward is still present but is now weaker, spoiled by side-effects or the deterioration of other sources of pleasure. Withdrawal may be exacerbated, but what counts most is the urgency of substance-bound behaviour that is enhanced to an overdrive level: in other words, the consistency between behavioural engagement and reward has been lost (Maremmani and Pacini 2003). The frequency of consumption has risen to a ceiling level, which by itself is not enough to constitute an isolated criterion but is a logical consequence of the increase of craving.

**Table 7.2** Stadiation of addictive processes

| | Stage I | Stage I-a | Stage II |
|---|---|---|---|
| Consumption mode | Consumption | Problematic use | Addiction |
| Post hoc satisfaction | + | +/– | – |
| 'High' | + | ++ | (+)/– |
| Withdrawal-related discomfort | – | +/– | (+) |
| Frequency of behaviour | (+) | ++ | +++ |
| Substance-elicited desire | + | + | +++ |

On the whole, we propose a control-over-stimulus area, comprising both use and problematic use, which can be indicated as a reversible state still rooted in the dynamics of reward. That leaves the 'out of control area' corresponding to addiction, which is rooted in an acquired, no longer reversible, chronic-relapsing change in the brain network relationship between reward and motivational drive (Bacciardi et al. 2013).

Treatments for addiction have a variety of psychobiological targets, according to which they may be classified (Maremmani and Pacini 2003; Pacini and Maremmani 2007a, b).

*Direct anticraving treatments*: these aim to restore the balance between desire and behavioural control. In addition to the obvious improvement to be experienced, patients are also relieved and amazed by recovering a substance-free perspective, which they had often given up after years of failures. Therapeutic engagement and motivation may be enhanced after realizing that one's brain has not gone wrong, or been born wrong, but that just a single piece of it is responsible for what is seen from the outside and experienced internally as moral disarray. Methadone, buprenorphine and other emerging treatments exert this kind of effect (Maremmani and Gerra 2010).

*Anti-reward treatment*: the psychological effect of such treatment continues to be incisive as long as the clinical picture shows it is still rooted in the dynamics of rewarding use (I and I-a stages) and may even help the gradual reversal of stage II pictures, so allowing a return to a state of behavioural control. Even so, it must be pointed out that interference with reward alone is unlikely to stop the course of addiction. Most addicts have already gone through the various phases of reward deterioration and have relapsed into it after detoxifying – a development that indicates that reward-centred logic is no longer dominant within that addiction. In fact, the best acting anti-reward regimen is provided gradually by a process of 'induction' into methadone or buprenorphine treatment, which is coupled with a state of narcotic blockade (due to high tolerance or stronger blockade at lower levels of tolerance), so producing a direct anticraving effect.

*Aversive treatments*: these are designed to abolish the chance to experience acute reward, as an anti-reward treatment, while also making this approach overlap with an aversive effect. Both the previously cited treatment modalities require external control over the treatment intake, since the psychobiological orientation of the patient is not favourable to self-administration. In fact, one reaction to be expected in response to reward impairment will be for the patient to act in such a way as to restore potential reward by discontinuing treatment.

Treatment for nonaddictive problematic use varies and may spring from different roots, either psychopathological or psychological, which underlie a problematic relationship with useful or rewarding stimuli.

Lastly, addicts differ from problematic users because they are expected to react to any treatment effort by presenting an ambivalent behaviour. Addicts, in fact, will ask for help because of the collateral damage done to their drug-related lifestyle or the need to change current states of intoxication but tend to keep away from treatment as an instinctive reaction, as if engaging in any treatment meant being kept in

a state of separation from the substance. In the absence of an inner substance-free perspective, such a reaction should be expected. Moreover, the reasons for requests for treatment should not be mistaken for what a nonaddicted person would look for in response to the same interventions: for instance, what addicts requiring detoxification are basically struggling with is not withdrawal but the absence of reward produced by tolerance. It should also be borne in mind that recovery may mean restoring the patient's global resources, only for him/her to engage in a new bout of addiction, instead of building up a barrier against addiction. While addicts may sincerely intend to stay free from addiction, they are often subject to a stronger drive, which can be defined as getting control over the substance, given that they can no longer do without it. This also explains why they often sign on for long-term programmes from which they drop out during the early phases and why they show enthusiasm for rapid and uncertain interventions but avoid long-term commitments.

## Appendix: Multiple-Choice Questions

1. Craving corresponds to
   - The perception of the stimulating agent
   - The positive quality of stimulation (liking)
   - The increase of liking for experienced drugs through time
   - *The abnormally urgent and overwhelming desire to stimulate oneself*
2. The liking of a drug, which induced addiction
   - Is always stronger than that of other drugs
   - *Is usually stronger and sharper*
   - Becomes highest than ever once addiction has developed
   - Depends on a general reward-deficient personality
3. Nonaddictive craving
   - Does not exist
   - *Does not actually make sense, although it is used to indicate amplified appetite for self-stimulation*
   - Is the craving for nonaddictive substances
   - Is the craving for legal substances
4. Addiction corresponds to a brain state
   - Forerunning the first contact with the drug
   - Starting at the time of first drug use
   - *Developing during drug use*
   - Developing after several relapses
5. Addictions to different substances
   - *Share a similar brain-imaging profile*
   - Concern different brain areas
   - Concern different cortical areas
   - Share a similar withdrawal-related brain state

6. The shared ground between addictions from different substances includes
   - *All of the following*
   - Late withdrawal
   - Cross-reactive craving
   - Reduction of cortical inhibiting activity
7. The release of dopamine in the nucleus accumbens
   - Is a key effect of dopaminergic drugs
   - Is a key effect of heavy drugs
   - *Is shared by all addictive stimuli*
   - Is mediated by a unique specific receptor
8. Once addiction has established
   - The effect of the substance is no longer possible
   - The effect of the substance is amplified
   - *The expectation of the effect is amplified*
   - The relevance of general reward is amplified
9. The addictive potential of stimuli depends on
   - The mechanism of action
   - The legal status
   - The potency
   - *The short latency of action*
10. Late withdrawal
    - *Is not specific of addiction*
    - Is specific of addiction
    - Is predictive of relapse
    - Is a milder trail of early withdrawal
11. Cortical inhibitory areas
    - Are underdeveloped in subject who then become addicted
    - Are atrophic in addicted persons
    - *Are inhibited by craving-related areas*
    - Are not recruited effectively by addicted persons
12. Cueing is
    - *An intense recall of appetite by drug-related memories*
    - The subconscious recall of drug-related memories
    - The persistence of drug-related memories
    - The recall of affectively relevant drug-related memories
13. The objective of anticraving treatment is
    - To suppress the desire for the drug
    - *To normalize craving to normal desire*
    - To suppress the urgency to get the drug
    - To suppress the fear of withdrawal
14. Craving during withdrawal
    - Is basically due to the fear of withdrawal
    - *Is basically due to the increase of appetition*
    - Is the irresistible component of craving
    - Is the core component of craving

15. Non-chemical addictions
    - Are not true addictions
    - *Share similar biological features with chemical addictions*
    - Are not chemically mediated, but psychologically
    - Are a side aspect of certain psychiatric disorders
16. The psychiatric syndrome closely resembling addiction is
    - *Mania*
    - Depression
    - Panic
    - Personality disorders
17. The best fitting model of addictive diseases can be identified in
    - A general neurotransmitter deficiency
    - Subcortical plastic changes in some input areas, affecting substance effects
    - *Subcortical plastic changes in some feedback areas, affecting substance-seeking behaviour*
    - A cortical area
18. Opiate withdrawal has a relevant biological overlap with
    - Depression
    - *Panic attacks*
    - Mania
    - Obsessive-compulsive disorder
19. Relapse differs from a simple new-use episode
    - *The brain reacts differently to the substance and starts back from the addictive stage*
    - The substance is the same
    - Doses are higher
    - The brain is still under withdrawal when relapsing
20. The most effective mechanisms against craving are
    - Motivational treatment
    - Blockade of the substance's effects
    - Direct receptor-mediated reduction of baseline craving
    - *The coupling between the previous two*

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# Sleep and Dreams

8

Theocharis Kyziridis and Ioannis Nimatoudis

## 8.1 Brief Historical Overview

Descriptions about sleep and dreaming can be found in texts of ancient civilizations such as those of Egypt and Greece. In Greek mythology, the state of sleep (Hypnos) was considered similar to that of death (Thanatos) (Norman et al. 2011). Both Aristotle and Hippocrates wrote about sleep; the former dedicated a book to sleep entitled *On Sleep and Sleeplessness* (Kirsch 2013). The Bible also contains mentions about dreaming through which prophecies occur, and Maimonides, a Hebrew scholar, gave instructions concerning sleep habits (Rosner 1965).

Major contributions toward understanding sleep were made though only during the twentieth century, and empirical studies were undertaken for the first time around 1950 (Hobson 1990) (Table 8.1). Current knowledge about sleep and dreaming is the result of research efforts made since only the previous century (Hobson 1990), and this was made possible after the discovery of electroencephalography (EEG) by Hans Berger in 1928. Using EEG to measure and record the brain electrical activity (Kirsch 2013), Berger showed that brain's rhythms were different between awake or asleep individuals (Berger 1930).

The anatomical localization of sleep was made possible by Constantin von Economo. His careful observations of patients during the epidemic of lethargic encephalitis led him to an important conclusion concerning the role of hypothalamus in sleep-wake cycle regulation: the anterior hypothalamus (AH) contained sleep-promoting neurons, whereas the posterior hypothalamus (PH) contained wakefulness-promoting neurons (Economo 1930). Nathaniel Kleitman's

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**Table 8.1** Important hallmarks in the history of sleep medicine (Lee-Chiong 2008)

| | |
|---|---|
| 1818 | John Cheyne (1777–1836) and William Stokes (1804–1878) described the respiration that bears their name |
| 1880 | Jean-Baptiste-Edouard Gelineau (1828–1906) described narcolepsy |
| 1907 | Rene Legendre and Henri Pieron (1881–1964) induced sleep in dogs by administering serum from sleepy dogs |
| 1920 | Nathaniel Kleitman (1895–1999) reported that increased sleepiness was a result of sleep deprivation |
| 1928–1930 | Hans Berger (1873–1941) discovered EEG and described beta waves for the first time |
| 1936 | Edmund Newton Harvey (1887–1959) and Alfred Lee Loomis (1887–1975) proposed sleep EEG classification (stages A, B, C, D, and E) |
| 1939 | Kleitman published his book *Sleep and Wakefulness* |
| 1944 | William Grey Walter (1910–1977) and F.J. Dovey first described delta and theta waves |
| 1945 | Karl-Axel Ekbom (1907–1977) described restless legs syndrome |
| 1949 | Giuseppe Moruzzi (1910–1986) and Horace Winchell Magoun (1907–1991) discovered reticular formation |
| 1953 | Eugene Aserinski (1921–1998) and Kleitman discovered REM sleep |
| 1960 | Gerald Vogel (1928–2012) described sleep onset REM periods in narcolepsy |
| 1965 | Clinical description of obstructive sleep apnea |
| 1986 | Carlos H. Schenck (1951–) reported on features of REM sleep behavior disorder |
| 1999 | Description of link of hypocretin and narcolepsy |

contribution is also important: he conducted sleep deprivation studies (Dement 2005) and, together with his student Eugene Aserinsky, described rapid eye movement (REM) sleep; this was followed by the discovery of atonia during it (Aserinsky and Kleitman 1953; Berger 1961). The different EEG stages of sleep had already been described (Loomis et al. 1937) as well as the promotion of arousal by the electrical stimulation of the reticular formation (Lindsley et al. 1949; Moruzzi and Magoun 1949). Finally, Jouvet with his colleagues established the role of relevant circuitry in the pons and discovered the characteristic elements of the "paradoxical" REM sleep (Jouvet and Michel 1959; Jouvet et al. 1959). Jouvet, who passed away in 2017, is considered a great pioneer in sleep research (Jones 2018).

## 8.2 Sleep in Humans and Animals

### 8.2.1 Definition of Sleep

Despite the enormous scientific advances, an exact definition of sleep has not been yet found, and its fundamental action remains largely unclear (Norman et al. 2011). Sleep is not a passive state or, to put it simply, just the absence of wakefulness and the reduction of motility and responsiveness to external stimuli. On the contrary, it is a reversible, active state which is essential for mental and physical well-being (Stenberg 2007; Weber 2017) and has behavioral and physiologic characteristics that differentiate it from wakefulness (Tables 8.2, 8.3, 8.4, and 8.5).

**Table 8.2** Behavioral characteristics of wakefulness and sleep (Chokroverty 2013)

| Characteristics | Wakefulness | Sleep |
|---|---|---|
| Posture | Erect, sitting, or recumbent | Recumbent |
| Mobility | Normal | Mildly reduced to absent with postural shifts (NREM)<br>Myoclonic jerks (REM) |
| Response to stimulation | Normal | Mildly to moderately reduced (NREM)<br>Moderately reduced to absent (REM) |
| Level of alertness | Alert | Unconscious but reversible |
| Eye position | Open | Closed |
| Eye movements | Waking eye | Slow eye movements (NREM)<br>Rapid eye movements (REM) |

**Table 8.3** Physiologic characteristics of wakefulness and sleep (Chokroverty 2013)

| | Wakefulness | Sleep |
|---|---|---|
| Electroencephalography | Parieto-occipital α-waves<br>Fronto-central β-rhythms | θ and δ-waves, sleep spindles, vertex waves and K-complexes (NREM)<br>θ waves and β-rhythms (REM) |
| Electromyography | Normal | Mildly reduced (NREM)<br>Markedly reduced to absent (REM) |
| Electrooculography | Waking eye movements | Slow eye movements (NREM)<br>Rapid eye movements (REM) |

**Table 8.4** Characteristics of wakefulness and sleep (Hobson and Pace-Schott 2002)

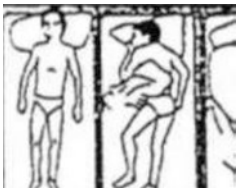
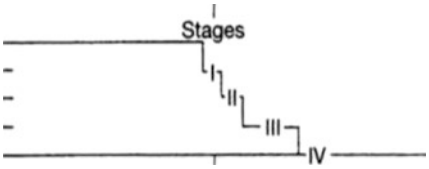
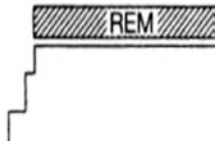
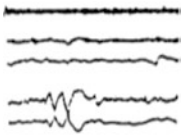
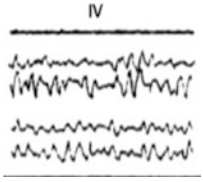
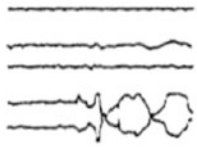
| | Wakefulness | NREM sleep | REM sleep |
|---|---|---|---|
| Behavior |  |  |  |
| Awake Polygraph |  | |  |
| EMG<br>EEG<br>EOG |  |  |  |
| Sensation/ perception | Vivid and externally generated | Dull or absent | Vivid and internally generated |
| Thought | Logical<br>Progressive | Logical<br>Perseverative | Illogical<br>Bizarre |
| Movement | Voluntary<br>Continuous | Involuntary<br>Episodic | Inhibited<br>Commanded |

**Table 8.5** EEG wave frequencies (Silber et al. 2010)

| | |
|---|---|
| Beta (β) | >13 Hz |
| Alpha (α) | 8–13 Hz |
| Theta (θ) | 4–7.9 Hz |
| Delta (δ) | <4 Hz |

### 8.2.2 Evolutionary Perspective

Sleep is universally present in the animal kingdom (Greenspan et al. 2001); all mammals and most of the animals sleep, and its deprivation usually leads to the need for recovery sleep (Cirelli and Tononi 2008). Sleep has a vital function at cellular level; thus all animals have an absolute need for it; from an evolutionary point of view, it seems to be important for the survival of animals (Reading 2013). Even unicellular organisms have a sleeplike behavior manifesting as sequential phases of activity and rest (Hobson 1990). Rest-activity cycle is a basic function of living organisms. Rest is a rather passive process that, in homeothermic vertebrates, evolved as sleep, providing both rest and a biological advantage through memory formation (Hobson and Pace-Schott 2002). Sleep is characterized by reduction of responsiveness to stimuli from the environment, reduction of mobility, and stereotyped postures (Tononi and Cirelli 2011), while wakefulness is a behavioral state characterized by response to stimuli and voluntary motor activation of animals (Scammell et al. 2017). Reptiles and birds have diminished responsiveness and EEG synchrony but no REM phase (with the exception of birds), and amphibians have none of the characteristic features of sleep in mammals (Hobson 1990). In order to speak about sleep in animals, they must present a minimum number of the following characteristics:

- A reversible state with motor repose and elevated sensory threshold.
- Protected sleeping site.
- Circadian organization.
- "Hunger"
- "Satiety".

Animals with lower number of these characteristics do not sleep in fact but have periods of rest and activity. It could be said that sleep in animals is a state of behavior alternative to wakefulness the regulation of which is based on circadian and homeostatic systems (Esteban et al. 2005).

### 8.2.3 Sleep During the Human Life Cycle

Approximately one third of the human life involves sleeping—90% of adults need at least 7 h of good sleep every day (Reading 2013). During life-span, sleep patterns and sleep requirement change (Table 8.6) following an order that depends upon maturation of the central nervous system (CNS) (Lavie et al. 2002; Roffwarg et al. 1966). Duration

**Table 8.6** Changes in content and length of sleep with age (Lavie et al. 2002)

| | Sleep time (h) | NREM Stages 1–2 (%) | NREM Stages 3–4 (%) | REM (%) |
|---|---|---|---|---|
| Infants | 13–16 | 10–30 | 30–40 | 40–50 |
| Children | 8–12 | 40–60 | 20–30 | 20–30 |
| Adults | 6–9 | 45–60 | 15–25 | 15–25 |
| Elderly | 5–8 | 50–80 | 5–15 | 15–25 |

of the sleep cycles shows correlation with brain size; rodents have a sleep cycle of a few minutes, while the duration is estimated to be some hours in large mammals (Weber 2017). The sleep of normal adults is fairly consistent as far as it concerns both the time spent in each stage and the pattern of stages across the night (Tononi and Cirelli 2011).

Newborns sleep approximately 16 h per day, in the form of short naps. These naps begin to disappear at about the age of 6 months (Parmelee 1961). Total sleep time and REM sleep proportion are reduced during early childhood and napping stops (Iglowstein et al. 2003). Slow-wave sleep (SWS) (a phase of NREM sleep) increases during the first year of life and reaches a peak. In adolescents and adults, it is reduced and by age 60 may even disappear (Tononi and Cirelli 2011). Elderly usually sleep less, have frequent awakenings, and wake earlier in the morning (Ehlers and Kupfer 1989).

## 8.3 Importance and Functions of Sleep

### 8.3.1 Importance of Sleep

Sleep serves important biological (immunity, hormonal regulation, thermoregulation) (Morrissey et al. 2004; Opp 2009; Van Cauter et al. 2008) and neurocognitive functions concerning emotion, memory, and reward (Lansink et al. 2008; Lena et al. 2005). Information processing and energy homeostasis are also among the important functions of sleep (Hobson 1990) (Table 8.7).

Its role in memory function is achieved through stabilization and enhancement of certain memory processes (Maquet 2001; Walker and Stickgold 2006) via memory consolidation; by this process, reorganization of new memories takes place first. After that, these memories are transferred to preexisting long-term memory networks (Wang and Morris 2010). This process may take place during sleep in humans (Diekelmann and Born 2010; Maquet 2001), and declarative (hippocampus-dependent) memory likely benefits from NREM sleep and particularly SWS (Born et al. 2006). Sleep seems to enhance changes taking place in neural networks after perceptual, motor, or emotional learning tasks (Maquet et al. 2003; Payne and Kensinger 2011; Schwartz et al. 2002; Sterpenich et al. 2007). The mechanism of such enhancement involves activation of the cells of two different brain regions: hippocampus proper (HC) and ventral striatum (VS). This coordinated activation of both HC and VS during NREM sleep may facilitate:

**Table 8.7** Sleep functions (Chokroverty 2013; Silber et al. 2010)

| |
|---|
| Restoration<br>• Body<br>• Brain tissue |
| Energy conservation |
| Adaptation to environmental conditions |
| Learning and unlearning |
| Memory consolidation |
| Synaptic and neural network integrity |
| Synaptic homeostasis |
| Thermoregulation |
| Immunocompetence |

- The replay of memories with contextual, emotional, and motivational components.
- The consolidation of memory-reward information.
- The selection of memories with a high storage priority (Lansink et al. 2008, 2009).

Apart from declarative memory, NREM sleep also consolidates motor skills; both are influenced by emotional relevance and motivational biases. This consolidation may be enhanced when linked with an anticipation of reward; thus memories could serve as salient stimuli for the neurons of ventral tegmental area (VTA), a region known as the reward center of the brain which is influenced by needs and memories (Fischer and Born 2009; Schultz 2010; Sterpenich et al. 2009; Wilhelm et al. 2011).

There seems to be a link between sleep and emotion regulation processes (Gujar et al. 2011; Lara-Carrasco et al. 2009; Pace-Schott et al. 2012; Talamini et al. 2013). REM sleep could possibly affect the emotional well-being in a negative way. This idea is based on studies showing that awakenings from an REM episode are associated with high scores in the Hamilton Depression Rating Scale (McNamara et al. 2010). Furthermore, depression is usually preceded by increases in REM density and decreases in REM latency. This might indicate that REM sleep, which is under circadian and homeostatic control (Wurts and Edgar 2000), may constitute a biomarker for depressive disease (Gottesmann and Gottesman 2007).

REM sleep may play a role in creative thinking and problem-solving by integrating information that is initially unassociated (Cai et al. 2009; Walker et al. 2002). Sleep may also facilitate insight since it can reconstruct new memory representations (Hobson and Pace-Schott 2002; Wagner et al. 2004). Furthermore, it may have a role of re-establishing metabolism of the cell and of cleansing brain from neurotoxins (Brown et al. 2012; Xie et al. 2013) benefiting as well the integrity and reorganization of neuronal synapses (Kavanau 1997; Krueger et al. 1995).

### 8.3.2 Effects of Sleep Deprivation

Sleep deprivation, which can be the result of various factors, such as physical disease or mental health problems, lifestyle factors, vocational demands, and others (Banks et al. 2017), may have detrimental effects (Table 8.8). It can lead rats to thermoregulation impairment, to metabolic dyscontrol (Bach et al. 2011; Hobson 1990), and, in extreme cases, even to death sooner than food deprivation, while humans, suffering from the rare genetic prion disease of familial fatal insomnia, usually die within 2 years (Higgins and George 2007).

The underlying pathophysiologic mechanism is rather the excess of wakefulness than the lack of sleep per se. Indeed, the excess of wakefulness seems to activate pathways that are harmful for the cell. Furthermore, there seems to be temporary dysfunction of the frontal lobe; the brain of sleep-deprived young adults has been shown to function like the brain of elderly people (Reading 2013).

Sleep deprivation may also increase blood pressure and the risk for diabetes. It can lead to obesity, growth hormone decrease (Van Cauter et al. 2008), and, along with poor sleep quality, deficits in both synaptic plasticity and memory processes probably leading this way to mood disorders (Casement et al. 2006; Prince et al. 2014). The most prominent effect of sleep deprivation in humans is neurocognitive impairment which may have serious consequences (Dinges 2006). If humans stay awake much longer than the usual 16 h a day, they are soon overcome by sleepiness and become cognitively impaired (Tononi and Cirelli 2011).

Even a few hours of sleep loss or just one night of sleep deprivation may cause impairment of tasks requiring sustained attention or the use of higher cognitive functions; lack of sleep makes the performance of these tasks inconsistent and unreliable without completely eliminating the capacity to perform them (Tononi and Cirelli 2011).

**Table 8.8** Consequences of sleep deprivation (Lee-Chiong 2008; Reading 2013)

| *Sleepiness* |
|---|
| *Increased morbidity and mortality* |
| • Increased risk for motor vehicle accidents |
| • Cardiovascular morbidity |
| • Endocrine dysfunction |
| • Immune dysfunction |
| • Neurological dysfunction |
| *Negative impact on mood* |
| *Cognitive dysfunction and performance difficulties* |
| • Increased reaction times |
| • Perseveration and reduced flexibility |
| • Impaired sense of humor |
| • Increased risk taking |
| • Impaired moral judgment |
| • Reduced emotional intelligence |
| • Increased “negativity” with enhanced memory for adverse events |
| • Increased distractibility |

### 8.3.3 Conclusions

Memory and learning processes seem to be specific to distinct NREM or REM sleep and dreaming states, and this makes them important for performance during wakefulness. There may also exist a difference among these states concerning their contribution to off-line reprocessing of emotional and reward information; REM sleep is probably responsible for emotional memory and synaptic consolidation, and NREM sleep may be more specialized in linking memory traces with motivational values (Diekelmann and Born 2010; Lansink et al. 2009; Payne and Kensinger 2011; Pennartz et al. 2004; Popa et al. 2010; Sterpenich et al. 2009; Wagner et al. 2001).

## 8.4 Sleep Architecture

### 8.4.1 Introduction

Sleep comprises two stages (NREM and REM), which take place approximately 4–6 times in one night (period of nearly 90 min) (Higgins and George 2007; Silber et al. 2010) (Fig. 8.1; Table 8.9). These two stages have distinct physiological parameters. NREM is the stage through which initiation of sleep normally takes place. It comprises four phases (light phases: 1, 2 and deep phases 3, 4, collectively known as SWS) based on EEG (Carskadon and Dement 2017).

SWS dominates the first third of sleep in adult humans (Chokroverty 2013) and usually occurs within an hour of sleep onset (Reading 2010). EEG during NREM

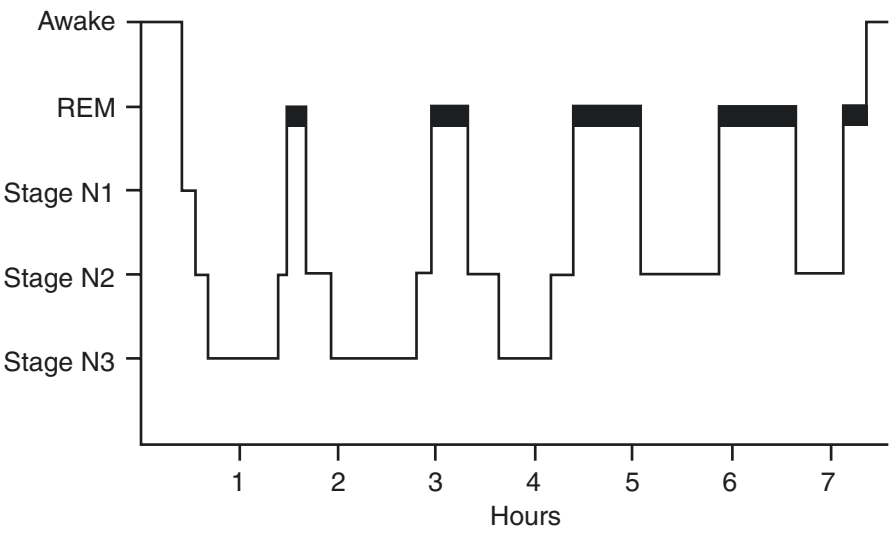



**Fig. 8.1** A typical night's sleep of a young adult (Silber et al. 2010)

**Table 8.9** Summary of various sleep states (Chokroverty 2013)

| *NREM sleep* | *75–80% of sleep time* |
|---|---|
| N1 stage | 3–8% of sleep time |
| N2 stage | 45–55% of sleep time |
| N3 stage (SWS) | 15–23% of sleep time |
| *REM sleep* | 20–25% of sleep time |

sleep is characterized as synchronized and has characteristic waveforms: sleep spindles, K-complexes, and high-voltage slow waves. Phase 1 of NREM sleep has the lowest arousal threshold; on the contrary, phase 4 has the highest (Carskadon and Dement 2017).

REM sleep, which follows one or more NREM periods (Weber 2017), accounts for around 20% of sleep and is characterized by EEG activation and wake-like activity, loss of muscle tone, episodic bursts of rapid eye movements (hence the name rapid eye movement sleep), and intense activation of the cortex and the limbic system (Carskadon and Dement 2017; Hobson and Pace-Schott 2002; Reading 2010). Loss of muscle tone and areflexia during this stage are the effects of inhibitory impulses from the brainstem. REM sleep, which predominates the last third of nocturnal sleep (Chokroverty 2013; Reading 2010), is also known as paradoxical, desynchronized, or wake-like. The reason for that is that the level of metabolic activity and the cortical EEG during this stage are similar to that observed during wakefulness usually corresponding to the vivid dreaming that takes place during this stage (Reading 2010) (Fig. 8.2).

Various mechanisms are responsible for the regulation of these two sleep stages while mammals are asleep (Datta and Maclean 2007). Under normal circumstances, humans first enter the sleep state via NREM sleep. Initially, the eyes drift slowly and the sleep position changes frequently. Individuals gradually lose awareness of the outside world and may even experience hypnagogic hallucinations and illusions of movements of the body in space. During NREM sleep, physiological changes take place. These changes include decreases in body temperature, blood pressure, and heart and respiratory rate and increases in the pulsatile release of growth and sex hormones from the pituitary gland and in the production of antibodies. This might imply that NREM sleep may be functionally associated with anabolic processes that benefit the somatic tissues (Pace-Schott and Hobson 2002).

## 8.4.2 Stages of Sleep

### 8.4.2.1 NREM Sleep: Stage 1

Sleep is usually entered through stage 1, and falling asleep takes place gradually accompanied by progressive disconnection from the environment. This transitory stage is characterized by loss of alpha activity; low-voltage, mixed-frequency EEG pattern; and prominent theta activity. Eye movements become slow and rolling, and

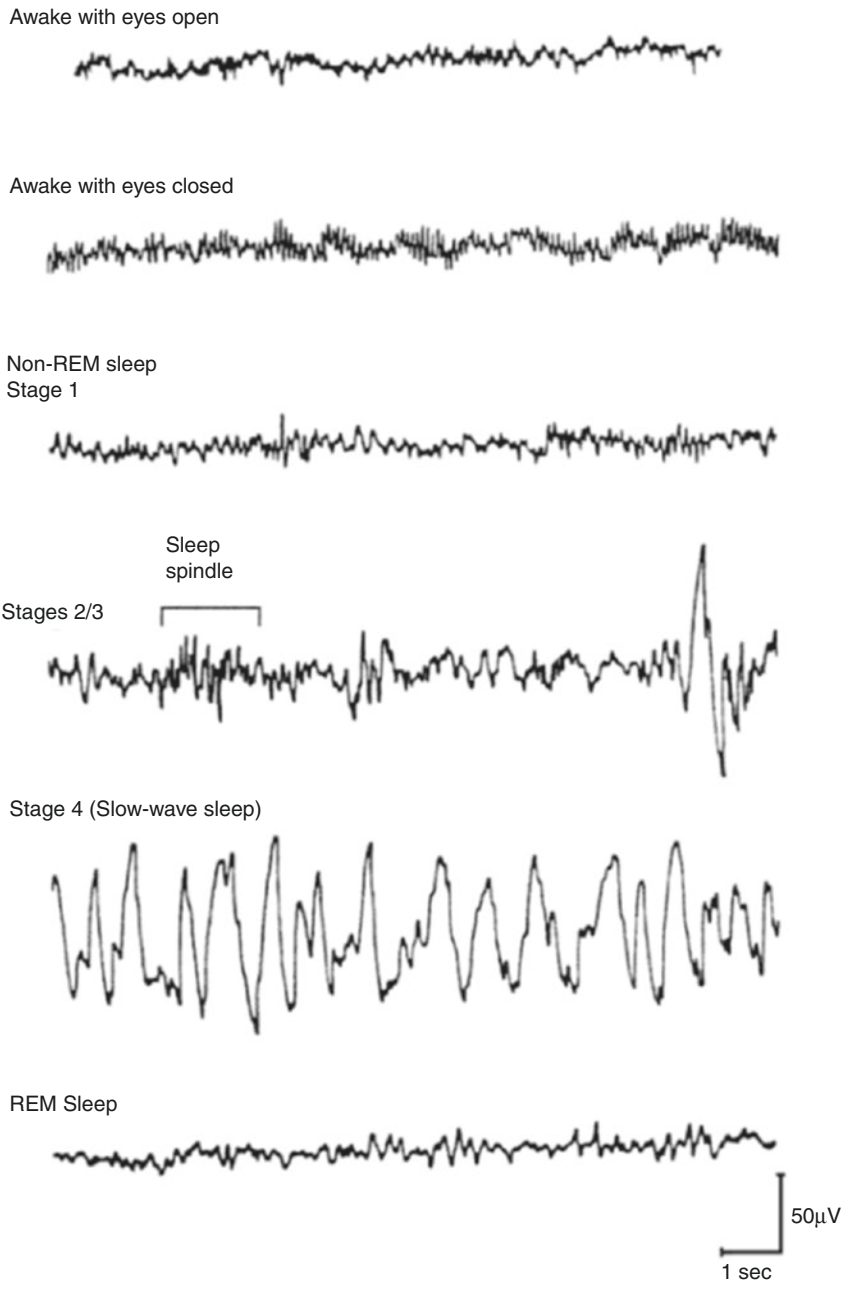



**Fig. 8.2** EEG recordings during wakefulness and sleep (Siegel 2002)

muscle tone relaxes even though sudden muscle contractions may take place occasionally; these may sometimes be accompanied by a sense of falling and dreamlike imagery. Awareness of sensory stimuli is reduced, and motor activity may persist for a few seconds (Reading 2013).

#### 8.4.2.2 NREM Sleep: Stage 2

Stage 2 follows after a few minutes. It is characterized by K-complexes and sleep spindles in EEG. Eye movements and muscle tone are further reduced. There is partial disconnection from the environment, and the arousal threshold is increased (Reading 2013).

#### 8.4.2.3 NREM Sleep: Stages 3 and 4 (SWS)

Stage 2 is followed, especially at the beginning of the night, by a period of SWS, which is characterized by slow waves in the delta range. Eye movements cease and electromyographic (EMG) activity decreases further. After deepening through stages 2–4, NREM sleep lightens and returns to stage 2, followed by REM sleep (Reading 2013).

#### 8.4.2.4 REM Sleep

EEG during REM sleep is similar to that during wakefulness or stage 1. Contrary to NREM, REM sleep is not subdivided into stages but comprises tonic and phasic components (Table 8.10). The first include penile erections, the activated EEG and a generalized loss of muscle tone, except for the extraocular muscles that drive the REMs and the diaphragm that keeps breathing. Phasic components include muscle twitches and irregular bursts of REMs. Behaviorally, REM sleep is deep sleep, with an arousal threshold that is as high as in SWS (Reading 2013).

**Table 8.10** Phenomena of REM sleep (Silber et al. 2010)

| |
|---|
| *Tonic phenomena* |
| Desynchronized EEG |
| Theta activity in hippocampus |
| Loss of voluntary muscle tone |
| Increased cerebral blood flow |
| Thermal regulation impairment |
| Dreaming |
| Erections of penis |
| Engorgement of clitoris |
| *Phasic phenomena* |
| Rapid eye movements |
| Transient muscle activity |
| Increased respiratory and heart rate |
| Ponto-geniculo-occipital waves |
| Sawtooth waves |

## 8.5 Neuroanatomy of Wakefulness and Sleep

Anatomically, brainstem, diencephalon, and telencephalon contain regions that regulate sleep and wakefulness (McGinty and Szymusiak 2017). Three functional systems regulate sleep:

- The homeostatic system, which is responsible for the regulation of intensity, amount, and duration of sleep, is mainly seated in the preoptic area.
- The ultradian system, regulating REM and NREM sleep alternation, is seated in mesencephalic structures and pons.
- The circadian system, responsible for the regulation of timing of wakefulness and sleep, is mainly seated in the AH (Borb and Achermann 2016; Economo 1930; Pace-Schott and Hobson 2002).

Multiple wake-promoting systems exist in mammals (Datta 1995). Each of these systems may be individually activated thus contributing to the maintenance of the general state of wakefulness. Wake-promoting neuronal groups are found in the basal forebrain (BF), the PH, and in the upper brain stem, whereas NREM sleep-promoting neurons are located in the AH and the BF (Jones 2003, 2005; McGinty and Szymusiak 2003). REM sleep-promoting areas include the meso-pontine reticular formation, thalamic nuclei, and the forebrain (Steriade and McCarley 1990) (Figs. 8.3, 8.4, and 8.5; Table 8.11).

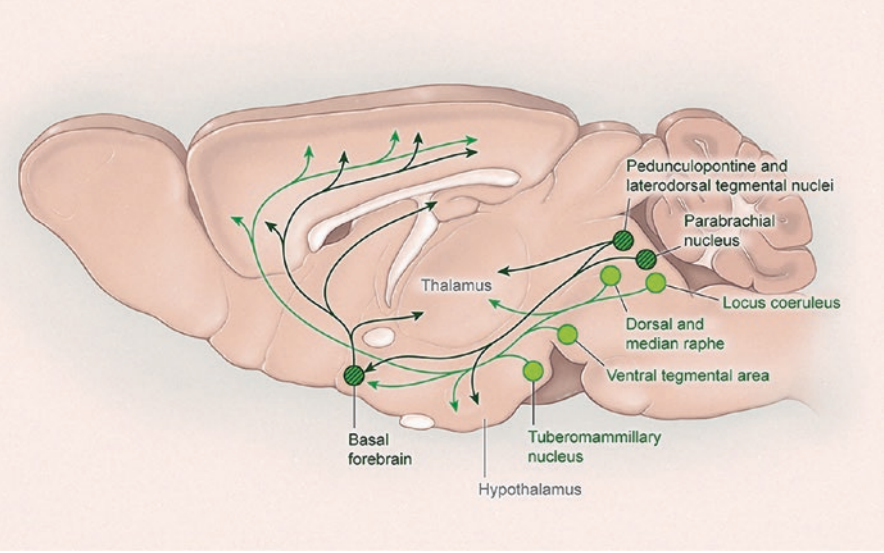



**Fig. 8.3** Wake-promoting pathways (Scammell et al. 2017)

The neuronal groups of REM sleep generation are cholinergic cell groups located in the dorsal part of the pons and in the medulla (laterodorsal tegmentum (LDT) and pedunculopontine tegmentum (PPT)) as well as in the medial pontine reticular formation (Tononi and Cirelli 2011). The critical neurons are localized mainly in the pontine tegmentum, as Jouvet showed, and these neurons have a wide distribution in various nuclei (Hobson 1990).

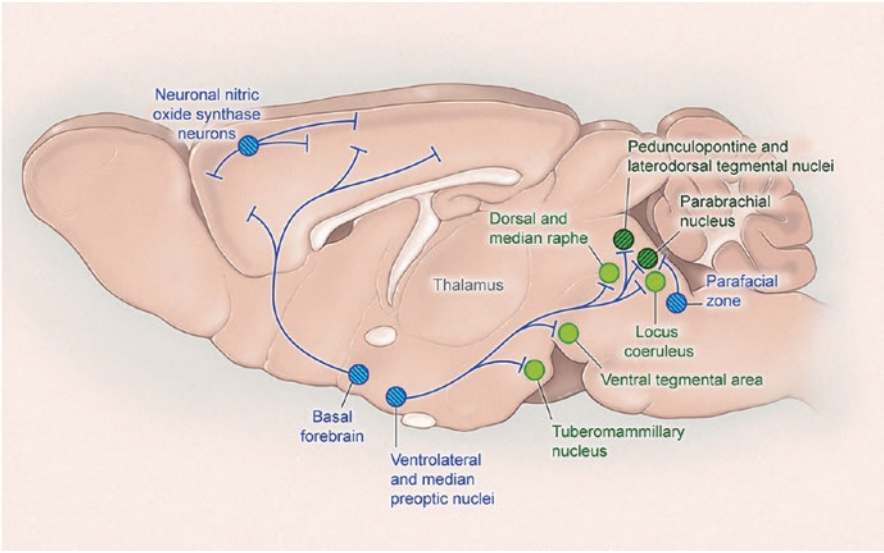



**Fig. 8.4** NREM sleep-promoting pathways (Scammell et al. 2017)

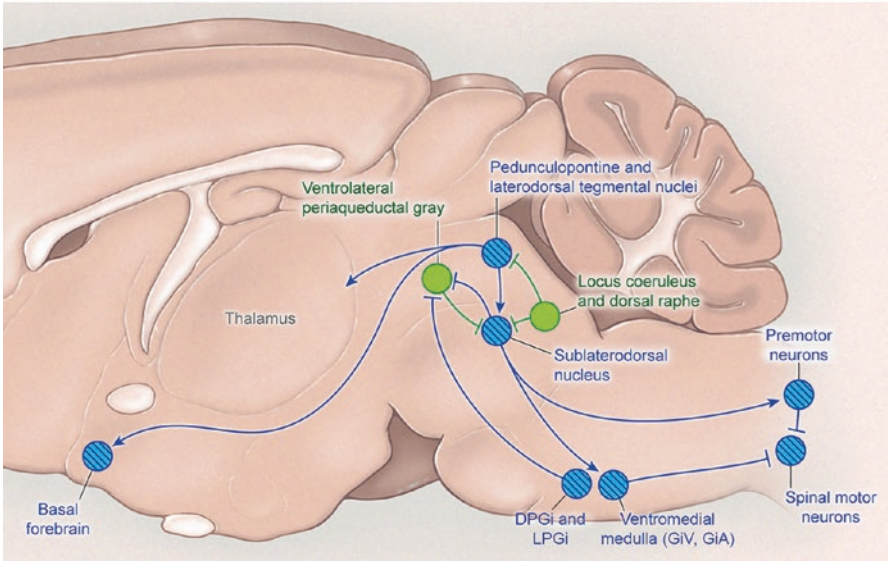



**Fig. 8.5** REM sleep-promoting pathways (Scammell et al. 2017)

**Table 8.11** Activity of wake and sleep centers (Lu and Zee 2010; Norman et al. 2011)

| | Wake | NREM sleep | REM sleep |
|---|---|---|---|
| Laterodorsal tegmental (LDT)/pedunculopontine tegmental (PPT) (acetylcholine) | ↑↑ | – | ↑↑ |
| Locus coeruleus (norepinephrine) (brain stem)<br>Dorsal raphe (serotonin)<br>Tuberomammillary nucleus (histamine) (forebrain)<br>Substantia nigra/ventral tegmental area (dopamine) | ↑↑ | ↑ | – |
| Lateral hypothalamus (orexin/hypocretin) | ↑↑ | – | – |
| Ventrolateral preoptic—cluster (galanin and GABA) | – | ↑↑ | – |
| Ventrolateral preoptic—extended (galanin and GABA) | – | – | ↑↑ |

Many of the aforementioned areas are under the control of the circadian clock which is located on the suprachiasmatic nucleus of the hypothalamus (SCN). This mechanism ensures that sleep occurs at the appropriate time of the 24-h light-dark cycle (Zee and Manthena 2007).

During REM sleep, increases in glucose metabolism or regional blood flow are found in the pontine tegmentum, thalamic nuclei, limbic, paralimbic, and temporo-occipital areas as shown by functional neuroimaging (Braun et al. 1997, 1998; Maquet et al. 1996; Nofzinger et al. 1997).

Neurochemically specific wake-promoting cell groups are found within the ascending reticular activating system (ARAS):

1. Noradrenergic cells in the locus coeruleus (LC).
2. Serotonergic cells in the raphe nuclei (RN).
3. Cholinergic cells in the PPT and LDT.
4. Glutamatergic cells in the midbrain.
5. Dopaminergic cells in the substantia nigra compacta (SNc) and ventral tegmental area (VTA).

These wake-promoting cell groups of pons and midbrain project dorsally to the thalamo-cortical system and ventrally to both the hypothalamo-cortical and basalo-cortical systems (Garcia-Rill 2002; Sakai and Crochet 2003).

The wake-promoting cell groups in brainstem ARAS are in functional cooperation with similar groups in the forebrain. There are at least five cellular groups in the forebrain, which can promote wakefulness either in coordination with the wake-promoting cells of the brainstem or independently (Alam et al. 2002; Deboer et al. 2003; Easton et al. 2004; Koyama et al. 2002; Mendelson et al. 2003; Parmentier et al. 2002; Takahashi et al. 2006; Vertes 2006). These forebrain cell groups include:

1. Histaminergic cells in the tuberomammillary nuclei (TMN) of the PH.
2. Orexin-containing cells in the lateral hypothalamus (LH).
3. Cholinergic cells in the BF.
4. Cells containing neuropeptide-Y; they are located on the SCN.
5. Glutamate-producing cells found in the ventromedial prefrontal cortex (vmPFC).

When these systems are activated, either by experimental procedures or spontaneously, they result in activation patterns of the cortex which is necessary to maintain wakefulness (Gerashchenko and Shiromani 2004).

The ARAS was initially described by Moruzzi and Magoun, who made the hypothesis that it was implicated in the regulation of wakefulness. This system contains two branches:

- (a) Cholinergic neurons from LDT and PPT of the dorsal midbrain and pons, thalamic relay nuclei-thalamic reticular nuclei-thalamocortical tract-cortex (b) Cholinergic neurons from ventral projection of LDT and PPT-BF-substantia innominata-medial septum-diagonal band of Broca-cerebral cortex
- Monoaminergic neurons to LH-BF-cerebral cortex (Lu and Zee 2010).

Each of the arousal systems may promote wakefulness independently. Nevertheless, these systems usually cooperate to generate behavioral arousal. Anatomically, they are characterized by the existence of many interconnections between them, which gives them a functional advantage; that is, even if one of these systems is injured, wakefulness will still occur. In fact, there are only a few brain regions in which lesions produce lasting reductions in arousal. One of them is the rostral reticular formation in the midbrain and PH. Lesions from strokes or tumors in this formation can produce severe hypersomnolence or even coma, probably from damage to many of the ascending monoaminergic and cholinergic pathways (Higgins and George 2007).

Sleep-active neurons have been found in the ventrolateral preoptic area (VLPO) and the median preoptic area (MNPO) in animal models (Gong et al. 2004). Many neurons in these nuclei fire most frequently during NREM sleep and to a lesser degree during REM sleep. During wakefulness, they are virtually silent (Takahashi et al. 2009).

Lesions of these VLPO neurons reduce sleep to a great degree. Furthermore, the sleep that does occur is light and fragmented. These observations suggest that MNPO neurons may help initiate sleep, whereas VLPO neurons may be necessary for the maintenance of sleep. Anatomically, the VLPO and MNPO are well positioned to promote sleep. The neurons in these nuclei contain the inhibitory neurotransmitter GABA and the inhibitory neuropeptide galanin (Gaus et al. 2002), and they innervate all the arousal-promoting regions, including the LDT/PPT, LC, DR, TMN, and also the orexin neurons. Thus, the VLPO and MNPO are hypothesized to promote sleep by coordinating the inhibition of arousal regions during NREM and REM sleep (Saper et al. 2005).

## 8.6 Neurochemistry of Wakefulness and Sleep

### 8.6.1 Introduction

Various neurotransmitters have been linked to the sleep-wake cycle regulation; the most recent discovery has been the finding of the link between wakefulness

**Table 8.12** Neurotransmitters in sleep and wakefulness (Lee-Chiong 2008)

| | |
|---|---|
| REM sleep | Acetylcholine<br>GABA<br>Glycine |
| NREM sleep | Adenosine<br>GABA<br>Norepinephrine<br>Peptides<br>Serotonin |
| Wakefulness | Acetylcholine<br>Dopamine<br>Glutamate<br>Histamine<br>Hypocretin<br>Norepinephrine<br>Peptides<br>Serotonin |

and orexin (hypocretin) which is produced in the LH (Norman et al. 2011). Neurotransmitter systems that promote wakefulness include:

- The cholinergic systems of the basal nuclei and the reticular formation in pons.
- The noradrenergic system in LC.
- The dopaminergic system in SN and VTA.
- The histaminergic system in PH (Pandi-Perumal and Kramer 2011) (Table 8.12).

Cholinergic neurons stimulate REM sleep, while the opposite is true for aminergic neurotransmitter systems (Hobson 1990).

## 8.6.2 Neurotransmitters of Wakefulness and Sleep

### 8.6.2.1 Acetylcholine (ACh)

Cholinergic agonists augment vigilance and promote fast activity in the brain cortex, while muscarinic receptor antagonists, such as atropine, reduce vigilance and produce dissociation between EEG activity and behavior (Norman et al. 2011). Ach has an important role in the control of vigilance, the function of neuromuscular and parasympathetic junctions, and cortical EEG activation (McCarley 2007; Steriade and McCarley 2005). Cholinergic neurons are important for REM sleep, wakefulness, cognition, learning, and memory. They are found in BF and brainstem. BF neurons project to the cortex and hippocampus promoting fast EEG rhythms. Brainstem neurons are found within the LDT/PPT nuclei projecting primarily to subcortical regions, such as the thalamus, hypothalamus, and BF (Gritti et al. 1997). These neurons are mainly active during wakefulness and REM sleep, and release of Ach is increased. During NREM sleep release of Ach is decreased (Lee-Chiong 2008).

REM sleep is believed by many researchers to be controlled by cholinergic neurons in the LDT/PPT. These are the same nuclei that contain wake-promoting cells, but a subpopulation of these cholinergic neurons are active in both wakefulness and REM sleep or are selectively active in REM sleep (el Mansari et al. 1989; McCarley 2007; Steriade 2004; Steriade and McCarley 1990).

Drugs that enhance ACh signaling elicit intense and long-lasting REM sleep when they are injected into the lateral pontine tegmentum (Baghdoyan 1997). Large lesions that include the LDT/PPT produce significant reductions in REM sleep (Steriade and McCarley 2005), suggesting that the LDT/PPT is necessary for REM sleep.

#### 8.6.2.2 Adenosine (ADE)

The stimulant action of caffeine is achieved through the blockade of ADE receptors, and this finding led to the hypothesis that there exists a link between ADE release and sleep (Norman et al. 2011). Administration of ADE has been shown to induce sleep-like behavior in cats and to increase NREM sleep in rodents (Stenberg 2007). ADE neurons are located in BF (Lee-Chiong 2008) and may promote sleep in response to high metabolic activity observed during wakefulness (Basheer et al. 2004). When cells have high levels of energy, ADE levels are low because it is phosphorylated to ATP. On the contrary, when cells are fatigued, ADE levels are high, and it acts as an inhibitory neuromodulator (Porkka-Heiskanen et al. 1997).

#### 8.6.2.3 Cytokines

Among cytokines, interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) have been shown to promote sleep (Imeri and Opp 2009). Administration of both cytokines into the preoptic area reduces firing rates of wake-active neurons and promotes NREM sleep (Alam et al. 2004; Kubota et al. 2002).

#### 8.6.2.4 Dopamine (DA)

DA mediates processes such as motor function, motivation, reward, and learning and has potent wake-promoting effects. Neuronal cells that produce DA are mainly found in the SN and VTA, but they have not been found to alter their rates of firing during wakefulness and sleep (Gaykema and Zaborszky 1996). Nevertheless, wakefulness has been found to be characterized by high extracellular levels of DA, while levels are lower during NREM sleep. This might suggest that some DA neurons are wake-active. Such neurons are found in the ventral periaqueductal area of the pons, and their lesions have been shown to lead to moderate reductions in wakefulness (Lu et al. 2006; Mignot and Nishino 2005; Nishino and Mignot 1997).

#### 8.6.2.5 Gamma-Aminobutyric Acid (GABA)

The SLD nucleus produces GABA or glutamate, and many of its neurons are active during REM sleep (Lu et al. 2006; Verret et al. 2005; Xi et al. 2004). These neurons give projections to both the ventromedial medulla and the ventral horn of the spinal cord, through which they may inhibit motor neurons. When SLD nucleus is

activated, the results are loss of muscle tone and REM sleep-like EEG activity. Inhibition of the same region promotes wakefulness and reduces REM sleep. Lesions of the SLD nucleus disrupt REM sleep atonia and reduce REM sleep (Hendricks et al. 1982; Sakai et al. 1979).

#### 8.6.2.6 Glutamate (Glu)

Glutamate is an excitatory neurotransmitter and the ARAS is probably glutamatergic (Stenberg 2007). Even though the firing patterns of cells in both the ARAS and the BF are not sufficiently characterized, it is known that they release glutamate and play an important role in wakefulness (Jones 2003, 2005).

#### 8.6.2.7 Histamine (His)

His is essential in wakefulness promotion, and older antihistamines that cross the blood-brain barrier are known for their sedating effects (Brown et al. 2001). His is found in the forebrain and the brainstem, regions which are innervated by the TMN. TMN fires mainly during wakefulness and less during sleep; thus His levels are higher when awake and lower when asleep (John et al. 2004; Monti 1993; Panula et al. 1984; Strecker et al. 2002; Watanabe et al. 1984). The crucial role of His for the initiation of arousal has also been shown in experimental models (John et al. 2004; Lin et al. 1989; Monti 1993).

#### 8.6.2.8 Melanin-Concentrating Hormone (MCH)

MCH is produced by REM sleep-active neurons found, mixed in with orexin neurons, in the LH (Koyama et al. 2003; Verret et al. 2005). Both neuronal cell groups innervate nearly the same target regions, including the DR and LC (Bittencourt et al. 1992). MCH neurons are inhibitory; they fire at a high rate during REM sleep, while, during NREM sleep, they fire at a much lower rate being completely inactive during wakefulness (Ahnaou et al. 2009).

#### 8.6.2.9 Monoamines

Monoamines, such as NE and 5-HT, cause excitation of motor neurons thus increasing muscle tone (Fedirchuk and Dai 2004; Lai et al. 2001). They inhibit REM sleep, and, during wakefulness and to some degree NREM sleep, the REM-active cholinergic neurons are inhibited by 5-HT, NE, and HA (Leonard and Llinas 1994). The interaction between cholinergic and monoaminergic neuronal groups forms the basis of the model explaining the NREM and REM sleep alternations during night (McCarley and Hobson 1975).

#### 8.6.2.10 Norepinephrine (NE)

The major site of NE is the LC. This neurotransmitter is helpful for arousal under conditions that require high levels of attention and task performance. Firing patterns of LC neurons are higher during wakefulness and lower during NREM sleep; during REM sleep, these neurons do not fire at all (Aston-Jones and Bloom 1981; Hobson et al. 1975; Rasmussen and Jacobs 1986). Furthermore, NE neurons in the ventral medulla have an active role during stress (Saper et al. 2005). NE projections to

arousal systems are excitatory, while those to sleep-promoting systems are inhibitory (Aghajanian and VanderMaelen 1982; Brown et al. 2002; Williams and Reiner 1993).

#### 8.6.2.11 Orexin (Orx)

Orexins (Orx) or hypocretins are excitatory neuropeptides discovered in 1998 (Norman et al. 2011). They are produced in the LH and PH, and their role in the sleep-wake cycle regulation is important (de Lecea et al. 1998; Sakurai and Sasaki 1998). Furthermore, the Orx neurons in the LH are related to emotional processing and motivated behaviors (Harris et al. 2005; Ponz et al. 2010; Schwartz et al. 2008; Thompson and Borgland 2011). Their absence may lead to problems such as transition to sleep at inopportune moments, which is the case in narcolepsy (Norman et al. 2011). Experimental animals lacking Orx or the receptor for this neuropeptide have been shown to have narcolepsy with cataplexy (Chemelli et al. 1999; Lin et al. 1999). Orx neurons innervate the LC and TMN (Peyron et al. 1998). Their firing patterns are high during wakefulness, especially during active exploration, and very low (they are practically silent) during NREM and REM sleep (Mileykovskiy et al. 2005), even though they may have occasional burst discharges during REM sleep of rodents (Mileykovskiy et al. 2005; Takahashi et al. 2008). Orx levels are highest during wakefulness (Zeitzer et al. 2003), and, when injected into the brain, they increase arousal and behavioral activity while suppressing NREM and REM sleep (Espana et al. 2001).

#### 8.6.2.12 Prolactin (PRL)

PRL neurons are found in LH and innervate hypothalamic areas, LC and DR. PRL is secreted during the second half of sleep. Experiments have shown increase of REM sleep after PRL injection and decrease of REM sleep in genetically PRL-deficient mice (Obal and Krueger 2004; Sassin et al. 1972).

#### 8.6.2.13 Prostaglandin D2 (PGD2)

Prostaglandin, which is probably synthesized in the basal meninges (Mizoguchi et al. 2001), has sleep-promoting properties. Injection of PGD2 in the preoptic area of experimental animals has been shown to lead to neuronal activation in the VLPO, increasing NREM and REM sleep (Scammell et al. 1998; Ueno et al. 1982). Furthermore, its levels in the cerebrospinal fluid are highest during the sleep period (Pandey et al. 1995) and increase with sleep deprivation (Ram et al. 1997).

#### 8.6.2.14 Serotonin (5-HT)

The relationship between 5-HT and sleep-wake cycle has been noticed since the 1950s when it was observed that chemicals inhibiting 5-HT catabolism enhanced SWS while those inhibiting 5-HT production led to insomnia (Jones 1972). 5-HT-producing neurons are found in the RN and innervate many brain regions that can influence sleep-wake cycle, such as the preoptic area, the BF, the hypothalamus, and the thalamus. Their firing patterns are highest during wakefulness, much lower during NREM sleep, and lowest during REM sleep. Thus, during wakefulness,

extracellular 5-HT levels are higher indicating that 5-HT promotes wakefulness (Jacobs and Azmitia 1992; McGinty and Harper 1976; Portas and McCarley 1994; Trulson and Jacobs 1979).

#### 8.6.2.15 Somnogens

They include substances that may function as natural sleep-inducing molecules, such as adenosine, cytokines, and prostaglandins (Obal and Krueger 2004).

#### 8.6.2.16 Vasoactive Intestinal Peptide (VIP)

VIP is a PRL-inducing factor (Stenberg 2007) that has been shown to increase REM sleep in experimental animals (Riou et al. 1982). In humans, VIP administration seems to stimulate REM sleep when given in doses high enough to stimulate PRL (Murck et al. 1996).

## 8.7 Neurophysiology of Wakefulness and Sleep

### 8.7.1 Cortical and Thalamic Activity During Wakefulness and Sleep

Even though BF, hypothalamus, or brainstem (all of them are subcortical systems) are essential in generating wakefulness and sleep and in regulating the transitions between them, both activity of the EEG and consciousness itself arise from interactions between these subcortical systems, the thalamus, and the cortex (Higgins and George 2007).

The thalamus and the cortex share information; cortical neurons relay information to the neurons of thalamus which, in turn, relay information to the cortex. These thalamic neurons have intrinsic electrical characteristics, and some of the cortical rhythms in NREM sleep are due to them (McCormick and Bal 1997). The thalamus contains:

1. Glutamatergic neurons that project to the cortex and relay sensory, motor, and limbic information to it.
2. GABAergic neurons in its reticular nucleus. They are innervated by the projection neurons and cortex and in turn inhibit the projection neurons.

These connections are believed to be responsible for some cortical rhythms, such as sleep spindles (Steriade et al. 1987).

NREM sleep is characterized by hyperpolarization of the thalamic neurons leading to burst firing and reduction of their responsiveness to sensory stimuli from the environment. On the contrary, REM sleep and wakefulness are characterized by depolarization of thalamic neurons. This is caused by ACh and results to spindle and slow-wave suppression. Furthermore, it promotes the transmission of single spikes that efficiently transmit information to the cortex and drive desynchronized cortical activity. Despite the fact that thalamus has an important role, even extensive damage to it does not change the general patterns of wakefulness, REM, and NREM sleep but impairs

consciousness and the ability to interact with the environment. Thus, it is believed that thalamus is not required for the basic generation of sleep states (Fuller et al. 2011).

Apart from the thalamus, GABAergic neurons are found within the cortex. They have wide projections, and they are active during NREM sleep, implying that they may broadly inhibit other cortical neurons, thus helping generate slow waves during NREM sleep (Gerashchenko et al. 2008). Furthermore, the intensity of cortical slow waves may reflect prior local activity and changes in synaptic strength, as slow waves during NREM sleep are increased over supplementary motor cortex after learning a motor task but decreased with arm immobilization (Vyazovskiy et al. 2008).

### 8.7.2 Process C and Process S: The Two-Process Model

This is a model that emerged in the mid-1980s and provided a useful macroscopic perspective on the dynamic control of wakefulness and sleep (Borbely et al. 2016; Daan et al. 1984). According to this model, process S refers to a homeostatic factor that accumulates during wakefulness and declines during sleep. It is defined as the drive to sleep depending on the duration individual is awake. It interacts with process C, a circadian process responsible for the regulation of the timing of wakefulness and REM sleep (Achermann 2004).

Since process C is a circadian process, it is under the control of both cues from the environment and the SCN, which regulates the circadian cycle of most physiologic rhythms, including sleep and wakefulness (Dibner et al. 2010). The neurons of SCN have a rhythmic function both individually and, especially, when coupled with other SCN neurons (Welsh et al. 2010). The synchronization of the activity of these neurons with the environmental light-dark cycle is achieved with the help of melanopsin. Melanopsin is a photosensitive molecule using luminance information and is found in retinal ganglion cells (Hattar et al. 2002).

The information arriving to SCN neurons is then transmitted to the adjacent subparaventricular zone (Kramer et al. 2001) passing through the dorsomedial nucleus of the hypothalamus and to brain regions that regulate sleep and wakefulness such as the LC, VLPO, and LH (Chou et al. 2003). Besides these, SCN neurons regulate the daily rhythm of body temperature. This is important since regulation of this rhythm entrains circadian activity throughout the body (Buhr et al. 2010).

Circadian rhythms and metabolism are closely linked. Disordered coordination of central and peripheral rhythms may give rise to problems, such as obesity and glucose intolerance which are common in people with shift work sleep disorder or insufficient sleep (Bass and Takahashi 2010).

### 8.7.3 Mechanisms That Regulate the Transitions Between Sleep and Wakefulness

A dynamic interaction among the systems that promote sleep and wakefulness takes place in various ways. The aim is to ensure rapid and complete transitions between sleep and wake states. The VLPO and other sleep-promoting preoptic neurons

inhibit monoaminergic and cholinergic wake-promoting neurons, and the preoptic neurons themselves are inhibited by NE, 5-HT, and Ach (Chou et al. 2003; Gallopin et al. 2004).

During wakefulness, regions containing arousal-promoting neurons are disinhibited. This is made possible through high monoaminergic and cholinergic tone which silences the VLPO. Conversely, during sleep, arousal regions are inhibited. This is achieved through the activation of preoptic neurons that disinhibit their own firing. These mutually inhibitory systems are probably reinforced by orexins. Orexins may stabilize wakefulness by enhancing activity in the arousal systems ensuring alertness and long periods of wakefulness despite rising homeostatic pressure across the day. During wakefulness (and, perhaps to a lesser degree, in NREM sleep), orexins may excite a variety of neurons that inhibit REM sleep, such as monoaminergic neurons, the vlPAG/LPT, and GABAergic inputs to the SLD (Arrigoni et al. 2006; Brown et al. 2001; Eggermann et al. 2001).

### 8.7.4 Activation of Emotional and Reward Circuits During Sleep and Dreaming

Neuroimaging, neurophysiological, and behavioral studies in both humans and animals have shown that, during sleep and dreaming, emotional and reward-related processes and networks are activated. Furthermore, lesion and pharmacological studies of dreaming and dream content analysis in humans also support such a hypothesis (Gaillard and Moneme 1977; Lena et al. 2005; Merritt et al. 1994 Nielsen-Bohlman et al. 1991; Perogamvros and Schwartz 2012; Schenck and Mahowald 2002; Solms 2000).

### 8.7.5 Neural Mechanisms of REM Sleep

REM sleep is characterized by the following events:

1. Cortical EEG activity pattern similar to that during wakefulness.
2. Loss of tone of the postural muscles resulting from the activation of neurons in the locus coeruleus alpha (LCα).
3. Rapid eye movements caused by the activation of neurons in the peri-abducens reticular formation (PAb).
4. Theta rhythm within the hippocampus produced via the activation of neurons in the pontis oralis (PO).
5. Field potentials in the pons (P wave) and spikes in the lateral geniculate nucleus and the occipital cortex. These waves emerge from activation of neurons in the caudo-lateral peribrachial area (C-PBL) of predator mammals and in the dorsal part of the nucleus subcoeruleus (SubCD) of prey mammals.
6. Myoclonic twitches, especially in the muscles of the face and the distal limbs, due to the activation of neurons in the nucleus gigantocellularis.

7. Fluctuations in core body temperature, cardiac and respiratory rate which result from activation of neurons in the parabrachial nucleus (PBN).
8. Penile erection in men and clitoral tumescence in women (Domhoff 2003; Higgins and George 2007; Kirsch 2013; Lee-Chiong 2008).

Each of these events is likely to be mediated by distinct cell groups in the brainstem (Vertes 1984). During REM sleep, aminergic cell activities are markedly reduced or absent, and cholinergic cell activities are comparatively high, even though much less than that during wakefulness (Datta et al. 2009; Lydic et al. 1983; McGinty and Harper 1976). To date, almost all studies have consistently demonstrated that the activation of cholinergic cells in the PPT is one of the most critical steps for the generation and maintenance of REM sleep (Datta et al. 2009).

### 8.7.6 Neural Mechanisms of SWS

Electrophysiological and behavioral signs of SWS-I in animals are comparable to those of stage II sleep in humans. The defining EEG signs of stage II sleep are the sleep spindles and the K-complexes. The former are waxing and waning waves in group sequences every 2–5 s. Sleep spindles are caused by the GABAergic neurons of the thalamic reticular nucleus (Steriade et al. 1993). The thalamus is also a gateway for most sensory and internal signals in their way to the cerebral cortex (Jones et al. 1985).

The thalamus contains two functionally different types of neurons:

- Thalamocortical relay neurons, through which incoming sensory information is transmitted to the cerebral cortex where they cause rhythmical excitation of the cortical neurons that ultimately generate cortical sleep spindles (Llinas and Steriade 2006).
- Thalamic reticular neurons, the activation of which has the opposite results.

The sleep spindle mechanism by thalamocortical relay neurons combines both passive and active physiological processes. The SWS/SWS-II generating mechanisms are active processes. The active steps of the SWS generating mechanisms, compared to the passive steps of the initiation of sleep, operate on shorter timescales. Yet, these behavioral states remain conducive to transfer short-term memory information from the cortex to the hippocampus and/or amygdala for the sorting and deleting steps of long-term memory formation processes (Datta 2006).

Studies have shown that lesions of cell bodies in the POA of the AH effectively suppress SWS in mammals (John et al. 1994; John and Kumar 1998; Srividya et al. 2006). A large population of cells within the POA are more active during SWS than during wakefulness or REM sleep (Alam et al. 1995; Koyama and Hayaishi 1994; McGinty and Szymusiak 2000; Suntsova et al. 2002; Szymusiak et al. 1998).

A study using functional magnetic resonance imaging (fMRI) in the behaving rat has demonstrated that the POA is more active than other parts of the hypothalamus and BF during SWS (Khubchandani et al. 2005). Immunohistochemical analysis of sleep-active neurons in the POA has revealed that the majority contain the inhibitory neurotransmitters GABA and galanin (Gaus et al. 2002; Gong et al. 2004; Gvilia et al. 2006). These sleep-active neurons innervate many wake-promoting areas of the brain, including the TMN, LH, LC, DRN, and PPT/LDT (Gritti et al. 1994). Thus, it is possible that the increased activity of SWS-active GABAergic cells in the POA could release GABA to targets within the wake-promoting areas of the brain.

Released GABA may then suppress activity in these areas in two different ways:

1. GABA receptor activation-mediated inhibition of wake-promoting cells.
2. Inhibition of presynaptic neurotransmitter release that is necessary for the activation of wake-promoting cells (Gottesmann 2002).

Neuropharmacological studies have shown that SWS may be also induced by sedative and hypnotic drugs that involve potentiation of POA GABAergic neurotransmission (Mendelson and Ziegler 2001; Sallanon et al. 1989; Tung et al. 2001).

### 8.7.7 Physiological Changes During Sleep (Table 8.13)

#### 8.7.7.1 Autonomic Nervous System

The sympathetic activity decreases during NREM and the tonic phase of REM sleep, while the parasympathetic increases and reaches a peak in SWS (Brandenberger et al. 2001; Trinder et al. 2001).

#### 8.7.7.2 Cardiovascular and Respiratory System

During sleep, cardiac output, blood pressure, and heart and respiratory rate are reduced. Episodes of arrhythmia may take place during REM sleep thus explaining the higher incidence of myocardial infarctions early in the morning (Verrier et al. 1996). Air exchange and ventilation decrease, whereas muscle relaxation increases resistance in the upper airways (Penzel et al. 2007).

#### 8.7.7.3 Endocrine System

Release of various hormones takes place during sleep. These include growth hormone, prolactin, cortisol, and adrenocorticotropic hormone (Freeman et al. 2000; Obal and Krueger 2004; Wagner and Born 2008) contrary to thyroid-stimulating hormone which is inhibited by sleep (Luboshitzky 2000). Generally, during sleep, increased secretion of anabolic hormones and synthesis of proteins and nucleic acid of the brain take place; the secretion of catabolic hormones is decreased (Nakanishi et al. 1997).

**Table 8.13** Physiological changes during NREM and REM sleep (Colten and Altevogt 2006)

| Physiological process | NREM | REM |
|---|---|---|
| Brain activity | Decreased | Increased in motor and sensory areas<br>Other areas similar to NREM |
| Heart rate | Decreased | Increased<br>Varies from NREM |
| Blood pressure | Decreased | Increased (up to 30 percent)<br>Varies from NREM |
| Sympathetic nerve activity | Decreased | Increased significantly |
| Muscle tone | Similar to wakefulness | Absent (atonia) |
| Blood flow to brain | Decreased | Increased from NREM<br>Depends on brain region |
| Respiration | Decreased | Increased and varies from NREM<br>Coughing suppressed |
| Airway resistance | Increased | Increased and varies from wakefulness |
| Body temperature | Regulated at lower set point than wakefulness; shivering initiated at lower temperature than during wakefulness | Not regulated; no shivering or sweating; temperature drifts toward that of the local environment |
| Sexual arousal | Occurs infrequently | Greater than NREM |

#### 8.7.7.4 Reproductive System

During REM sleep, men may experience nocturnal penile tumescence, and women may have increased vaginal blood flow and engorgement of clitoris (Abel et al. 1979; Schmidt and Schmidt 2004).

#### 8.7.7.5 Thermoregulation

Body temperature is reduced following a decrease in hypothalamic temperature set point. Sweating and shivering are also reduced (Krauchi 2007; Lack et al. 2008).

## 8.8 Neurobiology of Dreaming

Dreaming, a universal human phenomenon, takes place in all stages of sleep. Usually, if one is not awaken during sleep, there is no recall of the dreams. Recall of dreaming depends on both brain activation during sleep and awakening conditions (Hobson and Pace-Schott 2002). Compared to memories of everyday life, memory for dreams is rather poor. This is due to the specific brain states in which dreaming occurs and its reduced sensory and contextual anchoring (Schwartz et al. 2002). Nightmares are frightening dreams that seem to be related to intense and anxiety-provoking situations of everyday life. They are more common in children and decrease in old age (Table 8.14) (Chokroverty 2013; Colten and Altevogt 2006).

**Table 8.14** Types of dreams (Schredl 2010)

| Dream types | Definition |
|---|---|
| REM/NREM dreams | Recollection of mental activity during REM/NREM sleep |
| Sleep-onset dreams | Recollection of mental activity during stage 1 of NREM sleep |
| Nightmares | REM dreams with strong negative emotions which cause awakening |
| Night terrors | Sudden arousal with intense anxiety out of SWS<br>Sometimes accompanied by short NREM dreams |
| Post-traumatic reenactments | REM or NREM dreams which replay the original traumatic experience in a less distorted way |
| Lucid dreams | REM dreams in which the dreamer is aware that she or he is dreaming |

The dreams of REM sleep account for about 80% of dreams during sleep, while the rest are taking place during NREM sleep (Lee-Chiong 2008). Neurobiology of dreaming involves activation of cells and synapses in the brainstem and transmission of the signals to the hemispheres (Chokroverty 2013), activation of higher visual centers, activation of limbic system, and loss of working memory (Hobson and Pace-Schott 2002).

Their content differs. It is more bizarre, irrational, and complex in REM sleep and looks more like problem-solving, simple, and realistic in NREM sleep (Higgins and George 2007; Lee-Chiong 2008). Dreams during REM sleep contain formed hallucinatory perceptions in practically every sensory modality. They are delusional and lack stability in orientation. The imagery is often bizarre, and there may exist images and events that are common in everyday life (Hobson and Pace-Schott 2002).

They contain people, animals, and things with various colors and shapes. They may also contain sounds and experiences with a sensory character (Nir and Tononi 2010). Self-reflection and self-control are absent. Emotions, especially fear or anxiety, are intensified, and volitional control is attenuated (Hobson and Pace-Schott 2002). Emotional involvement levels are high even though negative feelings, such as sadness, are rare (Fosse et al. 2001; Foulkes et al. 1988; Hobson et al. 2000).

Dreams reflect our personality, interests, and anxieties of everyday life, our past, and our current waking concerns (Schredl and Hofmann 2003) and are quite stable during adulthood (Domhoff 1996, 2003). They are usually novel constructions and rarely reproductions of past events (Fosse et al. 2003; Schwartz et al. 2002). Contrary to NREM dreams, REM dreams are easier to remember. They are also easier to remember if subjects are awaken immediately after the onset of REM dreams (Chokroverty 2013).

Administration of dopaminergic agents in humans has been shown by pharmacological studies to elicit vivid dreams (Balon 1996; Thompson and Pierce 1999). On the other hand, administration of $D_2$ antagonists (a common mechanism for almost

**Table 8.15** Theories of function of dreaming (Chokroverty 2013)

| |
|---|
| Activation of neural networks of brain |
| Restructuring and reinterpretation of data |
| Memory consolidation |
| Removal of useless information |
| Dreams as epiphenomenon |
| Iterative programming |
| Guardian of sleep |
| Compensation |
| Reverse learning hypothesis |
| Mastery hypothesis |
| Mood regulation |
| Systemic desensitization |
| Threat simulation theory |

all antipsychotics) reduces vivid dreaming (Gaillard and Moneme 1977) and nightmares (Lambert 2006). This dopaminergic theory of dreams has been criticized though (Doricchi and Violani 2000), and effects of dopamine on dreaming may be a result of its interactions with other neuromodulatory systems, such as cholinergic cells of BF that activate cortical and limbic structures (Perry and Piggott 2000). Other theories of dreaming include the cognitive and the activation synthesis hypothesis (Lee-Chiong 2008).

Dreams are believed to be associated with memory-related processes and activation of neural networks in CNS (Lee-Chiong 2008). Their neurobiological significance is as yet unknown even though various theories have been postulated (Table 8.15). Nevertheless, there is no scientific evidence that dreams foretell the future (Hobson and Pace-Schott 2002).

## 8.9 Clinical Aspects

### 8.9.1 Introduction

Sleep disorders are considered an important aspect of public health. Depending on their etiology, they are categorized into two broad groups: those of primary etiology and those that have an underlying neurologic disease or mental health disorder (Chokroverty 2009; Mitler et al. 2000; Saper and Scammell 2013).

### 8.9.2 Circadian Rhythm Sleep Disorders

Patients with circadian rhythm sleep disorders (CRSL) have adequate sleep quantity and quality, but they cannot sleep when they want or they are expected to do so; this may lead both to insomnia and excessive daytime sleepiness. Jet lag and shift work are two common causes of CRSD (Silber et al. 2010). The exact pathophysiologic basis is not fully elucidated but likely involves genetic and molecular mechanisms (Iwase et al. 2002; Reid et al. 2001; Toh et al. 2001).

### 8.9.3 Fatal Familial Insomnia

This is a rare, prion disease defined by agrypnia excitata syndrome. Patients cannot sleep and concurrently have overactivation of the sympathetic nervous system. There is no treatment for the disease, and patients die from it (Guaraldi et al. 2011; Montagna et al. 2003).

### 8.9.4 Insomnia

It is estimated that insomnia is the most common sleep disorder (Ohayon 2002) and many of those complaining for it may have an underlying psychiatric disorder (Ohayon 1997). It can lead to many adverse effects, such as anxiety and mood disorders, fatigue, and problems in daily functioning. In clinical practice, insomnia is a term used to denote difficulties in falling or staying asleep. Insomnia is believed to be a disorder of increased physiological arousal since, contrary to what was generally believed, arousal and sleep are not mutually exclusive states (Nofzinger et al. 2004). Potential mechanisms include stress response, inhospitable environment (temperature, light, noises), homeostatic factors, and maladaptive coping mechanisms (Silber et al. 2010).

### 8.9.5 Narcolepsy

Narcolepsy, a disease of REM sleep mechanism, is characterized by excessive sleepiness due to activation or disfacilitation of sleep-active or wake-active neurons, respectively. Most patients with narcolepsy exhibit also a sudden loss of muscle tone, which is called cataplexy (Siegel 2009). Apart from cataplexy, there are two other REM-related symptoms that define the disease: hypnagogic hallucinations and sleep paralysis (Guilleminault and Anagnos 2000). The majority of narcolepsy cases are caused by the loss of hypocretin-containing hypothalamic cells (Thannickal et al. 2000), and this has been shown in brains of patients with the disease (Nishino et al. 2000; Thannickal et al. 2000).

### 8.9.6 Obstructive Sleep Apnea

This disorder is caused by dysfunction of the upper airway or the control mechanisms of the respiratory system (Silber et al. 2010). Factors predisposing to obstructive sleep apnea include small upper airway, such as in obesity and in lesions of the upper airway, reduction of dilator activity of the upper airway muscles (may be caused by alcohol and drugs, such as benzodiazepines, and neurological disorders), and increased resistance of chest wall in obesity (Reading 2013).

### 8.9.7 Parasomnias

Parasomnias are sleep disorders characterized by abnormal behaviors during sleep (Howell and Schenck 2012). REM sleep behavior disorders are parasomnias

occurring during REM sleep; instead of the normal atonia in this stage, patients have increased muscle tone resulting in overt motor behavior during dreaming (Schenck and Mahowald 2002). Parasomnias during NREM sleep are characterized by the concurrent occurrence of wake and sleep states (Bassetti et al. 2000). The underlying pathophysiological mechanisms of parasomnias are not fully known. Clinically, they are characterized by instinctual and exploratory behaviors, such as oriented locomotion, aggression, sexual behaviors, feeding, chewing, or swallowing (Morrison et al. 1992; Vetrugno et al. 2006; Winkelman 2006).

### 8.9.8 Sleep-Related Movement Disorders

#### 8.9.8.1 Restless Legs Syndrome (Willis-Ekbom's Disease)

Various movements have been described to occur when falling for sleep or during sleep. Restless legs syndrome (RLS) is the most common disease in this group. Its pathophysiology is not fully known yet, but it is likely due to dopamine dysregulation. Iron may also be implicated since it is cofactor for the production of dopamine (Raman 2013) and has been shown to be reduced in the SN of patients with RLS (Allen et al. 2001; Connor et al. 2003). CNS pathology might exist since it is known that centrally active dopamine antagonists exacerbate the disease. Studies also indicate a possible pathology of subcortical areas or of subcortical inhibition of flexor reflex (Bara-Jimenez et al. 2000; Tergau et al. 1999).

#### 8.9.8.2 Periodic Limb Movement Disorder

This is a disease entity characterized by periodic, stereotyped limb movements during sleep, usually in N1 and N2 stages (Raman 2013).

### 8.9.9 Sleep and Psychiatric Disorders

#### 8.9.9.1 Sleep and Alcohol

Alcohol is frequently used as hypnagogic substance since it results to decreased sleep latency and increased SWS during the first hours of the night. However, later in the night, alcohol ingestion leads to nightmares and sleep fragmentation (Pressman 2007). Chronic alcohol use leads to increased sleep latency, poor quality of sleep, and exacerbation of preexisting sleep disorders (Stein and Friedmann 2006).

#### 8.9.9.2 Sleep and Anxiety Disorders

Many patients suffering from anxiety complain about sleep disorders, especially insomnia, which, in turn, may lead to further anxiety. This leads to a vicious cycle: insomnia deteriorates anxiety and mood symptoms suggesting that there may exist a common pathophysiologic mechanism (Mellman 2006, 2008; Ohayon et al. 1998; Ohayon and Roth 2003).

#### 8.9.9.3 Sleep and Bipolar Disorder

Patients with hypomania and/or mania have a reduced need for sleep (Plante and Winkelman 2008; Wehr 1991). Furthermore, a decrease in sleep may lead to

hypomania or mania in patients with bipolar disorder, while the opposite is true for bipolar depression (Bauer et al. 2006). Sleep disturbances may also be common prodromal signs of both mania and depression (Jackson et al. 2003). This connection between sleep disturbances and mood disorders has been proposed by research to form a closed loop (Harvey 2008) with circadian (Li et al. 2013; Roybal et al. 2007; Wirz-Justice et al. 2009) and neuroendocrine (Spiegel 2000) underlying mechanisms.

#### 8.9.9.4 Sleep and Depression

Circadian dysfunction may be partially responsible for the initiation or maintenance of mood disorders. Depression has a diurnal variation and may be alleviated by sleep deprivation, which could possibly be explained by circadian or homeostatic processes (Boivin et al. 1997). Misalignment between circadian and sleep phase can deteriorate mood (Danilenko et al. 2003); this could likely explain mood-related problems in jet lag or shift work (Kolla and Auger 2011), as well as severity of unipolar depression (Hasler et al. 2010). Furthermore, prior wakefulness seems to deteriorate mood (Boivin et al. 1997). Sleep deprivation may alleviate depressive mood in patients immediately even though this effect is usually of short duration (Barbini et al. 1998; Giedke and Schwarzler 2002). Researchers have attempted to explain this effect by dopaminergic (Ebert and Berger 1998), noradrenergic (Payne et al. 2002), circadian (Wirz-Justice et al. 1981), and homeostatic mechanisms (Endo et al. 1997). On the other hand, insomnia is an independent risk factor of subsequent onset of major depression (Buysse et al. 2008; Ford and Kamerow 1989; Johnson et al. 2006; Riemann and Voderholzer 2003).

#### 8.9.9.5 Sleep and Psychotic Disorders

Insomnia is common in patients with schizophrenia and may be a clinical prodromal sign of first-episode psychosis or relapse (Benca et al. 1992; Chouinard et al. 2004). These patients usually have short REM latency and SWS deficits (Zarcone et al. 1987) (Table 8.15).

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# Genetics and Behaviour

9

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## 9.1 Introduction

Behavioural genetics constitutes a wide research field focusing on genetic, as well as environmental contributors to phenotypic variance of behaviour.

There are different research methods to explore genetic contribution to behaviour:

(a) Animal studies: these are based on animal models simulating human behaviour, e.g. aggressive, impulsive, etc. Selective breeding or genetic manipulation allows studying gene effects on brain development and behaviour.
(b) Heritability studies: these involve quantitative research techniques aiming at determining heritability, e.g. genome-wide linkage studies of multiple alleles segregating within family members. Heritability studies include family, twin and adoption studies.
(c) Molecular genetic studies: these focus on the identification of susceptibility genes, e.g. association between DNA polymorphisms and behavioural traits. The most promising susceptibility alleles are the ones altering gene expression and thus protein levels. Molecular genetic studies include linkage and

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association studies. The latter constitute a common approach in the field of behavioural genetics. Roughly, they search for significant differences in genetic variant frequencies between individuals characterised by a specific behaviour and healthy controls.

(d) Mechanism studies: these focus on the investigation of the underlying biological mechanisms triggered by gene polymorphisms.

Still, it is almost impossible to base phenotypic expression of behaviour strictly on genes. A broad range of environmental factors is also influential. Thus, it is widely accepted that genetic factors (nature) and environmental factors (nurture) interact with each other. As a result, environmental factors can trigger behaviours for which there is a genetic predisposition (Caspi et al. 2002; Reif et al. 2007; Cicchetti et al. 2012). Gene-environment interaction or genotype-environment correlation (rGE) may be (a) passive, in which there is an association between inherited genotype and childhood environment, e.g. antisocial parents provide both genetic component and an environment promoting the development of antisocial behaviour, and (b) evocative, in which one factor promotes the other, e.g. a child genetically predisposed for aggression will manifest aggressive behaviour provoking others' harsh responses, which evoke in turn further manifestation of child's aggressive behaviour (Jaffee and Price 2008).

Behaviour varies between individuals, a phenomenon called "population variance". Such variance is statistically represented by a bell curve, depicting a "normal distribution". The tails of normal distribution represent individuals with low or high extremes of variance. The term "heritability" is used to describe the proportion of phenotypic variance that may be attributed to genetic factors, e.g. "heritability of 0.50" means that 50% of the variance across the population is explained by non-specific genotype differences. On the other hand, the term "environmental variance" is used to describe the proportion of phenotypic variance that can be explained by environmental factors.

The aim of this chapter is to provide recent research evidence for the association between genes and behaviour. In this first section, a short introduction revises basic knowledge of genetics and provides descriptive information about behaviours and personality traits studied in relation with genetics.

### 9.1.1 Genetic Variation

Humans are diploid organisms with 23 pairs of chromosomes, 22 somatic and 1 pair of sex chromosomes (female, XX; male, XY). Chromosomes contain all genetic information, coded for by DNA. DNA consists of two strands. Each strand consists of nucleotides. There are four main nitrogenous nucleotide bases, adenine (A), thymine (T), guanine (G) and cytosine (C). Purines consist of A and G while pyrimidines of T and C. These bases couple with each other forming base pairs (bp). Adenine pairs with thymine and guanine with cytosine, in such the two DNA strands are held together forming a double helix, which resembles graphically a ladder.

A DNA segment coding for a specific protein is called "gene", while the sum of genes forms one's "genome". Gene DNA sequences are not fully identical among all people. For instance, at a particular DNA position, one may have adenine whereas another guanine. This DNA variation is called "allele", resulting in wide phenotypic differences among humans. Each individual is a carrier of two alleles, since chromosomes are paired. One allele is of maternal and the other of paternal origin. An individual is homozygous when alleles are identical. When alleles are different, then there is heterozygosity for that particular gene allele. In most cases, individuals are heterozygous.

Alleles detected in at least one out of a hundred (1%) in a population constitute "DNA polymorphisms". Polymorphisms are the result of DNA damage or incorrect DNA replication. In cases of DNA alterations with deleterious effects, i.e. mutations, severe diseases may emerge. Such mutations are usually rapidly eliminated from a population, since mutant carriers are less likely to reproduce. In a broader sense, DNA polymorphisms are not associated with emerging pathology. They are rather the reason why each person is unique. Depending though on polymorphism, protein amount or protein structure may be altered. In this case, the polymorphism is considered "functional". Functional polymorphisms mapping at important sites may be associated with human traits and disorders. The most common polymorphisms are (a) single nucleotide polymorphisms (SNPs): these are formed by variation in a single nucleotide at a specific position. When a purine is changed into another purine or a pyrimidine into another pyrimidine, the polymorphism is called "transition". When a purine is changed into a pyrimidine, the polymorphism is called "transversion". Although there are some triallelic SNPs (i.e. three different base variations), for most SNPs, there are only two different alleles. Single nucleotide polymorphisms may be found at different locations within the genome, and most of them are "silent", caused by synonymous nucleotide changes leaving protein amino acid sequences unaltered (non-synonymous nucleotide changes are the ones altering amino acid sequence and possibly protein's function). Still, a SNP located at a gene's promoter region could be functional, affecting gene expression; (b) short insertion and deletion polymorphisms (INDELs): these constitute insertions (i.e. nucleotide gain, lengthening overall fragment) or deletions (i.e. nucleotide loss, shortening overall fragment) of up to 50 nucleotides at a single locus; and (c) variable-number tandem repeats (VNTRs): these are formed by genetic elements repeated in tandem arrays. They include micro- and minisatellites, primarily distinguished based on size and repeat pattern. Microsatellites or short tandem repeats (STRs) or simple sequence repeats (SSRs) consist of repeated nucleotide sequences ranging from 2 to 6 bp. Minisatellites consist of repeated sequences ranging from 11 to 65 bp.

In case of behavioural genetics, the term "risk allele" is used to describe polymorphic alleles associated with a specific behavioural phenotype. Still, it is extremely difficult to associate a specific behaviour strictly with a certain allele. Behavioural traits normally distributed in a population are attributed to multiple genes interacting with each other. Each gene shows relative limited effects, either enforcing or limiting a trait. Furthermore, gene expression is based on many other expressed genes. Altogether, "polygenic inheritance" (i.e. a complex gene pattern,

in some cases across different chromosomes) is involved in the phenotypic expression of human behaviour and personality. Lastly, "linkage disequilibrium" (LD) refers to the non-random association of alleles at two or more loci. Neighbouring alleles tend to co-segregate, i.e. be inherited together. Table 9.1 includes a brief glossary of genetic terms and abbreviations used in this chapter.

**Table 9.1** Brief glossary of genetic terms and abbreviations

| Terms and abbreviations | Definition |
|---|---|
| Diploid | A cell/organism with two sets of chromosomes, one of maternal and one of paternal origin |
| Chromosome | Structure located in the cell nucleus and formed by DNA coiled tightly around histones, the proteins supporting chromosome's structure |
| XX | Female |
| XY | Male |
| DNA | Deoxyribonucleic acid composed of nucleotides, encoding genetic information carried by chromosomes |
| DNA replication | Production of two identical DNA replicas from one original DNA molecule |
| Nitrogenous nucleotide bases | Adenine (A), thymine (T), guanine (G), cytosine (C) |
| Purines | Adenine (A) and guanine (G) |
| Pyrimidines | Thymine (T) and cytosine (C) |
| bp | Base pair, formed by nucleotide bases' coupling (adenine pairs with thymine and guanine with cytosine) |
| kb | Kilobase, unit equal to 1000 bp |
| Double helix | Two DNA strands coiled around each other |
| Genome | Sum of genes in an individual |
| Gene | DNA segment coding for a specific protein |
| Locus | The exact position of a gene on a chromosome |
| Gene's promoter region | DNA region initiating gene transcription (i.e. the first step of gene expression), in which a DNA segment is copied into messenger RNA (mRNA) |
| Gene's coding region | DNA sequence composed of exons, coding for a protein |
| Exon | DNA sequence encoding RNA, produced after introns have been removed via RNA splicing |
| Intron | DNA sequence removed by RNA splicing |
| Codon | Nucleotide triplet coding for an amino acid |
| Initiation or start codon | Nucleotide triplet defining the beginning of translation, i.e. protein formation. The most common start codon is AUG, coding for amino acid methionine |
| Amino acid | Structural units forming proteins |
| Allele | Gene variation due to different nucleotide arrangement, resulting in wide phenotypic differences (each individual carries one allele of maternal and one of paternal origin) |
| Major allele | The most common allele in a population; in most cases it is the ancestral, also called "wild" allele |
| Minor allele | The second most common allele in a population |

**Table 9.1** (continued)

| Terms and abbreviations | Definition |
|---|---|
| Genotype | The combination of two alleles at a specific locus |
| Homo-/heterozygous | Due to chromosomal diploidy, there are two alleles for any given gene. Carriers of identical alleles at a specific position are homozygous, whereas carriers of different alleles are heterozygous for that particular gene |
| Alleles in phase | In diploids, "alleles in phase" or "gametic phase" refers to allele combination at different loci on the same chromosome, representing the original combination of maternal and paternal alleles |
| Risk allele | Allele associated with a specific behaviour or personality trait |
| Differential susceptibility | Vulnerability or protective effects provided by a gene under specific environmental conditions |
| DNA polymorphism | Allele detected in at least one out of a hundred in a population |
| SNP | Single nucleotide polymorphism formed by variation in a single nucleotide at a specific position |
| Transition | SNP, in which a purine is changed into another purine or a pyrimidine into another pyrimidine |
| Transversion | SNP, in which a purine is changed into a pyrimidine |
| Silent SNP | SNP caused by synonymous nucleotide changes leaving amino acid sequence unaltered |
| Functional SNP | SNP caused by non-synonymous nucleotide changes, altering amino acid sequence and possibly protein's function<br>SNP located at gene's promoter region, affecting gene expression |
| INDEL | Short insertion and deletion polymorphism, including insertions or deletions of up to 50 nucleotides at a single locus |
| VNTR | Variable-number tandem repeat formed by genetic elements repeated in tandem arrays |
| Microsatellite | Short tandem repeat (STR) or simple sequence repeat (SSR) consisting of repeated nucleotide sequences of 2–6 bp |
| Minisatellite | VNTR consisting of repeated nucleotide sequences of 11–65 bp |
| Polygenic inheritance | Complex gene pattern, in some cases across different chromosomes, affecting phenotypic expression |
| LD | Linkage disequilibrium, i.e. non-random association of co-segregating alleles at two or more loci |

## 9.1.2 Behaviour and Personality

### 9.1.2.1 Behaviour

Behaviour is defined by the way an individual acts and functions in response to internal or external stimuli and under specific circumstances. Behaviours are divided into "innate" and "learned". Innate behaviours are governed by genes. An example of human innate behaviour, or fixed action pattern, is a baby's smile when it's looked at. Such a response makes it attractive and maximises the chance of gaining parental care. Although learned behaviours have a genetic background as well, they are also determined by experience and environmental influences. Examples of learned behaviours include habituation, imprinting, classical conditioning, operant conditioning, observational learning, play and insight learning (reasoning).

Different behaviours have been studied in relation with gene polymorphisms, among which impulsive, suicidal, aggressive, antisocial and criminal. Behaviours laying at the extremes of normal distribution are maladaptive and often associated with psychiatric disorders.

### Impulsive Behaviour

Impulsive behaviour is characterised by acting without foresight and is associated with a preference for immediate reward, decision-making without realising risky aspects of a decision and poor volitional control (Evenden 1999). In other words, different aspects of impulsivity include non-planning impulsiveness (i.e. behaving without taking future consequences into consideration), cognitive or attentional impulsiveness (i.e. deciding rapidly without focusing on an assignment) and motor impulsiveness (i.e. acting without thinking) (Patton et al. 1995).

Impulsivity as a personality trait is associated with impulsive behaviour. "Adaptive" impulsivity may be a positive personality trait when there is a demand for immediate confrontation with a crucial situation. In short, impulsive actions that turn out beneficial may be characterised as "spontaneous", "unconventional" or "bold", although their true nature remains impulsive. On the other hand, there is "maladaptive" impulsivity, which is dysfunctional, leads to negative consequences and may be associated with aggressive behaviour.

Heritability of trait impulsivity was estimated at around 45–50% (Pedersen et al. 1988; Hur and Bouchard Jr. 1997). The role of heritability in the manifestation of impulsivity was shown to increase with age. Additionally, heritability of risk-taking was shown to increase with age, though only in males (Anokhin et al. 2009). Behavioural expression of impulsivity was associated with suicidal, aggressive and antisocial behaviour. Additionally, impulsive behaviour constitutes a shared phenotype among different psychiatric disorders, such as attention deficit hyperactivity disorder (ADHD), impulse control and addictive disorders.

### Suicidal Behaviour

Suicidal behaviour or suicidality includes thoughts and actions aiming at causing own death. *S*uicide ideation always precedes a suicide attempt and may be originally expressed by a vague death wish. As suicide ideation becomes more intense, a suicide plan, including suicide method, place and time, may be organised. A suicide attempt is an intentional act aiming at causing own death, without succeeding. Lastly, suicide is defined as an intentional fatal act causing own death.

Suicidal behaviour is more common within the context of psychiatric disorders, such as major depressive disorder and schizophrenia (Nock et al. 2008). There seems to be a genetic contribution to suicidal behaviour independent of the genetic contribution to psychiatric disorders. Many genes were implicated in the manifestation of suicidal behaviour (Clayden et al. 2012). Family history of suicidal behaviour is a severe risk factor for suicidal behaviour, while heritability of serious suicidality was estimated at around 55% (Mann et al. 2001). According to some, suicidal behaviour may constitute another form of aggressive behaviour, in which aggression is directed towards one's self. Suicide attempts may be more related to impulsivity, while completed suicide may be more related to aggression.

### Aggressive Behaviour

Aggressive behaviour constitutes a broad phenotype, ranging from verbal to physical aggression, including offensive behaviour against others and objects' destruction. Aggression is categorised into two major subtypes: (a) proactive or instrumental. This form is associated with premeditated, controlled assault. Therefore, it is considered as predatory, offensive aggression, aiming at gaining something or achieving a goal, and is related to psychopathy. Proactive aggressive behaviour is more closely related to antisocial and criminal behaviour; (b) reactive or impulsive. In this case, aggressive behaviour is neither planned nor well considered and is almost always accompanied by intense negative emotions, e.g. fear, anxiety, anger, hostility, increased psychomotor activity and excitation of autonomic nervous system. Reactive aggression is usually provoked by external stimuli, such as insults, threats, physical attacks, and is more closely related to affect dysregulation and impulsive behaviour (Vitiello and Stoff 1997). When reactive aggression constitutes a response to threats posed by others, then it is considered "defensive" and thus beneficial. On the contrary, "dysfunctional" reactive aggression is often disproportionate to the stimulus, associated with reduced control over aggressive impulses and closely related to frustration (Crick and Dodge 1996; Raine et al. 2006).

Aggressive behaviour is far more common in males compared with females. Heritability, which was confirmed by meta-analyses of twin and adoption studies, may be more pronounced during adulthood compared with childhood, during which environmental factors are probably equally important. The genetic component of aggressive behaviour was shown to account for 40–60% of the variance (Miles and Carey 1997; Rhee and Waldman 2002; Craig and Halton 2009).

### Antisocial Behaviour

Antisocial behaviour constitutes a broad phenotype, characterised among others by aggressive behaviour, criminal behaviour, delinquency and psychopathy (Baker et al. 2007). Antisocial behaviour can be studied under a different perspective, depending on its definition and measurement tools, and is best considered a dimensional phenomenon, a continuum, within which different manifestation and diverse severity may be observed. Altogether, there seems to be a strong association between the clinical manifestation (e.g. aggressive behaviour), the legal aspects (e.g. criminal behaviour, court conviction) and the personality traits (e.g. hostility, dishonesty, psychopathy) related to antisocial behaviour.

Antisocial personality traits include beliefs and attitudes aiming at using or harming others. Still, someone with antisocial personality traits does not necessarily perform aggressive or illegal acts. Since the relation between antisocial personality traits and aggressive or criminal behaviour is not bidirectional, genetic studies should differentiate aggressive versus non-aggressive antisocial behaviour.

Antisocial behaviour is far more common in males compared with females (Craig and Halton 2009). Still, the effect of genetic factors on the manifestation of antisocial behaviour seems to be higher in females during childhood. This sex difference disappears throughout adolescence and in adulthood, since the effect of genetic and environmental factors becomes roughly the same in both sexes (Jacobson

et al. 2002). Quantitative genetic studies yielded diverse results, possibly due to heterogeneous definition and assessment of antisocial behaviour. Roughly, the genetic component of antisocial behaviour was shown to account for 40–60% of the variance (Gunter et al. 2010; Fergusson et al. 2011).

**Criminal Behaviour**

Criminal behaviour, defined as "an act violating public law" or as "failure to act according to public law", was mainly studied within the context of antisocial behaviour/antisocial personality disorder.

### 9.1.2.2 Personality

Personality is formed by a pattern of relatively permanent traits and unique mental, emotional and behavioural characteristics providing consistency and individuality to one's behaviour. A personality "trait" is a relatively stable characteristic, enduring and consistent across a variety of situations, as well as typical for an individual. Traits are considered to predispose a person to respond in a certain way, regardless of the situation. For instance, an individual with high trait anxiety is prone to interpreting ambiguous stimuli as more threatening, while an individual with high trait anger is prone to reacting with anger towards situations that are least provoking. On the other hand, "state" is a temporary emotional-personality change, constituting a reaction to different stimuli.

Cloninger introduced the Temperament and Character Inventory (TCI), a self-report personality questionnaire, based on his "psychobiological model of personality". According to Cloninger, personality consists of temperament (i.e. heritable-stable traits) and character (i.e. traits influenced by learning and experience, maturing throughout life). Temperament has four dimensions: (a) novelty seeking, (b) harm avoidance, (c) reward dependence and (d) persistence. Character consists of three dimensions: (a) self-directedness, (b) cooperativeness and (c) self-transcendence (Raeymaekers and Van Broeckhoven 1998).

Currently, another widely used taxonomy of personality traits identifies five major personality dimensions: (a) neuroticism, (b) introversion-extraversion, (c) agreeableness, (d) conscientiousness and (e) openness to experience. Each personality trait is represented by a normal distribution. Based on twin studies, heritability of aforementioned dimensions was estimated at around 40% (Borkenau et al. 2001). Neuroticism constitutes a dimensional trait with six different facets: (a) anxiety, (b) depression, (c) hostility, (d) self-consciousness, (e) impulsiveness and (f) vulnerability (Miller et al. 2009). Altogether, twin studies revealed that genetic factors contribute to phenotypic expression of all aforementioned personality facets, accounting for 41–61% of the variance (Jang et al. 1996).

Personality traits laying at the extremes of normal distribution are putatively maladaptive and may predispose to the manifestation of psychiatric disorders. For instance, anxiety-related traits increase vulnerability for the development of anxiety disorders. Different personality traits have been studied in relation with gene polymorphisms, among which trait anxiety, trait impulsivity, trait anger, novelty seeking, sensation seeking, harm avoidance and psychopathy.

### Novelty Seeking

High novelty seeking individuals appear quick-tempered, impulsive, curious, exploratory, enthusiastic-excitable, disorderly and extravagant. According to Cloninger's Tridimensional Personality Questionnaire (TPQ, the old version of TCI, measuring novelty seeking, harm avoidance and reward dependence), individuals scoring high in novelty seeking are characterised by impulsive and exploratory behaviour, while those scoring low tend to be rigid, frugal, reflective, stoic and low-tempered. Novelty seeking was correlated with extraversion (Lepine et al. 1994; Tsuchimine et al. 2009). Novelty seeking and extraversion were correlated in turn with suicide ideation and attempt (Brezo et al. 2006). Heritability of novelty seeking was shown to account for 36% of the variance (Heiman et al. 2004).

### Sensation Seeking

Sensation seeking is defined as an individual's need for novel, varied, sensory and mental experiences (Zuckerman et al. 1972) and is expressed by four facets: (a) experience seeking, characterised by an attraction towards new experiences (e.g. through travel or various lifestyle choices); (b) disinhibition, characterised by a tendency towards sensation pursuit (e.g. alcohol or sexual intercourse); (c) thrill/adventure seeking, characterised by an engagement in adventurous activities (e.g. extreme sports, reckless driving); and (d) boredom susceptibility, characterised by an aversion to boredom, routine and repetition as well agitation when there is lack of a variety of stimuli.

Sensation seekers pursue new sensations, feelings and experiences in all life aspects, including personal and professional life. Although risk is not the driving force, risk can be underestimated or even considered an additional stimulant for acquiring desired sensations. Behaviours associated with thrill and adventure components of sensation seeking are referred to as "thrill" or "adrenaline seeking behaviours". Individuals exhibiting dysfunctional sensation seeking may engage in sexual risk-taking and gambling.

It was shown that sensation seeking is a highly heritable trait. In males, highly heritable sensation seeking facets included experience seeking (60%) and disinhibition (59%), while thrill/adventure seeking was the least heritable facet (34%). In females, highly heritable facets included thrill/adventure seeking (62%) and disinhibition (52%), while boredom susceptibility was the least heritable facet, accounting for 29% of the variance (Stoel et al. 2006). Sensation seeking was correlated with novelty seeking (McCourt et al. 1993).

### Harm Avoidance

Harm avoidance is characterised by anticipatory worry, fear of the unknown, cautiousness, self-doubt, shyness and fatigability. Individuals exhibiting this trait are often characterised as cautious, fearful, discouraged, insecure, negativistic-pessimistic, asthenic and reserved with strangers (Cheung 2007). Harm avoidance was positively correlated with neuroticism and negatively correlated with novelty and sensation seeking (Cloninger 1986; McCourt et al. 1993). Harm avoidance and neuroticism were associated with suicide ideation and attempts (Brezo et al. 2006). Heritability of harm avoidance was shown to account for 36% of the variance (Heiman et al. 2004).

**Psychopathy**
Psychopathy is a personality trait characterised by lack of empathy (i.e. response congruent to the other's emotional state) and remorse. Psychopathy is related to antisocial behaviour and was shown to have a genetic component ranging from 50% to 80% (Retz et al. 2004; Gunter et al. 2010).

## 9.2 Genes and Behaviour

This second section focuses on the association between different gene polymorphisms and behaviour/personality. Emphasis was given on human studies, since data from animal studies cannot be easily interpreted in relation to humans. Some animal studies will be presented when there is no available data on humans. Due to the large amount of literature, emphasis was drawn away from genes that have not been extensively studied (Clayden et al. 2012). For instance, although the norepinephrine system has been associated with aggression, genes for which there is lack of consistent evidence, e.g. norepinephrine transporter gene (Kim et al. 2006a), will not be described. Overall, focus was placed on meta-analytic studies, whenever these were available.

### 9.2.1 Serotonergic System

The serotonergic system is involved, among others, in mood and behaviour regulation. There is evidence for the implication of the serotonergic system in the manifestation of impulsive (Bevilacqua and Goldman 2013), suicidal (Mann et al. 2001), aggressive and antisocial behaviour (Lesch and Merschdorf 2000).

Specifically, it was serotonergic system hypofunction that was associated with impulsive and risk-taking behaviour (Mann 2003). Low 5-hydroxyindoleacetic acid (5-HIAA) levels in cerebrospinal fluid (CSF), indicative of serotonergic system deficiency, were associated with suicidal behaviour within the context of different psychiatric disorders, independent of diagnosis (Asberg et al. 1986; Olivier and van Oorschot 2005). Furthermore, different serotonergic gene polymorphisms were associated with suicidal behaviour (Arango et al. 2003).

The serotonergic system was particularly implicated in the manifestation of aggressive behaviour (Craig and Halton 2009). The theory of a negative association between serotonergic activity and aggression, i.e. low serotonin activity is related to increased aggression levels (Olivier and van Oorschot 2005), was supported by the anti-aggressive effects of selective serotonin reuptake inhibitors (SSRIs) (Fuller 1996; Reist et al. 2003) and other anti-aggressive drugs with serotonergic function, called "serenics", which are under investigation (Miczek et al. 2002; Olivier and van Oorschot 2005). Still, such a direct association may be an oversimplified hypothesis due to serotonin receptors' wide variety, as well as serotonin system's complex regulation (de Almeida et al. 2005).

Lastly, it should be mentioned that research evidence relating different behavioural phenotypes to serotonergic system's dysfunction emphasises the detrimental effects of environmental stressors on the serotonergic system. Tables 9.2, 9.3, 9.4, and 9.5 present meta-analyses of studies investigating serotonergic genes in relation with behaviour and personality.

**Table 9.2** MAOA gene polymorphism and behaviour

| Gene (chromosome location) | Encoded protein | Polymorphism | Alleles | Behavioural phenotype | Meta-analyses |
|---|---|---|---|---|---|
| MAOA (Xp11.3) | Monoamine oxidase A | MAOA-uVNTR, 30 bp repeat element | MAOA-H: high-activity allele, transcribed 2–10 times more efficiently<br>MAOA-L: low-activity allele | Suicidal behaviour | Meta-analysis of five studies (862 suicidal cases versus 1239 healthy controls)<br>Results: no association (Clayden et al. 2012) |
| | | | | Aggressive/ antisocial behaviour | Meta-analysis of five studies (around 2570 males)<br>Results: childhood adversity/abuse was associated with antisocial behaviour in male MAOA-L genotype carriers (Kim-Cohen et al. 2006) |
| | | | | | Meta-analysis of 31 studies (case and healthy control number not mentioned)<br>Results: MAOA-L was proven a risk allele for broadly defined antisocial behaviour (Ficks and Waldman 2014) |
| | | | | | 1. Meta-analysis of 20 studies of strictly male or mixed male-female, mainly non-clinical populations (11,064 participants)<br>Results: male MAOA-L carriers with a background of childhood maltreatment (e.g. domestic violence, physical/sexual abuse and parental neglect) exhibited higher levels of aggression/violence, non-violent antisocial behaviour as well as aggressive/violent antisocial behaviour during childhood/adolescence, as well as during adulthood<br>2. Meta-analysis of 12 studies of female, mainly non-clinical populations (7588 participants)<br>Results: an interaction was observed between MAOA-H genotype and childhood maltreatment (e.g. domestic violence, physical/sexual abuse and parental neglect) in relation with antisocial outcomes. This finding depended though on meta-analysis' study inclusion and requires further investigation (Byrd and Manuck 2014) |

**Table 9.3** SLC6A4 gene polymorphisms and behaviour/personality

| Gene (chromosome location) | Encoded protein | Polymorphisms | Alleles | Behavioural phenotype | Meta-analyses |
|---|---|---|---|---|---|
| SLC6A4 (17q11.1–q12) | Serotonin transporter | 5-HTTLPR, 20–23 bp repeat element | L: long allele; it was associated with increased gene transcriptional efficiency and exists as LA and LG (low-expressing)<br>S: short allele; it was associated with reduced gene transcriptional activity and is therefore considered low-expressing | Suicidal behaviour | Meta-analysis of 12 studies (three studies of completed/nine studies of attempted suicide; 1168 suicidal cases versus 1371 healthy controls)<br>Results: S allele was proven a risk factor for suicide attempt (Anguelova et al. 2003) |
| | | | | | 1. Meta-analysis of 18 studies (1521 suicide attempters and completers versus 2429 healthy controls)<br>Results: no association; subanalysis of 15 studies of only Caucasian populations revealed again no association |
| | | | | | 2. Meta-analysis of two studies of patients with a schizophrenia spectrum disorder (146 suicide attempters and 374 non-attempters) and two studies of patients with alcohol dependence (107 suicide attempters and 166 non attempters), leading to a meta-analysis of four studies altogether (258 suicide attempters versus 291 non-attempters)<br>Results: S allele was proven a risk factor for suicide attempt in patients diagnosed with the same psychiatric disorders (the association was significant only in patients with alcohol dependence, when diagnostic categories were considered separately) |
| | | | | | 3. Meta-analysis of five studies (190 violent attempters/suicide completers versus 733 healthy controls)<br>Results: association between S allele and violent suicide behaviour (no association when non-violent attempters were compared with healthy controls) (Lin and Tsai 2004) |

| Gene (chromosome location) | Encoded protein | Polymorphisms | Alleles | Behavioural phenotype | Meta-analyses |
|---|---|---|---|---|---|
| | | | | | Meta-analysis of 39 studies (3096 suicidal cases versus 5936 healthy controls)<br>Results: overall association between 5-HTTLPR polymorphism and suicidal behaviour, independent of psychiatric diagnoses (Li and He 2007) |
| | | | | | Meta-analysis of 31 studies (6324 suicidal cases versus 10,285 healthy controls)<br>Results: no overall association<br>Subanalysis of 25 studies of suicide attempters revealed an association between S allele and suicide attempt (S allele increased risk for suicide attempt by 13%)<br>Subanalysis of six studies of suicide completers revealed no association (Clayden et al. 2012) |
| | | | | Aggressive/ antisocial behaviour | Meta-analysis of 18 studies (case and healthy control number not mentioned)<br>Results: S was proven a risk allele for broadly defined antisocial behaviour (Ficks and Waldman 2014) |
| | | | | Trait anxiety | Meta-analysis of 26 studies (7657 participants)<br>Results: no association (slight association, provided the fact that trait anxiety was assessed by a particular scale addressing the five-factor model of personality) (Schinka et al. 2004) |
| | | STin2, 17 bp repeat element | STin2.9: contains nine copies<br>STin2.10: contains ten copies<br>STin2.12: contains 12 copies and constitutes a more potent positive transcriptional regulator | Suicidal behaviour | Meta-analysis of 10 studies (case and healthy control number not mentioned)<br>Results: no association (Li and He 2007) |

**Table 9.4** Serotonin receptor gene polymorphisms and behaviour

| Gene (chromosome location) | Encoded protein | Polymorphisms | Alleles | Behavioural phenotype | Meta-analyses |
|---|---|---|---|---|---|
| 5-HTR1A (5q11.2–13) | Serotonin 1A receptor | rs6295: C(-1019)G SNP | C G: it was associated with higher receptor expression | Suicidal behaviour | Meta-analysis of four studies (three Caucasian/one Asian population; 957 suicidal cases versus 957 healthy controls) Results: no association, even when only suicide completers were included in analysis (Angles et al. 2012) |
| | | | | | Meta-analysis of six studies (2022 suicidal cases versus 2135 healthy controls) Results: no association (Clayden et al. 2012) |
| | | | | | Meta-analysis of nine studies (seven Caucasian/one Asian/one Mexican population; 2366 suicidal cases versus 2943 healthy controls) Results: no association, even when only Caucasians were included in analysis (Gonzalez-Castro et al. 2013a, b) |
| 5-HTR1B (6q14.1) | Serotonin 1B receptor | rs6296: G861C SNP | G: G/G genotype was associated with higher receptor binding C | Suicidal behaviour | Meta-analysis of seven studies (789 suicidal cases versus 1247 healthy controls) Results: no association (Kia-Keating et al. 2007) |
| | | | | | Meta-analysis of ten studies (2947 suicidal cases versus 4066 healthy controls) Results: no association, even when suicide completers were excluded from analysis (Clayden et al. 2012) |

| | | | | | |
|---|---|---|---|---|---|
| 5-HTR2A (13q14–q21) | Serotonin 2A receptor | rs6313: T102C SNP | T<br>C | Suicidal behaviour | Meta-analysis of nine studies (three studies of suicide attempters; 596 suicidal cases versus 1003 healthy controls)<br>Results: no association (Anguelova et al. 2003) |
| | | | | | Meta-analysis of 25 studies (1954 suicidal cases versus 2860 healthy controls)<br>Results: no association, even when analysing different subgroups, e.g. Europeans, Asians, suicidal ideation versus healthy controls, suicide attempt versus healthy controls, violent versus non-violent, etc. (Li et al. 2006) |
| | | | | | Meta-analysis of 18 studies (3759 suicidal cases versus 5692 healthy controls)<br>Results: no association, even when suicide completers were excluded from analysis (Clayden et al. 2012) |
| | | | | | Meta-analysis of 23 studies [2566 suicide attempters and completers versus 3989 healthy controls, as well as 612 suicidal cases and 1129 healthy controls included in a previous meta-analysis (Li et al. 2006); 13 Caucasian/six Asian/four populations of other ethnic origin]<br>Results: no association, even when Caucasian and Asian populations, as well as schizophrenia patients, were analysed separately (Gonzalez-Castro et al. 2013a) |
| | | | | | Meta-analysis of 13 studies [1729 suicide attempters diagnosed with a psychiatric disorder (710 Asians/1019 European-Americans); 1794 non-suicide attempters diagnosed with a psychiatric disorder (759 Asians/920 European-Americans); 2398 healthy controls (906 Asians/1492 European-Americans)]<br>Results: no association when suicide attempters were compared with healthy controls, even when data were analysed separately based on ethnicity<br>No association when suicide attempters were compared with non-attempters diagnosed with the same psychiatric disorders, even when data were analysed separately based on ethnicity<br>Analysis taking psychiatric diagnosis into consideration revealed an association between C/C genotype and suicide attempt in schizophrenia patients. Genotype C/C was not proven a risk factor for suicide attempt in bipolar and in patients with alcohol dependence (Wang et al. 2015) |
| | | rs6311: G-1438A SNP | G<br>A | Suicidal behaviour | Meta-analysis of seven studies (six Asian populations, further data not shown)<br>Results: genotypic analysis with allele A combined [(AA+AG)/GG] revealed an association with suicidal behaviour (Li et al. 2006) |
| 5-HTR2C (Xq23) | Serotonin 2C receptor | rs6318: C68G SNP | C<br>G | Suicidal behaviour | Meta-analysis of seven studies (2297 suicidal cases versus 3431 healthy controls)<br>Results: no association (Clayden et al. 2012) |

**Table 9.5** TPH1 gene polymorphisms and behaviour

| Gene (chromosome location) | Encoded protein | Polymorphisms | Alleles | Behavioural phenotype | Meta-analyses |
|---|---|---|---|---|---|
| TPH1 (11p15.1) | Tryptophan hydroxylase, isoform 1 | rs1800532: A218C SNP | 218A (U allele) 218C (L allele) | Suicidal behaviour | Meta-analysis of seven studies (Caucasian populations only; 898 suicide attempters and completers versus 1179 healthy controls)<br>Results: association between 218A allele and suicide-related behaviours (Rujescu et al. 2003b) |
| | | | | | Meta-analysis of seven studies (Caucasian populations only; 860 suicidal cases versus 1279 healthy controls)<br>Results: association between 218A allele and suicide-related behaviours (Bellivier et al. 2004) |
| | | | | | Meta-analysis of 21 studies (4829 suicidal cases versus 7945 healthy controls)<br>Results: no overall association; association between 218A allele and suicide attempt (Clayden et al. 2012) |
| | | rs1799913: A779C SNP | 779A (U allele): it was associated with lower CSF 5-HIAA levels 779C (L allele) | Suicidal behaviour | Meta-analysis of eight studies (1512 suicidal cases versus 3408 healthy controls)<br>Results: no association (Clayden et al. 2012) |
| | | rs1800532 (A218C SNP) together with rs1799913 (A779C SNP) | Described above | Suicidal behaviour | 1. Meta-analysis of 15 studies of A218C and/or A779C (3585 suicide attempters and completers versus 2295 healthy controls)<br>Results: no overall association<br>2. Meta-analysis of nine studies of psychiatric patients (two alcohol dependence/seven major depression, bipolar disorder and schizophrenia; 625 suicide attempters versus 1475 non-attempters)<br>Results: no association (Lalovic and Turecki 2002) |
| | | | | | Meta-analysis of 34 studies of A218C and/or A779C (3922 suicidal cases versus 6700 healthy controls)<br>Results: overall association between A218C/A779C SNPs and suicidal behaviour (different alleles implicated, based on different study characteristics) (Li and He 2006) |
| | | | | | Meta-analysis of 13 studies of psychiatric patients (three schizophrenia/two bipolar disorder/two major depression/three alcohol dependence/one borderline personality disorder/two mixed diagnoses; 1272 suicide attempters versus 1727 non-suicide attempters)<br>Results: no association, independent of mental health status (Saetre et al. 2010) |

#### 9.2.1.1 Monoamine Oxidase A Gene (MAOA)

**The MAOA Gene Polymorphism**

The monoamine oxidase A, MAO-A, is a mitochondrial enzyme in neuronal presynaptic terminals, implicated in the degradation of biogenic amines, i.e. the neurotransmitters dopamine, serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine, after reuptake from the neuronal synaptic cleft. Decreased brain MAO-A levels were associated with impulsive aggression and mental retardation in a study of a Dutch family and specifically in male carriers of a MAOA gene mutation (C936T MAOA stop codon) of maternal origin (Brunner et al. 1993a,b). Additionally, low MAO-A activity in different cortical and subcortical regions detected by positron emission tomography was related to trait aggression, accounting for more than 30% of variance (Alia-Klein et al. 2008).

The MAOA gene, linked to the short arm of X chromosome (Xp11.3), is mainly expressed in catecholaminergic neurons (Hunter 2010). There is a functional polymorphism within the gene's promoter region, located 1.2 kb upstream of the MAOA coding region. This length polymorphic region (MAOA-LPR), a VNTR (MAOA-uVNTR) consisting of a specific 30 bp nucleotide sequence repeated 2, 3, 3.5, 4 or 5 times, was shown to influence gene's transcriptional activity. It was reported that high-activity MAOA gene variants (MAOA-H), containing alleles with 3.5 or 4 copies, were transcribed 2–10 times more efficiently than low-activity MAOA gene variants (MAOA-L), containing alleles with 2, 3 or 5 copies. Thus, the nucleotide repeat number was shown to affect MAO-A enzyme abundance, since MAOA-H genotype was associated with higher, while MAOA-L genotype with reduced MAO-A expression and therefore increased synaptic serotonin levels (Sabol et al. 1998; Buckholtz and Meyer-Lindenberg 2008; Guo et al. 2008).

**The MAOA-uVNTR Polymorphism and Behaviour/Personality**

The MAOA-L allele was associated with personality traits related to aggressiveness and impulsivity in a community male sample (Manuck et al. 2000). Furthermore, it was suggested that MAOA-L allele association with trait aggression in both healthy males and females may be mediated by increased sensitivity towards negative experiences (Eisenberger et al. 2007). The MAOA-L allele was also associated with antisocial and aggressive/violent behaviour in different psychiatric populations, such as in patients diagnosed with substance abuse and cluster B personality disorders (Reif et al. 2007), as well as in male criminal alcoholics with increased CSF testosterone levels (Sjoberg et al. 2008).

The MAOA genotype was shown to moderate the effects of childhood maltreatment on the manifestation of antisocial behaviour in adulthood. Specifically, male MAOA-L carriers with a background of childhood maltreatment were more prompt to the development of antisocial behaviour compared with male MAOA-H carriers. This was the outcome of a core longitudinal study, emphasising the combined effect of genetic and environmental factors on behavioural outcome (Caspi et al. 2002). Further studies of gene-environment interactions showed that the MAOA-L genotype predicted aggressive behaviour in males with a history of traumatic life events,

e.g. separation from parents or family violence, especially during the first 15 years of life (Frazzetto et al. 2007), the presence of at least one short MAOA allele (MAOA-L, 2 or 3 copies) in males and one or two long MAOA alleles (MAOA-H, 3.5, 4 or 5 copies) in females was associated with higher levels of delinquency in adolescents with a history of maltreatment (Aslund et al. 2011), and MAOA-L genotype was associated with aggressive behaviour in males under high provocation (McDermott et al. 2009).

On the other hand, MAOA-L was proven a risk allele for violent behaviour in a population of psychiatric patients, independent of childhood adversity (Reif et al. 2007), while others found no interaction between MAOA genotype and childhood adversity (Haberstick et al. 2005; Huizinga et al. 2006). Lastly, there were studies that did not find an association between MAOA genotype and aggressive/antisocial behaviour at all (Haberstick et al. 2005; Jacob et al. 2005; Widom and Brzustowicz 2006; Prichard et al. 2007a; Weder et al. 2009).

Altogether, different meta-analyses revealed an association between MAOA-L allele and aggressive/violent/antisocial behaviour, while MAOA-H was shown to be the low-risk allele. The first one, a meta-analysis of five independent studies (around 2570 males), reported that childhood adversity (domestic violence, parental neglect, physical or sexual abuse, harsh discipline, etc.) was associated with antisocial behaviour in male MAOA-L genotype carriers (Kim-Cohen et al. 2006). A subsequent meta-analysis of 31 studies confirmed MAOA-L as a risk allele for aggressive and antisocial behaviour (Ficks and Waldman 2014). Lastly, a more recent extended meta-analysis investigated the effect of the interaction between childhood adversity and MAOA genotype on later manifestation of aggressive-antisocial behaviour in both males and females. The meta-analysed studies were mainly conducted in non-clinical populations. Firstly, 20 studies of strictly male or mixed male-female samples (11,064 participants) were meta-analysed. Results revealed that male MAOA-L carriers with a background of childhood maltreatment and other adversities exhibited higher levels of aggression/violence, non-violent antisocial behaviour as well as aggressive/violent antisocial behaviour during childhood/adolescence, as well as during adulthood. When early environmental adversity was more closely investigated, it was shown that MAOA-L genotype increased the risk for aforementioned behavioural outcomes specifically in cases of childhood maltreatment (e.g. domestic violence, physical/sexual abuse and parental neglect), and not in cases of other childhood adversities (e.g. separation, marital difficulties, parental psychopathology). Secondly, 12 studies of female populations (7588 participants) were meta-analysed. Overall, results did not reveal any significant interaction between MAOA genotype and maltreatment/other adversities, predicting aggressive/antisocial outcomes. An interaction was observed between MAOA-H genotype and childhood maltreatment in relation with antisocial outcomes. This association depended though on study inclusion and therefore requires further investigation (Byrd and Manuck 2014).

On the other hand, a meta-analysis of five studies (862 suicidal cases versus 1239 healthy controls) investigating the association between MAOA-L (three copies), MAOA-H (four copies) and suicidal behaviour did not reveal any significant associations (Clayden et al. 2012) (Table 9.2).

### 9.2.1.2 Serotonin Transporter Gene (SLC6A4)

#### The SLC6A4 Gene Polymorphisms

The serotonin transporter, SERT or 5HTT, is a monoamine transporter protein at serotonergic neurons' cell body and synaptic terminals, regulating synaptic signalling by removing serotonin from synaptic cleft back to presynaptic neurons.

The transporter is coded for by the gene "solute carrier family 6 member 4" (SLC6A4), located at chromosome 17 (17q11.1–q12) (Nakamura et al. 2000). The polymorphism "5-HTTLPR" constitutes a 20–23 bp repeat element in gene's promoter region (44 bp insertion/deletion), giving rise to up to 14 different alleles (Nakamura et al. 2000). The most common and best studied alleles include the "long" ("L", 16 copies, 528 bp) and the "short" ("S", 14 copies, 484 bp) variant (Heils et al. 1996; Hariri and Weinberger 2003). Homozygosity for the long variant (L/L) was associated with increased transcriptional efficiency compared with the L/S and S/S genotypes (Heils et al. 1996; Cadoret et al. 2003), resulting in higher amounts of serotonin transporter and thus higher serotonin reuptake in blood platelets and lymphoblasts. Contrary, the S allele was associated with reduced SLC6A4 gene transcriptional activity (Lesch et al. 1996; Greenberg et al. 1999), since the S/S genotype corresponded to almost half of SERT protein levels compared with the L/L genotype (Collier et al. 1996). Still, another study reported no association between the 5-HTTLPR genotype and serotonin transporter binding (Jacobsen et al. 2000). Lately, a common polymorphism (rs25531), a single-base substitution (SNP A/G), was reported within the first of two 22 bp imperfect repeats of the L allele. This SNP gives rise to the LA and the LG allele. Thus, together with the S allele, the locus is considered triallelic. The LG allele carries a binding site for a transcription factor (AP2) that possibly suppresses gene expression. Thus, similarly to the S allele, the LG was considered a low-expressing allele (Hu et al. 2006).

Another SLC6A4 gene polymorphism is a 17 bp VNTR in the second intron (STin2), a triallelic polymorphism existing in the form of 9 (STin2.9), 10 (STin2.10) and 12 (STin2.12) copies. Allele STin2.12 was proven a more potent positive transcriptional regulator compared with STin2.10 (MacKenzie and Quinn 1999).

#### The 5-HTTLPR Polymorphism and Behaviour/Personality

Studies of 5-HTTLPR polymorphism in a Japanese (Sakado et al. 2003) and a Korean male population (Lee et al. 2003b) showed that the S/S genotype was associated with higher levels of trait impulsivity compared with the L/S and the L/L genotype. Similarly, in another study of a non-clinical Caucasian population recruited from the University of Oslo, S/S carriers showed higher levels of impulsivity compared with L/S carriers displaying intermediate and L/L carriers displaying lower levels of impulsiveness. The effect of S allele on the expression of impulsivity was sex-dependent, since males were more likely to exhibit impulsiveness (Walderhaug et al. 2010). On the other hand, a study of a non-clinical Caucasian-Brazilian population did not find any association between the 5-HTTLPR polymorphism and impulsivity (Lage et al. 2011).

A study of German suicide completers with undefined psychiatric diagnoses reported an association between the S allele and violent suicide (Bondy et al. 2000a). The same association was reported in another study of suicide attempters (40 with and 11 without a history of a major psychiatric disorder) (Courtet et al. 2001). Contradictory reports supported an association between the L allele and suicidal behaviour within the context of affective disorders (Du et al. 1999), while other studies did not find any association between the 5-HTTLPR polymorphism and suicidal behaviour (Anguelova et al. 2003). A meta-analysis including nine studies of suicide attempters and three studies of suicide completers analysed a total number of 1168 suicidal cases in comparison with 1371 healthy controls. The results supported an association between the S allele and suicidal behaviour. Still, further analysis showed that this association was credited to studies of suicide attempters only, since meta-analysis of 991 suicide attempters confirmed an association between suicidal behaviour and the S allele, while meta-analysis of 177 suicide completers did not (Anguelova et al. 2003). The following meta-analysis of 18 studies (1521 suicidal cases versus 2429 healthy controls) did not find any association between the 5-HTTLPR polymorphism and suicidal behaviour. In order to rule out confounding effects of ethnicity, a separate analysis included only Caucasians. Again, no significant association was revealed. The same meta-analysis focused only on psychiatric patients, comparing patients with and without suicidal behaviour (4 studies of mood disorder patients, 258 suicide attempters versus 291 non-attempters; 2 studies of schizophrenia/schizoaffective patients, 146 suicide attempters versus 374 non-attempters; 2 studies of alcohol-dependent patients, 107 suicide attempters versus 166 non-attempters). The results revealed a significant association between the S allele and suicide attempts in patients with a positive psychiatric history. Lastly, meta-analysis of five studies (190 cases of violent suicide attempters or completers versus 733 healthy controls) revealed a significant association between the S allele and violent suicidal behaviour. Additionally, S allele frequency was higher in violent compared with non-violent suicide attempters (Lin and Tsai 2004). A subsequent meta-analysis of 39 studies (3096 suicidal cases versus 5936 healthy controls) confirmed overall association of the 5-HTTLPR polymorphism and suicidal behaviour, suggesting though that based on study design and genotypic analysis, both the S and the L allele contribute to risk (Li and He 2007). Lastly, an even more recent meta-analysis of 31 studies (6324 suicidal individuals versus 10,285 healthy controls; 25 studies of suicide attempters, 6 studies of suicide completers) confirmed an association between the S allele and suicidal behaviour in attempted suicide only, emphasising once more the phenotypic heterogeneity between suicide attempt and completed suicide. Based on results, the S allele increased risk for suicide attempt by 13% (Clayden et al. 2012).

In regard to aggression, a study reported a significant association between genotypes with low-expressing alleles (S/S, S/LG and LG/LG) and aggressive behaviour in children aged 5–15 years (Beitchman et al. 2006). Another study emphasised the importance of gene-environment interaction, since a highly adverse childhood environment was associated with later manifestation of violent behaviour only in psychiatric patients being S/S and S/L carriers. Vice versa, the L/L genotype was

considered a protective factor against manifestation of violence in adults with a high childhood adverse environment index (Reif et al. 2007). This finding was confirmed in male Caucasian offenders with a history of childhood ADHD. The S allele and the S/S genotype were associated with violent behaviour, explaining 5% of the variance of violent behaviour (Retz et al. 2004). Lastly, a study of a Chinese population of convicted criminals reported an association between the S/S genotype and violent crime, but not antisocial personality disorder (Liao et al. 2004). On the other hand, there were studies that reported no association between the 5-HTTLPR genotype and aggressive behaviour in children (Davidge et al. 2004). Altogether, a recent meta-analysis of 18 studies of the 5-HTTLPR polymorphism confirmed an association between the S allele and the increased risk for antisocial behaviour. Still, the authors noted an effect of publication bias on results, since it was shown that there was a trend towards more publications reporting positive associations (Ficks and Waldman 2014).

Lastly, the S allele (both S/S and S/L genotype) was also associated with neuroticism, reflected by increased trait anxiety (Lesch et al. 1996), specifically within the context of cluster C personality disorders (Jacob et al. 2004). In addition, a study reported an association between the S allele and different aspects of neuroticism, such as trait anxiety, affective temperament (depressive, cyclothymic, irritable and anxious), guilt, hostility and somatisation in a non-clinical Hungarian sample (Gonda et al. 2009). Still, an association between the 5-HTTLPR polymorphism and neuroticism was not always confirmed (Ball et al. 1997). A meta-analysis of 26 studies (7657 subjects) did not reveal a significant association between the 5-HTTLPR genotype and trait anxiety. However, a slight association was indicated, provided the fact that anxiety was assessed by a particular scale addressing the five-factor model of personality (Schinka et al. 2004).

#### The STin2 Polymorphism and Behaviour/Personality

Based on a post-mortem study of Croatia/Southern Slavic suicide victims, the lower activity STin2.10 allele was associated with suicidal behaviour (Jernej et al. 2004). Altogether though, a meta-analysis of ten studies (case and healthy control number were not reported) failed to support an association between the STin2 polymorphism and suicidal behaviour (Li and He 2007).

According to a study of children displaying aggressive behaviour, in several cases within the context of ADHD, oppositional defiant and conduct disorder, STin2.10 allele frequency was significantly lower compared with STin2.12 allele frequency. Still, this difference was not statistically significant when aggressive children were compared with a control population of healthy adults (Davidge et al. 2004).

The STin2 polymorphism was also studied in relation to different personality traits, measured by the Eysenck Personality Inventory and the TCI. Carriers of the 10-repeat allele scored lower in neuroticism and harm avoidance, while they scored higher in extraversion. Contrary to STin2.10 carriers, STin2.12 carriers scored higher in harm avoidance and lower in extraversion and novelty seeking (Kazantseva et al. 2008) (Table 9.3).

### 9.2.1.3 Serotonin Receptor Genes

#### The Serotonin Receptor 1A Gene (5-HTR1A)

The serotonin receptor family includes at least 14 different 5-HT receptors (Hoyer et al. 2002). The serotonin receptor 5-HTR1A is a protein regulating serotonin release by functioning both as a presynaptic autoreceptor in dorsal and medial raphe nuclei serotonergic neurons and a postsynaptic heteroreceptor in non-serotonergic neurons.

The 5-HTR1A receptor is encoded by a gene located at chromosome 5 (5q11.2–13) (Kobilka et al. 1987). There is a common functional SNP (rs6295) in 5-HTR1A gene promoter, C(-1019)G (Wu and Comings 1999). The G allele was associated with higher receptor expression, leading to increased negative feedback inhibition in raphe nuclei serotonergic neurons (mediated by 5-HTR1A autoreceptors) and thus decreased serotonergic activity (Lemonde et al. 2003).

In a study of a Hungarian population, G/G carriers displayed significantly higher impulsivity levels, compared with G/C and C/C carriers (Benko et al. 2010).

The G allele was also recognised as a risk factor for completed suicide in a population of French-Canadian origin (Lemonde et al. 2003) and for suicide attempt in a Polish study (Sawiniec et al. 2007). Still, the latter association was not supported in Ukrainian families of suicide attempters (probands and both parents) (Wasserman et al. 2006) and in a Mexican population of suicide attempters (Gonzalez-Castro et al. 2013b).

The first meta-analysis of four studies of the C(-1019)G polymorphism in relation to suicidal behaviour (three Caucasian and one Asian population; 957 suicidal cases versus 957 healthy controls) did not find any association between the G risk allele and suicidal behaviour (Angles et al. 2012). Lack of an association was confirmed in a subsequent meta-analysis of six studies (2022 suicidal cases versus 2135 healthy controls) (Clayden et al. 2012), as well as in a more recent meta-analysis of nine studies (seven Caucasian, one Asian and one Mexican population; 2366 suicidal cases versus 2943 healthy controls) (Gonzalez-Castro et al. 2013b).

Furthermore, the C(-1019)G polymorphism was investigated in relation with personality traits. The G allele was associated with different anxiety- and depression-related personality traits, such as neuroticism and harm avoidance, in a non-clinical German population (Strobel et al. 2003), though such an association was not always supported (Koller et al. 2006). Another study also failed to report an association between the C(-1019)G polymorphism and different personality traits in a German population of suicide attempters and healthy controls, as well as in an Italian population of patients diagnosed with a mood disorder (Serretti et al. 2009).

Lastly, a few studies of other SNPs, such as *Pro16Leu* (rs1800041, amino acid proline is substituted by amino acid leucine at codon 16), Gly272Asp (rs1800042, amino acid glycine is substituted by amino acid aspartic acid at codon 272) (Anguelova et al. 2003) as well as a C to T transition (rs878567) (Gonzalez-Castro et al. 2013b), did not reveal an association with suicidal behaviour.

### The Serotonin Receptor 1B Gene (5-HTR1B)

The serotonin receptor 5-HTR1B is a protein functioning both as a presynaptic autoreceptor in serotonergic neurons, as well as a postsynaptic heteroreceptor in non-serotonergic neurons. The activation of 5-HTR1B autoreceptor modulates neuronal function by inhibiting serotonin release, preventing neuron's overstimulation. There is evidence that 5HTR1B heteroreceptors modulate offensive aggression (Olivier and van Oorschot 2005).

The 5-HTR1B receptor is coded for by a short intronless gene located at chromosome 6 (6q14.1). Several gene polymorphisms have been described, among which a G861C SNP (rs6296). Although G861C is a silent SNP, it is in LD with other functional polymorphisms. There is some evidence that G861C, or another allele in LD with G861C, affects receptor binding (Sanders et al. 2002). Based on a post-mortem study, homozygosity for the G allele was associated with higher receptor binding compared with the G/C heterozygous genotype (Huang et al. 1999).

Although a study found an association between the G allele and history of suicidal behaviour within the context of personality disorders (New et al. 2001), other studies of the G861C SNP did not prove 5-HTR1B a risk gene for manifestation of suicidal behaviour in a Japanese (Nishiguchi et al. 2001), a German (Rujescu et al. 2003c) and a Slavic/Croatian population (Stefulj et al. 2004b). Altogether, lack of an association between the G861C polymorphism and suicidal behaviour was confirmed by a meta-analysis of seven studies (789 suicidal cases versus 1247 healthy controls), in which results were not affected by study heterogeneity, age, gender or ethnicity (Kia-Keating et al. 2007), as well as by a meta-analysis of ten studies (2947 suicidal cases versus 4066 healthy controls) (Clayden et al. 2012).

A study of children displaying aggressive behaviour, in several cases within the context of ADHD, oppositional defiant and conduct disorder, reported a trend towards higher C allele frequency in these children compared with a control population of healthy adults (Davidge et al. 2004), an observation that requires though further verification. Increased C allele frequency was also observed in a Finnish cohort of antisocial alcoholics compared with non-antisocial alcoholics and healthy controls (Lappalainen et al. 1998). Contrary, a previous post-mortem study did not reveal an association between the G861C genotype and pathological aggression (Huang et al. 1999).

### The Serotonin Receptor 2A Gene (5-HTR2A)

The serotonin receptor 5-HTR2A is a G *protein*-coupled receptor, regulated by many different interacting proteins and distributed in many different central nervous system areas. This receptor has been implicated in the manifestation of affective and cognitive disorders (Zhang and Stackman Jr. 2015).

The receptor is encoded by the 5-HTR2A gene located at chromosome 13 (13q14–q21). There is a silent SNP in exon 1 (rs6313) as a result of a T/C substitution at position 102. The polymorphism T102C is in almost complete LD with the promoter G-1438A SNP (rs6311), which is also non-functional. Still, a post-mortem study of suicide victims and healthy controls showed that the T102C and the G-1438A SNP affected serotonin binding in both study groups. Specifically, the

haplotype 102T/-1438A was associated with increased serotonin binding compared with the haplotype 102C/-1438G (Turecki et al. 1999). Other 5-HTR2A gene SNPs include rs6314 (within gene's coding region; amino acid histidine is substituted by amino acid tyrosine at codon 452, His452Tyr), rs7322347 (an intron 2 SNP, T/A), rs643627 (A/G) and rs594242 (C/G).

Studies of the association between the T102C polymorphism and suicidal behaviour were rather controversial, indicating the C as the risk allele (Zhang et al. 1997), T as the risk allele (Gonzalez-Castro et al. 2013a, b) or no association at all (Bondy et al. 2000b). A meta-analysis of nine studies (596 suicidal attempters and completers versus 1003 healthy controls) did not find any association between the T102C polymorphism and suicidal behaviour (Anguelova et al. 2003). A subsequent meta-analysis of 25 studies (1954 suicidal cases versus 2860 healthy controls) investigated the association between the T102C polymorphism and suicidal behaviour performing several subanalyses, e.g. Europeans only, Asians only, suicidal ideation versus healthy controls, suicide attempt versus healthy controls, violent versus non-violent, etc. Overall, study findings did not support an association between the T102C polymorphism and suicidal behaviour (Li et al. 2006). Lack of an association was confirmed by another meta-analysis of 18 studies (3759 suicidal cases versus 5692 healthy controls) (Clayden et al. 2012).

An even more recent meta-analysis of 23 studies, including 2566 suicide attempters and completers versus 3989 healthy controls (13 Caucasian, 6 Asian and 4 populations of other ethnic origin), as well as 612 suicidal cases and 1129 healthy controls included in a previous meta-analysis (Li et al. 2006), reported no association between the T102C polymorphism and suicidal behaviour, after using allelic models for both C and T allele. No associations were found even when Caucasian and Asian populations were analysed separately, as well as when only schizophrenia patients were considered (Gonzalez-Castro et al. 2013a). A latest meta-analysis of 13 studies [1729 suicide attempters diagnosed with a psychiatric disorder (710 Asians/1019 European-Americans); 1794 non-suicide attempters diagnosed with a psychiatric disorder (759 Asians/920 European-Americans); 2398 healthy controls (906 Asians/1492 European-Americans)] conducted two separate analyses. In the first one, suicide attempters were compared with healthy controls. Results indicated that the C/C genotype was not associated with suicide attempt, even when data was analysed separately based on ethnicity. In the second analysis, suicide attempters were compared with non-attempters diagnosed with the same psychiatric disorders. Again, there was no association between the T102C polymorphism and suicide attempt, even when different ethnic groups were analysed separately. Still, when data was analysed separately based on psychiatric diagnosis, the C/C genotype was proven a risk factor for suicide attempt in schizophrenia patients. On the other hand, this association was confirmed neither in bipolar patients nor in patients with alcohol dependence (Wang et al. 2015).

Although a few data on other polymorphisms, such as His452Tyr and G-1438A, did not reveal an association between 5-HTR2A gene polymorphisms and suicidal behaviour (Anguelova et al. 2003), a meta-analysis of seven studies (six Asian populations) conducting genotypic analysis with the G-1438A SNP allele A combined

[(AA+AG)/GG] reported a significant association with suicidal behaviour (Li et al. 2006). The G-1438A polymorphism was also not associated with different personality traits, such as novelty seeking and harm avoidance. Still, an association was found between the A-1438A genotype and impulsive behaviour assessed by a behavioural task (go/no-go task) in healthy Japanese study participants (Nomura et al. 2006), as well as contradictory evidence for an association between the A-1438A genotype and low levels of impulsive behaviour in a German population of patients with alcohol dependence. The latter association was independent of the presence of comorbidity with a personality disorder (Preuss et al. 2001).

Another study of a non-clinical Caucasian Hungarian population investigated the relation between a set of different 5-HTR2A SNPs and aggressive traits. An association was reported between the intronic SNP T/A (rs7322347) and aggressive traits, in such T/T genotype carriers displayed more aggressive traits compared with allele A carriers (Banlaki et al. 2015).

Lastly, a study of German suicide attempters, diagnosed with an affective, schizophrenia spectrum or borderline personality disorder, searched for an association between different 5-HTR2A gene polymorphisms (rs643627, rs594242 and rs6311) and inwardly/outwardly state and trait anger, as well as aggressive behaviour. Results showed that the A-C-T haplotype (polymorphism/allele, rs643627/A, rs594242/C and rs6311/T), the C-T haplotype (polymorphism/allele, rs594242/C and rs6311/T) and the T allele (rs6311) decreased risk for suicidal behaviour. Additionally, the rs6311 SNP was associated with trait anger, in such the risk genotype C/C was related to higher levels of trait anger, specifically anger turned inwards. Additionally, the C allele was associated with decreased aggressive behaviour inhibition (Giegling et al. 2006).

#### The Serotonin Receptor 2B Gene (5-HTR2B)

The serotonin receptor 5-HTR2B is a G protein-coupled receptor coded for by a gene located at chromosome 2 (2q36.3–q37.1) and expressed, among others, in the brain (Bonaventure et al. 2002). Its function is currently under investigation, although presynaptic 5-HTR2B receptors were shown to regulate serotonin reuptake (Launay et al. 2006) and were also implicated in mesolimbic dopaminergic activity modulation (Auclair et al. 2010).

There is a functional stop codon (C20T, Q20*), most probably limited to the Finnish population, causing RNA decay and 5-HTR2B expression blockage. In a study of a Finnish population of violent criminal offenders, Q20* carriers showed no cognitive deficits and committed crimes mediated by high impulsivity levels (Bevilacqua et al. 2010).

#### The Serotonin Receptor 2C Gene (5-HTR2C)

The serotonin receptor 5-HTR2C is again a G protein-coupled receptor, implicated among others in mood, anxiety and reproductive behaviour regulation. The receptor is coded for by a gene located at X chromosome (Xq23). There is a SNP (rs6318) in the gene's coding region, C68G, leading to an amino acid substitution (cysteine is substituted by serine at codon 23, Cys23Ser).

Although one study indicated an association between the serine variant and trait impulsiveness in males displaying repeatedly self-harming behaviour (Evans et al. 2000), another study of suicide completers belonging to two different ethnicities, German and Slavic, did not reveal any association between the C68G SNP and suicidal behaviour (Stefulj et al. 2004a). Absence of an association between the C68G polymorphism and suicidal behaviour was confirmed by a recent meta-analysis of seven studies (2297 suicidal cases versus 3431 healthy controls) (Clayden et al. 2012).

Lastly, a study of a German population of suicide attempters and healthy controls, as well as of Italian patients diagnosed with a mood disorder, did not reveal an association between the C68G polymorphism and different personality traits (Serretti et al. 2009) (Table 9.4).

#### 9.2.1.4 Tryptophan Hydroxylase 1 Gene (TPH1)

##### The TPH1 Gene Polymorphisms

Tryptophan hydroxylase, TPH, is an enzyme that regulates serotonin availability by catalysing the rate-limiting step in serotonin biosynthesis. The isoform 1, TPH1, is coded for by TPH1 gene, located at chromosome 11 (11p15.1), and is expressed in a variety of tissues. Still, there are contradictory results regarding its expression in the brain (Zill et al. 2007; Gutknecht et al. 2009).

There is a SNP (rs1800532) in intron 7, A218C. The 218A allele is also referred to as "upper"/U allele and constitutes the minor allele, while the 218C is also referred to as "lower"/L allele. Originally, the A218C SNP was not shown to alter TPH1 amino acid sequence (Nielsen et al. 1997). Later, and based on a post-mortem study of suicide victims and healthy controls, 218A allele was considered the high activity allele, since it was associated with significantly higher TPH1 immunoreactivity. Still, the A218C polymorphism was not shown to affect only TPH1 production but 5-HTR2A receptor regulation as well, since the 218A allele was associated with decreased 5-HTR2A receptor density. (Ono et al. 2002).

Another SNP (rs1799913) in intron 7 is the A779C transversion. Accordingly, the allele 779A is referred to as U allele and was related to lower CSF 5-HIAA levels in healthy males (Jonsson et al. 1997), while the allele 779C is referred to as L allele. The A779C SNP, which was also not shown to alter TPH1 amino acid sequence (Nielsen et al. 1997), is in almost complete LD with the A218C SNP in Caucasian populations (alleles 218C and 779C are in phase).

##### The A218C Polymorphism and Behaviour/Personality

Altogether, studies of the A218C SNP in relation to suicidal behaviour led to great discrepancy both in Caucasian, as well as in Asian populations (Rujescu et al. 2003b). The 218A allele was associated with suicidal behaviour within the context of affective (Mann et al. 1997; Souery et al. 2001) and other psychiatric disorders (Abbar et al. 2001), although the latter finding was not confirmed in Caucasian suicide completers of French-Canadian origin (Turecki et al. 2001), in a family-based study of Israeli adolescent suicide attempters diagnosed with different psychiatric

disorders (Zalsman et al. 2001) as well as in a German population of suicide attempters diagnosed with different psychiatric disorders (Rujescu et al. 2003b). On the contrary and based on a post-mortem study of Croatia/Southern Slavic suicide victims, it was the lower activity 218C allele that was associated with suicidal behaviour, especially in combination with the lower ten repeat allele of STin2 (SLC6A4 gene) polymorphism (Jernej et al. 2004).

A meta-analysis of seven studies of Caucasian populations only (898 suicidal cases versus 1179 healthy controls) revealed an association between the 218A allele and suicide-related behaviours (Rujescu et al. 2003b). A subsequent study restricted again to Caucasian populations meta-analysed data from seven studies (860 suicidal cases versus 1279 healthy controls), confirming the association between the 218A allele and suicidal behaviour (Bellivier et al. 2004). A more recent meta-analysis of 21 studies (4829 suicidal cases versus 7945 healthy controls) confirmed partly previous outcomes, since results indicated that the 218A allele was associated only with suicide attempt, and not with completed suicide (Clayden et al. 2012).

Furthermore, homozygosity for the 218A allele was associated with higher aggression and more intense tendency towards unprovoked anger in males (Manuck et al. 1999), as well as with higher levels of proactive aggression (Hennig et al. 2005). The 218A allele was also associated with trait anger, state anger and anger temperament in a German population (Rujescu et al. 2002).

#### The A779C Polymorphism and Behaviour/Personality

Although evidence was provided for an association between the 779C allele and non-impulsive suicide attempts (Nielsen et al. 1998), results regarding the implication of both A779C and A218C polymorphisms in the manifestation of suicidal behaviour were altogether rather controversial. A meta-analysis of 15 studies (1290 suicide attempters/completers versus 2295 healthy control subjects) investigating the A779C and/or the A218C polymorphism in relation to suicidal behaviour revealed no significant associations. The same meta-analysis searched for an association between the two TPH1 SNPs and suicidal behaviour only in patients with psychiatric diagnoses (9 studies; 625 suicide attempters versus 1475 non-attempters), confirming absence of any association between the SNPs and suicidal behaviour (Lalovic and Turecki 2002). Previous results were confirmed by a meta-analysis of 13 studies (1272 suicide attempters, 1727 non-suicide attempters, all participants were diagnosed with a psychiatric disorder), which did not find any association between the A779C/A218C polymorphisms and suicidal behaviour (Saetre et al. 2010).

Contradictory results were provided by a subsequent meta-analysis of 34 studies (3922 suicidal cases versus 6700 healthy controls), which reported a strong overall association, regardless of alleles, between the TPH1 A779C/A218C polymorphisms and suicidal behaviour. The same meta-analysis revealed though no association between the promoter A-6526G SNP (rs4537731) and suicidal behaviour (Li and He 2006). Lastly, a more recent meta-analysis of eight studies (1512 suicidal cases versus 3408 healthy controls) found again no association between the A779C polymorphism and suicidal behaviour (Clayden et al. 2012).

Homozygosity for the 779C allele was associated with low CSF 5-HIAA levels in a Finnish population of impulsive alcoholic violent offenders (Nielsen et al. 1994), as well as with impulsive aggression in males diagnosed with personality disorders (New et al. 1998). Lastly, the 779A allele was associated with trait anger, state anger and anger temperament in a German population (Rujescu et al. 2002) (Table 9.5).

#### 9.2.1.5 Tryptophan Hydroxylase 2 Gene (TPH2)

The tryptophan hydroxylase isoform 2, TPH2, is expressed in brain serotonergic neurons. The enzyme is encoded by a gene located at chromosome 12 (12q21.1) (Zill et al. 2007). There is a TPH2 gene SNP, C1473G, which has been studied only in animal models. Homozygosity for the G allele in mouse strains was associated with reduced TPH2 activity and lower 5-HT levels (Zhang et al. 2004b). On the contrary, mice homozygous for the C allele showed higher TPH2 activity, which was associated in turn with higher levels of inter-male aggression (Kulikov et al. 2005).

Although TPH2 SNPs have been studied in relation with psychiatric disorders (Walitza et al. 2005; Zhang et al. 2005), further investigation is required regarding their association with aggressive behaviour in humans (Zhang et al. 2006).

### 9.2.2 Dopaminergic System

The dopaminergic system is involved, among others, in motor control, motivation, emotional stability, reward and cognition. Thus, impulsive, compulsive or addictive behaviours could be related to dopaminergic gene dysregulation.

There is evidence for the implication of dopamine in the manifestation of aggression (de Almeida et al. 2005), since antipsychotic drugs display anti-aggressive effects (Groleger 2007). It has been suggested that dopamine is implicated in the initiation of aggressive behaviour, whereas serotonin in its termination (Olivier and van Oorschot 2005). On the contrary, novelty and sensation seeking were associated with lower dopamine system activity (Cloninger 1986). The Table 9.6 presents meta-analyses of studies investigating dopaminergic genes in relation with behaviour and personality.

#### 9.2.2.1 Dopamine Receptor Genes

##### The Dopamine 2 Receptor Gene (DRD2)

Dopamine's function is mediated by dopamine receptors, among which the dopamine 2 receptor, D2R, also known as the "antipsychotic dopamine receptor", since it constitutes the main target receptor of all antipsychotic drugs.

The D2R receptor is encoded by the DRD2 gene, located at chromosome 11 (11q22–q23). There is a DRD2 gene TaqI restriction fragment length polymorphism (RFLP), giving rise to alleles A1 and A2 (Grandy et al. 1989). Its functional significance has not been fully elucidated yet. Different studies reported an association

**Table 9.6** Dopaminergic gene polymorphisms and personality/behaviour

| Gene (chromosome location) | Encoded protein | Polymorphisms | Alleles | Behavioural phenotype | Meta-analyses |
|---|---|---|---|---|---|
| DRD4 (11p15.5) | Dopamine 4 receptor | 48 bp VNTR | S: short alleles, 2R-5R<br>L: long alleles, 6R-10R | Novelty seeking | Meta-analysis of 20 studies (3907 individuals)<br>Results: no association (Kluger et al. 2002) |
| | | | | | 1. Meta-analysis of 14 studies (21 separate samples; 2720 individuals)<br>Results: no association between 7R allele and novelty seeking<br>2. Meta-analysis of ten studies (12 separate samples; 1719 individuals) grouping all long alleles together<br>Results: association between long alleles and novelty seeking (Schinka et al. 2002) |
| | | | | Novelty seeking<br>Extraversion<br>Trait impulsivity | Meta-analysis of 36 independent non-clinical adult samples (around 5600 individuals); included studies had grouped 48 bp VNTR into short and long alleles<br>Results: no association between long alleles and personality traits, even when European samples were analysed separately (Munafo et al. 2008) |
| | | **rs1800955**: C-521T SNP | C<br>T | Novelty seeking | Meta-analysis of four studies (677 individuals)<br>Results: association between C/C genotype and novelty seeking (Schinka et al. 2002) |
| | | | | Novelty seeking<br>Extraversion<br>Trait impulsivity | Meta-analysis of 11 independent non-clinical adult samples (around 1600 individuals)<br>Results: association between C/T and T/T genotype and novelty seeking, as well as trait impulsivity (T allele carriers displayed lower novelty seeking and trait impulsivity levels). No association with extraversion (Munafo et al. 2008) |

(continued)

**Table 9.6** (continued)

| Gene (chromosome location) | Encoded protein | Polymorphisms | Alleles | Behavioural phenotype | Meta-analyses |
|---|---|---|---|---|---|
| COMT (22q11.21) | Catechol-o-methyltransferase | rs4680: G472A SNP (Val158Met) | COMT-L: corresponds to methionine and is associated with low enzyme activity COMT-H: corresponds to valine and is associated with high enzyme activity | Suicidal behaviour | Meta-analysis of 6 studies (519 suicide attempters and completers versus 933 healthy controls) Results: association between COMT-L allele and suicidal behaviour (Kia-Keating et al. 2007) |
| | | | | | Meta-analysis of ten studies (1324 suicidal cases versus 1415 healthy controls) Results: no association (Calati et al. 2011) |
| | | | | | Meta-analysis of 12 studies (2723 suicidal cases versus 1886 healthy controls) Results: no association, even when Caucasians and suicide attempters were analysed separately (Tovilla-Zarate et al. 2011) |
| | | | | | Meta-analysis of nine studies (3226 suicidal cases versus 3055 healthy controls) Results: no association (Clayden et al. 2012) |
| | | | | Aggressive/violent behaviour | Meta-analysis of 15 studies (2370 schizophrenia patients) Results: presence of at least one COMT-L allele increased risk for manifestation of violent behaviour in male schizophrenia patients by around 50% (Singh et al. 2012) |

between the A1 allele and reduced D2 receptor activity in different brain areas (Noble et al. 1997), an association between the A1 allele and decreased receptor density (Pohjalainen et al. 1998) as well as an association between the A1 allele and increased dopamine synthesis, perhaps due to decreased D2R receptor expression (Laakso et al. 2005).

A study of more than 2500 adolescents and young adults showed that contrary to the homozygous A1/A1 and A2/A2 genotype, the heterozygous A1/A2 genotype was associated with serious and violent delinquency only in males (Guo et al. 2007). These findings were discussed within the context of "heterosis". Based on this phenomenon, it is heterozygous rather than homozygous individuals manifesting a trait to a greater or lesser extend (Comings and MacMurray 2000). Elsewhere, the A1 genotype (A1/A1 homozygosity or A1/A2 heterozygosity) was related to aggressive-violent behaviour (Chen et al. 2005).

#### The Dopamine 4 Receptor Gene (DRD4)

The dopamine receptor 4, D4R, is a D2R-like receptor coded for by the DRD4 gene at chromosome 11 (11p15.5). There is a VNTR in exon III, namely, a 48 bp sequence repeated two (2R) to ten (10R) times. Different alleles vary in regard to number of repeats, nucleotide sequence and variant order, leading to different receptor products containing 32–160 amino acids at the corresponding position. Allele frequencies vary greatly between different populations. It was shown that the 4R allele is the most commonly found, together with the 7R and the 2R allele, while alleles 3R, 5R, 6R and 8R are rare. Alleles up to 5R are considered "short", while the rest, including the 7R allele, "long" (Lichter et al. 1993; Chang et al. 1996; Ding et al. 2002). The 7R allele was associated with decreased in vitro gene expression and receptor binding compared with short alleles (Asghari et al. 1994; Asghari et al. 1995).

There is another DRD4 gene polymorphism, namely, a C-521T SNP (rs1800955) in the promoter region, which is in LD with 48 bp VNTR. This SNP was shown to affect gene's transcription, since the T allele was associated with up to 40% lower transcription levels compared with the C allele (Ronai et al. 2001).

Lastly, there is a tandem 120 bp duplication located 1.2 kb upstream from the initiation codon, giving rise to the long (L) and the short (S) allele. It was shown that the S allele was associated with increased transcriptional activity compared with the L allele (D'Souza et al. 2004).

#### The DRD4 48 bp VNTR and Personality

A study of the DRD4 48 bp VNTR and its association with novelty seeking in a non-clinical Israeli population reported that 7R allele carriers scored significantly higher in novelty seeking (Ebstein et al. 1996).

Another study supported an association between the 48 bp VNTR and novelty seeking in a sample of white Americans, mainly male (95%, mostly male siblings). Instead of examining the 7R allele as previously described, participants were subgrouped into long or short allele carriers, and it was shown that long allele carriers displayed higher levels of trait novelty seeking (Benjamin et al. 1996). The same

association was replicated in another healthy female population, recruited from Japan (Ono et al. 1997), as well as in other Asian (Tomitaka et al. 1999; Lee et al. 2003a) and German (Strobel et al. 1999) populations.

Still, there were studies that were not able to confirm aforementioned results (Baron 1998; Lusher et al. 2001). Contradictory findings were also reported, supporting an association between the 5R allele and high novelty seeking in healthy Japanese individuals (Tsuchimine et al. 2009), an association between the short 2R and 5R alleles and high novelty seeking in a Finnish population (Ekelund et al. 1999) as well as no associations at all in a non-clinical Korean (Kim et al. 2006b) and different Japanese populations (Mitsuyasu et al. 2001; Tochigi et al. 2006).

A former meta-analysis of 20 studies (3907 individuals) applied two different meta-analytic methods. The results did not confirm an association between the 48 bp VNTR and novelty seeking (Kluger et al. 2002). Another meta-analysis published shortly after the previous one reviewed data from 14 studies (21 separate samples, 2720 individuals) and revealed no association between the long 7R allele and novelty seeking. The same study meta-analysed data from ten studies (12 separate samples, 1719 individuals) grouping all long alleles together. In this case, results revealed a significant association between long repeat alleles and high novelty seeking (Schinka et al. 2002). Lastly, a more recent meta-analysis included data from 36 independent non-clinical adult samples (around 5600 individuals). The studies included in this meta-analysis had grouped 48 bp VNTR into short and long alleles and investigated them in relation with novelty seeking, extraversion and trait impulsivity. The results showed absence of an association between long alleles and aforementioned traits, even when samples of European origin were analysed separately. Furthermore, this analysis revealed significant heterogeneity between employed studies (Munafo et al. 2008).

In another study of a mixed population consisting of young men recruited from Harvard University, the 7R allele was proven a significant predictor of sensation seeking, including thrill and adventure seeking (Campbell et al. 2010). Similarly, in a Russian study, 7R allele carriers had higher thrill seeking elements, delinquency and short temper. Still, this was observed only in males, while when social parameters (parental monitoring of youths, exposure to violence) were taken into account, the interaction between thrill seeking and the 7R allele, as well as the gender effect, were no longer significant (Dmitrieva et al. 2011).

Lastly, a study of a Japanese population revealed an association between the 2R-4R short alleles and higher neuroticism levels, including anxiety, depression and vulnerability (Tochigi et al. 2006).

### The DRD4 C-521T SNP/120 bp Duplication and Personality

A meta-analysis of four studies (677 individuals) confirmed an association between the C-521T SNP C/C genotype and high novelty seeking (Schinka et al. 2002), a finding that was confirmed by a recent meta-analysis of 11 independent non-clinical adult samples (around 1600 individuals), which reported a significant association between the C-521T SNP and novelty seeking, as well as impulsivity. Namely, T allele carriers (C/T or T/T genotype) displayed lower levels of aforementioned

traits, while the C-521T SNP accounted for 2% of the phenotypic variance. Still, the latter polymorphism was not related to extraversion (Munafo et al. 2008).

Lastly, a study of the tandem 120 bp duplication in regard to novelty seeking was performed in four different clinical samples, one diagnosed with bipolar disorder, one with alcohol dependence and two with depression. Combined data revealed an association with novelty seeking. Specifically, individuals genotyped as S/S scored higher in novelty seeking, including impulsivity, extravagance and disorderliness. Still, due to the fact that the S allele is rare, one could assume that it would not contribute greatly to population variance (Rogers et al. 2004) (Table 9.6).

#### 9.2.2.2 Dopamine Transporter Gene (SLC6A3)

##### The SLC6A3 Gene Polymorphism

The dopamine transporter 1, DAT1, is a protein regulating dopamine synaptic levels by limiting dopamine receptor activation and facilitating neuronal dopamine reuptake.

This protein is coded for by the gene "Solute Carrier Family 6, member 3" (SLC6A3), located at chromosome 5 (5p15.3). Several DAT1 gene polymorphisms have been described. Among these, there is a 40 bp VNTR most commonly repeated nine (DAT1*9R) and ten (DAT1*10R) times. Less abundant alleles include 3, 7 and 11 repeats (Vandenbergh et al. 1992). There is evidence that this polymorphism may be functional, altering gene expression (Fuke et al. 2001). Although it was found that healthy DAT1*10R/10R genotype carriers showed lower striatal transporter binding (Jacobsen et al. 2000) and DAT1*9R allele carriers increased striatal dopamine transporter availability (van Dyck et al. 2005), contradictory findings were also reported (Heinz et al. 2000).

##### The DAT1 40 bp VNTR and Behaviour

Contrary to the DAT1*9R/9R genotype, the DAT1*10R/10R and the DAT1*10R/9R genotypes were associated with serious and violent delinquency in males (Guo et al. 2007), as well as with aggressive-violent behaviour (Chen et al. 2005). Still, not all studies were able to confirm an association between the DAT1 genotype and violent behaviour (Reif et al. 2007).

Lastly, DAT1 gene, together with other dopamine-related genes, was implicated in the aetiology of ADHD, which is characterised by impulsive behaviour (Khan and Faraone 2006).

#### 9.2.2.3 Dopamine Beta-Hydroxylase Gene (DBH)

Dopamine beta-hydroxylase, DBH, is an enzyme involved in norepinephrine synthesis by catalysing dopamine hydroxylation. Previous studies showed that low plasma norepinephrine levels were associated with antisocial behaviour (Rogeness et al. 1982; Gabel et al. 1995).

The DBH gene is located at chromosome 9 (9q34.2). There is a C1021T SNP, accounting for about 35–52% of the variance of DBH plasma levels. A German study reported an association between the C1021T SNP and personality traits.

Patients diagnosed with more than two personality disorders and genotyped as T/T displayed higher neuroticism levels, as well as higher levels of neuroticism's facet "anger hostility". The same individuals displayed higher novelty seeking levels, as well as higher levels of novelty seeking's facets "impulsiveness" and "disorderliness" (Hess et al. 2009).

#### 9.2.2.4 Catechol-O-Methyltransferase Gene (COMT)

##### The COMT Gene Polymorphism

Catechol-o-methyltransferase (COMT) is an enzyme catalysing catecholamine methylation. This o-methylation constitutes a major degrading pathway of catecholamine neurotransmitters dopamine, epinephrine and norepinephrine. Brain COMT activity regulates active dopamine and norepinephrine amounts.

The gene coding for COMT is located at chromosome 22 (22q11.21). There is a functional SNP in exon 4 (rs4680, G472A transition), resulting in an amino acid change, i.e. valine is substituted by methionine at codon 158 of membrane-bound COMT (Met158Val) and at codon 108 of soluble COMT (Met108Val). The G472A polymorphism was shown to decrease enzyme thermostability and therefore activity three- to fourfold. Specifically, genetically polymorphic COMT enzyme activity may be low (COMT-LL, corresponding to Met/Met genotype), intermediate (COMT-LH, corresponding to Met/Val genotype) or high (COMT-HH, corresponding to Val/Val genotype). Altogether, carriers of the more active form of the enzyme display less dopamine for neurotransmission (Lachman et al. 1996; Stahl 2003).

##### The G472A Polymorphism and Behaviour/Personality

The COMT-LL genotype was associated with violent suicide attempts (e.g. hanging, shooting, etc.) but not with non-violent (e.g. drug overdose, gas suffocation, etc.) in a German psychiatric population, independent of diagnosis, compared with healthy controls. Additionally, the latter study found a correlation between the COMT genotype and state anger assessed by the State-Trait Anger Expression Inventory. Specifically, the COMT-HH genotype was related to inward anger expression (higher scores in "Anger-In") while the COMT-LL genotype with outward anger expression (higher scores in "Anger-Out") (Rujescu et al. 2003a). Still, an association between the G472A polymorphism and suicidal behaviour was not confirmed in another mixed (mainly Caucasian) (Russ et al. 2000) and in a Mexican population (Tovilla-Zarate et al. 2011).

Altogether, a meta-analysis of six studies (519 suicide attempters and completers versus 933 healthy controls) revealed a significant association between the COMT-L allele and suicidal behaviour, which was not affected by age or ethnicity. Several studies reported though a gender effect on the association between the G472A polymorphism and suicidal behaviour, reporting COMT-L allele to be more abundant in male compared to female suicidal cases. In accordance, aforementioned meta-analytic results were shown to be affected by the proportion of females to males in both suicidal cases and healthy controls, a gender effect that requires further investigation (Kia-Keating et al. 2007). On the contrary, a subsequent meta-analysis of ten

studies (1324 suicidal cases versus 1415 healthy controls) considering both allele frequency and genotype did not report an association between the G472A polymorphism and suicidal behaviour. The meta-analysis of three among ten studies, which compared suicide attempters versus non-suicide attempters diagnosed with the same psychiatric disorders (mood disorders and schizophrenia), showed again lack of any association (Calati et al. 2011). A following meta-analysis of 12 studies (2723 suicidal cases versus 1886 healthy controls) did not find any association between the risk COMT-L allele and suicidal behaviour, even when Caucasians and suicide attempters were analysed separately (Tovilla-Zarate et al. 2011). Lastly, a meta-analysis of nine studies (3226 suicidal cases versus 3055 healthy controls) confirmed lack of an association between the G472A polymorphism and suicidal behaviour (Clayden et al. 2012).

In regard to aggressive behaviour, one study of unselected women showed that COMT-LL carriers displayed lower levels of physical aggression compared with COMT-HH carriers (Kulikova et al. 2008). Altogether, although there was discrepancy in study findings, the G472A polymorphism (in particular COMT-HH genotype) may be associated with aggressive traits [for review see Calati et al. (2011)].

There was one meta-analysis that included 15 studies of the G472A polymorphism in relation with violent behaviour within the context of schizophrenia (2370 schizophrenia patients). Based on results, the presence of at least one COMT-L allele increased risk for violent behaviour in male schizophrenia patients by around 50%. No association was found in females or when data from male and female patients was pooled together (Singh et al. 2012).

Other studies focused on the relation between the COMT genotype and personality traits. There were reports of an association between the COMT-HH genotype and high levels of extraversion, the COMT-HH genotype and the "exploratory excitement" component of novelty seeking in healthy individuals (Reuter and Hennig 2005) as well as the COMT-HH genotype and novelty seeking in a non-clinical female Chinese population (Tsai et al. 2004b). In accordance with previous findings, a study of a non-clinical German population revealed an association between the G472A polymorphism and sensation seeking in females. Specifically, female subjects genotyped as COMT-HH showed higher levels of sensation seeking, including disinhibition, boredom susceptibility and thrill and adventure seeking, compared with subjects genotyped as COMT-LH and COMT-LL (Lang et al. 2007).

Since harm avoidance was correlated inversely with novelty and sensation seeking (McCourt et al. 1993), aforementioned results were not supported by a study of a Korean population, reporting a different association between the COMT genotype and harm avoidance again only in females. Specifically, females carrying the COMT-LL genotype showed the lowest harm avoidance levels, whereas the COMT-LH genotype was associated with intermediate and the COMT-HH with higher harm avoidance levels (Kim et al. 2006c). Lastly, there was some evidence for an association between the COMT-LL genotype and neuroticism in females, which was drawn though from a study employing a selected population (high or low scorers) (Eley et al. 2003).

Altogether, the COMT G472A polymorphism was shown to exhibit a sexually dimorphic effect, relating to personality traits only in females. A plausible explanation could be the correlation between the COMT-HH genotype and low oestrogen levels, which were in turn associated with lower thrill and adventure seeking levels in healthy females (Balada et al. 1993). Still, the latter observation is again not in accordance with previously presented studies [for review of the G472A polymorphism studies in relation to personality traits, see Calati et al. (2011)] (Table 9.6).

### 9.2.3 Genes Involved in Sexual Behaviour

#### 9.2.3.1 Arginine Vasopressin Receptor 1A Gene (AVPR1A)

Arginine vasopressin (AVP), also called "antidiuretic hormone" (ADH), is a hormone regulating body water retain. Recent evidence suggested though that AVP may be also implicated in social, sexual and reproductive behaviour (Insel 2010).

The arginine vasopressin receptor 1 gene, AVPR1A, is located at chromosome 12 (12q14.2), and its polymorphisms have been studied in relation with reproductive behavioural motifs in other mammals (Young 2002). One study extended research of AVPR1A polymorphisms in humans. A large population consisting of 2085 males and females was genotyped at two different gene loci, c.-5518 AVPR1A (TC)x(TG)y and c.-2481 AVPR1A (AGAT)7_16. Alleles were grouped as short, medium and long for each polymorphism, giving rise to six possible genotypes: short/short, short/medium, short/long, medium/medium, medium/long and long/long. It was observed that males genotyped as long/long AVPR1A (TC)x(TG)y and females genotyped as long/long AVPR1A (AGAT)7_16 showed an increased probability of beginning sexual intercourse at an earlier age, i.e. before the age of 15 (Prichard et al. 2007b).

#### 9.2.3.2 Oxytocin Receptor Gene (OXTR)

Oxytocin is a protein involved in attachment processes, such as social, familiar and maternal bonding, as well as in sexual reproduction. Its function is mediated by oxytocin receptor, OXTR, encoded by a gene located at chromosome 3 (3p25.3).

A large population consisting of 2085 males and females was genotyped at gene locus 1170*712 OXTR (CA)10_15. Alleles were grouped as short and long, giving rise to three genotypes: short/short, short/long and long/long. Based on results, it was more probable for females genotyped as long/long not to use oral contraceptives and to have children at a younger age (Prichard et al. 2007b).

### 9.2.4 Other Genes

#### 9.2.4.1 Nitric Oxide Synthase Gene (NOS1)

Nitric oxide, NO, is an abundant neurotransmitter in emotion-regulating brain areas. The neuronal nitric oxide synthase, NOS-I, is coded for by NOS1 gene, located at chromosome 12 (12q24.3). The NOS1 is a complex gene, containing multiple

protein-coding exons, as well as a variable region with multiple first exons (Zhang et al. 2004a).

There is a highly polymorphic CA dinucleotide repeat (180–210 repeats) within the promoter region (exon 1f), termed NOS1 Ex1f VNTR. Alleles containing 180–196 repeats were defined as short/S and were associated with decreased gene expression, while alleles containing 198–210 repeats were defined as long/L and were associated with maximal gene expression. The NOS1 Ex1f VNTR polymorphism was also shown to dysregulate many other different genes (Reif et al. 2009).

A study of more than 3200 probands (mixed population consisting of healthy controls, patients diagnosed with personality disorder or ADHD, suicide attempters and criminal offenders) reported that the S alleles were associated with psychiatric disorders manifesting impulsive behaviour as a common phenotype, such as ADHD and cluster B personality disorders. Additionally, S alleles were associated with suicidal and aggressive/criminal behaviour, phenotypes relating to impulsivity (Reif et al. 2009).

Still, the implication of NOS1 Ex1f VNTR in the manifestation of impulsiveness warrants further research. The same, above-mentioned, research group assessed impulsiveness and empathy in a male population consisting of criminal offenders with a history of a psychiatric disorder but without acute psychopathology. Previous results were not fully replicated, while there were also contradictory outcomes, since it was heterozygous S/L individuals displaying the highest impulsivity levels, a phenomenon previously described as "heterosis". On the other hand, homozygous S/S carriers displayed the lowest impulsiveness levels and the highest empathy levels. Conflicting results were attributed to behavioural phenotypes and measures being related but not identical, as well as to employment of a different study population, in the latter case with high psychiatric comorbidity (Retz et al. 2010). Another explanation for outcome diversity could be the fact that environmental factors may moderate the effect of gene polymorphisms on behavioural phenotype. In an effort to clear the issue, the same research group conducted a longitudinal study of children (mean age 15 years) followed up as adults (mean age 18 years). Based on study outcomes, a hypothesis was formed. Short alleles were considered risk alleles for trait adaptive impulsivity, i.e. fast decision-making and excitement seeking, while the S/S risk genotype was associated with behavioural measures of impulsivity. These findings applied for male participants. On the other hand, maladaptive impulsivity, i.e. disinhibition and thoughtlessness, was associated again with the S/S risk genotype, though only in participants with a history of stressful life events, specifically increased perceived maternal rejection and beliefs that parents showed lack of love, appreciation and care towards them. Altogether, environmental stressful events could mediate the phenotypic outcome of the risk S/S genotype, turning adaptive impulsivity into dysfunctional (Reif et al. 2011).

#### 9.2.4.2 Androgen Receptor Gene (AR)

The androgen receptors mediate testosterone's (i.e. hormone implicated in the development of primary male sexual characteristics) and dihydrotestosterone's (i.e. hormone regulating secondary male characteristics) function. The androgen

receptor gene, AR, is located at X chromosome (Xq12) and presents with a triallelic polymorphism [GCA locus or AR_(CAG)n], giving rise to short, medium and long alleles. Caucasian males homozygous for the medium allele showed more severe antisocial traits. However, it should be noted that this association was rather weak (Prichard et al. 2007a).

#### 9.2.4.3 Nuclear Receptor 4A2 Gene (NR4A2)

Nuclear receptor subfamily four group A member 2, NR4A2, is a protein possibly functioning as a transcription factor involved in dopamine neuron development (Sacchetti et al. 2001). It is encoded by a gene located at chromosome 2 (2q24.1). There was some evidence for an association between the long/long NR4A2 (AC) genotype and antisocial traits in females, a finding that requires though further verification (Prichard et al. 2007a).

#### 9.2.4.4 Transcription Factor AP-2 Beta Gene (TFAP2B)

Transcription factor AP-2 beta, TFAP2B, is a protein acting both as a transcriptional activator and repressor, mediating monoaminergic neuron development and regulating gene expression. The corresponding gene is located at chromosome 6 (6p12.3). There are two polymorphisms in strong LD, TFAP2B (AACA) and TFAP2B (TC) (Prichard and Easteal 2006).

The TFAP2B (CAAA) polymorphism, an intron 2 tetranucleotide repeat (CAAA), repeated four or five times, was associated with different personality traits, such as somatic anxiety and indirect aggression (Damberg et al. 2000). In another study, the short/long genotype of TFAP2B (TC locus) was associated with antisocial traits in females (Prichard et al. 2007a).

#### 9.2.4.5 FK506 Binding Protein 5 Gene (FKBP5)

FK506 binding protein 5, FKBP5, is a heat shock protein 90 co-chaperone, regulating the activity of glucocorticoid receptors and as a result the hypothalamic-pituitary-adrenal axis. The corresponding gene, located at chromosome 6 (6p21.31), has been studied in regard to dysregulated stress response in affective and anxiety disorders (Gillespie et al. 2009).

There are four FKBP5 gene SNPs (rs3800373, rs9296158, rs1360780 and rs9470080) in strong LD, giving rise to six haplotypes. Among these, haplotypes H1 and H2 are considered functional. Three possible diplotypes may be formed, derived from the combination of these two functional haplotypes, H1/H1, H1/H2 and H2/H2.

Study of the aforementioned FKBP5 gene SNPs in a population of substance-dependent African-Americans revealed an association between H1/H1 diplotype and suicidal behaviour, though only in participants with a history of childhood trauma (Roy et al. 2010), while another study reported that the less common H2/H2 diplotype was associated with increased risk for aggressive-violent behaviour in male prisoners with a background of physical abuse (Bevilacqua et al. 2012).

#### 9.2.4.6 Brain-Derived Neurotrophic Factor Gene (BDNF)

Brain-derived neurotrophic factor, BDNF, is a member of the neurotrophin superfamily, a nervous system growth factor implicated in neuronal differentiation, growth, survival and death, affecting multiple neurotransmitter systems, among which the serotonergic and the dopaminergic. It is encoded by a gene located at chromosome 11 (11p14.1). There is a functional SNP (rs6265), G196A, resulting in an amino acid substitution (valine is substituted by methionine at codon 66, Val66Met). The more common G allele codes for valine, while the A allele codes for methionine. An in vitro study indicated that the G196A polymorphism was functional, since the A/A genotype was associated with decreased BDNF neuronal secretion (Egan et al. 2003).

The first meta-analysis of 12 studies (1202 suicidal patients diagnosed with psychiatric disorders versus 1699 non-suicidal patients diagnosed with the same psychiatric disorders and 451 healthy controls) investigating the relation between the G196A polymorphism and suicidal behaviour showed that the low-functioning A allele constituted a risk allele. The association between the A allele and suicidal behaviour was more significant in Asian populations (Chinese, Japanese, Korean) as well as when suicide attempters were compared with non-suicide attempters diagnosed with the same psychiatric disorders (eight studies) (Zai et al. 2012). Contrary to previous findings, a subsequent meta-analysis of seven studies (1700 suicidal cases versus 2584 healthy controls) did not reveal a significant association between the G196A polymorphism and suicidal behaviour (Clayden et al. 2012).

A study of a non-clinical German population focused on the association between the G196A polymorphism and different personality traits. Based on results, the BDNF genotype explained 1.9% of the variance of trait anxiety. Specifically, trait anxiety was significantly higher in G/G carriers (Lang et al. 2005).

In another study, the G allele was associated with increased neuroticism levels, explaining 4% of the genetic variance. Specifically, and in regard to six neuroticism facets, the association was confirmed between the G allele and increased anxiety, depression, self-consciousness and vulnerability (Sen et al. 2003). Similarly, G/G genotype carriers within a German population showed higher neuroticism levels compared with G/A and A/A carriers. It should be noted though that the latter findings failed to reach statistical significance (Lang et al. 2005). Another study of a healthy Japanese population reported an association between the A/A genotype and extraversion, though only in females (Itoh et al. 2004), while a recent genome-wide association study confirmed the association between the G196A polymorphism and extraversion (Terracciano et al. 2010).

On the other hand, a study of a healthy female Chinese population failed to confirm any association between the G196A polymorphism and different personality traits (novelty seeking, harm avoidance, reward dependence and persistence) (Tsai et al. 2004a).

Altogether, a meta-analysis of four studies (non-clinical population consisting of 607 individuals) investigated the relation between the G196A polymorphism and harm avoidance. Results showed that the A/A genotype was associated with a

trend towards higher harm avoidance. The same meta-analysis investigated the association between the G196A polymorphism and neuroticism pooling five studies (non-clinical population consisting of 1633 individuals). According to the results, the G/G genotype was associated with higher neuroticism levels (Frustaci et al. 2008).

Lastly, a study of a non-clinical Korean population investigated both COMT G472A polymorphism and BDNF G196A polymorphism in relation to sensation seeking and reported no significant associations when the two polymorphisms were considered separately. On the contrary, focus on the combined effect of COMT and BDNF polymorphisms on sensation seeking revealed a significant association with only one sensation seeking facet. Specifically, among female homozygous or heterozygous COMT-L carriers, female BDNF G/G carriers displayed higher boredom susceptibility levels (Kang et al. 2010) (Table 9.7).

#### 9.2.4.7 Nerve Growth Factor Gene (NGF)

The nerve growth factor, NGF, is a neurotrophic factor involved in neuronal growth and survival of basal forebrain cholinergic neurons. Although the NGF complex consists of α, β and γ subunits, it is the β subunits exhibiting NGF stimulating function.

The NGF gene is located at chromosome 1 (1p13.2). There is a non-synonymous C104T SNP (rs6330) giving rise to the more common C allele coding for alanine and the T allele coding for valine. This amino acid substitution (alanine is substituted by valine at codon 35, Ala35Val) may affect NGF secretion (Syed et al. 2007).

A study of a non-clinical German population revealed a gender-specific effect of the C104T polymorphism on state-trait anxiety levels. Specifically, females genotyped as C/C showed increased anxiety levels compared with heterozygous carriers. Contrary to females, males genotyped as C/C displayed lower anxiety levels compared with heterozygous carriers. Still, results were not significant in both females and males, when homozygous C/C were compared with homozygous T/T individuals (Lang et al. 2008).

#### 9.2.4.8 Cholinergic Receptor Nicotinic Alpha 4 Subunit Gene (CHRNA4)

The cholinergic system is involved in neural plasticity and associated with learning. The nicotinic acetylcholine receptors constitute a receptor family, whose members are formed by diverse combinations of five different subunits (α1–α10 and β2–β4). The neuronal receptor α4β2 is the main receptor found in mammalian brain (Gotti et al. 2009). The α4 subunit is encoded by the CHRNA4 gene, located at chromosome 20 (20q13.2–13.3). There is a synonymous SNP (rs1044396) in exon five, a C to T transition, giving rise to two alleles. Although the SNP does not cause any amino acid change, there is evidence that it affects receptor sensitivity (Eggert et al. 2015).

**Table 9.7** Brain-derived neurotrophic factor gene polymorphism and behaviour

| Gene (chromosome location) | Encoded protein | Polymorphism | Alleles | Behavioural phenotype | Meta-analyses |
|---|---|---|---|---|---|
| BDNF (11p14.1) | Brain-derived neurotrophic factor | rs6265: G196A SNP (Val66Met) | G: the more common coding for valine<br>A: coding for methionine; A/A genotype was associated with decreased BDNF neuronal secretion | Suicidal behaviour | Meta-analysis of 12 studies (1202 suicidal patients diagnosed with a psychiatric disorder versus 1699 non-suicidal patients diagnosed with the same psychiatric disorders and 451 healthy controls)<br>Results: association between A allele and suicidal behaviour, which was even more significant in Asian populations (Chinese, Japanese, Korean), as well as when suicide attempters were compared with non-suicide attempters diagnosed with the same psychiatric disorders (Zai et al. 2012) |
| | | | | | Meta-analysis of seven studies (1700 suicidal cases versus 2584 healthy controls)<br>Results: no association (Clayden et al. 2012) |

In a study of a non-clinical sample, contrary to T allele carriers, C/C carriers displayed higher levels of negative emotionality, specifically anxiety and emotional instability, in combination with more intense harm avoidance and behavioural inhibition (Markett et al. 2011). A German study of a large population (1673 subjects) obtained from a German multicentre study of nicotine dependence genetics confirmed aforementioned results, reporting an association between the C allele and higher harm avoidance, as well as increased neuroticism levels (Bey et al. 2016).

Lastly, a study of maltreated children showed that the rs1044396 polymorphism moderated the effects of maltreatment on childhood personality outcome. Children carrying the T/T genotype displayed higher neuroticism levels when they had a background of childhood maltreatment. Contrary to maltreated, non-maltreated children carrying the T/T genotype displayed lower neuroticism levels and higher levels of openness to experience (Grazioplene et al. 2013).

## 9.3 Conclusions

### 9.3.1 Discrepancy in Study Outcomes

Association studies within the research field of behavioural genetics have provided in several cases controversial or inconsistent results. There are different issues in regard to study design, leading to outcome discrepancy and difficulties in interpreting findings. Inadequate study strategies may lead to false-positive, probably on chance, or false-negative results. Several factors should be taken into consideration when studying genetic background of behaviour and personality:

1. *Ethnicity*: studies of diverse ethnic groups, showing different allele variant frequency, should pay considerable effort in sample selection so as to avoid bias (Li and He 2007). For instance, research outcomes of MAOA, one of the most studied genes in relation to aggression, were characterised by both discrepancy and inconsistency, partly due to different MAOA allele frequency in diverse ethnic groups (Lea and Chambers 2007). Furthermore, it should be noted that the risk MAOA-L allele is not uncommon, occurring in 40% of the population (Brunner et al. 1993a, b; Hunter 2010).

   Additionally, different allele frequencies between cases and healthy controls in case-control study designs may also confound results. For instance, the frequency of the 5-HTTLPR S allele was shown to be significantly different between Caucasian and Asian healthy controls. In this sense, family-based designs could provide a more appropriate study approach (Lin and Tsai 2004).

   Lastly, the discovery of population-specific mutations associating with behavioural characteristics emphasises the importance of exact description of study populations' genetic background (Brunner et al. 1993a, b; Kelsoe 2010; Zai et al. 2012).

2. *Demographics*: in case of genes with a sexually dimorphic effect, such as the COMT gene, or X-linked genes, such as the MAOA gene, several studies recruited selected samples in regard to sex, possibly limiting results to these particular populations (Manuck et al. 2000; Tsai et al. 2004b; Kulikova et al. 2008). Specifically, MAOA-H/MAOA-L heterozygosity is only present in females, while males are always homozygous, due to the presence of one X chromosome. Since MAOA expression in heterozygous cases has not been fully elucidated yet, many studies excluded all females or included strictly female homozygous allele carriers (Kim-Cohen et al. 2006; Alia-Klein et al. 2008; Derringer et al. 2010; Ficks and Waldman 2014). Furthermore, only a few researchers have provided data on allele frequency in males and females separately, hindering analysis of a plausible gender effect on study outcomes (Lin and Tsai 2004).

   Age is another important variable, specifically in research of gene polymorphisms and personality traits. For instance, novelty seeking diminishes with age, as most personality traits do. In order to avoid bias, recruited individuals should be preferably under the age of 45 (Lusher et al. 2001; Lang et al. 2005). Furthermore, socio-economic or cultural differences may also affect study outcomes in regard to personality traits (Campbell et al. 2010; Kang et al. 2010).
3. *Methodological issues*: studies employing large populations may be at risk of finding false associations, while studies of small populations may fail in revealing statistically significant results. Furthermore, contrary to studies of unselected populations, studies employing selected samples may lead to overestimation of a genetic association, since they focus only on the extremes of normal distribution (Munafo et al. 2008).

   Different definition of a behavioural phenotype may also result in inconsistent findings across studies. For instance, it should be noted that self-report measures of aggression may reflect trait aggression, without reflecting aggressive acts. Additionally, most behaviours and personality traits constitute a continuum that may be defined by a different genetic background. For instance, animal studies suggested that trait aggression may be positively associated with serotonergic activity, whereas impulsive/violent state aggression may be negatively associated with serotonergic activity (Olivier and van Oorschot 2005). Another example is the behavioural spectrum of suicidal behaviour, ranging from death wish to completed suicide. Within this spectrum, suicide attempt constitutes also a broad phenotype, including failed suicide (strong intent of dying, usually careful planning, lethal/violent suicide methods) and suicide gesture (less intent of dying, usually a reaction to acute interpersonal conflicts, less lethal/non-violent suicide methods) (Mann 1998). In this sense, genetic background of severe/violent suicidal behaviour may be different from genetic background in cases of milder/non-violent suicidal manifestations (Lin and Tsai 2004). Accordingly, suicide completers may constitute a distinct group from suicide attempters (Clayden et al. 2012). Lastly, diversity in assessment tools, employed for measuring a specific behaviour or a personality trait, was also shown to moderate results (Schinka et al. 2004). Altogether, each study should describe clearly the

behaviour being studied in a particular population, by defining assessment tools and what these measure.

4. *Common pathophysiology*: the possibility of a common pathophysiology underlying extreme manifestation of a specific behaviour and psychiatric disorders should not be overlooked. For instance, alcohol dependence and anorexia/bulimia nervosa are examples of psychiatric disorders characterised by impulsive behaviour. Both disorders were associated with the G-1438A 5-HT2A polymorphism. Additionally, there was evidence that the COMT gene may be a risk gene for schizophrenia. Based on a meta-analysis, presence of at least one COMT-L allele (G472A polymorphism) increased risk for violent behaviour in male schizophrenia patients by around 50% (Williams et al. 2007; Singh et al. 2012).

   Similarly, suicidal behaviour has been mostly studied within the context of different psychiatric disorders, e.g. affective, schizophrenia spectrum, personality and substance use disorders, since 90–95% of suicidal individuals are diagnosed with at least one psychiatric disorder (Gonzalez-Castro et al. 2013a, b). Research has provided evidence for a genetic component for most psychiatric disorders that usually involves the serotonergic and the dopaminergic system. Therefore, it cannot be excluded that risk genes for impulsive, aggressive or suicidal behaviour overlap with susceptibility genes for psychiatric disorders, confounding results. Others suggested that serotonergic system dysfunction may predispose to both suicidal behaviour and psychiatric disorders. In such a case, only psychiatric patients carrying a particular risk allele would manifest suicidal behaviour (Lin and Tsai 2004). Still, although suicidal behaviour has been associated with both TPH1 (Courtet et al. 2005) and SLC6A4 gene (Li and He 2007) independent of psychiatric diagnosis, others failed to confirm this association, claiming that psychiatric history is a major confounding factor. The latter assumption was based on the fact that genetic associations were not confirmed when suicidal versus non-suicidal psychiatric patients were compared (Saetre et al. 2010).

   Altogether, due to comorbidity between specific behaviours, e.g. suicidal and aggressive behaviour, and psychiatric disorders, case-control analyses carry mental health status as a confounding factor. Thus, differentiating the genetic component of a behaviour from the genetic component of a psychiatric disorder may prove a difficult challenge (Schild et al. 2013).

5. *Common comorbidity*: common comorbidity between psychiatric disorders suggests that a certain biological substrate may be shared. Thus, elucidating genetics of a behavioural phenotype present within the context of different diagnostic categories may prove difficult, since the genetic contribution to the behavioural phenotype may be masked by the genetic contributor to comorbid psychiatric disorders.

6. *Environmental factors*: study results have not always supported the association between a gene polymorphism and a particular behaviour or personality trait, such as in case of the MAOA-uVNTR polymorphism and aggressive/antisocial behaviour (Jacob et al. 2005; Huizinga et al. 2006; Widom and Brzustowicz 2006). This may be partly attributed to the fact that the effects of the MAOA

gene polymorphism on the manifestation of aggressive/antisocial behaviour were shown to be moderated by environmental factors, specifically childhood maltreatment (Caspi et al. et al. 2002; Hart and Marmorstein 2009; Derringer et al. 2010). Therefore, studies investigating gene effects without considering history of stressful environmental factors may not be able to reveal an association between a gene polymorphism and a particular behaviour.

7. *Allele grouping:* in case of the DRD4 48 bp VNTR, most studies grouped alleles into short (up to 5) and long (6, 7, 8) repeats. Still, the 7R allele is evolutionary younger than the common 4R allele and has increased in frequency due to positive selection. Thus, it may not be so simply related to other long alleles. Additionally, the 7R allele is extremely rare in Asians; thus it could not possibly contribute to the manifestation of novelty seeking (Kluger et al. 2002).

In regard to the TPH1 gene polymorphisms, diverse A218C and A779C polymorphism alleles have been associated with the manifestation of suicidal behaviour. Therefore it cannot be excluded that the "causative" risk allele is another one, until now unknown, which is not in strong LD with the TPH1 genetic variants implicated so far in suicidal behaviour. As a result, the TPH1 genetic variant associated with suicidal behaviour may depend on the original haplotype carrying the unknown risk allele (Lalovic and Turecki 2002).

Furthermore, several SNPs are not functional and may be in strong LD with other "causative" polymorphisms, located perhaps at different chromosomes. Additionally, a single polymorphism probably accounts for a small proportion of the variance, contributing minorly to the manifestation of a behaviour or expression of a personality trait. Thus, a haplotype approach could be more elucidating (Kluger et al. 2002). For instance, a study of suicide completers investigated the association between three different TPH1 SNPs (A218C; promoter region A-6526G; promoter region G-5806T) and the more extreme manifestation of suicidal behaviour. These three SNPs were in strong LD and were not found to be related to suicidal behaviour when they were analysed separately. On the contrary, when haplotype analysis was conducted, considering all three SNPs simultaneously, the haplotype -6526G-5806T-218C was more abundant in violent suicide completers compared with healthy controls. Based on results, haplotype analysis provided increased statistical power for the identification of a risk locus. Furthermore, although the A218C SNP alone does not seem to be functional, the risk haplotype could affect protein binding (Turecki et al. 2001).

### 9.3.2 Meta-analyses

Individual studies may lack sufficient statistical power to detect small gene effects. As a result, meta-analyses have been extensively applied in the field of behavioural genetics to investigate a global effect with a greater statistical power, based on studies using smaller sample sizes. Meta-analyses are additionally used to search for sources of heterogeneity between different studies, excluding studies with

significant contribution to the magnitude of an association. Although they were proven a useful tool for quantitative summarisation of heterogeneous and/or small sample size studies, meta-analyses are prone to false-positive results due to publication bias (Anguelova et al. 2003). Publication bias is attributed to the fact that studies reporting positive associations are more likely to get published compared with studies reporting negative outcomes (Bellivier et al. 2004). Inclusion of less negative studies, as well as unpublished negative studies, may lead to meta-analyses' undersampling. Thus, studies reporting non-significant associations are equally important as studies with positive findings, in order to avoid overestimation of an association (Munafo et al. 2008). For instance, there was a meta-analysis of the TPH1 A218C polymorphism in relation to suicidal behaviour that pooled data from only one study reporting a positive and six studies reporting a negative association. Overall results revealed a positive association (Bellivier et al. 2004). The one research field that does not seem to be affected by publication bias is genetics of suicidal behaviour (Anguelova et al. 2003).

Still, there were cases of similar meta-analyses, reporting contradictory results, such as in the case of the association between the BDNF G196A polymorphism and suicidal behaviour (Clayden et al. 2012; Zai et al. 2012). Contradictory results may be explained by factors similar to the ones causing heterogeneity between individual studies:

1. *Ethnicity*: pooling samples from different ethnicities is a source of heterogeneity. For instance, genetic distinct populations, such as the Ashkenazi population, were shown to be a significant source of heterogeneity in meta-analyses (Bellivier et al. 2004). Therefore, there were meta-analyses that took ethnicity into consideration, pooling data from studies of Caucasian populations only (Rujescu et al. 2003b; Bellivier et al. 2004).
2. *Methodological issues*: diversity in assessment tools of behaviour and personality was shown to moderate results (Schinka et al. 2004). Therefore, meta-analyses should include studies applying the same measuring tools. For instance, a meta-analysis of the DRD4 48 bp VNTR in relation to novelty seeking based on studies assessing novelty seeking explicitly by Cloninger's TPQ questionnaire (Kluger et al. 2002) revealed different outcomes from a meta-analysis pooling studies independent of assessment scales (Schinka et al. 2002). Lastly, different meta-analytic methods may also contribute to contradictory findings. There were meta-analyses applying fixed effects model, which assumes the same true genetic effects, while other meta-analyses used the random effects model, which assumes normally distributed effects. The latter model may be more advantageous, considering and parameterising in between study variability (Lin and Tsai 2004).
3. *Non-homogeneous phenotypes*: as previously mentioned, human behaviour and personality constitute a spectrum. For instance, suicidal behaviour includes both non-violent and violent suicide. Pooling all suicidal cases together may be a reason why there were negative results among meta-analyses pooling suicide attempters and completers together, instead of analysing them separately (Lalovic and Turecki 2002; Kia-Keating et al. 2007). Contrary to suicidal behav-

iour, another meta-analysis did not prove broad definition of antisocial behaviour to be a cause of heterogeneity among studies (Ficks and Waldman 2014).

4. *Different psychiatric history*: a meta-analysis clearly showed that psychiatric diagnosis (mixed psychiatric populations or psychiatric populations with unclear diagnosis) is a significant source of heterogeneity (Wang et al. 2015). For instance, inclusion of suicidal bipolar patients was shown to moderate meta-analytic results, while inclusion of suicidal patients with different psychiatric diagnoses was not (Bellivier et al. 2004). Altogether, psychiatric history may contribute to outcome diversity, at least in case of genetic studies of suicidal behaviour (Tovilla-Zarate et al. 2011).
5. *Environmental factors*: since behavioural and personality outcome is not affected by genetic factors alone, moderating effects of environmental factors should be taken into consideration. Meta-analyses of studies of gene-environment interactions probably constitute a crucial step towards drawing more certain conclusions (Taylor and Kim-Cohen 2007; Ficks and Waldman 2014).

### 9.3.3 Closing Remarks

Psychopathology may be viewed as the extreme manifestation of behaviours and personality traits normally distributed in a population. A future aim of behavioural genetics is prediction of the probability that an individual with a specific genetic variation will manifest impulsive, suicidal, aggressive or antisocial/criminal behaviour, behaviours often expressed within the context of different psychiatric disorders. Accordingly, elucidation of the genetics of personality could contribute to early diagnosis and intervention in case of personality disorders (Mulder et al. 1999). Lastly, a wedge issue in regard to behavioural genetics would be adducing evidence of genotypic data explaining aggressive/violent behaviour in legal trials of criminal defendants (Bernet et al. 2007). Genetic studies of criminal behaviour raised severe legal issues. In 2009, a court in Italy lightened the sentence of a man convicted for murder by 1 year, based on scientific evidence linking his violent behaviour to "abnormal genes". Others suggested though tougher sentences in cases of evidence linking criminal behaviour with genetic background, arguing that a genetically determined behaviour will probably be repeated and cannot be treated.

Still, research is a long way before contributing to aforementioned goals. To date, reported associations between gene polymorphisms and behavioural/personality outcomes were proven relatively weak. Furthermore, the influential effect of different study inclusion on meta-analytic outcomes underlines discontinuity in results (Schild et al. 2013; Vassos et al. 2014). Associating a single gene polymorphism with behaviours and personality traits was proven a non-accomplishable task until now. Both human behaviour and personality are of complex origin, the result of genes interacting with each other, as well as with environmental factors. Additionally, behaviour and personality traits manifest themselves in a continuum. Complex phenotypes lying on a continuum are most probably attributed to polygenic inheritance.

Altogether, studies of the association between specific alleles and behaviours/personality traits have mostly contributed to exclude the theory of a single gene's major contribution. "Missing heritability" has been attributed to variants, possibly rare variants with greater effects, which have not been discovered yet, or to gene-gene interactions (Manolio et al. 2009; Zuk et al. 2012). Since a research approach focusing on separate risk alleles was proven unfruitful, genome-wide association studies of large populations (thousands) assaying multiple SNPs could constitute a more effective approach for the identification of candidate genes (Schild et al. 2013; Vassos et al. 2014).

Lastly, behavioural genetics alone are in danger of failing in contributing substantially to effective drug treatment. A certain "risk" allele may not always correspond with high or low protein activity. As a result, the mechanism mediating the effects of a risk genotype remains in several cases unknown. Thus, supplementary studies, enlightening the effects of gene polymorphisms on pathophysiology and focusing on epigenetic regulation, are required.

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# Psychobiology and Psychoanalysis

# 10

Elias Andreoulakis and Ioanna Ierodiakonou-Benou

## 10.1 To Link or Not to Link?

The question whether psychobiology and psychoanalysis can be bridged goes back to the very birth of psychoanalysis. Sigmund Freud, the founder of psychoanalysis, started his career as a neuroscientist; he was trained as a neuroanatomist and originally studied some—conservatively speaking—neurological disorders such as aphasia and cerebral palsies in children before turning to the "neuro-psychoses of defense" and the "studies on hysteria" and the development of psychoanalysis. Freud strongly believed that psychoanalytic ideas could be eventually corroborated by answers provided by biology. He aimed to put psychoanalysis among natural sciences in order to strengthen the validity of his formulations and gain wider acceptance within the scientific community.

This passionate effort of his is illustrated in his writing the *Project for a Scientific Psychology*. In this work, Freud conceptualized mental phenomena in the framework of hydraulic psychic energy and the phenomena of accumulation of excessive amounts of energy and the consequent pressure to discharge. In this context, he described different types of neurons receiving input from inside or outside and exhibiting excitatory, secretory and inhibitory functions (McCrone 2004; Freud 1966).

Freud's initial enthusiasm for the project was soon followed by intense frustration that made him discard "the project" and refrain himself from publishing it. The *Project for a Scientific Psychology* was eventually published after his death, in 1954. However, in this work, Freud had already introduced fundamental concepts of the psychoanalytic theory.

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After abandoning his initial endeavor, Freud turned to a pure psychological theory. The reason for this seemed to be that neuroscience was not technically sufficient at that time to provide the answers he was seeking for. In addition, strict localization approach that was prevailing at his time did not satisfy him (Schore 1997; Northoff 2012). Nevertheless, he did not give up the belief that such a quest would become fruitful in the near future.

Thereon, psychoanalysis and neuroscience followed a rather divergent course for most of the twentieth century. As Kandel points out, "*psychoanalysis represented a revolution in our thinking about the brain in the first half of the 20th century*" but although "*it still represents the most coherent and intellectually satisfying view of the mind it has not evolved scientifically*" mainly in that it suffers from a lack of objective measures and methods to test its theoretical formulations in an experimental setting rather than the analytic situation itself, which is subjective and thus renders susceptible to observer bias. "*As a result, psychoanalysis enters the twenty-first century with its influence in decline*." Although Kandel acknowledges that "*we are very much at the beginning*," he argues that the biological foundation of many psychoanalytic concepts might be feasible in the near future, judging from the pace of advance in neuroscience (Kandel 1999). Kandel also argues that much of the unease hampering the dialogue between neuroscience and psychoanalysis might be due to a misconception regarding the way genes work and emphasizes on the mutually influenced interplay between "*nature*" and "*nurture*" by highlighting the *dual function of genes*:

1. Genes demonstrate a *template* function (to ensure reliable replication) which is vulnerable to no other influence (environmental or social) than mutations.
2. However, genes also have a *transcriptional* function (protein production) which can be regulated in response to environmental factors (epigenetic regulation), including learning. In that sense, "*Behaviour itself can also modify gene expression and produce sustained alterations in neuronal connectivity and functioning*" (Kandel 1999).

Kandel regards a dialogue between psychoanalysis and neuroscience as feasible, meaningful, and necessary "*if psychoanalysis is to have any future*" within the evolving sciences of the brain. He has outlined some areas in which neuroscience could contribute to psychoanalysis, such as preconscious and unconscious mental processes, psychological causality and its relation to psychopathology, early experiences and the predisposition for a mental disorder, brain structural changes in response to psychotherapy, and the potential for a synergistic effect of psychopharmacology in adjunction to psychoanalysis (Kandel 1999).

Kandel proposed "*a new intellectual framework*" (Kandel 1999) for a dialogue between neuroscience and psychiatry—applicable both for a dialogue involving psychoanalysis—based on certain principles:

1. "*All mental processes, even the most complex psychological processes, derive from operations of the brain*" and "*even those disturbances that are clearly environmental in origin are disturbances in brain function*."

2. "*Genes, through their protein products, determine the pattern of neuronal interconnections in the brain and, thus, the functioning of neurons. Consequently, genes influence behaviour. In other words, one component of major mental illnesses, either inherited or acquired, is genetic… Genetic illnesses (e.g., schizophrenia) are expressions of altered genes, whereas illnesses acquired as learned behaviour (neuroses) involve the modulation of gene expression by environmental stimuli, leading to the transcription of a previously inactive gene*."
3. That said, "*altered genes do not, by themselves, account for all of the variance of a given major mental illness and thus, an important contribution of social or developmental factors should also be acknowledged*."
4. In addition, "*environmental factors as well as behaviour—learning, in particular—can, in reverse modify the expression of genes and consequently the neuronal connectivity and functioning*."
5. Kandel regards psychotherapy as "*a learning process that can produce long-term changes through a significant modification on genes expression that results in structural and functional changes in the brain*" (Kandel 1999).

As stated above, psychoanalysis and neuroscience have been in a state of mutual disregard and avoidance during most of the twentieth century, but this appears to be changing over the last two decades. A mutual interest on behalf of both neuroscientists and psychoanalysts regarding the bridging of the two disciplines has emerged (Yovell et al. 2015). Thus, a century after, the interest in continuing Freud's initial endeavor has reemerged, on the ground of recent technological advances that allow in vivo study of the brain in function.

Recent advances in neuroscience have also led to a reframing of brain functioning conceptualization. Strict localization approach has given its place to a function-based and a diffuse dynamic localization approach. The modular approach of highly specialized segregations of neurons has been reconsidered in the light of findings concerning complex interconnections and interactions in the context of neuronal integration, i.e., the hierarchical organization and coordination of neuronal activity across various interconnected brain areas (Northoff 2012). Research focused on brain connectivity—anatomical, functional, and effective (Friston 2011)—is thought to be able to enhance the convergence between psychoanalysis and neuroscience by providing insightful information on the circuitries and mechanisms underlying mental functions (Salone et al. 2016). Northoff proposes that neuroscientific research may now go beyond the function and localization-based approach, moving from the "Neural *Correlates* of Psychodynamics" to the "Neural *Predispositions* of Psychodynamics," which he relates with the brain's *resting-state activity* and its "*spatiotemporal structure*." The latter reflects the two essential characteristics of the resting-state activity, namely, the low-frequency fluctuations and the patterns of functional connectivity. According to Northoff, the "spatiotemporal structure" of the brain's resting-state activity may be parallelized to the Freudian conceptualization of the "psychological structure" of the mental apparatus, in that both concepts reflect a process and a dynamic organization rather than a strictly anatomical entity. In addition, spatiotemporal structure of the resting-state activity

may provide a model related with the ego functions and dreams (Northoff 2012). Northoff also suggests a direct link between abnormalities of the "spatiotemporal structure" of the resting state and psychopathological symptoms such as ego disturbances and auditory hallucinations observed in schizophrenia (Northoff 2015).

In the context of this revitalized interest, several researchers have revisited Freud's ideas linking them with current neuroscientific findings (Carhart-Harris and Friston 2010; Carhart-Harris et al. 2008; Fotopoulou et al. 2012; Kandel 1999; Kaplan-Solms 2000), while others challenge this revisiting on Freudian ideas arguing that new insights provided so far are not unique to psychoanalytical concepts but can be embedded in the cognitive, affective, and social neuroscience (Ramus 2013). There are also some psychoanalysts who consider that the time for a rapprochement between neuroscience and psychoanalysis has come (Schore 1997; Fonagy 2003; Kernberg 2004). However, the issue of rapprochement has not been free of confrontation and has given rise to several concerns as will be discussed later on.

This revitalized interest in the quest for a rapprochement between psychoanalysis and neuroscience has led to the emergence of a bridging interdiscipline named *neuropsychoanalysis* (Nersessian and Solms 1999). Neuropsychoanalysis aims to link psychoanalysis with neuroscience and understand the human mind by investigating its functions in a cross-species context (Panksepp and Solms 2012). Although the proponents of neuropsychoanalysis argue that the investigation of neural networks associated with complex behaviors is essential for the thorough understanding of the latter, they refrain themselves from the prevailing reductionism and the temptation to make hasty inferences concerning causality regarding the relationship between human behavior and the functioning in certain brain areas (Panksepp and Solms 2012).

As mentioned above, the meaningfulness of a dialogue between psychoanalysis and neuroscience represents a matter of debate, probably representing a new era of what might lead to the—hopefully fruitful—"controversial discussions of the twenty-first century." Many questions and concerns have risen, such as: Is this bridging legitimate? Is it feasible? Would it be meaningful and beneficial for both disciplines, i.e., neuroscience and psychoanalysis?

A fruitful controversy has begun regarding the aim to engage psychoanalysis and neuroscience in a dialogue within the framework of neuropsychoanalysis, with arguments raised for (Yovell et al. 2015; Canestri 2015; Panksepp and Solms 2012; Pugh 2007; Mancia 2007) and against the newborn interdiscipline (Blass and Carmeli 2007, 2015; Carmeli and Blass 2013; Pulver 2003; Ramus 2013).

While proponents argue that neuropsychoanalysis is consistent with Freud's conceptualization and represents a legitimate continuation of his legacy, opponents challenge such an inference as contradicting the broader spirit of his work (Blass and Carmeli 2015).

Solms and colleagues, leading proponents of bridging psychoanalysis with neuroscience by means of neuropsychoanalysis, argue that such a dialogue should be fostered on the grounds that psychoanalysis and neuroscience essentially study the same entity, which they call as "*mindbrain*," speaking of a "*dual-aspect monism*." At the same time, however, they acknowledge that neither discipline can

be sufficient in exploring and describing this entity on its own. They argue in favor of a mutually respectful dialogue and collaboration between the two disciplines that "*does not eliminate each other's unique perspective*." They admit that psychoanalysis and neurosciences are and will continue to be two inherently different disciplines that employ different methodologies to investigate two complementary aspects of the human mind—the subjective and the objective—"*neither of which is reducible to the other or more real than the other*" (Yovell et al. 2015; Solms and Turnbull 2002). The very essence of "mindbrain" and "dual-aspect monism" has been challenged (Blass and Carmeli 2015; Karlsson 2010), particularly by Blass, Carmeli, and colleagues who have extensively stressed important and plausible concerns (Blass and Carmeli 2007, 2015; Carmeli and Blass 2013). Blass and Carmeli challenge the very essence of "dual-aspect monism" postulated by Solms and colleagues although they acknowledge that there is indeed an inherent tie and a mutually influenced relationship between the mind and the brain and that mental phenomena can be "correlated" with brain functions. They would prefer the term "correlated" as less reductionistic compared to "mapped to a biological substrate." Besides challenging the opinion that neuroscience and psychoanalysis study the same entity, Blass and Carmeli argue that even if this argument is accepted, it could not be a sufficient condition for an in depth and mutually influencing dialogue, as in many other approaches that might share the same study object with psychoanalysis. Exerting further criticism on dual-aspect monism, Blass and Carmeli argue that psychoanalysis and neuroscience do not share the same research question, since psychoanalysis studies the subjective experience, whereas neuroscience studies the objective part (brain function). They argue that "*the analyst not only seeks to discover patient's meaning but also goes beyond this by trying to make them manifest themselves in the analytic setting in order for them to be amenable to working through. To this end, they argue, biology has nothing to say*."

Blass and Carmeli also consider neuroscientific findings as irrelevant to psychoanalysis using some metaphors to further illustrate and corroborate their view. In specific, they argue that the study of the piano structure and function though related with the music produced would be irrelevant to study of the music itself as the study of chemicals would be irrelevant to the painter. In line with this, they raise plausible concerns against a materialistic and reductionistic approach which would contradict the very essence of Freud's spirit as illustrated in the following passage: "*It will soon be clear what the mental apparatus is; but I must beg you not to ask what material it is constructed of. That is not a subject of psychological interest… We shall leave entirely on one side the material line of approach*" (Freud 1969).

Blass and Carmeli also criticize some of the neuroscientific findings as general psychological but also do not consider the knowledge gained from neuroscience as necessary for psychoanalysis, arguing that the analyst should not ask for external information sources so that he can understand what is happening in the patient's mind and what his/her subjective meanings are. They conclude by arguing that neuroscientific findings are not only irrelevant (as not studying the same entity or addressing the same research question) but even harmful to

psychoanalysis, particularly if neuroscientific knowledge is to interfere with the practice of psychoanalysis (Blass and Carmeli 2015). This is indeed a matter of concern to which we will come back later on.

Proponents of the dialogue argue that this could be mutually beneficial; on one hand, the psychoanalytic theory can provide a conceptual framework guiding neuroscientific research, whereas, on the other hand, the neuroscience may contribute to the neurobiological foundation of psychoanalytic theory and concepts. Consequently, this might lead to a fruitful revisiting of both psychoanalytic theory and practice (Yovell et al. 2015).

At this point, some authors—although not entirely against a dialogue—speak of a somehow one-sided benefit as they argue that psychoanalysis might help neuroscience in a better targeted research, whereas the knowledge derived from neuroscience would be meaningful to a to a cognitive neuroscientist but not a psychoanalyst (Mechelli 2010). Others agree that neuroscience could be beneficial for the psychoanalytic theory, in that neuroscience might help psychoanalysis sort and systematize the knowledge within the abundance of psychoanalytic ideas and answer essential questions, such as "how therapy cures" (Fonagy 2003) or by providing evidence that would enable choosing between competing analytic theories whereas it is also stressed that it would be irrelevant and would have nothing to offer to psychoanalytic practice (Pulver 2003).

There is some skepticism concerning the validation of psychoanalytic theory by means of neuroscientific evidence. Pulver as well as Blass and Carmeli acknowledge that psychoanalytic models of explanations cannot be incongruent to the new findings of neuroscience (Blass and Carmeli 2007; Pulver 2003). That said, it is also stressed that neuroscience should not represent the "final court of appeal for psychoanalytic models" (Blass and Carmeli 2007). Similarly, Mitchell (1995) argues that it is communication within the psychoanalytic community that can provide the necessary "testing-ground" for psychoanalytic theory and practice. In addition, Blass and colleagues also plausibly argue that psychoanalysis should not restrict and redirect its interest only in concepts (such as certain drives and motives), the existence of which has been confirmed and mapped biologically (Blass and Carmeli 2007, 2015). Despite the disagreement concerning the role of neuroscience in validating or revisiting (or probably discarding) certain formulations of the psychoanalytic theory, the proponents of neuropsychoanalysis have also refrained themselves from assigning a decisive role to neuroscience. As they state, this is not only because any new findings might be proved to be wrong in the long run but also because any findings leading to a proposal for a revisiting of psychoanalytic theory and practice should always be tested within the analytic situation (Yovell et al. 2015).

There are also some concerns raised in terms of methodology and the feasibility of a meaningful dialogue. Regarding the cross-validation of psychoanalytic concepts, Mechelli plausibly stresses that a necessary assumption is that the concepts under investigation many of which have been so far unique to psychoanalytic thinking have to be defined in such a manner that would make them widely acceptable. In addition, a fully objective interpretation of neuroscientific findings might be flawed by the researcher's theoretical predisposition. Moreover, neuroscientific

findings have to be consolidated and freed from controversies in order to serve as a testing-ground knowledge base (Mechelli 2010).

One important barrier in bridging psychoanalytic concepts and neuroscience lies in the arduous task to link the subjective experience of a person (first-person experience) with the observation of his/her brain function from a third-person (investigator) perspective. In an attempt to overcome this barrier, Norhoff and colleagues recommended the employment of a strategy termed as "first-person neuroscience" which aims to "*preserve the individual contents*" of psychological states as obtained from first-person perspective but at the same time, "*make them amenable to objectification and quantification*" in order to be accessible to systematic data gathering and investigation "*without compromising their complexity and richness*." To this end, self-rated instruments such visual analogue scales or semi-structured interviews might be used in order to transcribe the first-person experience into measurable and reliable data. Northoff goes on to point to the need for a further development in assessment tools, namely, "first-person questionnaires" (Northoff and Heinzel 2006; Northoff et al. 2007).

A point of convergence is that opponents of neuropsychoanalysis admit that "*neuroscientific findings can help demarcate the limits of psychoanalysis*," in that they can identify the cases where the benefit of psychoanalysis is limited by brain abnormalities that render a patient less capable of "*meaningful expression*" (Blass and Carmeli 2007). That said, they clarify that this should be not be taken as a categorical argument that "psychoanalysis has nothing to say" in cases of severe brain damage and hold that there always remains a psychic meaning in the patient's behavior no matter how this behavior is related with certain brain lesions (Blass and Carmeli 2015).

Concerning the interference of neuroscientific findings with psychoanalytic practice, Blass and colleagues criticize Solms' and colleagues' argument presented by means of a clinical illustration in which neuroscientific knowledge on the unfeasibility of retrieval of early traumatic memories due to certain neuronal dysfunction is conveyed to the analysand. They consider this as a consolatory and nonanalytical practice despite the relief of anxiety or guilt it might provide to the patient. They argue that "*when information and consolation are introduced into the analytic setting to calm latent anxieties to the neglect of the dynamic sources of the anxieties, the dynamic sources remain untouched*" (Blass and Carmeli 2015). This is the main argument concerning the potential harmfulness of a dialogue between neuroscience and psychoanalysis as stressed by Blass and Carmeli. We agree that acquisition of neuroscientific knowledge on behalf of the analyst is one thing, while conveying such a knowledge to the patient is another.

In response to the necessity of a dialogue between neuropsychoanalysis and psychoanalysis in order to avoid scientific isolation of the latter, Blass and Carmeli (2015) argue that "*the spirit of psychoanalysis should not be distorted in order to belong to the mainstream*".

Another potential benefit proposed by those who argue in favor of neuropsychoanalysis is that neuroscience could help psychoanalysis further demonstrate its therapeutic efficacy in an evidence-based context, by identifying structural or

functional changes in the brain in response to the therapy. However, as Mechelli plausibly stresses, neuroanatomical changes are of a quantitative nature and cannot be fully informative about the nature or the quality of the analytic experience or the effectiveness of treatment (Mechelli 2010). We would corroborate and go on to say that effectiveness of treatment is also to be assessed in terms of insight acquired, growth gained, and the improvement achieved in patient's living and relating with others besides the assessment of his/her functioning in various domains of life.

## 10.2 Neuroscientific Findings in Relation to Psychoanalytic Theory

We will now turn to the presentation of some current neuroscientific findings that are linked to essential aspects of the psychoanalytic theory.

### 10.2.1 The Unconscious

The study of the unconscious and its dominant role in mental life represents a cornerstone in psychoanalytic theory, which is also unique to psychoanalysis, in that the conceptualization of unconscious (encompassing phantasies, emotions, and motivation) has been fundamentally different from its view in cognitive neuroscience. In that context, some authors prefer to refer to "*non-conscious*" instead of unconscious processes to discriminate cognitive from emotional and motivational aspects of the unconscious (Berlin 2011).

Moving closer to the psychoanalytic conceptualization of unconscious, the interest in unconscious processes has been expanded recently from the study of cognitive functions, such as memory and learning, to the exploration of emotions and motivation within the evolving fields of affective and social neuroscience.

As for the "cognitive" part of the unconscious, it has been found that unconscious perception of subliminal stimuli can induce motor responses or, at a more complex level, activate high-level cortical areas to induce an appropriate behavioral response. In addition, semantic priming and associative learning have been found to take place outside awareness. Notably, besides unconscious cognitive processes, there is sufficient evidence that emotion processing can also occur outside conscious awareness; subliminal (thus not consciously perceived) emotionally valenced stimuli can activate emotional circuits including, but not restricted to, the amygdala (Berlin 2011). It has also been found that conscious interfering in the processing of a stimulus can eliminate the conscious perception of the emotional valence of the stimulus. In other words one could say that conscious interfering, particularly exerted by the prefrontal cortex, can *repress* information toward the unconscious. In addition to the interaction between cognitive and unconscious emotional processing, it has been found that unconscious emotionally valenced stimuli can influence motivation, social judgment, and

goal-directed behavior. Decisions seem to be influenced by unconscious processes more than we believed (Berlin 2011). Recent reviews have challenged the so far prevailing role of consciousness on the setting and pursuing personal goals and documented the presence of what has been described as "unconscious will," which initiates the perseverance of personal goals before or even outside conscious attending to them (Custers and Aarts 2010; Dijksterhuis and Aarts 2010). Conscious decision-making is thought to be more precise but with less capacity to integrate larger proportion of information compared to unconscious thinking. Thus, it is proposed that conscious thinking might be more suitable for simple matters, whereas unconscious processing might offer better choices under complex conditions (Berlin 2011).

The increased interest in the study of all the aspects of the unconscious has led to the exploration of its neurological substrate. Schore assigns the neurological substrate of the dynamic unconscious to the right hemisphere, which he considers as the "nest" for sexual and aggressive impulses. He also argues that repression of such impulses an interhemispheric inhibition exerted by the left hemisphere upon the right. However, such an inhibition can be feasible only after the left hemisphere has established dominance over the right, i.e., after the age of 4. This led Schore to conclude that the formation of the unconscious in the early years of life must rely on mechanisms other than repression (Schore 2003). In contrast, Kaplan-Solms and Solms challenge the linking of the right hemisphere with the capacity for repression based on their clinico-anatomical studies in patients with damage in the perisylvian area of the right hemisphere. These patients demonstrated greater ego-deficits, and thus less capacity for repression, compared to their left-hemisphere counterparts (Kaplan-Solms 2000).

### 10.2.2 Defense Mechanisms

It is stressed that the complex emotional-cognitive interaction underlying the constitution of defense mechanisms can be better explored in the context of neuronal integration (Northoff et al. 2007).

#### 10.2.2.1 Regression

It has been postulated that the *sensorimotor regression* (as typically observed in catatonia) might be related with disruption in the function of a neural circuit involving the orbitofrontal, the premotor, and the medial prefrontal cortices. The orbitofrontal cortex has also been highlighted in constituting defenses that are relatively more mature (Northoff et al. 2007).

#### 10.2.2.2 Repression

Although the neural mechanism underlying *repression* is still unknown, it has been observed that people with longer "utilization brain duration," i.e., the critical time period of neural activation in order for a stimulus to become conscious, might be more prone to repression (Berlin 2011).

#### 10.2.2.3 Suppression

Compared to repression, *suppression*, i.e., the conscious casting unbearable thoughts or emotions away from awareness, has been associated with increased activation of dorsolateral prefrontal cortex and reduced activation of the hippocampus. It has also been found that as long as suppression is constantly repeated, it can evolve to repression (Berlin 2011).

### 10.2.3 Memory and the Unconscious

It is stressed that the unconscious as a storage of content related—though not limited—to memories can plausibly be linked to the structures involved in memory (Mancia 2006).

Memory encompasses a dual system consisting of overlapping and usually working together subsystems, namely:

(a) *Explicit* or *declarative* memory, which is conscious and encodes autobiographical and other factual information on people, objects, and places. The medial temporal lobe and particularly the hippocampus complex are essential for its function (Milner et al. 1998). However, it has also been stressed that after sufficient time, the storage or retrieval of explicit memory no longer depends on hippocampus but on the neocortex instead (Squire and Alvarez 1995).
(b) *Implicit* memory, which involves unconscious information of many kinds involving different brain areas (following in parenthesis below).

In specific, implicit memory involves (a) *procedural* memory for skills and habits (striatum); (b) *priming* (neocortex); (c) *classical conditioning*, further related to *emotional responses* (amygdala) and the *skeletal musculature* (cerebellum); and, finally, (d) *associated learning* (reflex pathways) (Milner et al. 1998). There occurs a significant interplay between the two subsystems as many learning processes involve both, whereas the repetition of a task can transform explicit memory to implicit, of procedural type (Kandel 1999). In addition, amygdala, involved in implicit memory, also exerts an influence on explicit memory, due to its involvement in emotion processing (Milner et al. 1998).

Linking memory with the unconscious, Kandel postulates that the part of the unconscious that does not contain conflict-evoking or repressed material but is concerned with habits and skills, either perceptual or motor (i.e., what he calls the "procedural unconscious"), can be mapped to the procedural implicit memory (Kandel 1999). On the other hand, the dynamic (repressed) unconscious might be linked with the circuit involved in explicit memory (Kandel 1999; Mancia 2006). Furthermore, given that amygdala matures earlier than the hippocampus, Mancia argues that early infancy experiences cannot be stored in the explicit memory (which is hippocampus-dependent) but are filed in the implicit memory since this is the only one available at that time (Mancia 2006). Besides early experiences of any kind, traumatic experiences (even of later time) cannot be filed in explicit memory

either due to a trauma induced loss of hippocampal neurons (McEwen and Sapolsky 1995). Such experiences are also thought to be filed in implicit memory, constituting what Mancia calls a *late unrepressed unconscious,* which is irretrievable by conscious effort though not because of repression (Mancia 2006). Mancia argues that these irretrievable experiences might be accessible through dreaming, as in the case of patients with bilateral hippocampal lesions who were failed to consciously recall the previous training for a memorizing game but mentioned dreaming about it (Stickgold et al. 2000).

### 10.2.4 Dreaming

In this part, we will refrain from dealing with the neurobiology of dreaming as a psychophysiological phenomenon and will be concerned with the neuroscientific findings that might provide insight regarding the function of dreaming, as the latter reflects the aspect of dreaming that psychoanalysis is concerned with. There are some findings that corroborate the Freudian conceptualization of the dreamwork. For instance, Mancia argues that there are neuroscientific findings that can confirm the "*derepression*" function of dreaming, i.e., bringing repressed material back to light. According to Mancia, such a function can be inferred from the reciprocal pattern of activation/deactivation observed during REM-related dreaming compared to deactivation/activation of the same areas, namely, the hippocampus and the dorsolateral frontal cortex, respectively, during voluntary repression. (It is a matter of terminology whether this should better be called suppression.) In addition, Johnson argues that there is strong evidence corroborating the "*wish-fulfilment*" function of dreams, as stressed by Freud (Johnson 2001).

### 10.2.5 Empathy

The discovery of the mirror neuron systems in the macaque monkey (di Pellegrino et al. 1992) and the verification of the existence of a similar system in humans (Rizzolatti 2005) have given the opportunity to view human beings no longer as a social and self-centered minds but as capable of interpersonal communion and other-centered participation at the very outset of life (as of infancy) in the context of "intersubjectivity" (Bråten 2007). In addition, the discovery of mirror neurons has enhanced the study of an issue closely related to psychoanalysis such as empathy.

#### 10.2.5.1 Actions

A circuit encompassing the middle temporal gyrus, the rostral inferior parietal lobule, and the ventral premotor cortex has been found to be involved in both the performance of one's own actions and the observation of the same actions by others (Keysers and Gazzola 2006). In addition, important properties of the mirror system, namely, (a) *selectivity* to a certain kind of a precise action as well as (b) a *somatotopical organization*, not only for actions but also *for the related sounds* have also

been found in humans (Gazzola et al. 2006). Another interesting finding is that mirroring might also be gender-specific as revealed in a study among male and female dancers (Calvo-Merino et al. 2005). However, in our opinion, it might warrant further clarification whether such a mirroring represents a gender-specific or a role-specific one.

#### 10.2.5.2 Sensations

Concerning sensations, it has been found that the somatosensory cortices are involved in both experiencing touch on oneself and viewing others being touched (Keysers et al. 2004). Similarly, anterior cingulate and insular cortices have been found to be involved in the both the first-person experience of one's own pain and the perception of others in pain (Jackson et al. 2005; Avenanti et al. 2005).

#### 10.2.5.3 Emotions

As for emotions, the anterior insula has been found to involve both in the experience of disgust and in the observation of disgust in others, whereas amygdala has been implicated in both the subjective experience of fear and in the perception of fear in others. However, Keysers and colleagues challenge the opinion that amygdala shows fear selectivity. Instead, they argue that amygdala is involved in processing of all facial expressions and that recognition of fear in fearful facial expressions might be confounded by factors such as focusing on the eye part of the picture or not or on the investigation method, i.e., photo with fearful expressions vs. video (Keysers and Gazzola 2006). They conclude that the role of amygdala in the experience of fear in both a first- and third-person perspective might be indirect, with amygdala representing an information providing part within a circuit involving other brain areas which might be more directly associated with fear than amygdala.

Concerning the understanding of the emotions of others from a third-person perspective, Damasio and colleagues consider a somatosensory representation of the body state of the person observed as a necessary condition (Damasio 2003b). In contrast, Keysers and Gazzola (2006) hold that somatosensory representations are important in the case of others' sensations but may not be central to our understanding of others' emotions and actions.

### 10.2.6 Empathy and Differentiation Between the Self and Others

Given the existence of a shared circuit involved in both first-person and third-person experience, there emerges the issue of differentiation between the representation of the self vs. the others.

Keysers and colleagues argue that there can be a discrimination between one's own experience and the perception of other's experience on the basis of a different pattern of activations among the (same) areas involved in both (Keysers and Gazzola 2006). Other authors argue that brain areas such as the right inferior parietal lobule and the posterior cingulate gyrus are involved in the explicit differentiation between

self and others (Decety and Sommerville 2003; Vogt 2005). Van Veluw and colleagues reviewed relevant studies and concluded that although there are regions of higher order prefrontal cortex involved in both self-representation and the presentation of others, there are also distinct neural circuits with different connectivity patterns separately involved in each kind of representation. In specific, regions involved in both representations were the superior temporal gyrus and the ventromedial prefrontal cortex. The medial prefrontal cortex, the temporoparietal junction bilaterally, the precuneus, and the middle temporal gyrus bilaterally were involved in the representation of others, whereas the right superior temporal gyrus, the right parahippocampal gyrus, the right inferior frontal gyrus/anterior cingulate cortex, and the left inferior parietal lobe were involved in self-representation. According to the authors, these findings may provide new insight into disorders such as autism, schizophrenia, and borderline personality disorder, in which a disruption of the self and other representations is profound (van Veluw and Chance 2014).

### 10.2.7 The Self

In addition to the finding that the medial prefrontal cortex is selectively activated during self-referential processing (Kelley et al. 2002), there has been a link between different facets of self-referential stimuli processing and certain areas within the cortical midline structures, more specifically, *self-representation* and orbitomedial prefrontal cortex, *self-monitoring* and supragenual anterior cingulate cortex, *self-evaluation* and dorsomedial prefrontal cortex, and *self-integration* and posterior cingulate cortex (Northoff and Bermpohl 2004). Northoff and colleagues conclude that the self is related with the neuronal connectivity and integration among different brain areas. They also postulate that certain areas along the cortical midline structures linked with certain aspects of the self, extending what has been mentioned above (for instance, the right posterior insula and right inferior parietal cortex—linked with self-agency—and the right parietal and ventromedial prefrontal cortex, linked with self-ownership-), might represent the neural correlate of what Damasio has termed as the "*core self*," i.e., the continuous interaction between intero- and exteroceptive stimuli that allows the self to be perceived as a unit (Northoff 2012; Northoff and Bermpohl 2004; Damasio 2003a).

### 10.2.8 The Ego and the Default Mode Network

Raichle et al. have introduced the notion of default mode network (DMN) to emphasize on the brain's intrinsic activity, i.e., activity not directly related to identifiable sensory or motor events (Raichle and Snyder 2007; Raichle et al. 2001). The DMN includes the medial prefrontal cortex, the posterior cingulated cortex, the inferior parietal lobule, and the medial temporal lobes (Raichle and Snyder 2007; Raichle et al. 2001; Buckner et al. 2008). The major nodes of DMN demonstrate a strong structural and functional connectivity (Greicius et al. 2009) that develops ontogenetically, as, for

instance, the medial prefrontal cortex and the posterior cingulated cortex are absent or underdeveloped in infants (Fair et al. 2008; Kelly et al. 2009).

DMN shows a competitive activity—antiphase relationship with reciprocal pattern of activation/deactivation—compared to another large-scale intrinsic network which is activated during cognitive tasks, occasionally referred to as the "*attention system*" (Fox et al. 2005).

Carhart-Harris and colleagues consider DMN as sitting at the top of the hierarchical organization of the brain and parallelize it with what they call "*the core of the ego*." They postulate that just like ego—by employing the secondary process—tries to bound the free energy of primary process (the latter entailed by the Id), so are higher cortical regions, the DMN and medial prefrontal cortex, in particular, trying to suppress the activity of lower limbic areas, i.e., the medial temporal lobe structures such as hippocampus, parahippocampus, amygdala, and endorhinal cortex, thus exerting a *top-down control*. In sum, Harris parallelizes the Freudian concept of ego and the default mode network based on:

(a) The integrated and compound nature of both.
(b) The parallelism in the course of their development and maturation (progressive development of functional connectivity among DMN parts over time).
(c) The conceptualization of the ego as an agency that acts as a recipient and regulatory agency (top-down control) of endogenous activity coming from the Id (bottom-up) related with drives, memories, and affects similar to the structural and functional connectivity between the cortical nodes of DMN and the lower limbic structures.
(d) The conceptualization of ego as the tonic reservoir of activity similar to the high resting activity and metabolism characterizing the DMN.
(e) The Freudian conceptualization of the ego as the "seat of the sense-of-self" and the involvement of the DMN in self-referential processing.

Carhart-Harris and colleagues conclude that such a synthetic approach could provide insight for disorders like anxiety, depression, and addiction (Carhart-Harris and Friston 2010, 2012).

## 10.3 Conclusive Thoughts

We think that inevitably, when translating from one language to another, some shades of the original meaning cannot be grasped, no matter the expertise competence of the translators. Similar to this is Bion's postulation regarding "*O*," or "*ultimate reality*," which can never be known; it can tentatively be inferred through its transformations, but there always be something that cannot be grasped. Hence, we think that there will also be something embedded in psychoanalytic understanding that cannot be fully conveyed to neuroscientific findings and vice versa. That said, we believe that a dialogue between the two disciplines remains meaningful. Arguing in favor of a mutually respective and collaborative dialogue between the two

perspectives, there come to our minds Bion's formulations regarding the "*language of substitution*" (which we would like to parallelize with the descriptive nature of the neuroscientific language), the "*language of achievement*" (which we would parallelize with the empathic understanding within psychoanalytic thinking and practicing), and his recommendation that the analyst should be sensitive to and employing both (Bion 1984a). In other words, we might say that neuroscience and psychoanalysis could provide insight deriving from different perspectives or "*vertices*" that could synergistically constitute a meaningful "*binocular vision*," to mention another Bion's formulation (Bion 1984a, b) we regard as applicable.

Thus, we think that although psychoanalysis and neuroscience do differ in terms of research question and aim, a dialogue between the two would still be meaningful, despite the limitations. Such a dialogue might not be that threatening for psychoanalysis, since there are always be an ultimate question, concerning the subjective meaning, which could be addressed only by psychoanalysis, no matter the progress in neuroscientific knowledge base. (Not to mention the fundamental difference lying in that psychoanalysis goes even further than addressing a question to dealing with dynamics that any answer evokes.)

In order to illustrate our postulation, we invite you to think of an imaginary dialogue between a patient and a neuroscientist. (At the moment, we put aside the concern regarding the provision of neuroscientific information to the patient, for the sake of the conversation.)

– Why do I feel so guilty?
– It's probably because your "guilt" circuit was activated.
– Ok, but what made it activate in the first place?

Even if the neuroscientist could provide an answer such as "an unconscious phantasy—probably an aggressive one—arose," he could not identify its qualitative characteristics, not restricted to its content, unless neuroscience could visualize one's unconscious thoughts, which is highly unlikely.

Even after overcoming this barrier, the neuroscientist would probably be faced up with another question "…And what made this fantasy come up in here and now?...".

This is a question that cannot be answered unless the dynamics concerning patients relating to others in all three dimensions, i.e., past, present, and transference, are put forward and the meaning the patients attributes to this knowledge gained is explored. Thereon, following the insight gained another question such as "now what?" might emerge, referring to the process of change, i.e., transforming knowledge gained to behavioral change. Another circle of resistances and dynamics to be elucidated and worked through by analysis. Another storm of anxieties to be "*held*" and "*contained*."

What we want to emphasize is that absolute convergence or even assimilation between the two disciplines should not be considered as meaningless or feared as harmful, since it is unfeasible in the first place. This is due to a fundamental difference between psychoanalysis and neuroscience in terms of both the nature

of the main question and aim to be addressed as well as the suitability and efficiency of each domain to provide a meaningful answer and working through. Psychoanalysis seeks to come up with answers concerning *why*, i.e., identify the subjective *meaning* of certain thoughts, fantasies, or behaviors; from another vertex, neuroscience can effectively provide some answers concerning *how*, by identifying the neuronal substrate and mechanisms correlated with certain mental phenomena. At this point, we would also like to stress parenthetically that tracking certain behaviors down to their neural substrate does not necessarily reflect a causal relationship. Cross-sectional studies of first-person experience and third-person observation are inherently incapable of providing inferences regarding causality in the first place; that is, in the context of a bidirectional interplay between neurobiology and behaviour, a certain behavior observed in a certain moment might be accounted for by a functional disruption in a certain neuronal circuit, but, conversely, it might also be the case that this behavior is the preceding cause, in that it might had previously modified the relevant neural circuits. Prospective studies would be helpful, but they have to overcome the barrier of setting the "zero" (starting) point of observation, among other complexities.

In line to the relevant arguments postulated in favor of neuropsychoanalysis stressed so far, we think that neuroscience could help elucidate and provide further scientific foundation and wide acceptance for some psychoanalytic concepts and formulations. We could mention "*repetition compulsion*," "*death drive*," "*innate aggression*," and "*primary envy*"; the Kleinian concepts of "*schizoid-paranoid*" and "*depressive position*," "*projective identification*," and "*empathy*"; and Bion's "*alpha function*," "*dreamwork*," the capacity for "*symbolization*," "*psychological thinking*," "*mentalization*," or even the "*transference/countertransference*" itself, to name some among a large list. In addition, neuroscience might provide insight and further validation regarding some aspects of psychoanalytic technique (or even the setting) such as whether the "*free association*" indeed enhances the emergence of unconscious content by eliminating conscious censorship or whether the "*evenly suspended attention*" or the "*reverie*" on behalf of the analyst reflects a brain state where the grasp of patient's unconscious meaning of communication is really enhanced, or even if "lying on the couch" and talking with no visual contact with and not frequent feedback from the listener indeed enhances the unfolding of early memories and anxieties, among others. That said, we do not argue that the abundance of empirical knowledge and clinical experience added so far is not enough to establish the psychoanalytic theory, setting and technique as valid and meaningful; nevertheless, neuroscientific cross-validation might not only provide psychoanalysis wider acceptance beyond the psychoanalytic community but it might also in some cases provide useful insight that might lead to a fruitful revisiting of certain aspects of psychoanalysis. On this ground, neuroscientific knowledge could also contribute to a richer dialogue regarding several issues—hopefully even the controversial ones—within the psychoanalytic community regarding both the theory and the technique of psychoanalysis and contribute to the scientific invigoration and evolution of the latter.

On the other hand, one thing that warrants attention is the use of any insight gained from neuroscience within the analytic practice in the context of the sessions. For instance, we think that including solid neuroscientific findings into psychoanalytic knowledge base is one thing, but conveying such knowledge to the patients is another; therefore we believe that such a practice should be employed with caution, not just in order to keep in line with the Freudian recommendation for "*abstinence*" (Freud 1958). Providing the patient with knowledge about certain limitations identified by the neuroscientific research (as Solms and colleagues showed in their case report, namely, inability to access early traumatic memories) might significantly diverge from the very spirit of psychoanalytic practice if employed thoughtlessly. Although this could ameliorate patient's anxiety, it might also hinder the working-through of the underlying dynamics. We think that any information provision should better not precede the extensive unfolding and working-through of the dynamics underlying any question posed. To take another example, however, tempting it might be for the analysts to provide neuroscientific evidence demonstrating the efficacy of psychoanalytic treatment, such a practice might compromise the working-through of the patient's ambivalence on entering or continuing analysis and engaging in an intimate human relationship—with all kinds of anxiety associated with it—or even addressing the possibility of the patient employing a "*reversible perspective*," as pointed out by Bion (1984a, b).

We generally agree that neuroscience might "*help demarcate the limits of psychoanalysis*" and identify patients most likely to benefit from psychoanalysis or brief psychodynamic psychotherapy; indeed, we think that neuroscience could contribute to a synthesis concerning the criteria employed to assess the applicability and potential benefit of a certain type of treatment among the psychodynamically originated therapies. Nevertheless, we think that the decisive role should be preserved for the clinical criterion and the risk of misuse of neuroscientific evidence that would lead to hasty categorical arguments for analyzable vs. non-analyzable patients should be acknowledged and managed.

As Fonagy points out, science progresses in an interdisciplinary context anyway. Thus, psychoanalysts cannot avoid being aware of recent developments in science, even if they are not consciously engaged in such a dialogue (Fonagy 2003).

Besides, Freud himself and many other prominent psychoanalytic thinkers have always been in a dialogue with philosophy or even the natural sciences. Why not with neuroscience then?

We think that there has emerged an ongoing fruitful dialogue between proponents and opponents of neuropsychoanalysis that can provide the psychoanalytic community with further insight. Both sides have admitted points of convergence and satisfactorily addressed their concerns alongside with a better clarification or even slight modification of their original arguments.

Conclusively, we think that despite the limitations and concerns, a dialogue between psychoanalysis and neuroscience would be meaningful and beneficial for both disciplines provided that a mutually respected attitude is safeguarded. We agree with Yovell et al. (2015) stressing that a deliberate negligence and isolation should be avoided. However, we also believe that analysts should be aware of

neuroscientific findings but at the same time they should be able to enter an "*as if not knowing*" state, in line with the recommendations of Freud for a self-imposed "*artificial blindness*" (Freud et al. 1972) and Bion for the "*abandonment of memory and desire*" within the analytic session (Bion 1984a). We think that the analysts should refrain themselves from using neuroscientific knowledge as a "*procrustean bed*" trying to fit patients' meanings into the prevailing theoretical model.

## Appendix

### Self-Assessment Questions

1. Sigmund Freud, founder of psychoanalysis:
   (a) Was an eminent psychologist who had nothing to do with neurobiology.
   (b) Essentially never gave up the belief that psychoanalytic ideas could eventually find biological evidence.
   (c) Had no interest in establishing psychoanalysis as a widely accepted discipline within medical science.
   (d) None of the above.
2. According to Kandel, neuroscience could contribute to psychoanalysis in:
   (a) Understanding preconscious and unconscious mental processes.
   (b) Clarifying psychological causality and its relation to early experience.
   (c) Identifying brain structural changes in response to psychotherapy.
   (d) All of the above.
3. According to Kandel:
   (a) Psychobiology and psychoanalysis have nothing in common to be studied.
   (b) There is a necessity for a scientific dialogue between neuroscience and psychiatry-psychoanalysis.
   (c) The time for a dialogue between neuroscience and psychoanalysis has not come yet.
   (d) None of the above.
4. Human behavior is determined by genes which are in no way influenced by environmental factors.
   True False.
5. Which of the following is true?
   (a) Psychoanalysis and neuroscience have always been in a state of mutual disregard and conflict.
   (b) Over the last two decades, there has risen a mutual interest of both neuroscientists and psychoanalysts regarding the bridging of the two disciplines.
   (c) Bridging between neuroscience and psychoanalysis should lead to a merging of the two disciplines in one.
   (d) None of the above.

6. "First-person neuroscience" aims to study:
   (a) The subjective experience of mental life by means of carefully designed first-person assessment tools.
   (b) A person's behavior observed by the most suitable (first-person) investigator.
   (c) A person's early experiences with parents and siblings (first-degree relatives).
   (d) None of the above.
7. It is unanimously accepted that neuroscientific findings represents the final "court of appeal" for psychoanalytic theory and practice.
   True False.
8. Neuropsychoanalysis aims:
   (a) To teach psychoanalysts how the brain operates.
   (b) To teach neuroscientists the dynamics that underlie human behavior.
   (c) To provide evidence that could help neuroscience and psychoanalysis engage in a mutually beneficial dialogue.
   (d) None of the above.
9. Dual-aspect monism as postulated by Solms and colleagues refers to.
   (a) The mind and brain seen as one and the same entity investigated from two complementary perspectives.
   (b) The existence of two contradictory opinions on how the brain operates.
   (c) The dual function of genes.
   (d) None of the above.
10. The "spatiotemporal structure" of the brain resting-state activity has been paralleled by Northoff with the Freudian non-anatomical conceptualization of the "psychological structure" of the mental apparatus.
    True False.
11. The discovery of mirror neurons has provided insight regarding:
    (a) Hallucinations.
    (b) Projections.
    (c) Empathy.
    (d) None of the above.
12. The existence in humans of a mirror neurons system similar to that discovered in monkeys is true for:
    (a) Actions.
    (b) Emotions.
    (c) Sensations.
    (d) All of the above.
13. According to current neuroscientific findings:
    (a) The "wish-fulfilling" function of dreaming can no longer be supported.
    (b) The "derepression" function of dreaming can be confirmed.
    (c) The interpretation of dreams renders clinically meaningless.
    (d) None of the above.

14. The default mode network (DMN):
    (a) Is responsible for the default answers brain utilizes when faced up with vague stimuli.
    (b) Is linked to the extrinsic view of brain function.
    (c) Is located in the limbic system.
    (d) None of the above.
15. Certain memories might be unable to enter consciousness due to:
    (a) Repression.
    (b) Acute loss of hippocampal neurons in case of traumas.
    (c) Suppression.
    (d) Any of the above.
16. DMN and the concept of Ego have been parallelized, based on:
    (a) The integrated and compound nature of both.
    (b) Their acting as a regulatory system exerting a top-down control.
    (c) Their representing a tonic reservoir of activity.
    (d) All of the above.
17. The existence of unconscious mental processes has been verified for cognitive but not emotional aspects.
    True False.
18. Among others, one thing that makes the absolute convergence between psychoanalysis and neuroscience unfeasible is that the latter cannot satisfactorily address and handle.
    (a) The how.
    (b) The why.
    (c) The where and what.
    (d) None of the above.
19. A dialogue between neuroscience and psychoanalysis might.
    (a) Help neuroscientists for a better targeted research.
    (b) Provide scientific foundation for some psychoanalytic formulations.
    (c) Provide insight about the effectiveness of certain aspects of psychoanalytic technical tools.
    (d) All of the above.
20. Neuroscientific findings could help clinicians decide between providing patients either psychoanalytic or psychopharmacological treatment.
    True False.

## Answers

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 1 | B | 6 | A | 11 | C | 16 | D |
| 2 | D | 7 | False | 12 | D | 17 | False |
| 3 | B | 8 | C | 13 | B | 18 | B |
| 4 | False | 9 | A | 14 | D | 19 | D |
| 5 | B | 10 | True | 15 | D | 20 | False |

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# Psychophysiology and Psychosomatics

# 11

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## 11.1 Psychophysiology

The discipline of psychophysiology concerns the study of the link between psychological processes and somatic physiology, which is the interface between mind and body (Cacioppo et al. 2007). Historically, most of research concerns the physiological responses and the function of the organ systems innervated by the autonomic nervous system, especially under stressful conditions (Lang et al. 2000), but more recent research has focused on the brain with the use of electrophysiological techniques and functional neuroimaging (Hugdahl 1984; Schwartz 1999; Striefel 1999; Bechtereva 2000; Gordon 2001).

Psychophysiology utilizes instruments and devices which record the activity of various physiological systems in the human body and compares these results with measures of psychological states. The main fields of psychophysiology research concern the study of emotions (Ekman et al. 1983; Panconesi and Hautmann 1996; Glynn et al. 2002; Davidson 2003; Corr and Perkins 2006; Critchley 2009; Stemmler and Wacker 2010; Quigley and Barrett 2014; Katz and Greenberg 2015), pain (Handwerker and Kobal 1993; Keefe and Smith 2002; Tiller 2006; Wachholtz et al. 2015), psychopathology (Fowles 1988; Steinhauer and Hakerem 1992; Carroll and Sheffield 1998; Wilhelm and Roth 2001; Corr and Perkins 2006; Tiller 2006; Stemmler and Wacker 2010), but also forensics (Yankee 1995; Furedy 1996).

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The term "psychophysiology" comes from the Greek *"ψυχή"* (psichi meaning the soul) plus "*φυσιο-*" (physio—meaning nature) and "*λογια*" (logia meaning the study of things). The term "psychosomatics" comes again from "*ψυχή*" plus "*σωματικός*" (somatikos meaning bodily function).

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### 11.1.1 Brain Psychophysiology

Brain psychophysiology includes the study of brain function with electroencephalography (EEG), functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), event-related potentials (ERPs) (Coles 1989), and other similar methods.

- EEG records electrical activity through the electrodes placed along the scalp, corresponding to the brain's spontaneous electrical activity. This activity corresponds to the summation of the synchronous activity of billions of neurons that have similar spatial orientation. Its diagnostic applications include the diagnosis of epilepsy, sleep disorders, coma, encephalopathies, and brain death. A routine clinical EEG lasts 20–30 min plus preparation time and usually uses the 10–20 system for the placing of the electrodes. For the first time, EEG was recorded by Hans Berger (1873–1941) in 1924. ERPs are derivatives of the EEG technique and involve the averaging of the EEG responses to the presentation of a visual, somatosensory, or auditory stimulus (Niedermeyer and da Silva 2004; Schreckenberger et al. 2004).
- MEG records the magnetic fields produced by the brain's electrical activity. For the first time, they were recorded by David Cohen in 1968 (Cohen 1968; Cohen and Cuffin 1983). The most important problem of biomagnetism is that the signal is relatively weak in comparison to the environmental noise and to the sensitivity of sensors. Event potentials can also be recorded with MEG.
- ERPs were recorded for the first time in 1935 by Pauline and Hallowell Davis (1896–1992). Grey Walter discovered the first cognitive ERP component, called the contingent negative variation (CNV) in 1964 (Walter et al. 1964), and the next year, Samuel Sutton, Margery Braren, and Joseph Zubin discovered the P3 (P300) component (Sutton et al. 1965). ERPs are one of the most widely used methods to study the physiological correlates of sensory, perceptual, and cognitive activity as well as the process of information. The pattern and the timing of responses and their components provide an image of brain function and the timing of information processing. After the P3, a number of other components were discovered including the ELAN, the N400, and the P600/SPS (Handy 2005).
- Magnetic resonance imaging (MRI) is used in radiology to image the anatomy and the physiology of the human body (McRobbie 2007). Essentially MRI scanners use strong magnetic fields, radio waves, and field gradients to form images of the body. The technique of the MRI is based upon the property of certain atomic nuclei to absorb and emit radio frequency energy when placed in an external magnetic field. In contrast to simple MRI, the functional MRI (fMRI) is used to record changing neural activity in different parts of the brain as a response to external stimuli (Heeger and Ress 2002). Blood oxygenation level-dependent (BOLD) fMRI measures the hemodynamic response to transient neural activity resulting from a change in the ratio of oxyhemoglobin and deoxyhemoglobin. Increased neural activity increases the demand for oxygen, and subsequently there is an increase in the amount of oxygenated hemoglobin

relative to deoxygenated hemoglobin. Other techniques include the arterial spin labeling (ASL) or weighting the MRI signal by cerebral blood flow (CBF) and cerebral blood volume (CBV) (Singer 1959).

Detailed description of the above methods and techniques is beyond the scope of the current chapter, and it can be found in specialized books and articles. However, it is important to note that in comparison to other imaging techniques (e.g., fMRI), electrophysiological methods have very high temporal resolution, on the order of milliseconds, but rather low spatial resolution on the scalp. However, on the contrary, electrophysiological methods measure the neural activity that occurs only at the surface of the brain and not at deep structures, and unlike PET and MRS, they cannot identify neurotransmitters, drugs, and metabolic indices. In research settings, structural MRI or functional MRI (fMRI) can be combined with EEG (electroencephalography) under the condition that the EEG equipment is MR compatible.

### 11.1.2 Pupillometry and Eye Movements

The testing of the eye pupil function gives information on the two components of the autonomic nervous system, that is, the sympathetic nervous system and the craniosacral or parasympathetic nervous system. These two parts of the autonomic nervous system exert opposite effects on the pupil (Ropper and Brown 2005).

One of the most interesting features of the eye is the pupil reaction to light, during which, acetylcholine acts on the muscarinic receptors of the sphincter muscle and leads to miosis (decrease of the size of the pupil). The dilator muscle of the pupil has an opposite function. The neurotransmitter released in the neuromuscular junction of the dilator muscle is norepinephrine, which through its effect on a-adrenergic receptors, leads to constriction of the dilator muscle and causes mydriasis. During miosis, acetylcholine is secreted in the dilator as well, inhibiting norepinephrine activity. Therefore the change of the pupil size as a response to a light stimuli is based on the functional balance between parasympathetic and sympathetic nervous systems (balance between acetylcholine and norepinephrine).

In the absence of a documented peripheral disorder, the contribution of peripheral structures is negligible in comparison to that of central ones (Fotiou et al. 2000b). So, the pupil reaction to light may be used either to test peripheral structures of the autonomic nervous system or, in cases in which peripheral structures are intact, to assess acetylcholine and norepinephrine function in the brain.

The assessment of the pupil reflex has been used to study the deficit of the parasympathetic supply to the pupil, among others, in alcoholics (Tan et al. 1984), pain (Chapman et al. 1999), HIV (Maclean and Dhillon 1993), depression (Sokolski and Demet 1996; Fountoulakis et al. 1999), generalized anxiety disorder (Bakes et al. 1990), and Alzheimer's disease (Scinto et al. 1994; Prettyman et al. 1997; Grunberger et al. 1999; Fotiou et al. 2000a; Granholm et al. 2003; Frost et al. 2013).

The critical point in this kind of research is the method used for the assessment of the pupil. Today, parasympatheticomimetic agents like methacholine 2.5% and pilocarpine 0.125%, 0.0625%, or 0.05% or mydriatic agents like tropicamide, cocaine 4%, epinephrine 0.001%, phenylephrine 10%, or hydroxyamphetamine are used. Important drawbacks of the method of direct application of these agents in the eye are that the eye epithelium may manifest different permeability across individuals and disorders and technical problems concerning the stability of the solutions applied and the characteristics measured (should one measure the difference in reaction to a standard dose of an agent-stimulus or the smallest dose that produces the minimum reaction?). It is obvious that the pharmacological methods of testing the pupil reactivity are poor and the results of studies that use these methods should be considered with caution.

On the contrary, optical methods which utilize recording of the pupil reaction to dark and light or the reaction to various stimuli are more reliable and provide a significant number of dynamic information, including speed, acceleration, and size at different time points (Fig. 11.1). These methods are noninvasive, do not depend on the condition of the epithelium or the stability of solutions, and measure a natural phenomenon, not a chemically induced one (Fotiou et al. 2000b). The variance due to the method itself is minimal.

Eye movement refers to both the voluntary and the involuntary movement of the eyes (Wehner 2005). Their function is to help in acquiring, fixating, and tracking visual stimuli (Henderson 2003). Rapid eye movement is a special type which occurs during REM sleep. In humans, there are three types of voluntary eye movement: smooth pursuit (following an object that moves), vergence shifts (movements of the eyes in opposite directions), and saccades (rapid movement of eyes while scanning a visual scene (Findlay 2009)), but also there are involuntary random jittering movements. All voluntary movements are under the control of the frontal lobe (Pierrot-Deseilligny et al. 2004). Eye movements can be recorded via electrooculogram (EOG) and direction-of-gaze methods.

### 11.1.3 Electrodermal Activity (EDA)

EDA was discovered for the first time in 1849 by Emil du Bois-Reymond (1818–1896). It refers to the continuous variation in the electrical characteristics of the skin. The combined changes between electrodermal resistance and electrodermal potential make up electrodermal activity. There are many terms which were used to denote this characteristic, including skin conductance, galvanic skin response, electrodermal response, psychogalvanic reflex, skin conductance response, sympathetic skin response, and skin conductance level (Bach and Friston 2013; Boucsein 2013).

As shown by Hermann and Luchsinger in 1878, the mechanism behind this variation in skin resistance is mainly sweating which is under the control of the sympathetic nervous system. As such, it is considered to be a measure of arousal. It was Marie Gabriel Romain Vigouroux (1831–1911) who in 1879 was the first to relate

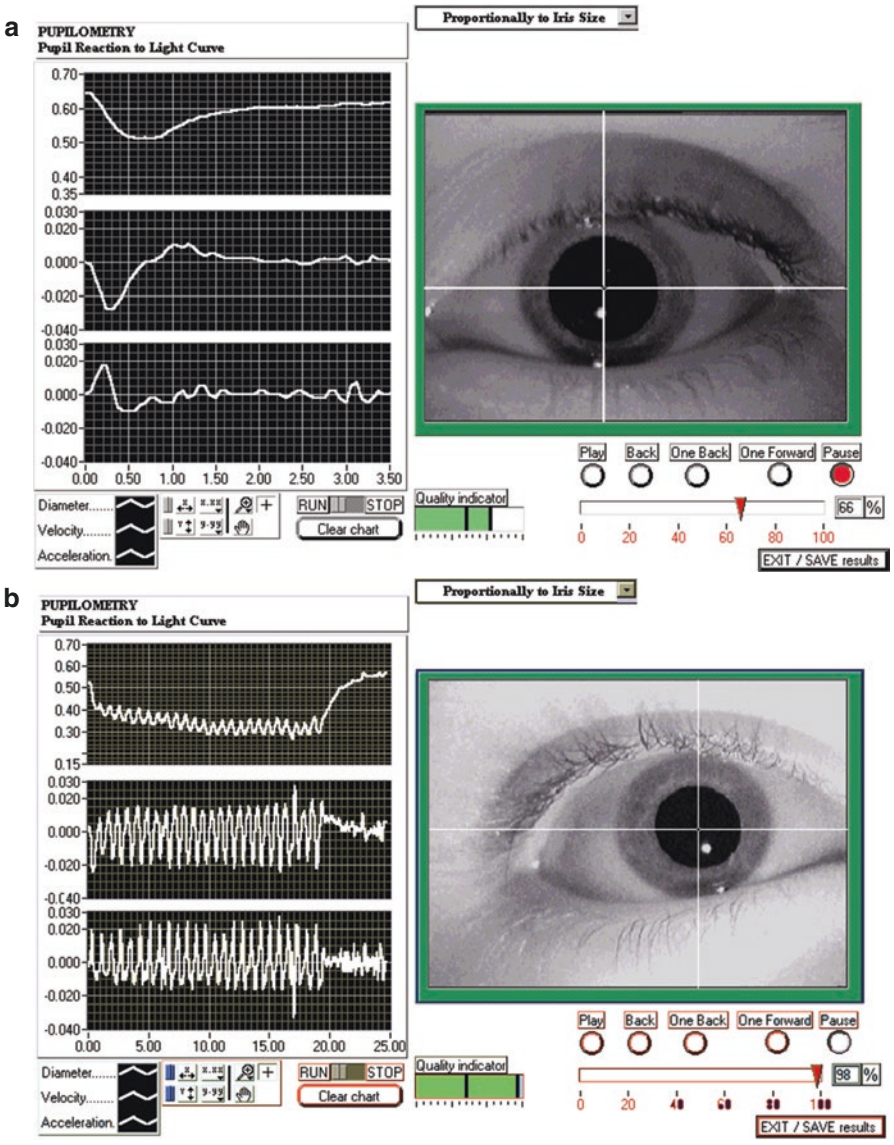


**Fig. 11.1** Pupillometry. (**a**) Pupil reaction to a single flash. (**b**) Pupil reaction to multiple flashes with 1 Hz. In both images the upper curve concerns the size change vs. time, the middle concerns the change in velocity, and the lower concerns the change in acceleration

EDA with psychological factors, while in 1888, Charles Samson Féré (1852–1907) showed that EDA could be changed by emotional stimulation and inhibited by drugs. In 1889 Ivan Romanovich Tarkhanov (or Ivane Tarkhnishvili; 1846–1908) observed spontaneous variations in skin electrical potentials and designed a device to measure these oscillations in real time.

EDA was used by the famous psychoanalyst Carl Gustav Jung (1875–1961) to evaluate the emotional sensitivities of patients to lists of words during word association testing and considered it to be a method to access the unconscious.

While EDA is highly responsive to emotions in some people, including fear, anger, startled response, orienting response, and sexual feelings, the relationship is inconsistent across different people and specifically different or flattened in psychopaths. This later fact makes problematic the inclusion of EDA in polygraphic lie detectors. Also external factors including temperature and humidity as well as medications and other internal (somatic) factors can lead to inconsistent results.

### 11.1.4 Other Psychophysiological Methods

The cardiovascular measures in psychophysiology include the recording of heart rate and its variability and cardiodynamics via impedance cardiography. The recording of somatic muscle activity includes electromyography and thermogram (Ioannou et al. 2014), while the assessment of the gastrointestinal tract includes electrogastrogram (Musial et al. 2008).

The main problem with most of the abovementioned methods is that they are sensitive to artifacts because of any physical activity or motion, they depend on the basal levels of arousal, and responsiveness differs significantly among individuals. Another very important issue is that they are very sensitive to medication status.

## 11.2 Stress

Stress is an organism's response to a stressor which is often an external factor such as an environmental condition. The term has its origins in physiology and engineering. Stress could be purely psychological in origin, or it could be mainly physiological or biological. Pure forms of stress are rare, and usually although one aspect could be predominant, stress includes both psychological and physiological/biological components (Goldstein and Kopin 2007).

Among scientists but also among lay people, stress is considered to be a major element of life and central to both mental and somatic health and disease. It is the universality of its unpleasant experience that makes stress so important both in science and in culture. These beliefs are dated back to antiquity and to a certain extend have been also incorporated in the theological teachings of major religions.

Homeostasis is a concept which refers to the equilibrium toward which most biochemical processes tend to or strive to maintain. The term was coined for the first time by Walter Cannon (1871–1945) in 1926. He made major contributions concerning the role of the sympathetic nervous system in the stress response. He also focused on more immediate (short-term) responses to stressors (Cannon 1926, 1932). Stressors tend to disrupt homeostasis in an extreme way, and as a response, the organism utilizes compensatory mechanisms and reserves to counterbalance the insult. This compensatory efforts usually consume resources to an unusual extend

and therefore could be considered as an additional source of stress. Hans Selye (1907–1982) almost immediately pointed out the ambiguity in defining stress and especially in discovering what is the cause and what is the effect (Selye 1978). He also coined the term "stress" for the first time, and soon after, in 1936, he developed the concept of the general adaptation syndrome, which corresponds to a simplified model of how organisms respond to stress (Fig. 11.2). It includes three phases: a non-specific mobilization phase (mainly sympathetic nervous system activity), a resistance phase (efforts to cope), and a recovery or an exhaustion phase (depletion of physiological resources) (Selye 1950, 1954). It was because of Hans Selye's prolific scholarship that the term "stress" was solidly embedded both in science and in lay culture.

The body reacts to stressful conditions with the activation of the sympathetic nervous system and the initiation of the fight-or-flight response. On the contrary, the role of the parasympathetic nervous system is to return the body to the normal physiological status and to facilitate the restoration of the reserves. The reaction eventually includes the activation of a variety of body systems and mechanisms, including the endocrine and the immune systems. But as Hans Selye argued, stress decreases the ability of the organism to adapt by consuming "adaptation energy" (Selye 1938). This term refers to complex abstract abilities and orientation rather than some specific mechanism or energy in the frame of physics (Gorban et al. 2016).

There is a widespread lay belief but also a number of theories suggesting there is a strong connection between stress and illness, both mental and somatic. According to theoretical approaches, both acute and chronic stress can lead to changes in physiology, which could create vicious cycles especially in combination with personality features or changes in behavior (Cohen et al. 2007; Jeronimus et al. 2014). As a result, the individual could become more susceptible to illnesses like the common cold (Cohen et al. 1997), morbidity, and mortality because of coronary heart disease as well as increased serum lipids (Calderon Jr. et al. 1999) and depression and

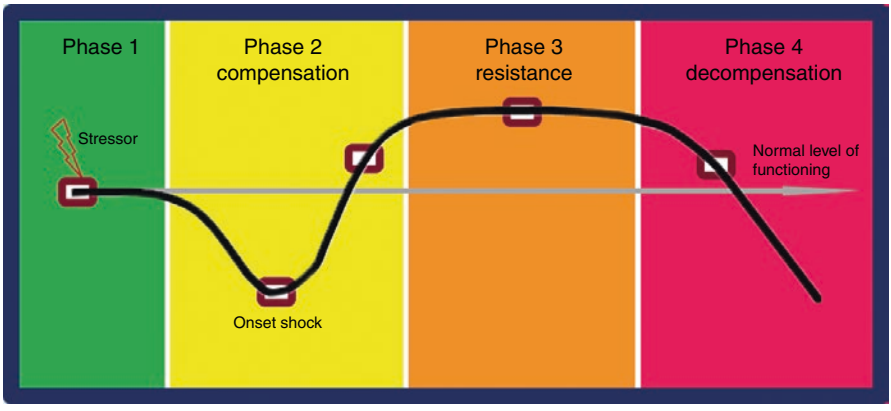


**Fig. 11.2** The general adaptation syndrome introduced by Hans Selye (1907–1982)

anxiety (Schlotz et al. 2011). Chronic stress increases the accumulation of visceral fat, which leads to hormonal and metabolic changes, thus causing a variety of health problems, especially cardiovascular (Shively et al. 2009).

It seems that the type of stressful condition in combination with early trauma, age, personality factors, and genetic vulnerabilities determine the overall outcome (Heim et al. 2000; Pace et al. 2006). Especially chronic stress seems to exert a worse effect on global health (Pinquart and Sorensen 2003; Schneiderman et al. 2005; Jeronimus et al. 2013, 2014). Age seems to be an important factor since experiencing of extremely stressful conditions at a young age increases future vulnerabilities (Miller et al. 2009). On the contrary, some people do not show any deterioration of their health even after prolonged periods of stress. This resilience is called "hardiness" (Kobasa 1982). Essentially most healthy individuals will not show any health deterioration even after chronic stress, and a factor which seems to be protective is the belief that stress will not (Keller et al. 2012; Richardson et al. 2012; Nabi et al. 2013). This is a strong evidence that psychological factors and reactions mediate the harmful effects of stress on somatic health. It is interesting to note that the above research findings suggest the presence of an intergenerational effect concerning early chronic stress (Miller et al. 2009).

Animal studies suggest that chronic exposure to a specific stressor leads to the development of tolerance concerning that specific stressor but also to a hypersensitivity toward novel stressors. The exact phenomenon of such a "sensitization" (meaning the enhanced response to the same stress over time) or "desensitization" (meaning the reduced response to the same stress over time) has not been elucidated yet, and it is unknown when, why, and how it might occur. However it is solidly known that the response to stress varies dramatically as a function of frequency and duration of the exposure to the stressful insult.

The mechanism of the response to stress from the periphery of the body is mainly mediated by the hypothalamic-pituitary-adrenal (HPA) axis (Fig. 11.3). It is triggered when the hypothalamus receives input from higher structures (e.g., cerebral cortex, limbic system, visceral organs) concerning the presence of stress and the deterioration of the supposed homeostatic state. In response to stress, the hypothalamus releases the corticotropin-releasing hormone (CRH) which stimulates the anterior pituitary gland, to release the adrenocorticotropic hormone into the bloodstream which in turn stimulates the adrenal glands to secrete cortisol but also norepinephrine (McEwen et al. 1997; Kaufman et al. 2000; Sanders and Straub 2002). The activation of the HPA axis lasts for as long as the stressor is present and insufficient amounts of cortisol exist in the bloodstream. As soon as the cortisol level is sufficiently high, the stressor is no longer present or some kind of new balance has been achieved, and the so-called homeostasis has been restored, cortisol itself causes inhibition of its release by binding on receptors in the pituitary gland and the hypothalamus but also as high as the hippocampus. In this way a feedback creates inhibition of further cortisol release. Cortisol is a steroid hormone of the group of glucocorticoids, and its primary function is to control and redistribute glucose consumption and subsequently energy and metabolism rates in favor of those body regions in need, depending on the

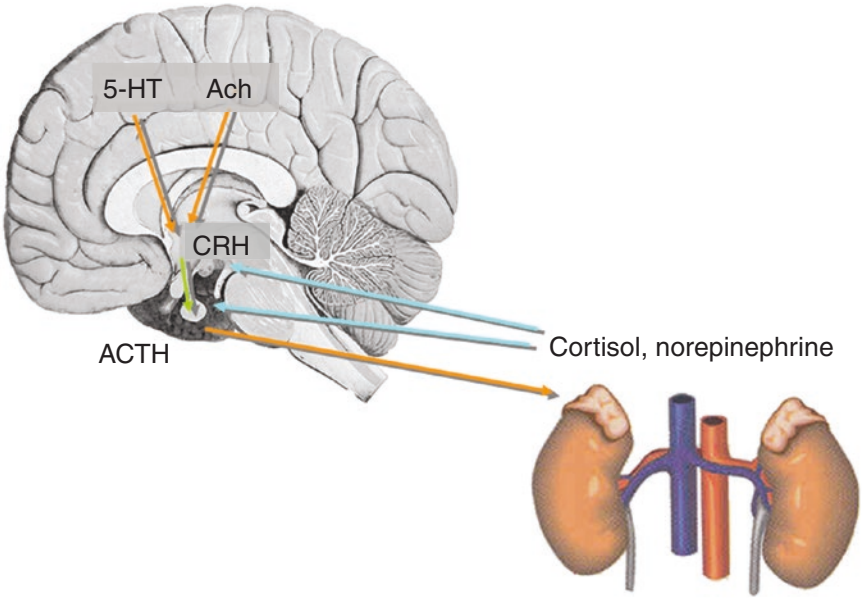


**Fig. 11.3** The hypothalamus-pituitary-adrenal (HPA) axis

situation. A second major effect of cortisol is the suppression of the immune system, so that energy resources are reserved for those body organs which take part in the fight or flight process. Energy is also conserved by the inhibition of growth and reproduction mechanisms. Under chronic stress this suppression of systems and functions could be chronic also, leaving the organism vulnerable to infectious insults (Miller 1985; Khansari et al. 1990; Wolf et al. 1994; Jessop et al. 1997; Poliak et al. 1997; Antoni et al. 2002; Karacabey et al. 2005; Adamo 2014; Gur and Bailey 2016).

This is the reason why the first biological marker which had been proposed in psychiatry was the dexamethasone suppression test (DST). It had been described as a biological marker for depression (Carroll et al. 1968; Fountoulakis et al. 2004; Yerevanian et al. 2004), it had also been associated with suicidal behavior, melancholic, and latter atypical features, but essentially it is a biomarker of stress, not of clinical depression. This test mainly reflects the HPA axis and norepinephrine activity (Greene and Dalton 1953; Carroll et al. 1968; Nuller and Ostroumova 1980; Mendlewicz et al. 1984; Stokes et al. 1984; Evans and Golden 1987; The APA Task Force on Laboratory Tests in Psychiatry 1987). The 1 mg DST protocol demands the administration of 1 mg dexamethasone per os at 23.00 of the first day and determination of cortisol serum levels simultaneously and the next day at 16.00 and 23.00. A subject is considered to be non-suppression if cortisol levels are above 5 μg/dl in either second day measurement. Nearly 4–10% of normal persons are reported to be DST non-suppressors (Watson et al. 1987; Sharma et al. 1988; Yeragani 1990). The reason for this is unknown; however, it has been

suggested that it is due to an underlying stressful situation since it probably reflects the degree of psychological pressure or discomfort of the subject and not a specific vulnerability or characteristic of depression (Ceulemans et al. 1985; Shuchter et al. 1986).

The effect of stress on the immune system is reported to be profound, although individual differences are significant and predictions at the patient level impossible (Cohen and Hamrick 2003; Irwin 2008). It is of course known that the immune system constitutes the body's defense against invading external pathogens but also against abnormal body cells like cancer cells. It includes a non-specific mechanism-based macrophages and granulocytes which release pro-inflammatory cytokines (tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6)). They do not demand the identification of the type of insult, and their function is to consume debris and invading organisms. There is also a second mechanism, which is specific and requires the identification of invading organisms and molecules and discriminating them from those of the body. The invading molecules and cells are called "antigens." B cells secrete specific antibodies which attack antigens, while T cells kill those body cells that host pathogens. Both types of immunity are controlled via the secretion of interleukins and cytokines from immune cells. In animals, acute exposure to stressors produces alterations in almost every aspect of immunity in a dose-dependent manner to the severity of the stressor. In humans, acute stress inhibits cellular immune responses and increases markers of inflammation (e.g., IL-6), and the overall impact when the stress is chronic puts the individual at increased risk for infectious diseases (Irwin et al. 2006)

The HPA axis and the autonomic nervous system connect the brain with the immune system. It seems that sympathetic activation suppresses the non-specific (cellular) immune mechanism while it might enhance the specific (humoral) mechanisms. It has also been reported that chronic stress might modify the sympathetic innervation (Sloan et al. 2007), while also disordered sleep and loss of sleep alter inflammatory function and have an adverse effect on disease progression (Lange et al. 2003).

However, it is important to stress that there is significant heterogeneity in the population which could at least be partially attributed to coping and personality as well as to idiosyncratic neuroendocrine and sympathetic activity. In spite of this problematic modeling, dealing with stress is important both for healthy and for patient populations. It is interesting that because the average individual feels comfortable talking about the stress he experiences, this is frequently the first thing discussed during a psychiatric consultation. Unfortunately, this is often more confusing than clarifying. Because of a number of methodological issues, it is almost impossible to scientifically prove that stress can cause any kind of somatic disorder. On the other hand, it is possible, and a number of studies support the suggestion that acute stress acts as a trigger on an underlying subclinical somatic condition. This, in turn, has shifted the focus from the stressor as a malignant insult to the vulnerability of the organism, both in psychological and in organic terms.

## 11.3 Psychosomatic Medicine

Although the term refers to the mind-body interaction in the development of somatic disorders, the lay interpretation during the last decades referred to the somatization type of disorders, and therefore in 1980, in the DSM-III, the term "psychological factors affecting physical conditions" replaced the previously used "psychophysiological (or psychosomatic) disorders." However, the term continues to be used in research, in journal titles, and in scientific associations, and also in 2003, the American Board of Medical Specialties and the American Board of Psychiatry and Neurology approved the specialty of psychosomatic medicine (Gitlin et al. 2004).

An early psychosomatic concept was proposed by Hippocrates (460–370 BC) who, in the frame of his fluid theory, suggested that fluid imbalance and the resulting disease could be caused by emotional upset. He was also the first to suggest a holistic approach in the treatment. Around the same time, Plato (427–348 BC), in his book *Timaeus*, suggested that trouble in the soul could bring trouble to the body, and, in *Charmides*, he quoted Socrates (470–399 BC) "…neither is it proper to cure the body without the soul." Aristotle (384–322 BC) wrote that emotions affect the body. Aretaeus of Cappadocia (first century BC) proposed that emotional problems constitute one of the six major causes of paralysis. The term "psychosomatic" was first coined in 1818 by Johann Christian August Heinroth (1773–1843) and "psychosomatic medicine" as a term was used for the first time by Felix Deutsch (1884–1964) in the early 1920s (Deutsch 1939).

The modern evolution of the psychosomatic concept followed a much different trajectory. While in the nineteenth century the diagnosis of spinal irritation was frequent in order to label somatization, this was later replaced by "reflex neurosis" which suggested that an affected organ could cause irritation in any other organ in the body through the nervous connections between organs. In the thought of physicians of the time, the uterus was the most important and frequently affected organ and the source of the problem. At the end of the nineteenth century, the reflex theory was abandoned in favor of the concept of a central disorder being responsible for symptoms, paving the way for the concept of the psychological origin of somatic symptoms in the early twentieth century (Shorter 1992). In this frame, George Miller Beard (1839–1883) coined the term "neurasthenia" in 1969, while the term "somatization" came from the false translation of the term "organsprache" coined by Wilhelm Stekel (1868–1940) in the 1920s (Marin and Carron 2002; Mai 2004).

The early twentieth century was marked by the theories of Sigmund Freud (1856–1939). In his early theories, libido and sexuality were utilized as a bridge between the body and the mind. Later, in the 1920s, Karl Abraham (1877–1925) and Sandor Ferenczi (1973–1933) further elaborated on these concepts with Georg Groddeck (1866–1934) going much further to the extremes and attaching a symbolic meaning to fever and hemorrhage in 1929. During the second half of the twentieth century, two main branches emerged, one concerned the contribution of psychological factors on the development of physical disorders (psychosomatics) and the second concerned the development of psychological disorders in somatic patients (consultation-liaison psychiatry and psychological medicine). Psychosomatics were initially

dominated by two conflicting theories. The first one, introduced by Franz Alexander (1891–1964) in the 1930s, was a theory of specificity suggesting that specific emotions led to specific cell and tissue damage, while the second was a non-specific one, suggesting that generalized anxiety and stress contributed to a number of un-predetermined somatic conditions. Franz Alexander considered intrapsychic conflict to constitute a stress factor, which even after suppression could lead organic pathology because the fight or flight response becomes chronic in spite of the suppression of the conflict (Alexander 1950). Depending on the specific predisposition the person carries, this prolonged alertness could lead to gastric ulcer, colitis, asthma, migraine, hypertension, or arthritis, but empirical data failed to recognize the same type of conflict behind the same somatic disease, thus making problematic the psychoanalytic approach to psychosomatics.

In 1939, Karen Horney (1885–1952) and, in 1948, James Halliday (1897–1983) shifted the emphasis on culture and its effect on the development of psychosomatic illness, mainly through the mother (Horney 1937).

An important contribution which later was solidly embedded in lay culture was made in 1954 by Helen Flanders Dunbar (1902–1959) who proposed that the ambitious, highly motivated male would be prone to coronary occlusion (Dunbar 1954). In 1959, two cardiologists, Meyer Friedman (1910–2001) and Ray H. Rosenman (1923–2013), proposed the existence of type A personality which is almost identical to the description of Dunbar and includes hostility as an important personality trait (Friedman et al. 1970). According to them, hostility was the main risk factor for the development of coronary artery disease. Around the same time, Harold Wolff (1898–1962) and Stewart George Wolf (1914–2005) reported that chronic hyperfunction or hypofunction activities of the mucosa of the gastrointestinal and respiratory systems could produce pathology and they correlated overfunctioning with hostility and underfunctioning with fear or sadness.

The patient's entire reactive patterning and his or her life history account for whether he or she reacts to stress by hyperfunctioning or hypofunctioning. Further on this theory of non-specific causation, Hans Selye suggested that the hormonal response to stress by the HPA could ultimately lead to the development of a number of organic diseases, which he considered to be a by-product of the attempt to adapt to stress. This was in sharp contrast with the prevailing theoretical model in medicine at that time, which demanded a specific cause to lead to a specific effect.

An important contribution was made in the late 1960s by two psychiatrists, Thomas Holmes and Richard H. Rahe. They developed the Social Readjustment Rating Scale (SRRS) (Holmes and Rahe 1967; Harmon et al. 1970; Rahe et al. 1971) on the basis of the medical records of over 5000 patients. Later they tested it in 2500 US sailors, and they reported a weak but significant correlation between scale scores and somatic illness (Rahe et al. 1970, 1972). An important contribution of the scale and this line of research was the identification of loss of spouse as the most intense stressor.

Already since the dawn of the twentieth century, Adolph Meyer (1866–1950) developed the psychobiological approach by emphasizing the interaction of developmental, psychological, social, and biological factors in mental health and disease.

This concept was further elaborated by Zbigniew Lipowski (1924–1997) (Lipowski 1967a, b, 1968), and eventually a vague but popular "biopsychosocial model" was proposed by George Engel (1913–1999) in 1977 (Engel 1977). Leon Eisenberg (1922–2009) suggested a developmental approach according to which the major brain structures and neural pathways are genetically specified, but the detailed connections are shaped and thus reflect social and interpersonal factors and the external environment in general (Eisenberg 1995). The last major contribution in the field came by Peter Sifneos (1920–2008) and John C. Nemiah (1918–2009) who coined the term alexithymia to describe a developmental arrest in the ability to express affect related to conflict, and as a result, psychosomatic symptoms emerge.

The most compelling data on psychosomatic medicine concern the impact of stress on atherosclerosis and cardiovascular disease in general which is now thought to correlate to an inflammatory process in vascular endothelium. The effect on immunity has profound consequences on a number of diseases including infections, autoimmune disorders, and cancer. The infectious diseases best studied include viral diseases such as herpes simplex, HIV, Epstein-Barr virus infections, and the common cold (Cohen et al. 1991). It seems that under stress, the immunologic suppression by glucocorticoids is not fully achieved, and specifically in rheumatoid arthritis patients, when chronic stress is present, there is an increase in IL-6, which correlates with symptoms of disease including fatigue, pain, and functional limitations (Davis et al. 2008). In cancer, human research linking stress to cancer onset and progression has produced inconsistent results. One recent study suggests there is a link between chronic stress and the expression of tumor-promoting peptides in women with ovarian cancer (Thaker et al. 2006). In cancer survivors, it has been reported that persistent fatigue is associated with elevated levels of markers of inflammation (Bower et al. 2002; Collado-Hidalgo et al. 2006), while treatment for cancer or hepatitis C with high doses of cytokines frequently induces sickness behaviors and depression. Interestingly, pretreatment with antidepressants prevents the manifestation of these symptoms (Dantzer 2001; Reichenberg et al. 2001; Konsman et al. 2002). High-dose interferon-α induces significant activation in the dorsal anterior cingulate cortex, which is responsible for affect generation and with cognitive control during highly demanding cognitive tasks (Reichenberg et al. 2001; Capuron et al. 2003). Such activations could lead to manic or psychotic symptoms and neurocognitive disorder (Fountoulakis et al. 2008).

There has also been a surge of interest in recent years in the phenomenon of emotional (or psychological) resilience (Lazarus 2006). Whereas serious traumatic stressors almost inevitably result in short-term symptoms and a decline in functioning, some individuals rebound especially quickly from such insults and go on to function extremely well, even in the face of ongoing chronic stress. Determination of individual differences in personality that characterize psychological resilience and the neurobiological mechanisms that underlie these observed differences is a subject of intense research scrutiny at the present time (Charney 2004). One intriguing report correlated the serotonin reuptake transporter gene with resilience (Caspi et al. 2003), but subsequent research failed to confirm it (Risch et al. 2009).

## 11.4 Consultation-Liaison Psychiatry (Psychological Medicine)

After the middle of the twentieth century, the prevalence of various psychiatric problems in medical patients became the focus of interest and research. The importance of assessing and understanding the personality of the medical patient in the long-term success of treatment and the overall outcome was stressed (Lipsitt 2001, 2003). Although the approach was initially psychoanalytic, more practical and operationalized approaches were dominant later. In spite of this, the overall prevalence of reasons for requests for assistance in patient management remained unchanged since the 1960s and included suicide, delirium and psychosis, hostility, depression, uncooperativeness, adverse events of medication, and preparation of patients for major events, including surgery. The first consultation-liaison psychiatry textbook was published in 1968 by John Schwab (1923–2010). However, recently, the focus of research has been on the relationship between chronic medical conditions and psychiatric disorders with a special focus also on economic outcomes. It is widely accepted that the co-occurrence of mental and somatic disorders constitutes a significant public health problem, since mental disorders are both risk factors for the development but also poor prognostic indicators of chronic medical illnesses (Evans and Charney 2003). This coexistence also worsens disability and has a huge impact on quality of life while at the same time increasing healthcare utilization and the overall cost. Another important consequence of mental-somatic comorbidity is poor adherence to all aspects of treatment including medication and lifestyle changes as well as safe behaviors in sex and drug abuse, thus increasing the overall mortality.

It is estimated that between 20% and 67% of medical patients also suffer from a mental disorder, a rate impressively higher from what is seen in the general population, with patients in general hospitals being at the highest risk. Depression and delirium are the most common mental disorders in this population with substance abuse being an additional significant problem. A general rule could be that mental disorders are 2–3 times more common in somatic patients in comparison to the general population.

Historically, the majority of consultation-liaison work is done within a general hospital setting, but recently with the increasing size of outpatient facilities, it embraces a variety of settings and deals with varying needs and problems. New challenges emerge as diagnostic, assessment, and therapeutic tools continue to evolve and change concerning the total field of medicine. On one hand this is extremely helpful, but on the other hand, it makes more difficult the synthesis of findings.

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# 12 Ethology, Evolutionary Psychology, Sociobiology, and Evolutionary Psychiatry

Kostas N. Fountoulakis

## 12.1 Introduction

The theory of evolution of species is one of the most celebrated pieces of science through the centuries. Although similar thoughts existed since antiquity, it was Charles Robert Darwin (1809–1882; Fig. 12.1) who established that all species of life have descended over time from common ancestors with his 1859 book *On the Origin of Species* (Darwin 1859). The theory of evolution is important not only because of its mere scientific value; it serves as a paradigm of what a scientific theory is and how it is developed in sharp contrast with religious or ideologically driven beliefs. Its effect on culture and society is so profound that it has been the focus of debate for more than a century and even the subject of a trial (the Scopes Monkey Trial in 1925). It is interesting that currently it is not taught in most medical schools not even in the frame of biology or genetics, while there is a significant number of academics who support the divine or "intelligent" design theory which does not meet the criteria to be considered a scientific theory.

Its scientific importance lies to the fact that it connects cellular biology, physiology, molecular biology, genetics, immunology, anatomy, microbiology, and literally every life science. It provides a conceptual framework which obeys to the laws of science and includes all Earth environment and all disciplines of human knowledge and activity. It suggests that while Earth itself is about 4.6 billion years old, there were molecules with the ability to self-duplicate since 4 billion years ago and single-celled organisms (prokaryotic) since 3.5 billion years ago. Multicellular organisms (eukaryotic) appeared some 1.7 billion years ago, while the first ancestors of humans evolved probably 2 million years ago (Fig. 12.2). It is very interesting to know that the genetic material of modern humans but also of all modern living beings is the end product of ancient natural experiments and loans from

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**Fig. 12.1** Charles Robert Darwin (1809–1882)

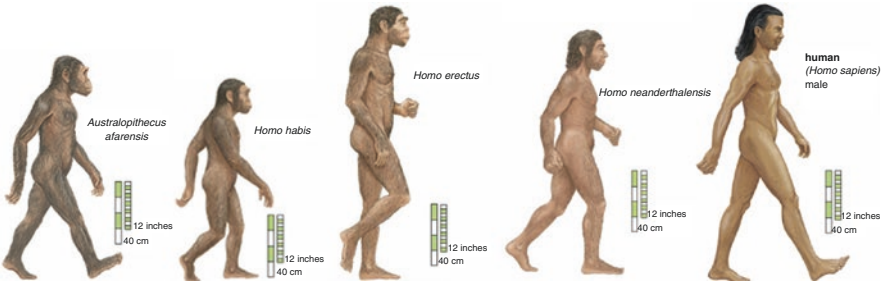


**Fig. 12.2** Evolution of modern humans (*Homo sapiens sapiens*). Modified from http://imgarcade.com/1/evolution-of-man-names-of-stages

other species and other kingdoms of life and not simply random mutations as a product of influence of external factors. Approximately 10% of the genes of modern humans come from retroviruses whose genetic material was insinuated into germ cells millions of years ago.

The Darwinian or evolutionary approach is of proven utility when we try to understand how behaviors evolved in parallel with genetic structure. In fact, genetics, environment, and behavior seem to be closely related since genetics determine

behavior which serves adaptation to the environment, but the feedback loops between these three domains are extremely complex and dynamic.

One important characteristic of the evolutionary approach to behavior and social structure is that it utilizes a somewhat "cynical" approach to interpret and understand things. This is often in contrast with the ethical-philosophical or even religious beliefs and concepts the average lay person but also probably the majority of the scientific community have. Phenomena like homicide or rape are considered under the concept that in order to exist, there must had been some evolutionary advantage in the far past for those who committed them, or at least they constitute residual out of frame behaviors. These approaches might bother since they seemingly deprive the ethical load of these acts and they seemingly justify and provide support or excuse for those engaging in similar behaviors. The source of individual differences is another such example of sociopolitically sensitive issues. Often individual differences are seen as a reason or a cause of social and hierarchical inequality, which is indeed not unusual in human society. The big question, however, is whether sociopolitical and ideological forces should dictate the outcome of scientific research. The reader should have in mind that the scientific method tries to elucidate the roots and the sources of behaviors without the bias that might come with millennia of social evolution and organization. This is the way science works in all fields, and this is why science was able to make the significant progress that changed human life in the last few centuries, prolonged life expectancy, improved quality of life, and reduced poverty. Also this is the way through which science might be able to reduce the manifestation of these unwanted behaviors and help to improve the humanity. After all, humanity is only partially a matter of genes; modern humans and chimpanzees differ in less than 5% of total genome (Varki and Altheide 2005), yet human and chimpanzee societies are radically different.

It is the cognitive and metacognitive processes that define what we are, how we see ourselves and the others, how we consider and respect them and their rights, and what we believe it is our place in the universe and among other species. These qualities made human beings aware of their existential dilemmas and tragedies and raised them above and beyond the basic instincts and biological pressure.

### 12.1.1 Ethology

The discipline of ethology concerns the study of animal behavior. It usually considers it to be an evolutionarily adaptive trait. The term "ethology" comes from the Greek word *Ἦθος* (ethos meaning "character") and *–λογία* (–logia meaning "the study or knowledge of"). The first to use the term was John Stuart Mill (1806–1873). In his 1843 book *System of Logic*, he advised the development of ethology as a field of science for the study of individual and national differences in character (Robson 1974). As the discipline we know today, it was introduced in 1902 by William Morton Wheeler (1865–1937), an American myrmecologist (he was studying ants) (Matthews and Matthews 2010). Typically, ethology studies a type of behavior across species rather than behaviors specific to a single specific species

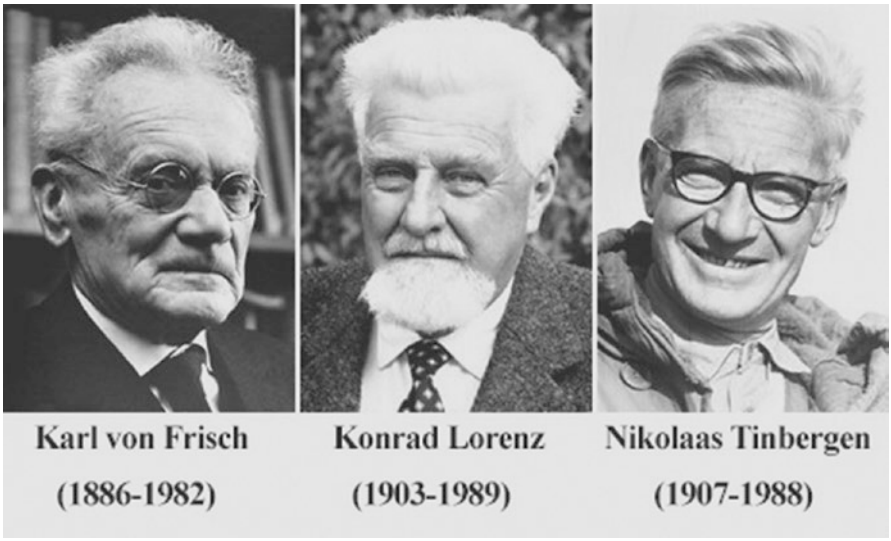


**Fig. 12.3** 1973 Nobel Prize in physiology or medicine

and in relationship to the known animal anatomy, physiology, neurobiology, and phylogenetic history.

Ethology was part of Darwin's work but was advanced mainly through the works of Charles Otis Whitman (1842–1910), Oskar Heinroth (1871–1945), and Wallace Craig (1876–1954) which were ornithologists. The discipline reached its highest fame when three scientists, Nikolaas Tinbergen (1907–1988), Konrad Lorenz (1903–1989), and Karl von Frisch (1886–1982), were awarded the 1973 Nobel Prize in Physiology or Medicine (Fig. 12.3).

### 12.1.2 Evolutionary Psychology

In this frame, evolutionary psychology studies behavior and psychological function from an evolutionary perspective. It assumes that human psychology and behavior is a direct product of evolutionary processes and constitute evolved adaptations, which follow the laws of Darwinian theory through natural or sexual selection (Williams 1966). This implies that not only the brain but also the mind and behavior follow these laws and rules and therefore evolutionary psychology can serve as a unifying theoretical approach for the behavioral sciences by putting research of psychological function in the frame of the human evolutionary past.

This concept has a number of other implications; it considers psychology to be part of biology rather than theoretical sciences and philosophy, which is true if one considers the fact that modern psychology emerged from anthropology and

the study of individual differences in the early nineteenth century. It also views the mind in the frame of computational theory and considers mental processes to be computational operations as responses to the environment. It utilizes elements and concepts from cognitive psychology, artificial intelligence, evolutionary biology, genetics, behavioral ecology and ethology, anthropology, archaeology, and zoology.

This computational approach to mind also suggests that every psychological function has evolved to solve a problem and that the complexity of needs and subsequently of evolved adaptations and solutions to these needs gave birth to broader psychological processes like reason, intelligence, emotion, or impulses and not vice versa as many philosophers imply. It also implies that modern humans have minds, which were evolved and are specifically equipped for behavioral adjustment and survival in the environment humans were facing during the Pleistocene and the Stone Age and not necessarily for the modern environment.

There is a number of behaviors, abilities, and psychological traits which could be good candidates to be considered as results of evolutionary procedures. They occur universally, that is, in all cultures and across the globe, and they concern basic cognitive abilities like expression, recognition, and interpretation of emotions and their behavioral dimensions including facial and hand gestures, discern kin from nonkin, select healthier and more fit mates, and cooperate with other members of the group or tribe. This approach has important although controversial applications in economic and political theory, health, law, and mental health among others (Dunbar and Barret 2007; Buss 2005).

### 12.1.3 Sociobiology

Sociobiology was introduced as a term in 1975 by Edward Osborne Wilson (1929–) (Wilson 1975). This constituted the highlight of a long process which took place in the late 1960s and early 1970s and attempted to bridge psychology, sociology, ethology, evolutionary and population biology, ecology, anthropology, game theory, and genetics (Barash 2003b). Among other issues, the word "psychobiology" has some political implications, and therefore the alternative term "behavioral ecology" is also used. Essentially, sociobiology differs very little from evolutionary psychology. At times and especially in the beginning, there was severe and vicious ideological criticism which included the broader spectrum of evolutionary psychology and sociobiology.

One major feature in the sociobiological approach is that natural selection occurs among genes, not at the level of groups or species. This has been shown among others by George C. Williams (1926–), William Donald Hamilton (1936–2000), and John Maynard Smith (1920–2004). Their work also introduced the term "inclusive fitness" to denote the sum of accumulated reproductive success of individual genes within family lines by passing the generations.

### 12.1.4 Evolutionary (Darwinian) Psychiatry

The Darwinian theory had a major influence on how health and disease are conceptualized and what might constitute the best treatment option. A number of medical conditions including obesity, anemias, autoimmune diseases, and hypertension were put in an evolutionary frame (Gluckman et al. 2009). According to this approach, mental health and disease should be understood as the end result of the interaction between the organism and the environment, with the addition that abnormal behaviors and symptoms could reflect either an extreme form of otherwise adaptive behaviors or the triggering of them in an out-of-frame or proportion way and under inappropriate conditions.

This is somehow different from the standard approach in clinical psychiatry and psychopathology where connections with recent events and reaction to recent problems in the frame of the individual patient's and core family are considered (proximate mechanisms). In contrast, evolutionary psychiatry stresses that variation (including variation in behavior) is not only normal but evolutionarily necessary and is concerned with the misfit of preexisting normal coping mechanisms which could cause maladjustment or disease if triggered in an inappropriate way or persist for longer than expected and especially in an environment and with social demands extremely different from those encountered by humans during the Pleistocene and the Stone Age (Fabrega 2002).

## 12.2 Historical Overview

The theory of evolution has a long history and roots in the antiquity. It exists in the teachings of the pre-Socratic Greek philosophers, especially Anaximander (610–546 BC) and Empedocles (495–430 BC), with his work *Περί φύσεως* (De rerum natura; *On the Nature of Things*). However, in contrast to them, Aristotle (384–322 BC; Fig. 12.4) utilized the idea of fixed natural unchanged and preexisting patterns, known as *μορφή* (morfi meaning form) or *είδος* (idos meaning species). He rejected any idea of changing or evolving forms and species and suggested that all naturally existing living or nonliving things were actually incomplete reflections of these preexisting ideal forms. He also introduced the concept of *ιεραρχική κλίμακα* (scala naturae; hierarchical scale), according to which both living beings and nonliving things are classified on an ideal pyramid with simple nonliving things at the base, plants and simpler animals at the lower levels, and humans at the top (Fig. 12.5). These ideas can be considered to be the early conceptualization of the "intelligent design theory"; they demand some kind of divine top-down cosmic order and in combination with Christianity came to dominate the western world until relatively recently.

With the Renaissance and since the seventeenth century, the method of modern science became gradually dominant and demanded the application of the same physical laws for all visible things without the contribution of any divine cosmic order. An important advance was the classification of plants and animals


**Fig. 12.4** Aristotle (384–322 BC)

in 1735 by Carl Linnaeus (1707–1778; Fig. 12.6) which showed the presence of a hierarchical nature in living organisms with the use of scientific method. Soon afterward in 1751, Pierre Louis Maupertuis (1658–1759) argued that natural changes that occur during reproduction could accumulate over several generations and eventually new species emerge, while Georges-Louis Leclerc, Comte de Buffon (1707–1788) proposed that the opposite could also happen, that is, a single "higher" species could degenerate into several "lower" species in the classification hierarchy. The grandfather of Charles Darwin, Erasmus Darwin (1731–1802), was the first to clearly propose that all animals could come from a single microorganism (filament). Jean-Baptiste Lamarck (1744–1829) developed his "transmutation theory" in 1809, which was based on the assumption that animal organs change because of use or disuse and these changes are inherited from parents to children (a theory called later "Lamarckism"). In sharp contrast, the English clergyman William Paley (1743–1805) in his 1802 book *Natural Theology or Evidences of the Existence and Attributes of the Deity* elaborated on the theory of the divine design (Paley 1802). Eventually the theory of evolution of species through natural selection was formulated by Charles Robert Darwin (1809–1882; Fig. 12.1) in his 1859 book *On the Origin of Species* (Darwin 1859). Probably Alfred Russel Wallace (1823–1913) had arrived at a similar theory

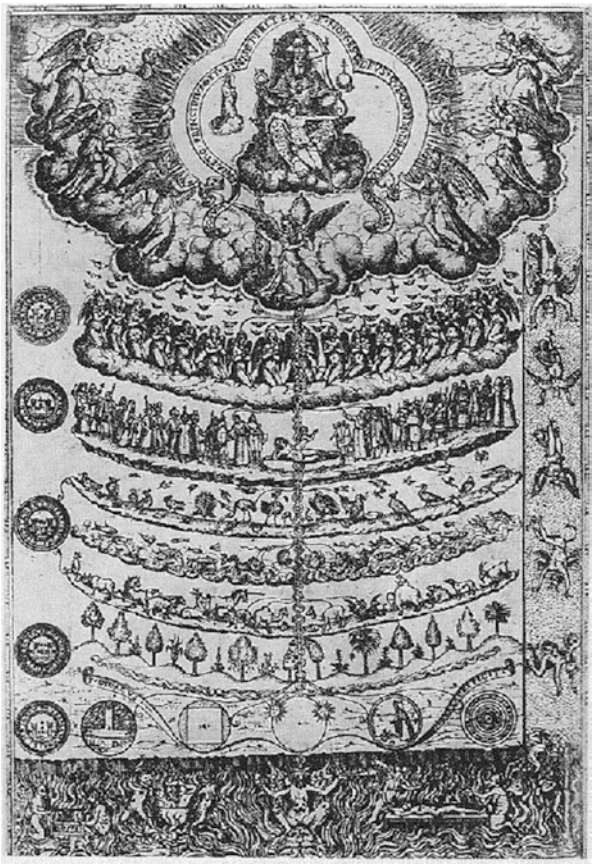

**Fig. 12.5** Ιεραρχική κλίμακα (scala naturae; hierarchical scale of nature): Drawing from *Retórica cristiana* by Fray Diego Valadés (1579)

more or less simultaneously with Darwin. Thomas Henry Huxley (1825–1895) also known as "Darwin's bulldog" for his support to the theory of Darwin provided evidence that humans and apes shared a common ancestry. This latter caused much criticism and disturbance since it was directly implying that neither humans as a species nor any specific human race have any special place in the universe; this was in sharp contrast with the religious and sociopolitical beliefs and ideas of the time.

Later, in the 1920s and 1930s but especially after the discovery of the DNA by James Watson (1928–) and Francis Crick (1916–2004) in 1953, the accumulated knowledge permitted a resolution of conflicts and discrepancies and the development of a revised and unified theory of evolution that applied generally to all branches of biology.

Essentially it was Charles Darwin who implied for the first time that behavior could obey to the same laws of evolution like biology, thus giving birth to evolutionary psychology. Two of his books concerned animal emotions and psychology (Darwin 1871, 1872).

**Fig. 12.6** Carl Linnaeus (1707–1778)

In the 1930s ethology emerged from the works of Nikolaas Tinbergen (1907–1988), Konrad Lorenz (1903–1989), and Karl von Frisch (1886–1982) which were awarded the 1973 Nobel Prize in Physiology or Medicine (Fig. 12.3). In 1975, Edward O. Wilson (1929–) introduced psychobiology (Wilson 1975, 2000, 1978), while mating and sexuality became the focus of evolutionary research during the 1980s and 1990s with the works of Donald Symons (1942–), Leda Cosmides (1957–), and John Tooby (1952–) (Barkow et al. 1995). In the 1970s Robert Ardrey compared human and animal behavior as similar in quality and directly comparable and relevant (Ardrey 2014).

## 12.3 Ethology

There is a variety of behaviors which are essential for the survival of the individual animal but also for the survival of the species. While usually behaviors serving the survival of the individual serve also the survival of the species, this is not always the case.

As a general rule, it can be said that animals learn to respond to stimuli which are relevant and neglect those which are irrelevant. This prerequisites that it is possible to distinguish between relevant and irrelevant stimuli, and as a consequence, new behaviors are learned and established. One possible mechanism through which these new behaviors are learned is associative learning as shown by Ivan Pavlov

(1849–1936). However, after repetition and by passing the time, responses tend to reduce in intensity with the emerging of habituation toward the stimuli.

Among the abilities and behaviors which are important for survival is the ability to recognize and discriminate the members of one's own species. This is fundamental and functions as a platform for a number of behaviors including collaboration, forming alliances, and mating.

Several animals if not most tend to live in groups of variable sizes. This gives birth to social behavior and requires advanced cognitive abilities. The end result is social life in groups which provides with better chances of survival and development. Living in groups provides better defense against predators, while predators could seek and attack their victims more easily. Searching for food is more efficient since larger areas can be covered and information can be exchanged concerning the location of resources.

Probably learning to identify one's own species only takes place in a very limited period of time. Konrad Lorenz called it "imprinting," after discovering it following extended observations in geese and other birds. He noticed that the young of birds follow their mothers spontaneously almost immediately after they are hatched. He also observed that this response could be triggered by an object other than the mother if it is presented instead of the mother during this critical period and for a few days after hatching. His photo walking and followed by young geese is iconic in the history of science (Fig. 12.7).

Another way of obtaining new behaviors and enriching one's own repertoire is "observational learning." Its simplest form is "imitation" which concerns the exact

**Fig. 12.7** The iconic image of Konrad Lorenz walking and followed by young geese

replication of an observed behavior. Usually the observed behavior is carried out by an individual with a higher status in the hierarchy of the group, usually an elder one. In this frame, the behavior is obtained by young low status and inexperienced members of the group, by copying the behaviors of elderly, high status, and experienced members (Horner et al. 2010). However, often there is targeted teaching which demands the "teacher" to deliberately modify its behavior so as to increase the probability the "pupil" will copy and imitate the observed behavior. Indeed the basic principles of teaching do exist in the animal kingdom (Hoppitt et al. 2008).

However, in the frame of group or social life, there is often conflict between members concerning social supremacy. Supremacy gives priority to resources but also to mating and therefore increases further the chances for survival and reproduction. On the other hand, group life has its disadvantages; it facilitates the spreading of disease and parasites, causes continuous conflict, and demands negotiations for the distribution of resources and privileges within the group.

There are also several unanswered questions concerning the existence of sterile subgroups within societies (e.g., in bees) as this seems to contradict essential rules of evolution as we understand it. Also several behaviors including altruism, self-sacrifice, or revenge are difficult to incorporate in a narrow theory of evolution. These behaviors demand to consider evolution not only at the level of the individual animal but also at the level of the species and for a time duration that exceeds the natural life of the individual and spreads across several generations. These proposed mechanisms are complex and currently not well understood; however, it seems that there exist mechanisms that under specific conditions put the interest of the group above the interest of the individual (Cummings et al. 1991).

There is much discussion and controversy on whether there is an optimal group size and how this could be defined. Animal groups tend to increase in size, but after exceeding a certain size, the benefits of social life degrade, and an equilibrium is achieved through the balance of benefits and conflicts (Sibley 1983).

## 12.4 Evolutionary Psychology

At the core of evolutionary psychology is the assumption that natural selection has provided humans with many psychological adaptations. This has happened with the same mechanisms and processes human anatomy and physiology adapted. In these adaptations the environment and the specific needs that stem from it are the determining factors.

### 12.4.1 Products of Evolution: Adaptations, Exaptations, By-Products, and Random Variation

The main task of evolutionary psychology is to understand how specific psychological mechanisms developed and exactly how they serve the survival of the species. These psychological mechanisms include also neurocognitive abilities like

understanding and interpreting gestures and emotions, discerning kin from nonkin, forming groups and developing cooperation and hierarchy, and identifying and preferring healthier mates, but also they include the involving in conflicts with mates, relatives, and other members of the group.

In general, it is expected that these mechanisms are either innate or easy to learn, and they are spread across cultures in a worldwide fashion. According to George C. Williams (1926–2010), an "adaptation" is characterized by an improbable complexity, species universality, and adaptive functionality (Williams 1966). Behaviors or traits that occur in all human societies and cultures universally around the world are good candidates to be evolutionary adaptations (Brown 1991). These are traits and behaviors related to language, neurocognition, and social and gender skills and roles (Smith 2011; Berent et al. 2008; Chomsky 2005; Sugiyama 2003; Schwartz et al. 2003). It is uncertain whether it is generally obligate or facultative (i.e., resistant or sensitive to typical environmental variation), but it is certain that at least some of them are shaped to a certain degree by the specific contemporary environment (Buss 2005; Barash and Lipton 2001).

Often, behavioral traits are not the products of evolutionary adaptation, but, peculiarly, they constitute by-products of some other behaviors with an adaptation essence. These by-products are called "exaptations" or "spandrels," and they manifest a random variation between individual persons (Buss et al. 1998).

### 12.4.2 Environment of Evolutionary Adaptedness

The set of recurring selection pressures which cause a specific adaptation to emerge are collectively called "environment of evolutionary adaptedness" (EEA) (Bowlby 1969).

The *Homo* genus appeared 2.5–1.5 million years ago while *Homo sapiens* 1.8–0.2 million years ago (Fig. 12.2). This time period is part of the Pleistocene, which is often colloquially referred to as the Ice Age and lasted from 2.5 million to 12,000 years ago. Its end corresponds to the end of the last glacial period, and its name comes from the Greek *πλείστος* and *καινός* meaning "mostly new." It is divided into four general stages or ages, the Gelasian, Calabrian, Ionian, and Tarantian. During that period, the Earth's climate was characterized by recurrent glacial cycles, and ice came to cover almost one third of the total Earth's surface. A large permafrost zone existed. The entrapment of large quantities of water in the glaciers caused a significant drop in the sea level which at times reached 100 m in comparison to the modern sea level. As a result the coastline was much different than today, and passages existed connecting lands which today are separated by sea (Fig. 12.8). Also the collective memory of cataclysms which survive in ancient myths, from Gilgamesh to Defkalion and to Noah, probably reflect abrupt changes in coastal line in the Mediterranean Basin, in the Black and Caspian Sea, as well as in the Red Sea and the Persian Gulf, because of glacier melting. It is to be noted that at that time, deserts were drier and more extensive.


**Fig. 12.8** The coastline during the Pleistocene with sea level 100 m lower than contemporary one. Large strips of land existed where today are sea, and there were passages connecting lands which today are separated by sea. Note the coastline in the Mediterranean Basin, the Black and the Caspian Sea, as well as around the Arabian Peninsula. These areas were probably land at the time and were probably the sites where catastrophic cataclysms occurred when the glaciers melted (image modified from http://www.genesisveracityfoundation.com/Iceage.html after permission). Modified from http://www.genesisveracityfoundation.com/Iceage.html

A major element in evolutionary psychology is the assumption that most of human psychological mechanisms evolved during the Pleistocene and constitute adaptations to survival and reproductive problems caused by the environment of that period. That environment both natural and social was radically different from the modern environment, and the societal structure and the needs were much different from contemporary needs. Humans lived in small hunter-gatherer groups with more stable group features, interpersonal interactions, and identity characteristics, and they were exclusively concerned with food selection and acquisition, selection of territory and physical shelter, as well as avoiding predators and environmental threats (Buss 2011). Differences in gender roles at that time might be behind the higher visuospatial cognitive capacity of males and the higher social cognition of females (Gaulin and McBurney 2003).

As a consequence to the fact that human psychological traits were developed in an environment much different from the modern one and with much different needs, often human psychology exhibits "mismatches" to the modern environment, which, however, is designed and constructed according to the needs and wishes of humanity. These mismatches can take the form of thoughts and biased beliefs but also behaviors (Ohman and Mineka 2001; Pinker 1999; Hagen and Hammerstein 2006). For example, present-day humans are inclined to trace patterns in a series of events even in cases such patterns do not really exist (in a series of random events) and to identify cheating rather than any other irregularity in the events (Gaulin and McBurney 2003).

Maybe several modern conditions including working in large anonymous bureaucratic groups and modern management methods could reflect mismatch and exploitation of instincts (Van Vugt and Ahuja 2011; Van Vugt and Ronay 2014). Another consequence similar to mismatch is the phenomenon of supernormal stimuli. Such a stimulus elicits a response which is far stronger than the same response when elicited by the specific stimulus for which it has originally been evolved. The concept was coined by Niko Tinbergen to refer to nonhuman animal behavior, but later Deirdre Barrett (1954–) carried it to modern human behavior. In this frame, television is a supernormal stimulus for social behavior and attention-grabbing action, junk food for the intake of important nutrients, and pornography of sexual behavior (Barrett 2007, 2010; Hagen and Hammerstein 2006).

### 12.4.3 Life History Theory

The life history theory starts with the obvious fact that each individual, no matter animal or human, does not have infinite time and energy budgets; on the contrary these are quite finite and precious. Thus, investing effort to solve one problem often precludes the investment in another. In oversimplified terms, the most contrasting investments are the investment in one's bodily growth, safety, and maintenance vs. parenting and kin investment. The first increases the chances of personal survival; the latter increases the reproductive success of genetic relatives. Therefore a trade-off between costs and benefits is always in place, while often investment in complex behaviors increases the success in the solving of more than one adaptive problems (Gadgil and Bossert 1970; Kaplan and Gangestad 2005; Roff 1992; Stearns 1992).

Individual features and characteristics determine the outcome of the trade-off between different investments. These characteristics include total energy, perceived life expectancy, and individual talents and preferences. Individuals might prefer parenting over mating or vice versa, while a perceived short life expectancy might push toward a strategy of immediate expenditure of resources, intense competition, and risk taking for mating (Daly and Wilson 2005a). Biological factors including hormonal might play a role in this trade-off. It is not clear whether it is cause or effect, but it has been reported that male testosterone levels drop with commitment in mateship and levels even fall further after the birth of children (Burnham et al. 2003).

### 12.4.4 Costly Signaling Theory

Communication is essential in all kinds of social interaction but also for interaction necessary for basic biological functions among members of the same species. Thus individuals also compete on how successfully they will communicate with others in order to be more successful in establishing alliances, achieving social status, and also mating. The reliability of the messages which individuals communicate to others is questionable since there is often an attempt to deceit; by this, the individual

might fulfill goals which otherwise would be out of their league. The ways of communication as well as the ability to understand and to trace deceit constitute important adaptations (McAndrew 2002; Miller 2000a; Zahavi 2006).

In this frame, costly signals tend to be honest signals (Zahavi 1975, 2006), since they are demanding in terms of investment and sent only by those who can afford. Activities like fighting or any type of physical contests for males or sex-analogous activities for females serve the purpose to send a honest and reliable message to the opposite sex about the condition of the individual. Complex and difficult to explain behaviors including generosity and altruism could be viewed in this frame (Miller 2007).

The costly signaling theory is linked to life history theory since the quality of the signal which an individual can communicate defines the individual's life history and the strategies he will adopt.

### 12.4.5 Balancing Selection

Balancing selection refers to a condition when selection does not choose a single solution to a problem and eliminates all others, but instead it permits genetic variation. This leads to the manifestation of different levels of adaptation to a specific environment or the same level of adaptation to different environments (Penke et al. 2007).

One mechanism of balancing selection is through environmental heterogeneity in fitness optima, that is, different environments favor the evolution of different behavioral patterns through a complex selection process including migration (Ebstein 2006; Penke et al. 2007; Chen et al. 1999; Eisenberg et al. 2008).

Another mechanism is frequency-dependent selection. This refers to the situation when two or more different strategies concerning the same adaptation problem are maintained within the same population, and they exist at a particular frequency relative to each other. This means also that the overall fitness of each strategy decreases with its increasing frequency of use in the population. An example of such a strategy is cheating, that is, using deceit to achieve adaptation goals (Mealey 1995).

### 12.4.6 Mutation Load

Genetic mutations are common and can be neutral or disruptive and could concern any body system or function. On average individual humans carry at least 500 brain-disruptive mutations each (Keller and Miller 2006). Through the process of natural selection, individual mutations or combination patterns could be eliminated through time; however purging is never complete, and mildly harmful mutations could survive for many generations. Most reflect older mutations, inherited from ancestors (Keller and Miller 2006), but the effect of increasing parental age in combination with very low infant mortality and the increasing rate of cesarean sections during the last few decades remain to be seen.

Random mutations and the genetic load they create could be the source of noise or variations in behavior (Buss 2006), and adaptive traits with an important role especially in mating, including emotional stability, conscientiousness, or intelligence, could be disrupted, or alternative facets or traits could manifest (Buss 2006).

### 12.4.7 Contingent Shifts According to Environmental and Phenotypic Conditions

While natural selection pushes toward the preference for a specific heritable trait which is adaptive for a specific environment, contingent shifts refer to the selection of psychological mechanisms which are flexibly responsive to changes in environmental or cultural conditions (Belsky 1999; Gangestad et al. 2006). This is related to the life history theory since this theory predicts changes in behavior after changes in environment or in personal achievements, e.g., parenting, but also as a response to individual characteristics, e.g., physical size and strength (Tooby and Cosmides 1990; Ishikawa et al. 2001).

### 12.4.8 Evolution of Emotion

As described in Chap. 1, affects and emotions serve two main aims:

- The first concerns the internal functioning of the individual and provides the individual with fast decisions which serve the survival of the individual but also of the species. Some of these decisions are easy to understand (e.g., fear of animals), but others are incomprehensible at least with a superficial approach (e.g., aesthetics and attraction to the opposite sex). In the same frame, emotions provide feedback concerning the behavior of the individual, and in this way, they enhance the expression of the specific behavior or preclude its future manifestations. For example, sadness constitutes the emotional response to loss, defeat, disappointment, or other adversities. Its adaptive function includes permitting withdrawal to conserve resources, asking for support from significant others and the autonomic arousal which might be present facilitates the search for the lost object or an appropriate substitute.
- The second aim is to communicate the internal emotional state of the individual to others, and this is achieved through facial expressions, gestures, bodily movements and posture, and verbal and nonverbal elements of voice. These ways of communicating emotions vary between cultures, but most of the repertoire is universal for human beings. They constitute a main source for the interaction with others, since the emotions of an individual influence the emotions, thoughts, and behaviors of others, produce positive or negative feedback, and give birth to circles of future interactions and reciprocal influence.

A modern understanding of the issue goes through a basic approach to brain function which could suggest that there are two distinct mental processes: logical thinking and emotions. While emotions are present also in animals, logical thinking is present primarily in humans, while some elements are also evident in the behavior of primates.

Emotional processes are evolutionary older and are characterized by speed and dominance. They lead to fast decision-making, on the basis of predetermined strong assumptions concerning the gross characteristics of the situation. For example, fear is triggered immediately and almost before conscious recognition of the stimuli, and it leads to the fast manifestation of a specific adaptive behavior (fight or flight). A snake will always trigger fear, no matter whether it is poisonous or not. On the contrary, logical thinking is slow, requires the conscious elaboration on the stimuli, and demands concentration and effort, and it is not as strong as emotions are, concerning the effect on behavior. Emotion is biased toward the triggering of those behaviors that serve the survival of the individual and the species, while logical thinking aims toward an "objective" assessment of the situation. In the language of artificial intelligence, the closest description which can be made today is that of "fuzzy" vs. "digital" systems.

The database of assumptions which the emotions use is of unknown origin, probably partially inherited and partially acquired through experience, and possibly it is characteristic of the species. Logical thinking is based mainly on training. Decisions based on emotions are stronger than those based on logical thinking, and when they are in conflict, the person faces a difficult dilemma, since it is very difficult for logical thinking to override emotional pressure.

The two processes, although independent in principle, they interact and influence each other. The emotional status causes bias in logical thinking, and logical analysis triggers emotions depending on the positive or negative outcome. This interaction is likely to happen at multiple levels (e.g., selective memory recall, reinforcement through new analysis, biased selection of possible solutions, etc.).

The interest in emotions from an evolutionary perspective was triggered by the publication of the book *The Expression of the Emotions in Man and Animals* by Charles Darwin in 1872 (Fig. 12.9). In that book, Darwin stresses the universal nature of emotions and the connection of mental states to the neurological organization of movement. Central to his understanding was a shared human and animal ancestry. This was in sharp contrast to the contemporary claims that there were divinely created human muscles to express uniquely human feelings. Darwin's original suggestion was that emotions evolved via natural selection and therefore have cross-culturally universal counterparts; a proposal confirmed almost a century later by the works of Paul Ekman (Ekman 1965, 1980, 1992a, b, 1993, 1994, 2003, 2009, 2016; Ekman and Friesen 1967, 1971; Ekman et al. 1969, 1987). According to Ekman humans share at least five basic emotions: fear, sadness, happiness, anger, and disgust. Furthermore, animals undergo emotions comparable to those of humans. It seems that social interaction based on emotions influences motivation and stimulates the reward systems (Belke and Garland 2007).

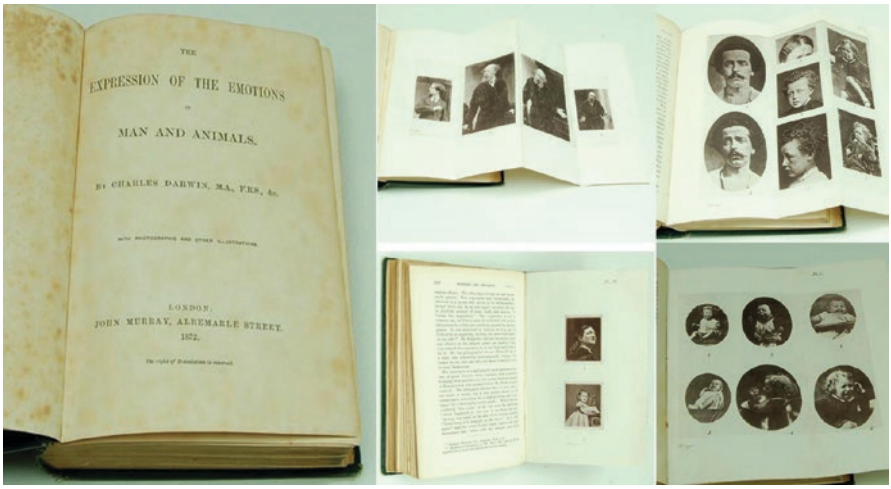


**Fig. 12.9** The book *Expression of the Emotions in Man and Animals* by Charles Darwin (1872) (images from Botterweg Auctions Amsterdam, after permission)

### 12.4.9 Mating and Parenting

Sexual function and mating are important for the survival of the species and more particular for the genes of the individual person. However the strategies to achieve this goal vary considerably among species and genders. According to the r/K selection theory (Huey and Pianka 1977) and the life history theory (Roff 1992; Stearns 1992), some species have many offspring, while on the contrary, others choose to have fewer offspring but invest much more in each one. Humans belong to the second category.

Angus John Bateman (1919–1996) argued that in most species, anisogamy, that is, the fact that males are able to produce millions of sperm cells while females only a relatively small number of eggs, results in different sexual behavior between genders. Females also spend many months in pregnancy. As a consequence, females are the limiting factor of parental investment. Males will compete for this limited female ability to give birth which is combined with higher nurturance of the offspring. Males themselves will overall invest less on the offspring (Bateman 1948). On the contrary, females exercise the ability to have high-quality males (choosiness). Additionally, human females exhibit concealed ovulation ("hidden estrus") which means that it is impossible for the male to know when the female is fertile. Subsequently, frequent mating and stable relationships are necessary to ensure paternity. The erectile ability from the part of the male might provide information concerning his health status, and because of this, it influences the mating choice of the female (Abbot et al. 2011).

This essentially means that females tend to choose males who care for the family and the offspring and its nurture and raising (Barash and Lipton 2001). In 1972

Robert Trivers (1943–) developed the parental investment theory (Trivers and Willard 1973; Trivers 1972) which further built on Bateman's principle. He suggested that there are different levels of parental investment between the sexes. According to his theory, females initially invest more, and this difference leads to different mating and reproductive strategies between males and females and eventually to sexual conflict in the form of sexual dimorphisms in mate choice (differences in behavior between the two sexes beyond the differences in sexual organs), sexual reproductive competition, and courtship displays (Barash and Lipton 2001). There are evolved mechanisms to attract select and secure mates (Workman and Reader 2008; Buss and Barnes 1986; Li et al. 2002; Schmitt and Buss 2001; Buss 1988), but there is also conflict between the sexes (Conroy-Beam et al. 2015; Peters et al. 2002; Botwin et al. 1997). Under specific conditions, females could adopt sexual behavior closer to that to males, but this is rather the exception (Buss 1989).

Same-sex sexual behavior or homosexuality seems impossible under a Darwinian point of view since it is related with low rates of reproduction and constitutes a "Darwinian paradox." However it is not a solely human phenomenon since it has been documented in hundreds of species (Garcia-Cardenas et al. 2015; Gunst et al. 2015; Leca et al. 2015; MacFarlane and Vasey 2016; Triana-Del Rio et al. 2015; Ungerfeld et al. 2014; Vasey et al. 2014). Its frequency is rather low, but the rates seem rather stable in all human populations. The role of environmental factors seems to be weak although there seems to exist some specific environmental conditions that may encourage transient homosexual behavior, e.g., captivity. On the other hand, there are data suggesting the influence of genetic factors, and some studies have pointed out relevant asymmetries in the distribution of both male homosexuality and female fecundity in the parental lines of homosexual vs. heterosexual males.

A number of hypotheses have been proposed to explain this paradox, although none of them has gained the full support of the scientific community. The following are the most important:

1. "Kin selection" which suggests that childless homosexuals might put more effort into helping raise nieces or nephews.
2. "Overdominance" which suggests the presence of a gene which when the person is heterozygous leads to a reproductive advantage (e.g., by increased female fertility or increased sperm motility) but when homozygous leads to homosexuality.
3. The "maternal effects hypothesis" suggests a fetus is influenced by the environment of the mother's womb, resulting in changes that predispose one toward homosexuality.
4. The "sexually antagonistic selection" hypothesis has the highest support from evidence currently. It suggests that there exist genes which are spread throughout the human population and they work by providing the one sex with a specific reproductive advantage while disadvantaging the opposite sex. Such a gene would promote fertility and subsequently reproductory fitness in females but homosexuality in males and vice versa (Camperio Ciani et al. 2008).

5. In animal species, in which the recognition cues of females and males overlap to a certain degree, homosexuality could be a consequence of an adaptive discrimination strategy to avoid the costs of making rejection errors (Engel et al. 2015).

In general it is supposed that the parents' investment depends on the probability of the offspring to survive. Furthermore, according to the Robert Trivers (1943–) and Dan Willard hypothesis (Trivers and Willard 1973), parents in good conditions tend to invest more on sons (who are best able to take advantage of good conditions), while parents in poor conditions tend to invest more in daughters (who are best able to have successful offspring even in poor conditions) (Veller et al. 2016; van Bodegom et al. 2013; Kaptijn et al. 2013; Kolk and Schnettler 2013; Venero Fernandez et al. 2011; Zadzinska et al. 2011; Cameron and Dalerum 2009; Cronk 2007; Koziel and Ulijaszek 2001; Chacon-Puignau and Jaffe 1996; Anderson and Crawford 1993).

According to Buss and Schmitt's sexual strategies theory and strategic interference theory, the differential parental investment observed in males and females led to the evolution of sexually dimorphic behaviors. When the strategies, priorities, and behaviors differ, then conflict between the sexes occurs, and as a result, emotional responses including anger or jealousy emerge (Buss and Schmitt 1993). Females generally react more negatively to emotional infidelity, while males will react more to sexual infidelity, especially also because fatherhood could not be proven until recently (Galperin et al. 2013; Buss 1995; Buss et al. 1992).

The "parental investment theory" is a branch of the "life history theory." It is evident that reproduction in general is costly for both sexes but especially for women. It demands the investment of significant resources, both in the form of time but also of material as well as of social resources (alliances and interactions). As a result the survival and the future reproductive output of the offspring are maximized at the cost of other options the parents have for their overall somatic health, fitness, reduced mating opportunities, and securing survival (Trivers 1972; Clutton-Brock and Vincent 1991; Hamilton 1964a, b). Step parental care could often be problematic because of priorities in favor of the biological child (the Cinderella effect) (Miller 2000b; Daly and Wilson 2005b, 1987 1991).

Evolution concerns the survival and proliferation of genes, and in this sense, the evolutionary success depends on the number of offspring, but this approach cannot explain a number of very frequent and important behaviors, e.g., altruism and self-sacrifice. In 1964, William D. Hamilton (1936–2000) proposed the inclusive fitness theory. In this theory he suggested that behaviors which harm the individual (e.g., self-sacrifice) could be considered to be adaptive in the frame of the group the individual belongs to, and in this way, they increase the chances of survival of the genes of the individual through the survival of family or relatives. Inclusive fitness is the sum of an organism's classical fitness (how many of its own offspring it produces and supports) and the number of equivalents of its own offspring it can add to the population by supporting others (Hamilton 1964a, b, 2001). It also explains our attitude toward more close to us species. This theory proposes an answer to the question concerning "altruism" in the frame of evolution. There is a number of

behaviors which are complex and difficult to understand in the frame of the classical evolution theory, and altruism is such an example. To explain their existence, a number of theories have been developed including evolutionary game theory, tit-for-tat reciprocity, and generalized reciprocity (Burt and Trivers 2006; Comins et al. 1980; Hamilton 1970, 1964a; Orlove and Wood 1978; Durand et al. 2011; Ferriere and Michod 2011; Abbot et al. 2011; Michod and Herron 2006; Michod 2006, 1996; Nedelcu and Michod 2006; Michod and Nedelcu 2003).

To further elaborate on the issue of non-selfish behaviors, one should consider the fact that from offspring to the wider family and eventually to wider groups, gene sharing and kinship are not an all or none phenomenon, but on the contrary, they spread on a continuum from close to distant relatives. Kin recognition is a complex ability with unknown characteristics, but it is well known that humans act generally more altruistically to close genetic kin compared to genetic nonkin (Lieberman et al. 2007). But this does not preclude collaboration with nonkin which can be achieved and maintained via mutually beneficial reciprocity. In this frame, natural selection favors strategies which improve the reputation and increase the chances of support from others. These strategies include a repertoire of social behaviors and emotions, including morality, guilt and friendship, as well as the ability to identify non-reciprocators (cheaters) (Fowler 2005).

### 12.4.10 Evolution of Language

An interesting ability of modern humans is the ability to speak, read, and write. Children learn to speak early without any specific training or intervention, and they are taught to read and write after specific training but again early and rather easily. However reading/writing and maybe speaking were not innate abilities of ancestral humans, although the use of sounds and gestures/behaviors is a common way for animals to communicate and to exchange crucial information.

There are several theories describing evolutionary pathways and mechanisms for the evolution of language, but all remain controversial (Workman and Reader 2008; Fitch 2010; Deacon 1997). The well-documented fact about language is that it is a universal characteristic of the human species and that children are not born with this ability, but seemingly effortlessly and without systematic training they learn to speak and comprehend language between years 1 and 4. These characteristics of language clearly suggest it is a distinctly human psychological adaptation, and it evolved in parallel with the body organs that support it (Pinker and Bloom 1990).

There are different theoretical approaches on the components and the foundation on which language evolved. Steven Pinker suggests the presence of an innate capacity of language in children (Pinker 1994), which is in accord with the ideas of Noam Chomsky (1928–) concerning the innate presence of a basic universal grammar. However, Pinker suggests that the acquisition of language is an adaptation while Chomsky suggests it is a spandrel (Workman and Reader 2008). Pinker argues that language is unique and characterizes only humans, it is an innate human ability rather than an invention, and it is separate from general intelligence and is based on

a distinct specialized mental module. On the other hand, Chomsky rejects the radical behaviorism of Skinner which argues that the brain is a "tabula rasa" (blank sheet) and subsequently language is fully acquired and taught. Also he argues that language is unique to humans and different from the ways of communication animals use (Chomsky and McGilvray 2012).

However although human languages share many common elements and structure, the universality of the nature of language has not been proved beyond doubt, and there are reports on the contrary. This debate is still unresolved. Additionally it is wrong to consider human language in the frame of the human species alone, and the idea of Chomsky that human language is completely different from the ways animals use to communicate with each other is an unproven and probably an extreme concept.

Animal communication is not identical with animal language, and it does not imply the presence of a language. However, animals use a variety of sounds or movements to communicate, and often they are complex enough to be considered as a form of language. It is important to note that the higher a species' position in the scale of evolution, the more specialized are the somatic organs which produce the sounds or the movements and of course the more evolved are the neurocognitive function and the content of communication. Almost all animals have specifically developed vocal cords in order to produce specific sounds. Therefore, language should be considered in the frame of extremely advanced general cognitive abilities which make possible the use of already existing organs (cords, fingers) for novel tasks in a creative way, which is easily passed from generation to generation through learning, but it is essential based on the innate ability to express and externalize mental procedures through their reflection on these sounds and movements (Fitch 2010; Deacon 1997). Such an expression could be considered to be a kind of "universal grammar" but in a less narrow definition. Although there was probably a selection pressure concerning language, it is unlikely such a pressure existed for reading/writing (Mabry 1995).

It is obvious that animal "language" lacks key elements which characterize the human language, but this depends on the species and how evolved they are. Some primates are even able to use lexigrams under experimental conditions (Gardner and Gardner 1969; Ward 1983), but normally the animal communication lacks the abstractive nature, the symbolism, the complex content, and the creativity which characterize human language. However it is not uncommon in nature that a quantitative difference, if extreme, could lead to a qualitative difference (Di Vincenzo and Manzi 2013; Traxler et al. 2012; Grodzinsky 2006, 2000; Fitch et al. 2005; Pinker and Jackendoff 2005; Hauser et al. 2002), while the continuum of language evolution is supported by research in primates which showed the presence of at least some human elements in their language (Ward 1983; Gardner and Gardner 1969; Patterson and Linden 1981).

### 12.4.11 Consciousness

Consciousness is another interesting neurobiological and psychological phenomenon. On one hand, it meets the criteria of species universality and of complexity as

determined by George Williams (Nichols and Grantham 2000), and on the other hand, its presence probably increases the overall fitness and survival (Herron and Freeman 2013). It is likely to be the end result of a number of highly adaptive evolutions in brain function (Eccles 1992), and it is not an all-or-none phenomenon. Its main purpose is to put the individual in a perspective concerning the place, the time, and the others, and therefore it is probably present in simpler forms and with somewhat more primitive and incomplete features and functioning also in pre-mammalian species (Baars 1993) with variable complexity and functionality (Gaulin and McBurney 2003).

Self-esteem is not part of consciousness per se, but it reflects self-awareness, that is, cognition about self at a second level. In evolutionary terms, it is essential as an estimation the individual makes concerning its place in social hierarchy. While consciousness positions the individual in terms of place, time, and the others, self-esteem positions the individual among humans and within the scale of social hierarchy. One approach could be that it constitutes a self-assessment in order to choose targets for the allocation of resources. The result is the so-called assortative mating, that is, mating with an individual of the opposite sex with similar qualities.

### 12.4.12 Personality

The description of temperament, character, and personality is beyond the scope of the present chapter and constitutes a very complex issue (Fountoulakis and Kaprinis 2006; Fountoulakis et al. 2016). Personality reflects individual differences between persons in terms of behavior, and individual behavior in humans manifests significant heterogeneity. These individual differences have been well documented in terms of social behavior, mating and other areas (Sugiyama 2005; Nettle 2006; Ozer and Benet-Martinez 2006; Thornhill and Gangestad 2008), and also in nonhuman species (Wolf et al. 2007; Gosling 2001), and they seem to be heritable to a significant extend (Plomin et al. 2008).

The question whether animals have these characteristics is still a matter of debate, although it is certain that individual differences exist also between individual animals in terms of behavior (D'Eath et al. 2009; Martin and Reale 2008; Reale et al. 2007; King et al. 2006; Whitney 1970). They seem to appear especially in social species, and this might mean that by presenting complex problems, it is the social environment that demands their existence and plays an essential role in manifestation as behaviors (Penke et al. 2007; Perilloux and Buss 2008).

Individual differences constitute an oxymoron for the evolutionary approach because heterogeneity is considered rather as the substrate on which natural selection acts or a starting point rather than the end product of natural selection itself (Gaulin and McBurney 2003). A general concept is that natural selection reduces rather than promotes individual differences. Therefore, the understanding of personality traits in the frame of evolutionary psychology manifests a number of important problems (Buss 1984, 1991, 2009) and has been relatively neglected, with some important exceptions (Buss 1984, 1991, 2009; Sheldon

et al. 2007; Segal and MacDonald 1998; MacDonald 1995; Nettle 2006; Wilson 1994; Wilson et al. 1996). On the other hand, when competition exists, individual differences are what matters, and they determine winners and losers. The ability to better monitor and assess these individual differences is also the product of adaptation (Buss 1996). Differences in personality among individuals could be considered as alternative strategies for the solving of adaptive problems which tend to recur (Buss 1996; Denissen and Penke 2008a, b; Hawley 1999; Nettle 2006).

For too long, individual differences were considered to be "noise" rather than "signal" in the big picture of evolution (Tooby and Cosmides 1990), but recent developments challenged this (Nettle 2006; Keller 2007). Apart from the standard life history, costly signaling, balancing selection, and contingent shift theories, a number of additional unique theories were developed specifically to deal with individual differences, such as social contract theory (Cosmides and Tooby 2005), sexual strategies theory (Buss and Schmitt 1993), error management theory (Haselton and Buss 2000), and adaptive cognitive biases (Haselton et al. 2005).

Individual differences are influenced by sex since, for example, it is reported that in the rhesus macaques, males are more aggressive, less socially affiliative, more impulsive, more prone to taking risks, and with higher mortality rates (Mehlman et al. 1994, 1997; Higley and Linnoila 1997; Higley et al. 1991, 1992). In mating, the strategies used differ not only between sexes but also among individuals of the same sex with some pursuing lifelong monogamy while others prefer frequent partner switching (Gangestad and Simpson 1990). Of course mixed strategies also exist. Similar differences exist concerning the pursuit of social status and the preference for a specific rank in social hierarchy (Hawley 1999; Lund et al. 2007b) as well as in the ability to detect deceit and cheaters (Ekman et al. 1999; Buss and Duntley 2008).

According to the life history theory which can provide a conceptual frame for the understanding of personality traits and their evolution (Figueredo et al. 2005; Kaplan and Gangestad 2005; Wolf et al. 2007), individuals make investments to solve adaptation problems, and the optimal trade-off between different allocations of resources depends on individual differences (Daly and Wilson 2005a). In this frame, personality disorders could be considered as behaviors stemming from perceiving different adaptational problems or from the presence of different qualities and resources which dictate different strategies (Daly and Wilson 2005a).

In a similar way, the costly signaling theory (Miller 2007) and the balancing selection with its key components "fitness optima" and "frequency-dependent selection" (Penke et al. 2007) could be also useful. It is reasonable to assume that some environments favor a risk-taking behaviors while others on the contrary favor more cautious harm avoidance behaviors (Camperio Ciani et al. 2007). A specific genetic substrate probably plays a role too (Ebstein 2006; Penke et al. 2007; Chen et al. 1999; Eisenberg et al. 2008). On the other hand, the mutation load theory is rather problematic since it tends to consider individual differences as random noise rather than alternative solution proposals, although there are opinions suggesting a more creative role in general for the mutation load (Buss 2006).

One personality which has been specifically the focus of research is psychopathy which corresponds to aspects of antisocial personality disorder. Frequency-dependent selection has been suggested as a mechanism which can explain the evolution of these traits and their survival in modern humans (Mealey 1995). The core characteristic of this personality is cheating with disregard of social norms and social solidarity. In this way these individuals exploit the strategy of cooperation the majority has. It is more frequent in males, and among other things, it involves the short-term seduction and abandonment of females (Mealey 1995). Another characteristic is the ability to identify potential victims (Buss and Duntley 2008).

More interesting is the way individual differences and personality traits could be understood in the frame of the theory of contingent shifts according to environmental and phenotypic conditions (Belsky 1999; Gangestad et al. 2006). Changes in behavior could come as a response to changing environment such as more aggression and higher risk taking in environment with few resources or mating opportunities or with more co-cooperativeness in dangerous environments. Such changes or facilitation of behaviors and psychological traits can also happen, not because of the environment but because of the emerging individual characteristics, a phenomenon called "reactive heritability" (Tooby and Cosmides 1990). Such an example is body size which tends to determine higher aggression in persons with large body sizes and more pacificity in individuals with small body size (Ishikawa et al. 2001). Another such example are the later-born children which are often more rebellious and less conscientious (Sulloway 1996).

The way individuals copy with the challenges posed by their participation in large groups is also variable and differs significantly from person to person. The position in social hierarchy is usually pursuit with prosocial and coercive strategies, depending on the personality (Hawley 1999). These strategies include deception and manipulation or, on the contrary, communication of positive personal characteristics and also with industriousness (Lund et al. 2007a), and to a significant extent, they correspond to the five-factor personality model (Buss 1992; Costa and McCrae 1985; McCrae et al. 2005). These personality factors were also viewed as motivational forces for the choice of specific strategies (Denissen and Penke 2008a, b).

Interestingly, the five-factor model was developed on the basis of the lexical theory of Gordon Allport (1897–1967) and Henry Odbert (Allport and Odbert 1936). The first such attempt had been made by Franziska Baumgarten-Tramer (1883–1970), who identified 1093 separate words in the German language as reflecting personality traits and mental disorders. This was of course incomplete as Gordon Allport and Henry S. Odbert showed in 1936, when they identified 17,953 such words in the English language and separated them into four categories or "columns." According to them, the first column included 4504 words that reflect personality descriptions. The second column with 4541 words reflected emotions, while the third column with 5226 words reflected social and pragmatic but not psychological evaluations of an individual and its position in society and its hierarchy. The last column with 3682 words included words with miscellaneous meanings and use. This theory is based on the assumption that the natural human language constitutes an important source for the identification of personality traits, because as Raymond Cattell

(1905–1998) suggested, in the course of the evolution of human culture, any behavior or personality concept which would be of importance in human social interaction should have been registered in language since it was the content of communication. The 16 Personality Factor Questionnaire (16PF) (Cattell et al. 1970) and the five-factor personality theory (Costa and McCrae 1985; McCrae et al. 2005) are both products of the lexical hypothesis. The main criticism argues that these imprints in human language are biased lay peoples trivial and superficial descriptions.

## 12.5 Evolutionary Social Psychology

Evolutionary social psychology is a rather recently developed scientific field and tries to understand the complex area of social behavior in the frame of evolutionary psychology and biology (Santrock 2005; Schaller et al. 2006). Essentially it constitutes the expansion of evolutionary psychology in the social domain.

Social psychology concerns the study of thoughts, feelings, and behaviors in a social environment, that is, in the actual, imagined, or implied presence of others (Allport 1985). Thus, it bridges psychology with sociology and pays attention to the phenomena that occur at the individual but also at the group level (Moscovici and Markova 2006). Its appearance followed the development of sociology in the late nineteenth century and emerged as a new discipline in the early twentieth century although some thoughts in this field existed already in the Arab scholar literature (Gergen 1973). At the core of its existence is the assumption that human behavior and social phenomena can be the focus of scientific research which follows the universal rules of science. One of the pivotal historical cases of social psychology was in the 1960s, the case of the Stanley Milgram (1933–1984) experiments on obedience to authority.

The basic concept in social psychology is "attitude" which is defined as a learned global evaluation of a person, object, place, or issue, and it determines action. It reflects approval or disapproval, favorability or unfavorability, or, in simple words, likes and dislikes (Bem 1970). Attitudes influence behavior, but they are often poor predictors of it. They could be conscious or unconscious (implicit), and they concern most of social interactions. The question whether attitudes are determined genetically or culturally and through learning and to what extent remains unanswered. Another important concept is "persuasion" which refers to the influencing of people by rational or emotive means in order to adopt a specific attitude (Myers 2010).

Social cognition and theory of mind is a field of research concerning the neurocognitive basis of social behavior. This refers to the ability of individuals to process and interpret stimuli relevant to the behavior of others, that is, their intentions, desires, and abilities, but also concerning the prediction of their future behavior. Collectively this is called "attribution" and can be ascribed as an internal (personality, character, etc.) or external (environmental) locus (Reisenzein 2015; Dunfield and Johnson 2015; Schreiber 2012; Seidel et al. 2010; Santiago and Tarantino 2002; Andrews 2001; Klin 2000; Block and Funder 1986; Kruglanski 1986).

A number of biases and errors in the attribution process have been described, and probably all of them are the product of evolution. These biases and errors include the tendency to overestimate the role of personality and underestimate the role of situations, to attribute dispositional causes for successes and failure and blaming victims for their suffering. Also bias is considered the false memory of having predicted events or the overestimation of true predictions after the outcome is known. Confirmation bias leads to search for information or interpretations that confirm preconceptions and disregard the others. All these protect the person from feeling vulnerable and mortal. It seems there is a kind of "white lies" everybody tells himself as a defense mechanism in order to keep psychological well-being, and maybe these "adjustment lies" are not functioning in depression (Andrews 2001). However biases are not identical with errors. Biases can help quick adaptation, but they could constitute errors under specific conditions. This is because the human brain utilizes heuristics in order to arrive at fast decisions to complex and demanding problems. Heuristics are cognitive shortcuts, and the whole procedure is based on the comparison of the situation faced with a prototype situation the people know of. This often demands a simplified and straightforward interpretation of the complex reality and the development of generalized mental representations called schemas. Schemas organize knowledge and guide information processing but often lead to the development of a generalized set of beliefs about groups of people or situations. If this comparison leads to a successful solution, then the bias and the schema lead to adaptation; if not it leads to an error or to a problematic stereotype and prejudice.

Another important concept is that of "social influence" which refers to the persuasive effects people have on each other and includes conformity (act or think like other members of a group), compliance (change in behavior due to a request or suggestion from another person), and obedience (change in behavior as a result of a direct command from another person). An interesting form of social influence is the so-called self-fulfilling prophecy which refers to the situation when a prediction is made; the person's behavior actually causes it to happen, e.g., when expecting hostility from others; the behavior of the person itself actually causes it, while it did not preexist.

Apart from the interaction between individuals and between individuals and groups, groups also interact with each other since they possess a distinct identity, rules to follow, and solidarity among members. A related phenomenon is the behavior of crowds which often leads to deindividuation, a term reflecting a state of altered self-awareness caused by feelings of anonymity (including large crowds, disguise, and online anonymity). This is associated with uninhibited and maybe dangerous behavior.

To put social psychology in an evolutionary perspective is both challenging and rewarding. An essential first observation is that there seems to be a lot of common features that link human cultures from around the world irrespective of how isolated they are from each other and similarities are more than differences (Brown 1991; Rosch 1973). For example, in all human cultures and societies, there are systems to recon kinship and treat individuals according to kinship status (Daly et al. 1997). While this is not the case for the vast majority of mammals, all human societies have

some kind of marital bond for the sharing of parenting (Daly and Wilson 1983; Broude 1994; Geary 1998). These cultural similarities exist alongside many cultural variations, which often seem very peculiar like the mating customs of the aboriginal tribe of Tiwi in Australia who manifests an interesting interplay between general human mating preferences and a particular social ecology (Hart and Pillig 1960).

Another example is that historically, in most cultures there is polygyny (one man and more than one wife), while a few permit polyandry (one woman and more than one husband). It is interesting that in spite of this modern societies are monogamous. It is standard procedure that when biologists find variations across species in behavior, they search for correlations with ecological factors (Alcock 2001). In general polyandry, though rare, can be explained by the presence of an environment with limited resources. In such environments (e.g., in the high Himalayas), it needs more than one male to support a female and her offspring successfully. In such places, often brothers marry the same woman (Platek and Shackelford 2007; Salmon and Shackelford 2008). On the contrary, in places rich in resources, the opposite phenomenon, that is, polygyny, is observed. Extreme polygyny is manifested in harems, and they are associated with societies with strict hierarchy in a rich environment (Crook and Crook 1988). However other factors apart from the physical environment play a role in the quality and characteristics of the marital bond. One such factor is the ratio males-to-females which can change because of war, migration, and other similar causes. In excess of females, later marriage, more divorce, and permissive sexual norms are observed. In excess of males, males are committed to more stable monogamy (Gangestad and Buss 1994; Kenrick et al. 2003).

It is interesting to note that in the great apes, all kinds of social organization are seen, from monogamy in gibbons to unimale polygyny in orangutans and gorillas and to multimale polygyny (or polygynandry) in chimpanzees where a group of males defends a group of females and their offspring (Foley and Lewin 2013; Lewin 2009).

In all human cultures, also the presence of status hierarchies is a basic characteristic of society with separations of casts and groups and variable restrictions and rules (Brown 1991). Anthropological and archaeological data suggest that originally, humans were living in small groups of hunter-gatherers with the size of 50–80 individuals on average and the members of each group were biologically related. These groups were characterized by less strict social hierarchy, members knew very well each other, and they were connected with (actual or fictive) bonds of kinship and were occupying large territories in an exclusive way (Barnard 1999; Maryanski and Turner 1992).

Within these groups, the genetic relatedness together with the long-term reciprocal exchanges usually developed trust and cooperation rather than market-like reciprocal exchange (Fiske 1992). Stigmas concerning disability or disease probably reflect fear of threat not only to the psychology of the individual but also to the collective group welfare (Kurzban and Leary 2001; Neuberg et al. 2000).

Also, an unknown individual not belonging to the group was considered to be a potential enemy, and although cordial exchange relationships with other groups were in place, outsiders were always considered to be a threat in terms of stealing,

kidnapping females, rape, or homicide (Chagnon 1988; Radcliffe-Brown 1913). Therefore it seems that evolution could have made humans to be cognitively inclined to divide other people into "with us" and "not with us" and to perceive the later as a source of danger and threat (Krebs and Denton 1997; Wilson 1978). However, since outsiders often did not constitute a threat but on the contrary they constituted opportunities for trade and development, a flexible response system would be more adaptive in comparison to a rigid one that would reject all outsiders. Such a flexible system would recognize the true value of the outsider and its place in the complex environment of the group (Kenrick 1994; Kenrick et al. 1994).

## 12.6 Sociobiology

Sociobiology attempts to predict social behavior by utilizing the tools and theories of evolutionary psychology (Haig 2002). Social life is the preferred mode of living in many species in nature. They prefer to live in groups and manifest characteristics of social life, some of them very complex, but the complexity of human societies is exceptional. This complexity is such that many individuals find it difficult to adjust to its demands and subsequently are concerned more with keeping up with the rules and laws of the society than with survival itself, which these rules are supposed to serve. According to Jean-Jacques Rousseau (1712–1778), "*social institutions are those that best know how to denature man, to take his absolute existence from him in order to give him a relative one and transport the I into the common unity*" (Rousseau 1979).

Through the history of human societies and since the strong prosocial teachings of Socrates (470–399 BC) and Confucius (551–479 BC), a number of theories evolved, which essentially were attacking the very concept of social organization itself, from the philosophical ideas of Jean-Jacques Rousseau to the anarchist political ideology of William Godwin (1756–1836) and Mikhail Alexandrovich Bakunin (1814–1876).

But one of the most fascinating ideas which appeared in the twentieth century was that of the "Noble Savage" which enjoyed wide acceptance, especially in the frame of the civil rights movement after WWII. It referred to an ideal human being, living in peace with nature and his neighbors, with no negative thoughts or feelings. It was preached by Margaret Mead (1901–1978) who claimed that she had found a tribe in Samoa with an ideal psychological and social behavior and lacked things like jealousy or rigid sex roles (Mead 1928). Her reports were proved to be completely false and biased (Shankman 2009; Freeman 1983). However this idea was appealing, since it suggested that humans are inherently good and moral and modern civilization was the cause of all negative things (a convenient external locus). This is of course very close to the ideas of Jean-Jacques Rousseau and his 1762 book *Emil* (Rousseau 1979). Around the same time Margaret Mead was developing her ideas, another concept, that of the "Blank Slate," was widespread. This suggested that all people were able to learn anything with an equal amount of effort and that there were no biological predispositions or inclinations. This reflected a

concept of radical equality at all levels and aspects, which took the step from civil rights equality to consider individuals being not only equal but essentially identical in all aspects. This was also suggesting that all individual differences were the product of social forces rather than inherent traits. This has its roots in Aristotle (384–322 BC), but it was shaped with the concept of "tabula rasa" by John Locke (1632–1704), although in a different frame and purpose. However the modern concept has important modern political implications. According to the modern concept of the "Blank Slate," in cases of state failure or in non-state societies, people organize in group for protection, and concepts like revenge and honor become extremely important (Pinker 2002; Rose 2001). This is in sharp contrast to the very influential collectivist anarchism theories developed by Mikhail Alexandrovich Bakunin.

Research has proved that humans have a strong predisposition to learn some behaviors over others and that individual differences do exist (Buss 2001). Therefore, it is pretty evident that as every living organism on Earth has a repertoire of "hard-wired" behaviors and instincts which serve survival, so do humans. For all species, these traits are evolutionary developed and determined. For humans, this evolution took place mainly during the Pleistocene, and contemporary behaviors constitute more abstract and refined versions of basic adaptation strategies (e.g., friendship evolved from sharing of resources) (Kenrick et al. 2003). All aspects of human mental life were developed during that period, and their properties, advantages, and problems can be traced back to then, from differences in cognitive function between sexes to the selective and representative but imprecise way memories are retrieved (Klein et al. 2002).

Social life is characterized by a way of life and behaviors which are often sharply different from a solitude way of life. Thus there is a constant conflict between the needs of the one vs. the needs of the many, and this is a problem evolutionary sociobiology needs to address, but it is often very difficult. The behaviors and restrictions when being part of a group might reduce that reproductive success or induce harm or even death to the individual. Eventually, however, through inclusive fitness, the survival and adaptation of the group and the society as a whole increase. The term "reciprocity" refers to the behaviors with which individuals exchange favors. The issue of altruism and other non-selfish or self-harming behaviors in the frame of inclusive fitness theory has been described above. Issues pertaining mating and polygamy have also been discussed above. The ability for empathy is a rapid way to induce cooperation and to facilitate reciprocal altruism (Burt and Trivers 2006; Dawkins 1976). The same holds for communication and "cheating." Reciprocity is essential for humans; failure to reciprocate reduces, while on the contrary, the reliable reciprocation increases social reputation. Especially for the study of reciprocal systems and cheating, the game theory paradigm known as the "Prisoner's dilemma" tries to model the development of cooperation among independently acting egoists (Barash 2003b).

It has been estimated that in order for the human fetus to be fully developed like the fetuses of other mammals and great apes, a gestation period of 18–21 months would be necessary. The reason why it has been restricted to only 9 months has been considered to be a side effect of upright bipedal walking which leads to a small

pelvis size which in turn limits the size of the fetus the human female can carry (Weiner et al. 2008; Charnov and Ernest 2006). This was called the "obstetrical dilemma," a term coined in 1960 by Sherwood Larned Washburn (1911–2000) (Wells et al. 2012; Washburn 1973, 1978, 1982; Washburn and McCown 1972). Another theory suggests that it is the result of limits in the metabolic burden the mother can take in favor of the fetus, and subsequently this puts a limit to how large and energetically expensive a fetus can be (metabolic crossover hypothesis) (Dunsworth et al. 2012). No matter what the cause is, the fact remains that the human newborn is extremely unprepared to survive by itself in nature and demands significant care and parental investment, thus pushing toward stable long-term mating relationships. This makes humans much more monogamous oriented than primates and other mammals.

Observations are consistent with the belief that humans are mildly polygamous by nature and this is a stable cross-cultural characteristic. Serial monogamy is a situation in between monogamy and polygamy (Barash and Lipton 2002; Platek and Shackelford 2007; Salmon and Shackelford 2008). Social norms do not permit departures from monogamy to manifest openly, especially for women. In spite of this, departures from monogamy are present for both sexes universally (Barash and Lipton 2002). This is also true for previously considered monogamous species, as DNA testing proved that 10–80% of offspring come from a father which is not the male social partner of the couple. This might also was the case for prehistoric humans as well, but in modern human societies, the rate is probably below 4% (Bellis et al. 2005). The globalization which started with the colonial era brought a gradual social homogenization, and while before, almost 90% of societies were polygynous, currently the vast majority are monogamous, and monogamy is also a feature, among others, which determines whether a society is modern or antiquated.

Polygyny was socially more dominant, and it is related to a number of differences between sexes. On average, men are physically larger and with a tendency toward competitive and often violent behavior. Females mature sexually earlier than men and often prefer men older than themselves. All these are also found in mammals where polygyny is the rule since through natural selection, males obtain characteristics which help them to compete with other males, with higher strength, status, and chances for success with advancing age, while females reproduce early and more frequently. These correspond to a pattern of "sexual dimorphism" and "sexual bimaturism." In monogamous species like gibbons, males and females are of the same size. In gorillas which live in unimale polygamy, males are 30% bigger (Foley and Lewin 2013; Lewin 2009).

Studies of old societies who accepted polygyny suggest that nearly all women were mated and reproductive. On the contrary, there was significant variability in men, with some men being nonreproductive bachelors, most being monogamous, and a few having a harem. This points to another fact that, although the physical tendency is toward polygamy, humans are clearly capable of monogamy, at least at the social level. Even their physical inclination toward polygamy seems to be less strong in comparison with most mammals. In evolutionary terms, as described

above, this could be explained by the fact that the human offspring is helpless at birth and takes several years to grow up, and this is more pronounced in comparison to the offspring of other mammals. Subsequently it needs more postnatal care and parental investment from both parents for several years until it grows up.

On the other hand, the tendency of females to seek multiple sexual partners is difficult to explain. It was also difficult to document until recently, because of the secretive way it was conducted in all species. This tendency occurs in spite of risking even violent behaviors from the side of the male and the high risk of abandonment. The probable explanation is that females try to improve the genetic quality of offspring while at the same time they keep the advantages of stable parenting through social monogamy.

The above are in accord with the presence of a lower threshold for sexual excitement in men which therefore are more susceptible to pornography, prostitution, and paraphilias. They are also more eager to engage in sexual activities with strangers, and they pay more emphasis on the physical attributes of the partner since these reflect fertility status. They pay less attention to intellectual attributes and are jealous and possessive. On the contrary, females seem to be more concern with male access to recourses. The mechanism for these choices is largely unconscious, at least concerning the deeper evolutionary goal.

Men are more inclined to physical aggression and violence than women, and much of their behavior is based on the show-off or physical strength. This is of course culturally enhanced, but it is based on inherent traits. There is no culture in which the sex images are the opposite and women are culturally expected to be more violent than men.

In nature physical aggression and violence is often linked with mating, even in the great apes. While in human society and culture, rape is linked to moral and political issues, in the animal kingdom, rape is probably the strategy followed by the otherwise socially and sexually unsuccessful individuals. In humans, the "domination hypothesis," introduced by Susan Brownmiller (1935–), suggests that rape is not sexually motivated, but instead, it is a conscious process of intimidation by which all men keep all women in a state of fear. This was a highly controversial theory in a clear feminist politico-ideological frame (Lalumiere et al. 2005), and one of the key arguments in favor was that no zoologist ever observed animals raping in their natural habitat. However this is far from true. At that time such evidence was available and in the following decades accumulated (Alcock 2001). Randy Thornhill (1944–) and Greg Palmer argued against this hypothesis and pointed out that the improved understanding of what motivates rape rather than ideological approaches likely helps prevent rape. They argued that sexuality is the motive behind rape since a disproportionate number of victims are very young women and suggested that rape is either an adaptation or a by-product of adaptive traits such as sexual desire and aggressiveness (Thornhill and Palmer 2000; Lalumiere et al. 2005; Figueredo et al. 2011). Furthermore, competition among males is probably more intensive in late adolescence and young adulthood, and this might explain the particularly high crime rates in these age groups (Rose 2001).

Parenting is a complex situation and task and demands a number of somatic but also intellectual abilities from the side of parents. Conflicts between parents but also among parents and offspring are frequent, and from an evolutionary perspective, this is also because their evolutionary goals and agendas are not identical. Parents share only half of their genetic material with each offspring which acts as a limiting factor in parental investment. The area of parent-offspring conflict is predictable and concerns mainly the tendency of the offspring to seeking and obtaining more investment than the parent has chosen to provide. In a reversal of situations, similar conflicts may occur when the offspring shows significantly less than expected inclination toward the parent and preference for other members of the family. The psychological dynamics within a family were the focus of psychological, sociological, and anthropological studies, and the conclusion is that they could be very intense as well as unconscious. Competition with same-sex parent and adjustment to opposite-sex parent can be considered under this view, as they can, even sophisticated psychoanalytic concepts like the "Oedipus concept."

A more complex social and psychological issue is stepparenting. Among animals, stepparenting is rare, and when it occurs, it might hide different aims from the side of the stepparent. When created experimentally, these families are very dysfunctional, and even murders happen. Infanticide and neglect of stepchildren are the rules rather than the exceptions (Power 1975; Hasegawa and Hiraiwa 1980; Barash 2003a).

While most human stepparents are clearly able to function and invest in their stepchildren, which is an important element especially in societies with high divorce rates, in evolutionary psychology, the term "Cinderella effect" (Daly and Wilson 2005b) refers to the alleged higher incidence of child abuse and mistreatment by stepparents in comparison with biological parents. Of course it refers to the famous Cinderella fairytale, and it is believed to be a direct effect of competition concerning mating and parental investment as described above. There is a wide belief that stepfamilies are emotionally conflicted more frequently in comparison to biological families. Non-biological parents have an inherent disinclination to invest in unrelated children. It is both interesting and disturbing that there are some data suggesting that even the accidental injury of children is higher when a stepparent exists but not in single-parent families when one of biological parents has left (Tooley et al. 2006).

One of the sensitive and delicate issues to deal with in a sociobiological perspective is religion and religiosity. Currently there is a controversy whether they are a consequence of evolved psychological adaptations or a by-product of other cognitive adaptations (Beit-Hallahmi 2012; D'Onofrio et al. 1999; Fountoulakis et al. 2008; Rossano 2006). It is to be noted however that primitive religious-like ceremonies have been observed in chimpanzees (Harrod 2014).

An issue which recently started to be the focus of interest and research is the fact that the more the culturally and technologically advanced a society is, the more it demands biologically determined secondary abilities, especially neurocognitive, from its members. This seems to be even more intensified and pronounced with the

informatics and electronics revolution of the last few decades (Geary 1995) and creates new challenges since human societies try to be simultaneously competitive but also inclusive and caring.

## 12.7 Darwinian (Evolutionary) Psychiatry

The Darwinian theory had a major influence on how health and disease are conceptualized and what might constitute the best treatment option. There is a newly emerged field, called "Darwinian medicine." It utilizes a different and novel approach to the consideration of symptoms and diseases and tries to provide with more rational and informed choices for treatment (Sims 2001; Rose 2001).

A number of medical conditions including obesity, anemias, autoimmune diseases, and hypertension were put in an evolutionary frame (Gluckman et al. 2009). A number of questions concerning "why we have this problem" might be answered in an evolutionary frame. For example, why modern humans manifest high rates of obesity? Is this a consequence of generations of humans living in an environment of limited resources and frequent famine which made important the accumulation of reserves? Is primary (essential) hypertension a consequence of adaption to low-salt diet which resulted in hyper-response to salt intake? Is maxillary sinusitis a problem of walking upright since the position of the duct for drainage is perfect for quadrupedal walking, but it is located too high when the head is erect as in bipedal walking? Are fever and diarrhea defense mechanisms to reduce the survival of pathogens inside the body and to eject them?

According to this approach, also mental health and disease could be understood as the end result of the interaction between the organism and the environment, with the addition that abnormal behaviors and symptoms could reflect either an extreme form of otherwise adaptive behaviors or the triggering of them in an out-of-frame or proportion way and under inappropriate conditions.

This is somehow different from the standard approach in clinical psychiatry and psychopathology where connections with recent events and reaction to recent problems in the frame of the individual patient's and core family are considered (proximate mechanisms). In contrast, evolutionary psychiatry stresses that variation (including variation in behavior) is not only normal but evolutionarily necessary and is concerned with the misfit of preexisting normal coping mechanisms which could cause maladjustment or disease if triggered in an inappropriate way or persist for longer than expected and especially in an environment and with social demands extremely different from those encountered by humans during the Pleistocene and the Stone Age (Fabrega 2002).

As psychiatry is part of medicine, so is Darwinian psychiatry a subset of Darwinian medicine. If this is so, it is important to see whether mental symptoms and disorders could be considered in the frame of evolutional adaptations.

The classic psychoanalytic theory of Sigmund Freud (1856–1939) is a very fruitful starting point. Especially his theory on the instincts of Eros (life and survival) vs. Thanatos (death and aggression) and the libidinal investing as well as the Oedipus complex have direct relevance to concepts and theories of evolutionary psychology as described above.

However, psychopathology is quite different from psychology of normal mental functioning. The big question is whether diseases and disorders like schizophrenia, manic depression (bipolar disorder), depression, and others can be analyzed and understood in an evolutionary frame.

The problem is perplexed by the problematic reliability of psychiatric diagnosis and the presence of a "gray zone" between normality and psychopathology. Although it is not standard approach, one could suggest that some psychiatric conditions could be considered to be clearly abnormal and psychotic symptoms are such an example. Experiences similar to psychosis are very rare in the general population, and the average person cannot "understand" how a psychotic person feels. On the other hand, some other conditions like anxiety disorders and depression seem to constitute an extreme version of normal experiences of grief and anxiety, at least in the way the patients experience them and the way the observer perceives. Thus, the inner experience of a depressed patient is quite understood by the average healthy person which in the past had experienced several periods of grief, mourning, and anxiety. A third group of conditions include behaviors and inner experiences which are frequently seen in the general population but in mental patients seem to exist in an unusually accumulated coexistence, and they manifest out of frame concerning the intensity and the environmental stimuli. These conditions include certain personality traits like antisocial behaviors, eccentric dressing and outlook, substance use, body modification, etc. For example, a large proportion of the population has used cannabis at least once, has been involved in minor stealing at least once especially during adolescence, dresses in an odd way occasionally, and has piercing and/or tattoo. When these characteristics accumulate in a single person and to an unusual degree, e.g., daily use of cannabis, habitual delinquency, whole-body cover of tattoos, and extreme piercing with health risks, then it is highly possible the person suffers from some kind of mental disorder.

If one views mental disorders with the above described way, then it is clear that it is highly unlikely to find an evolutionary explanation for the first category. This is reasonable since there is no apparent evolutionary advantage in hearing voices or seeing visions at any age and at any frequency. Such conditions are probably related to a deep primary disruption in the functioning of the brain and subsequently of the mental apparatus. Some delusional ideas, however, could be conceptualized as extreme forms of caution and efforts toward harm avoidance. The only way out could be to find some kind of fitness advantage in the healthy members of families of patients with psychotic disorders. Although there are assumptions that creativity and high intelligence run together with manic depression and schizophrenia in

families, this has never been proven. An impressive example of the coexistence of high intelligence and schizophrenia in a family is Albert Einstein (1879–1955) and his son Eduard (1910–1965; Fig. 12.10). Another example of the coexistence of greatness and multiple mental disorders and suicidality is the Hemingway family (Fig. 12.11).

**Fig. 12.10** Eduard Einstein (1910–1965)

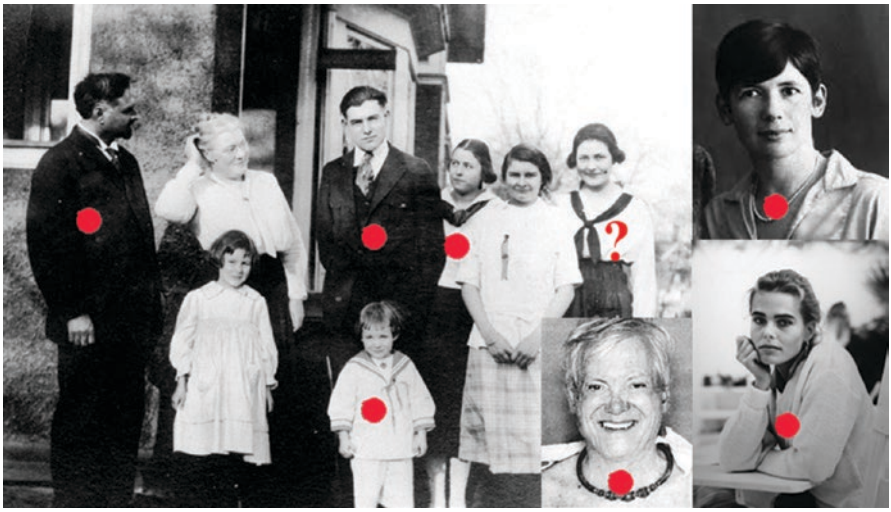


**Fig. 12.11** Members of the Hemingway family c. 1917. Main photo: Clarence (father), Grace (mother), and offspring (Carol, Ernest, Leicester, Ursula, Madelaine "Sunny," and Marceline). Right top: Pauline Pfeiffer (wife). Right bottom: Gregory (son). Left bottom: Margaux (granddaughter). Red dots mark those who died by suicide. The question mark stands for a possible suicide for Marceline

For the other two categories, however, an evolutionary approach is highly possible. Since affect is an adaptation which serves both fast unconscious decisions and communication with peers, mood and anxiety disorders can be conceptualized as an extreme form of communication, a "cry for help." An alternative explanation could be that depressed individuals attempt to preserve their position within the social group but the same time avoid risky and costly behaviors by sending out signals to ask for help (Allen and Badcock 2003). Suicide could be conceptualized as the triggering of a behavior where the individual sees no fitness-enhancing opportunities and death is the only right action since it will conserve resources for kin and enhance inclusive fitness. Substance abuse on the other hand as well as behavioral addictions (e.g., gambling) could be considered to be a by-product of the evolution of the "behavioral and habits formation systems," which permit the individual to acquire new and adaptive behaviors and habits. However the interaction of these systems with the presence of supernormal stimuli (drugs, carbohydrates, games etc.), which have a higher than expected effect both on the attentional grab and also at the biochemical level, leads to the formation of addictions. This is neither an adaptation nor an exaptations (spandrels), but rather a mismatch, that is, a mechanism which had been developed to function in a different environment, is dysfunctional today at least in vulnerable individuals.

On the contrary, the case of antisocial behavior and body modification as well as extreme cases of provocative and bizarre way of dressing probably constitute exaptations (sprandels) since they are based on behaviors which had developed in order to promote fitness but currently are expressed for a different reason. Usually this reason is overt or hidden aggression which takes the form of physical aggression or provocative show-off of a violation of social norms. In most cases there is no gain in terms of better adaptation or fitness; on the contrary the individual could be highly dysfunctional.

There are two significant problems when one tries to put the above in a comprehensive frame for clinical psychiatry. First, in order to have behaviors and experiences "out of proportion" and "out of frame," regardless of their initial evolutionary relevance, there should be some kind of dysfunction of controlling mechanisms. Again the concept of a brain dysfunction at the core of mental disorders seems to be essential even for the evolutionary approach, which, never the less, can explain the source of individual symptoms.

The second problem is political/ideological again, but it is at the root of the whole establishment, and the problem is strengthened by the approach itself. If there is an evolutionary explanation behind many antisocial behaviors, then these constitute essentially normal nonpsychiatric variations rather than abnormal conditions. On the contrary, a more conservative approach would argue that if supernormal stimuli are, at least partially, responsible for many mental problems, then these stimuli are "unnatural" and should be eradicated from human societies (wide suppression policies).

The detailed answer to both these issues is beyond the scope of the present chapter. However, one should have in mind that persons with antisocial behaviors are fully responsible for their acts in front of the law; therefore everybody accepts their "civil right" in the choosing of these behaviors but also in the accepting of their consequences. There is a huge debate whether self-destructive behaviors (including suicide) should be considered as "civil rights" or mental disorders, but the prevailing attitude is in favor of the second.

Concerning supernatural stimuli, an approach in favor of a wide eradication of this kind of stimuli from human societies does not take into consideration the fact that essentially modern societies are based on the presence of supernatural stimuli and demands. This is often the cause of mismatch conditions, where new "health problems" arise, and behaviors are triggered under inappropriate situations while focusing on the wrong target. Such examples are the demands of living in megacities with very complex social roles and dynamics, the cognitive load and demands the modern education and especially modern educational methods including multimedia and the Internet pose on the human mind, and the need for accuracy and precision in occupational tasks. Another interesting feature of modern life is that a significant number of stressors and threats are not visible and material, as they used to be in the past, but, on the contrary, are abstracted, theoretical, complex, and difficult for the average individual to understand in full. For example, during the Pleistocene, the danger was predator animals, while today it is the distant risk of having a disease which will give symptoms sometime in the future, the danger for economic problems, etc. The fact is that while biological evolution is slow (and Darwinian), cultural and societal evolution (which is Lamarckian) is very fast.

## 12.8 Criticism

While ethology is based on observation, a major problem in evolutionary psychology and sociobiology is that they depend too much on reasoning and less on the analysis of data. Very few theories can be experimentally tested or prospectively studied. Of course they follow the rules of science, but it is doubtful that many of the theories which have been developed could fulfill the falsificationism criterion proposed by Karl Popper (1902–1994) (Popper 1959). Probably while isolated statements do not fulfill the criterion, the whole theoretical framework does, but it is rather underdeveloped and conclusions are difficult.

Apart from the epistemological, there is a number of ideological-political issues which make the application of evolutionary principles to human behavior controversial (Confer et al. 2010). The first is the widespread objection to the Darwinian theory of evolution in general. Then there is the bitter controversy on the importance of nature vs. nurture in the shaping of human behavior. Inevitably these lead to important politico-ideological conflicts, and the evolutionary approach to human behavior has been accused of developing and spreading malevolent political or moral ideas, of justifying existing social hierarchies and "reactionary policies," and of giving support to racist and sexist attitudes.

The obvious problem with this kind of criticism is the well-known "naturalistic fallacy." This biased way of thinking identifies "natural" with "good" (Moore 2004). This is behind lay beliefs that "natural remedies" are good and medications are toxic and that a natural way of life in nature is better for human health. Of course these are in sharp contrast with the improvement of life and the impressive increase in life expectancy as a result of "unnatural" and technological advances during the last few decades. Still, it is a very popular way of viewing things not only among lay people

but also among many health and social sciences professionals and philosophers. Darwinism has been a particular problem for this way of viewing things, because it is directly destroying the romantic viewing of nature and the anthropocentric consideration of the universe.

An essential characteristic of politico-ideological criticism is that it mixes epistemology and the results of science with morality and ethics. Is the wolf in the *Little Red Riding Hood* a "bad" and "unmoral" being? Of course the tale is a metaphor; however it reflects our tendency to utilize an anthropomorphic and anthropocentric way when viewing nature. There is nothing moral, good, or bad in the natural relationship between wolves and sheep, the first being the predators and the second being the prey. The description of similar structures and phenomena in human society and related underlying psychological phenomena in the individual human being is neither good nor bad, as long as there is proof that this is the scientific case.

The human society and the human culture were both developed in order to control these behaviors and create a more friendly environment for human beings to live, and both society and culture fight constantly with the most primitive and aggressive aspects of human nature.

As discussed before, there is a long anti-societal and anti-civilization ideology, with deep roots in irrationalism, which however differs as a concept from anti-rationalism and non-rationalism, and in simple words, it interprets the world through wishful thinking (intuition) but simultaneously keeping in touch with reality, e.g., as in the writings of Friedrich Wilhelm Nietzsche (1844–1900). An example of anti-rationalism is the teachings of Saint Augustine of Hippo (354–430). Often irrationalism, non-rationalism, and anti-rationalism coexist in most ideological and philosophical thoughts, since their major concern is not scientific theories and scientific explanation and understanding of the world but the effect such progress might have on various aspects of humanism and especially in the rejection of the perceived special top position humans have in the hierarchical pyramid of the universe.

Last but not least, one should always have in mind that the topics discussed in this chapter are sensitive in terms of humanity and politics and have been used both ways by completely opposing sociopolitical groups. This sensitivity and dangerousness is impressively shown in the life and works of the Nobel Laureate Konrad Lorenz. Lorenz joined the Nazi Party in 1938, and he was also a university chair at the University of Königsberg under the Nazi regime. At the same time, he published articles in accord with Nazi ideology, especially "racial hygiene" couched in pseudoscientific metaphors and with anti-Semitic content. This led to accusations that his scientific work had been contaminated by Nazi sympathies. During the WWII, he served as a military psychologist, conducting racial studies in occupied Poznań under Rudolf Hippius, on the biological characteristics of "German-Polish half-breeds" in order to determine whether they were psychologically and physically fit to be allowed to reproduce humans. His real contribution to this project is unknown, and this 2-year period is not mentioned in his memoirs. Because of the above, in 2015, the University of Salzburg posthumously rescinded an honorary doctorate

awarded to him in 1983 and also accused him of using his work to spread "basic elements of the racist ideology of National Socialism" (Burkhardt 2005; Föger and Taschwer 2001; Kalikow 1983; Nisbett 1976). In sharp contrast, Karl von Frisch lost his academic position in 1933 when the Nazi regime passed the Civil Service Law, and he was proved to have 1/8th Jewish ancestry. He had also attracted negative attention for employing Jewish assistants and for practicing "Jewish science." He also worked actively to help Polish scientists who arrested by the Gestapo (Deichmann 1992).

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# Biological Psychiatry and Psychopharmacology

13

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## 13.1 General Considerations

Biological psychiatry is an approach to psychiatry that aims to understand mental disorders in terms of the biological function of the brain and to establish their biological basis. It is interdisciplinary in its approach and includes basic neuroscience, psychopharmacology, biochemistry, genetics, epigenetics and neuropsychophysiology. Although it has its roots in the text of the Hippocratic school, for the first time the term was coined officially in 1953 (Bennett 1953; Gerard 1955a, b; Rioch 1955; Tourney 1969; van Praag 1971). The difference between biological psychiatry and neurology is that while biological psychiatry deals with the general neurobiological characteristics of diseases of the brain without gross abnormal findings, neurology deals with those disorders with gross and often easily observed pathology in the brain. The two disciplines overlap and also complement each other in the fields of neuropsychiatry and especially in behavioural neurology and psychogeriatrics, particularly when dealing with dementias.

The modern explosive development of the field happened in the 1950s with the introduction of psychotherapeutic medication, that is, antipsychotics and antidepressants. In 1965 the first biological theory concerning a mental disorder was

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developed (Schildkraut 1965), and since then this particular approach was proven valuable in the development of novel treatment modalities that changed the lives of hundreds of millions of mental patients worldwide and made the deinstitutionalization effort and the end of the big asylums possible.

The current chapter will attempt a very brief but comprehensive introduction to biological theories on the etiopathogenesis of major mental disorders as well as a brief description of contemporary available psychopharmacological agents.

## 13.2 Biological Models of Major Mental Disorders

### 13.2.1 Schizophrenia

Although most of cases of schizophrenia are sporadic, it also runs in families, and the overall genetic component is quite strong with a heritability greater than 60–80% (Hilker et al. 2018; Cardno and Gottesman 2000; Cardno et al. 2012; Kendler 1983; Sullivan et al. 2003). The lifetime risk for schizophrenia in the general population is around 1%, with the lifetime risk of relatives of patients being several times higher: siblings 10%, offspring 13% and parents 6%. The lifetime risk for children with both parents being patients is close to 50% (Gottesman and Shields 1982; Kendler 1993; Kendler et al. 1994).

Thus, and since no gross pathology is identifiable, it is generally accepted that a more subtle and probably nonuniform and complex pathology does exist (Selemon 2001). In the late 1950s and early 1960s, the dopaminergic theory of schizophrenia was developed (Davis et al. 1991; Howes et al. 2015; Carlsson et al. 2001), on the basis of the empirical discovery of antipsychotics and findings suggesting they produce their therapeutic effect by blocking the D2 dopamine receptors (Kapur and Seeman 2001). Following this, the hypothesis was that schizophrenia is a result of abnormal dopamine receptor density (Snyder 1976; Matthysse 1973), but so far there is little direct evidence to support a primary pathology in the dopamine system as the etiological factor in schizophrenia especially since D2 up-regulation could be due to antipsychotic treatment (Silvestri et al. 2000). Subsequently a refined dopamine hypothesis was developed in the 1990s suggesting a subcortical hyperdopaminergic activity being secondary to cortical hypodopaminergic activity, in particular in the frontal regions (Grace 2000; Davis et al. 1991). There is no change in the D2 density in extrastriatal subcortical brain regions (Kambeitz et al. 2014), the data concerning the D1 receptor density are inconclusive (Hirvonen et al. 2006; Kosaka et al. 2010; Abi-Dargham et al. 2012; Okubo et al. 1997a, b; Karlsson et al. 2002), and the data concerning the dopamine transporter density are also negative (Chen et al. 2013; Howes et al. 2012). A recent meta-analysis found a small increase in the density of the D2 and D3 receptors but reported also that heterogeneity between studies was large (Howes et al. 2012). Another meta-analysis reported no change in receptor densities in the thalamus, temporal cortex or substantia nigra (Kambeitz et al. 2014).

However, there seems to be a 14% increased striatal dopamine synthesis and a higher occupancy of D2 receptors by dopamine in patients with schizophrenia especially under stress (Howes et al. 2012; Abi-Dargham et al. 2009; Laruelle et al. 1999; Pogarell et al. 2012; Kegeles et al. 2010; Mizrahi et al. 2014; Catts et al. 2013; Fusar-Poli and Meyer-Lindenberg 2013). On the other hand, it seems that increasing the dopaminergic activity has some beneficial effect on negative symptoms (Laruelle et al. 1999), which is suggestive of regional rather than global changes in dopaminergic activity in the brain (Laruelle 2014).

It has been shown that there is no linear relationship between the D2 occupancy, clinical response and side effects. Response appears with occupancy above 50% and extrapyramidal side effects when it reaches 75% or more (Howes et al. 2009a; Howes and Kapur 2009; Nordstrom et al. 1993). However this has been challenged by the EUFEST study which suggested that for first-generation antipsychotics, extrapyramidal adverse events might appear at lower occupancy than the therapeutic effect (Boter et al. 2009).

It is possible that the alterations in the dopaminergic activity are state rather than trait features and are related with the acute phase and could be consequences of the treatment rather than core features in the etiopathogenesis of schizophrenia (Hietala et al. 1999; Howes and Kapur 2009; Howes et al. 2009b, 2013; Meyer-Lindenberg et al. 2002; Reith et al. 1994; Shotbolt et al. 2011).

A dysfunction in the activity of excitatory amino acids and their receptors has also been proposed. This model is based on animal studies and suggests that glutamate acting on the NMDA receptor in combination with dopaminergic activity on the D2 receptor in combination leads to a balanced intracellular signal at postsynaptic neurons in the striatum. In this way there is an optimal connection and communication between the basal ganglia and thalamus to cortex. In case either activity is dysfunctional and more specifically there is an increase in dopaminergic activity or a decrease in glutamatergic activity, psychosis could emerge (Carlsson and Carlsson 1990a; Carlsson and Carlsson 1990b). Several authors have hypothesized that in schizophrenia, there is a primary glutamatergic dysfunction in the prefrontal cortex, which results in reduced GABAergic activity in the ventral tegmental area (VTA) and eventually to a reduced inhibition of dopaminergic activity in the striatum (Garbutt and Vankammen 1983). Following this reduced tonic inhibition exerted by the thalamic mediodorsal nucleus, the dopaminergic activity increases which is the main cause for the emergence of positive symptoms of schizophrenia (Jones et al. 1988). According to this theory, the dopamine dysfunction seen in schizophrenia could be secondary to a primary glutamatergic dysfunction (McGuire et al. 2008; Stone et al. 2010).

The nature of this glutamatergic dysfunction is unclear but probably is due to a NMDA receptor hypofunction (Stone 2011). Such a deficit has been reported to exist in the left hippocampus in unmedicated patients (Pilowsky et al. 2006). However, the data concerning the existence and exact functionality of this dopamine-glutamate systems interaction are inconclusive, and the effect of glutamate and GABA on dopamine function seems to depend on the specific conditions (Reid et al. 1988; Ishita et al. 1988; Onteniente et al. 1987; Penit-Soria et al. 1987;

Chéramy et al. 1978; Garbutt and Vankammen 1983). Additionally, molecular imaging studies did not confirm the presence of differences in glutamatergic activity between patients with schizophrenia and controls (Kim et al. 2015). An alternative explanation is that NMDA dysfunction makes the dopamine system more sensitive to the effects of psychological stress and causes it to react in an abnormal way (Aalto et al. 2002; Kegeles et al. 2000, 2002, 2010).

Another important element for consideration is the observation that after overstimulation of either NMDA or non-NMDA receptors, excitotoxicity might appear because of the uncontrolled influx of CA2+ ions through the NMDA receptor channels which open (Choi et al. 1988; Rothman and Olney 1987). This could be the cause behind a variety of brain disorders of the neurodegenerative type (Olney 1989). This autoexcitotoxic mechanism could be responsible for the death of postsynaptic cells that house the glutaminergic receptors during early life, leading to schizophrenia (Olney and Farber 1995; Coyle and Puttfarcken 1993).

Metabolic imaging studies suggest the presence of lower metabolism in the frontal lobes, a condition known as 'hypofrontality' (Daniel et al. 1989; Ingvar and Franzen 1974; Liddle et al. 1992; Ragland et al. 1998; Spence et al. 2018; Volz et al. 1997; Weinberger et al. 1986; Yurgelun-Todd et al. 1996).

The overall research findings are split, and while some of them suggest the presence of a neurodevelopmental static encephalopathy (Munn 2000), others point to an ongoing neurodegenerative disorder maybe of the type of acceleration of brain ageing (Schnack et al. 2016). The neurodevelopmental hypothesis is supported by reports on the relationship between obstetric complications and the development of schizophrenia in the offspring (Dalman et al. 1999; Geddes and Lawrie 1995; Hultman et al. 1999; Jones et al. 1998) and also by the finding of ectopic neurons and abnormal cytoarchitecture in the PFC and the entorhinal cortex (Glausier and Lewis 2013; Catts et al. 2013; Eastwood 2004). On the other hand, neurodegenerative theories stress the neurotoxic effect of hyperdopaminergic activity (Lieberman et al. 1990) and the static type of existing encephalopathy, that is, the relative lack of progression in gross brain structural pathology (Csernansky and Bardgett 1998; Pearlson and Marsh 1999).

It is certain that in chronic patients, there is a widespread dysfunction in white matter connections (Kubicki et al. 2007) and significant reductions in neuropil (Eastwood 2004; Glausier and Lewis 2013; Konopaske et al. 2014; Selemon and Goldman-Rakic 1999) and synaptic proteins (Arnold 2006; Kleinman et al. 2011), resulting in fewer synaptic connections in specific brain regions (Glausier and Lewis 2013; Konopaske et al. 2014; Schmidt and Mirnics 2015). This impaired connectivity affects the communication between the default, the affective, the ventral attention, the thalamic and the somatosensory networks and all of them with the frontoparietal network (Dong et al. 2018).

On the other hand, there is much controversy over the presence or not of an enlargement of lateral ventricles (Andreasen et al. 1990; Johnstone et al. 1976; Raz and Raz 1990; Van Horn and McManus 1992; Chua and McKenna 1995; Weinberger et al. 1979) and a reduction in overall brain size (Andreasen et al. 1986; Harvey et al. 1993; Andreasen et al. 1990; DeMyer et al. 1988). Some authors suggest these

are localized rather than global findings affecting specific brain areas like the head of the hippocampus (Csernansky et al. 1998) and only in a minority of patients with more severe and chronic form of the disorder.

As already mentioned, mental disorders are not characterized by abnormalities in gross brain morphology, and schizophrenia is not an exception. However, pathological studies suggest the presence of subtle changes in cellular morphology in the prefrontal cortex (PFC), the thalamus and the medial temporal lobe and more specifically a reduction in neuropil volume (Lewis et al. 1999a, b; Selemon and Goldman-Rakic 1999; Arnold 2006). Other studies reported an increase in neuronal density in the PFC without any change in the total number of neurons, which is in accord with neuropil volume reduction (Akbarian et al. 1995; Daviss and Lewis 1995; Pakkenberg 1993; Rajkowska 1997; Rajkowska et al. 1998; Selemon et al. 1998). Such findings however were not found in the hippocampus (Arnold 2006; Glausier and Lewis 2013; Harrison 2004). Some but not all studies report an increase in microglia in the PFC and in the white matter (Bernstein et al. 2015). The finding of ectopic neurons and indications of the presence of some kind of abnormal cytoarchitecture in the PFC and the entorhinal cortex (Glausier and Lewis 2013) provide support for the concept of neurodevelopmental disorder (Catts et al. 2013; Eastwood 2004).

The literature on postmortem studies of NMDA receptors is inconclusive (Humphries et al. 1996; Sokolov 2002; McCullumsmith et al. 2012).

From psychophysiological findings, it is important to note that in almost half of the patients with schizophrenia, there is an intrusion of saccadic movements in smooth pursuit, that is, while following a target across the visual field (Holzman et al. 1997). Successful treatment does not seem to correct this, and it seems also to constitute an endophenotype since it is found also in unaffected relatives of patients (Iacono and Clementz 1993).

In the field of genetics, while the literature is rich, so far it has failed to identify specific genetic loci in a reliable way, since findings are almost never replicated. GWAS are more promising and so far have provided some data supporting the association between the DRD2 (dopamine D2 gene), GRM3 (mGluR3 gene), NRG (neuregulin gene), DTNBP1 (dystrobrevin-binding protein 1 gene) and RGS 4 (regulator of G protein-signaling 4 gene), as well as other genes related to the glutamatergic system. These studies strongly support a polygenic contribution of a very large number of small allelic effects (Schizophrenia Working Group of the Psychiatric Genomics C 2014; Bigdeli et al. 2016; Collier et al. 2016; Devor et al. 2017; Wockner et al. 2014). Epigenetic processes seem also to play a significant role since there seems to exist a differential DNA methylation profile in leucocytes and in the brain in patients with schizophrenia (Kundakovic et al. 2016; Pidsley and Mill 2011).

### 13.2.2 Bipolar Disorder (Manic Depression)

The first biological theory of mood disorders was the monoamine deficiency hypothesis for depression (Schildkraut 1965; Maas 1975; Van Praag and Leijnse 1963),

while later, the cholinergic-noradrenergic imbalance hypothesis included acetylcholine in a broader model for mood disorders (Davidson 1972; Tarsy et al. 1972; Janowsky et al. 1972). More complex models include state changes (depending on the polarity of the mood episode) in the excitatory amino acid function in specific areas of the cortex (Fountoulakis et al. 2008a). However, in spite of decades of extensive research, there is no definite proof for either a deficiency or an excess of either the quantity or the overall functioning of biogenic amines in specific brain structures in bipolar patients (Cannon et al. 2006a, b; Anand et al. 2011; Zavitsanou et al. 2004, 2005; Fountoulakis 2015a). The picture is especially problematic since the only class effect concerning the treatment of bipolar patients exists with antipsychotics exclusively against acute mania, while antidepressants do not seem to be efficacious against bipolar depression (Fountoulakis et al. 2011, 2012 Fountoulakis et al. 2017a, b, c, d; Rosa et al. 2011). A more complex profile for those agents with proven efficacy against bipolar depression seems necessary with an effect on norepinephrine reuptake and 5HT-1A agonism (Fountoulakis et al. 2012, 2015; Wiste et al. 2008; Young et al. 1994).

There are some data suggestive of a possible deficit in GABA and developmental/synaptic neurochemical systems in BD (Torrey et al. 2005; Benes et al. 2000, 2001) with a 60% decrease in NMDA receptor density (Woo et al. 2008b), but other studies failed to confirm any involvement of the GABAergic system (Cotter et al. 2002; Bielau et al. 2007; Bitanihirwe et al. 2010; Woo et al. 2008a). On the other hand, mania has been associated with reduced glutamate levels in the anterior cingulate cortex (ACC) (Moore et al. 2007). There are evidence supporting the decrease in the expression of specific NMDA subunits and associated proteins in the dorsolateral prefrontal cortex (Mueller and Meador-Woodruff 2004) and maybe in regions of the hippocampus (McCullumsmith et al. 2007; Beneyto et al. 2007; Toro and Deakin 2005), as well as in the perirhinal cortex (Beneyto et al. 2007), and the thalamus (Clinton and Meador-Woodruff 2004), but not in the orbitofrontal cortex of bipolar patients (Toro and Deakin 2005). The abnormal composition of NMDA receptors might lead to slower NMDA kinetics and eventually to disorganization (Fountoulakis 2012).

The presence of volumetric changes in the brains of BD patients is present as early as the prodromal phase but seems to increase with the duration of illness (Farrow et al. 2005; Hajek et al. 2005; Hirayasu et al. 1999; Kaur et al. 2005; Lyoo et al. 2006; Lagopoulos et al. 2012; Strakowski et al. 2002). The literature so far suggests that patients with BD manifest an enlargement of the third and lateral ventricles (Soares et al. 2005), white matter hyperintensities (Moore et al. 2001; Silverstone et al. 2003; Marlinge et al. 2014) and reduced grey matter in the prefrontal cortex, the hippocampus and the cerebellum (Moorhead et al. 2007; Soares et al. 2005; Blumberg et al. 2006) as well as a volume reduction in the left cingulate cortex (CC) (Bruno et al. 2006; Lyoo et al. 2006) or the right CC (McDonald et al. 2004). There is a large body of literature pointing to a specific vulnerability of the left anterior CC (ACC) and in particular its subgenual part (sgACC) (Atmaca et al. 2007; Lyoo et al. 2004; Sassi et al. 2004) or left posterior CC (PCC) (Hirayasu et al. 1999; Houenou et al. 2007; Wilke et al.

2004). However some studies report a right or bilateral ACC (Bruno et al. 2004; Cannon et al. 2006a) or a left or bilateral PCC volume decrease (Farrow et al. 2005; Kaur et al. 2005; Lim et al. 1999; Lochhead et al. 2004). While in schizophrenia a loss of brain volume is evident already at onset, in BD this happens latter. This is especially true concerning grey matter, while on the contrary, the loss of white mater volume might happen first and be present already at onset (Berk et al. 2010; Vita et al. 2009; Bora et al. 2010; Strakowski et al. 1993). Therefore, it is possible that white matter pathology is the prominent finding during the early stages (Lim et al. 2013; Lin et al. 2013), while grey matter loss follows years later (Arango et al. 2012; Strakowski et al. 2002). There are evidences that at least three variables might influence the volumetric changes in BD, the presence of cognitive decline (Bruno et al. 2006), response to treatment (Sassi et al. 2004; Cannon et al. 2006a; Atmaca et al. 2007; Bearden et al. 2007) and genetic background (McDonald et al. 2004), but overall the literature on neuroimaging data at different stages of BD is limited, and most of the data are cross-sectional (Lim et al. 2013; Balanza-Martinez et al. 2005) which make generalizable conclusions difficult.

Unfortunately the functional neuroimaging studies are usually restricted to the depressive phase of the illness simply because when patients are in an acute manic phase, it is very difficult to provide the level of collaboration needed to apply this kind of examination. Overall they suggest a state-dependent increased activity in the left dorsal ACC during acute mania (Blumberg et al. 2000) and a decreased activity in the same area during acute bipolar depression (Drevets et al. 1997). Activation studies provided with inconclusive results (Chang et al. 2004; Gruber et al. 2004; Rubinsztein et al. 2001; Benabarre et al. 2005; Altshuler et al. 2005; Blumberg et al. 2003; Roth et al. 2006; Pavuluri et al. 2007; Malhi et al. 2007).

A significant part of the total contribution on the neuropathology of BD is based on the material provided by the Stanley Neuropathology Consortium (Cotter et al. 2002; Knable 1999; Raedler et al. 1999; Torrey et al. 2005; Webster et al. 2005; Zavitsanou et al. 2004, 2005).

The results of these studies are inconclusive since some of them report an approximately 20–30% reduction in the volume in the ACC cortex as well as in the glial cells, with some layers the volume loss being above 60% (Ongur et al. 1998; Bouras et al. 2001; Chana et al. 2003; Torrey et al. 2005; Webster et al. 2005; Savitz et al. 2014), but other studies failed to confirm these findings (Miller et al. 2006; Benes et al. 2000, 2001; Cotter et al. 2001). A meta-analysis reported a 31% decreased density of non-pyramidal neurons bilaterally in layer II of the ACC in BD patients but reported no differences in glia numbers with 2D cell counting but significant glial reduction in layers III, V and VI when using 3D cell counting (Todtenkopf et al. 2005). Proteins related to the number and functioning of synapses such as synaptophysin, complexin II and growth-associated protein-43 (GAP-43) may be reduced in the ACC (Eastwood and Harrison 2001), suggesting a progressive destruction of excitatory rather than inhibitory synapses (Auer et al. 2000), and non-GABAergic cells may be selectively vulnerable to oxidative stress in patients with BD (Buttner et al. 2007).

The role of genetics in the development of BD is well known, and there is significant support in the literature from family, twin and adoption studies. It is also known that the mechanisms through which genetic factors play a role are complex, probably with several of them interacting with the environment, and thus BD is not a Mendelian disease (Andreassen et al. 2013), but instead, it manifests significant genetic heterogeneity. So far one of the greatest problems is that studies suffer from poor replicability and explain only around 70–80% of the genetic variance. Overall mood disorders have a reduced penetrance (less than 100%) which increases with age. Little is known about the role of epigenetics and imprinting in BD (Fountoulakis 2015a).

Interestingly there seems to be a significant genetic overlap between BD and schizophrenia (Fountoulakis et al. 2012; Cross-Disorder Group of the Psychiatric Genomics C et al. 2013; Andreassen et al. 2013).

Family studies indicate a morbid risk of BD in first-degree relatives of bipolar probands between 3% and 8% that is significantly higher in comparison with the general population. Twin studies often pool together unipolar and bipolar disorders and report 2–4 times higher risk for monozygotic twins in comparison with dizygotic. When BD is contrasted with unipolar depression, the genetic load appears to be higher for BD. Again, as in family studies, unipolar depression is the most common mood disorder in monozygotic cotwins of bipolar probands. Concerning adoption studies, only a few exist, and their results are inconclusive (Kelsoe 2009).

A meta-analysis reported that six pathways (corticotropin-releasing hormone signaling, cardiac beta-adrenergic signaling, phospholipase C signaling, glutamate receptor signaling, endothelin 1 signaling and cardiac hypertrophy signaling) and nine genes (CACNA1C, DTNA, FOXP1, GNG2, ITPR2, LSAMP, NPAS3, NCOA2 and NTRK3) were found to relate with BD (Nurnberger Jr. et al. 2014). Another review concluded that the expression profiles of BD-associated genes do not explain the majority of structural abnormalities observed in BD (McCarthy et al. 2014).

A GWAS study in 1461 BD patients reported that after genotyping for 372,193 single nucleotide polymorphisms (SNPs), the strongest results concerned myosin5B (MYO5B) and tetraspanin-8 (TSPAN8) and possibly the epidermal growth factor receptor (EGFR), but the results failed to replicate. Further analysis with the use of controls from the Wellcome Trust Case Control study reported that the results pointed to SNPs related with the voltage-dependent calcium channel, L-type, alpha 1C subunit (CACNA1C) gene (Sklar et al. 2008; Wellcome Trust Case Control 2007). Another GWAS confirmed the involvement of ion channel structural and regulatory genes, including voltage-gated ion channels and the broader ion channel group that comprises both voltage- and ligand-gated channels in the pathogenesis of BD (Askland et al. 2009).

In accord with the above are a number of studies concerning the genes related with NMDA receptors (Mundo et al. 2003; Itokawa et al. 2003; Avramopoulos et al. 2007; Martucci et al. 2006; Fountoulakis et al. 2012). These studies suggested that BD is associated with an abnormal structure of the NMDA receptor because of lower contribution of NR2A subunits, with predominance of more immature forms resulting in disordered receptor properties and slower kinetics. These slower

kinetics might make NMDA receptors incapable of dealing with the increased speed of stimuli during manic episodes leading to disorganization (Fountoulakis et al. 2012).

### 13.2.3 Unipolar Depression

Overall the literature suggests that depressed patients manifest impairments in attention and concentration probably as a non-specific accompanying feature but the contribution of comorbid anxiety is unknown. Failure to activate the left anterior cingulate gyrus (which suppresses interference) accompanied by an overactivation of the dorsolateral prefrontal and the visual cortex probably constitutes the neurobiological substrate of this impairment (Abrams and Taylor 1987; Golinkoff and Sweeney 1989; Watts et al. 1990; Mialet et al. 1996; Austin et al. 1992; Cornblatt et al. 1989; George et al. 1997; Mayberg 1997; Mayberg et al. 1999). The deficits in memory functions are isolated on explicit but not implicit tasks and include short-term memory, recognition and verbal and visual memory, spatial working memory and immediate or delayed recall. Also depressed patients tend to recall more negative memories. A dysfunction in the temporal cortex and the hippocampus is probably behind memory problems (Burt et al. 1995; Cutting 1979; Massman et al. 1992; Richards and Ruff 1989; Heller et al. 1997; Herrmann et al. 2001; Austin et al. 1992; Beats et al. 1996; Sweeney et al. 2000; Shah et al. 1998; Bremner et al. 2000; Mervaala et al. 2000; von Gunten et al. 2000; Sheline et al. 1996). Concerning executive functioning, patients with depression suffer from deficits among others, in set shifting, working memory, inhibition and updating, and these deficits seem to persist even after remission at least in a subgroup of patients and are not related to medication status. A dysfunction in the dorsolateral and the medial prefrontal cortex, the orbitofrontal cortex and the anterior cingulate regions is probably behind these impairments (Channon and Green 1999; Friedman 1964; Silberman et al. 1983; Elliott et al. 1996, 1997; Degl'Innocenti et al. 1998; Trichard et al. 1995; Heller and Nitscke 1997). In general the severity of neurocognitive deficits seems to correlate with the severity of depression. Psychotic features may specifically cause further deterioration in a 'qualitative' way irrespective of the overall symptoms severity (Jeste et al. 1996; Nelson et al. 1998; Basso and Bornstein 1999; Lesser et al. 1991). Successful treatment improves neurocognitive function irrespective of medication status (Thompson 1991; Frith et al. 1983).

In the area of neurotransmitters, the role of monoamines and especially of serotonin in the successful treatment of depression has been solidly proven, but the initially conceived monoamine deficiency hypothesis concerning the etiopathogenesis of depression (Coppen 1967; Maes and Meltzer 1995; Bunney Jr. and Davis 1965; Schildkraut 1965; Delgado 2000; Heninger et al. 1996; Kapur and Mann 1992) should not be considered valid any more, since tryptophan and catecholamine depletion studies provided negative results (Abbott et al. 1992; Delgado et al. 1994; Delgado 2000; Price et al. 1997, 1998; Miller et al. 1996; Hirschfeld 2000; Belmaker and Agam 2008; Homan et al. 2015). The abnormal findings concerning the 5-$HT_{1A}$

and 5-$HT_2$ receptors are probably due to the long-term treatment with antidepressants, while the initial findings concerning the serotonin transporters failed to replicate (Parsey et al. 1998; Meyer et al. 1999; Meltzer et al. 1999). The literature is inconsistent concerning noradrenergic receptors and overall the dopaminergic, cholinergic, GABAergic and glutamatergic systems, but they are much less researched in comparison to the serotonergic.

Stress could be the intermediate factor between depression and pathological findings, possibly through the development of hypercortisolaemia in combination with a dysfunction in neuroprotective systems, especially BDNF (Duman et al. 1997; Fuchs and Flugge 1998; Sapolsky 2000; Coplan et al. 2014; Lyons et al. 2001; Sheline et al. 2003). Stress might also dysregulate several neuroendocrine systems, with a specific effect on thyroid function (Haggerty Jr. et al. 1993; Staner et al. 1992; Legros et al. 1985; Rao et al. 1996). Especially early severe stress, e.g. maternal deprivation, might predispose for the development of adult depression (Rots et al. 1996; Smith et al. 1997; Suchecki et al. 1993; Zhang et al. 2002).

The brains of severely depressed and maybe refractory patients manifest local volumetric deficits and more specifically ventricular enlargement, cortical atrophy and sulcal widening especially in the prefrontal cortex, the amygdala and the hippocampus (Drevets et al. 1997; Siegle et al. 2012; Shah et al. 1998, 1999; Vakili et al. 2000; Mervaala et al. 2000; Sheline et al. 1996, 1998; McEwen 2000; Sheline et al. 2003; Fujita et al. 2000; Pearlson et al. 1997; Botteron and Figiel 1997; Duman and Charney 1999; Bremner et al. 2000). They seem to be reversible with successful treatment suggesting the loss of volume is mainly due to neuropil volume reduction rather than loss of neurons (Korte et al. 1998; van Winkel et al. 2014; Fujita et al. 2000).

Functional brain imaging in patients with depression during the resting state shows that there is an abnormally increased connectivity in the brain's default mode network and a decrease in the connectivity in the central executive network suggesting a dysregulation in the recruitment as well as the deactivation of regions and circuits responsible for the control of emotions. This includes a reduction in the activity of the DLPFC, in combination with an increase in the activity in the VMPFC as well as in the amygdala (Gudayol-Ferre et al. 2015; Posner et al. 2016; Watters et al. 2018; Biver et al. 1994; Baxter Jr. et al. 1989; Galynker et al. 1998; Rive et al. 2013; Drevets et al. 1992; Greicius et al. 2007; Mayberg et al. 2000, 2005; Motzkin et al. 2015; McGrath et al. 2013; Zhang et al. 2016; Brody et al. 2001).

Pathological studies report the presence of structural disturbances in the parahippocampal cortical regions with malformations in the entorhinal lamination, reduction in neuronal size and alterations in the prefrontal regions and the temporal lobe (Duman et al. 1997; Fuchs and Flugge 1998; Rajkowska et al. 1999, 2001; Sapolsky 2000; Bernstein et al. 1998; Altshuler et al. 1990; Goodwin 1997; Rajkowska 1997).

A number of psychophysiological abnormalities pointing to ANS dysfunction have been reported, but the most important findings concern sleep disturbances and more specifically the premature loss of slow-wave deep sleep which is a consequence of reduced REM latency (<65 min) and reduced SWS, particularly during the first sleep cycle, the increase in nocturnal arousal and awakenings (sleep

fragmentation), the reduction in total sleep time and the increased phasic REM sleep. Increased REM density seems to be specific for depression (Benca et al. 1992; Brunello et al. 2000; Lauer et al. 1991; Reynolds 3rd and Kupfer 1987; Riemann et al. 2001).

The genetics of unipolar depression are extremely complex and based on a mixture of a great number of genes of both large and small effect, which are transmitted in a variety of ways (Ament et al. 2015). The concordance rate of mood disorders for MZ twins is around 70–80% suggesting the role of epigenetic and maybe environment-gene interactions. Overall genetic data collectively suggest that genes explain approximately 30% of the aetiology of major depression (Wray and Gottesman 2012). In general it seems that early-onset depressions are more heritable. Unfortunately although a number of genes have been proposed as candidate genetic markers, including the SERT gene (SLC6A4), the results are inconclusive and rather negative so far (Culverhouse et al. 2018). GWAS studies seem promising but more studies of this kind are needed.

### 13.2.4 Alzheimer's Disease (AD)

AD is a neurodegenerative disorder, with a complex aetiology, especially concerning sporadic cases. Risk factors include ageing, gender and genetic and environmental factors, but the overall prediction power is relatively low. Neuropathological and imaging data point to the hippocampus as the early location of anatomical change (Jack Jr. et al. 1999).

Imaging studies have revealed marked atrophy (30–40% in comparison with controls) in the hippocampus (Kesslak et al. 1991), the parahippocampal gyrus (Ikeda et al. 1994), the amygdala (Lehericy et al. 1994), the subiculum and the perihippocampal clefts (De Leon et al. 1992). This loss of brain volume is reported to correlate with the severity of dementia (Fox et al. 1999). Functional imaging data suggest a pattern of hypometabolism which is most prominent in the temporoparietal and frontal cortical association areas while the primary visual and sensory motor cortices are typically spared (Haxby et al. 1986; McGeer et al. 1986a, b, c; Hirsch et al. 1997; Bartenstein et al. 1997; Weber et al. 1997; Holman et al. 1992) and suggested that hypoperfusion in the temporoparietal areas correlated with the global severity of the disease (Imran et al. 1999; Robert et al. 1992; Ashford et al. 2000).

At the pathological level, the disease is characterized by significant neuronal loss which is more striking with a reduction of up to 40% in the size of the hippocampus, amygdala, thalamus and anterior temporal lobe (Pantel et al. 1997). It is also characterized by the accumulation of amyloid-β (Aβ) protein in the brain. This protein can be found both in the brain parenchyma and on the walls of the leptomeningeal and parenchymal vessels. The core protein of amyloid plaques, Aβ, is a 4-kDa peptide, derived from the much larger beta-precursor protein (βPP). It is coded in chromosome 21, exists in several isoforms, is synthesized as an integral membrane molecule (Kang et al. 1987; Ashall and Goate 1994) and is secreted as a product of

proteolytic cleavage of βPP (Selkoe 1994). An additional pathological characteristic is the presence of neurofibrillary changes. Amyloid accumulation and neurofibrillary changes could be diffuse or could form neuritic plaques and neurofibrillary tangles, which are both considered to be hallmark lesions of AD in which the post-mortem diagnosis is based on them (Fox et al. 1985; Khachaturian 1985; Mirra et al. 1991; Braak and Braak 1991). Neuritic plaques have a complex structure and include abnormal neurites with paired helical filaments and activated glial cells (Wisniewski et al. 1989, 1990; Wisniewski and Wegiel 1995). The neurofibrillary tangles consist of abnormal accumulations of abnormally phosphorylated tau within the perikaryal cytoplasm of certain neurons (Perl 2010).

The mechanisms behind the development of the typical AD neuropathology are not well understood. Overall the data suggest that a low-grade chronic inflammatory process is active in AD, with activated microglia being the main factor. Centrally located Aβ aggregates are surrounded by astrocytes. However, microglia and astrocytes are associated with neuritic plaques but are lacking from most diffuse plaques. The fibril formation is influenced by Aβ peptide concentration, pH, length of Aβ peptide, as well as by interaction with other proteins (Selkoe 1994; Kisilevsky and Fraser 1997). The processes involved include neurotoxicity of fibrillar Aβ, oxidative injury and immune activation. Thus, it seems that activated glial cells produce substances contributing to the production and the fibrillization of Aβ as well as to neuronal injury (Akiyama et al. 1991; Eikelenboom et al. 1998; McGeer et al. 1994; Overmyer et al. 1999). A number of interleukins are present in neuritic plaques, including interleukin 1 alpha (IL-1α), interleukin 1 beta (IL-1β), interleukin 6 (IL-6) and tumour necrosis factor (TNF) (Eikelenboom et al. 1994; McGeer and McGeer 1999) which all have been shown promote an altered processing of βPP leading to the production of Aβ (Griffin et al. 2006; Sheng et al. 1996; Wood et al. 1993; Del Bo et al. 1995; Forloni et al. 1992; Ohyagi and Tabira 1993; Vasilakos et al. 1994), which Aβ in turn, in a vicious cycle, stimulates glial cells to produce cytokines and basic fibroblast growth factor (BFGF) (Araujo and Cotman 1992; Meda et al. 1995). A number of studies implicated IL-1 in memory deficits and reduced long-term potentiation in the ageing rat hippocampus (Lynch 1998) and in hippocampal cell damage (Araujo 1992). Activated microglia secretes a number of additional neurotoxic factors, including eicosanoids, free radicals, nitric oxide, proteases, protease inhibitors and excitotoxins (Eikelenboom et al. 1994; Espey et al. 1997; Giulian et al. 1995; McGeer et al. 1989).

Since ApoE ε4 allele is considered an important risk factor for the development of AD, its possible relationship with Aβ aggregation has been studied (Corder et al. 1993; Saunders et al. 1993). ApoE is involved in the transport and cellular uptake of lipid complexes via the low-density lipoprotein receptor (LDL-R) and the low-density lipoprotein receptor-related protein (LRP) receptor (Mahley 1988; Rebeck et al. 1995). It binds to Aβ and is co-localized with it in plaques (Strittmatter et al. 1993b; Namba et al. 1991), an observation which leads to the suggestion that there is a possible LRP-mediated uptake of ApoE/Aβ complexes and the risk for the development of AD associated with the ApoE genotype could be related to the clearance of the Aβ from the neuropil (Rebeck et al. 1995),.

The earliest and most consistent neurochemical abnormalities to appear in the brains of AD concern the cholinergic system (Mesulam et al. 1983). The decline in cholinergic transmission is not uniform throughout the brain. There is a significant reduction in the basal forebrain cholinergic system (30–90% loss of neurons), but typically there is no loss in other cholinergic-rich areas, particularly the brainstem (Mesulam 1996). This loss of neurons results in a dramatic reduction of choline acetyltransferase (ChAT) in the temporal lobes with a less marked reduction in frontal lobes. Biopsy studies suggest that the decline in cortical ChAT activity occurs within the first year after the onset of clinical signs (Davis et al. 1999; Bowen et al. 1983). Postmortem and PET studies reported the presence of an accompanying reduction in the density of presynaptic nicotinic receptors in the cortex and parahippocampal gyrus (Perry et al. 1995; Nordberg 1996). It is important to note that muscarinic activity remains relatively intact.

The basis for the selective vulnerability of basal forebrain cholinergic neurons, as opposed to other populations of cholinergic neurons, remains unclear. The data so far point to the depletion of neurons in the basal nucleus of Meynert as the core issue concerning the declining cholinergic activity (Ezrin-Waters and Resch 1986; Ferreira-Vieira et al. 2016).

There is the hypothesis that cholinergic degeneration is, in part, the result of impaired nerve growth factor (NGF) signaling and transport to the basal forebrain cholinergic neurons (Cuello et al. 2010; Tuszynski et al. 2015). Other studies proposed that there is a decrease in the number of neurons expressing tropomyosin receptor kinase A (TrkA) in the nucleus of Meynert, again as a result of cholinergic neuronal loss, and since TrkA interacts with Aβ, the decrease leads to apoptosis and the formation of amyloid plaques (Boissiere et al. 1997; Zheng et al. 2015). Another finding is that acetylcholinesterase AChE activity is reduced in AD (Herholz et al. 2000; Kuhl et al. 1999; Geula and Mesulam 1996) and that this reduction correlates well with reductions in regional cerebral blood flow or glucose metabolism, particularly in temporolateral regions of the cortex (Herholz et al. 2000). It is not clear whether this reduction is part of a vicious cycle of Aβ and P-tau dysregulation (Garcia-Ayllon et al. 2011).

The progressive loss of noradrenergic neurons in the locus coeruleus has been documented using postmortem as well as biopsy tissue samples (Mann 1998), but there is little relationship between the extent of loss of noradrenaline in the locus coeruleus and the cognitive deficits seen in AD (Palmer et al. 1987a, b; Palmer and DeKosky 1993). Interestingly, the loss of noradrenergic innervation greatly exacerbates AD pathogenesis and progression (Gannon et al. 2015). There are some data suggesting that the norepinephrine system mediates the effect of chronic stress in the pathogenesis of dementia (Ross et al. 2015).

There are several reports indicating widespread serotonergic dysfunctions early in AD, although the overall picture is less consistent (Bowen et al. 1983; Palmer et al. 1987a). A significant reduction equal to 30–40% in the number of 5-HT-positive neurons in the median and dorsal raphe nuclei is reported (Chen et al. 2000; Aletrino et al. 1992; Halliday et al. 1992; Kovacs et al. 2003; Yamamoto and Hirano 1985; Zweig et al. 1988). There is little evidence that changes in serotonergic transmission

contribute significantly to the neurocognitive deficits seen in AD and probably play a role in the development of affective and behavioural symptomatology that accompany AD (Court and Perry 1991). Postmortem analyses reveal significant reductions in 5-HT levels in the frontal (Arai et al. 1984; D'Amato et al. 1987; Palmer et al. 1987a) and temporal cortex (Palmer et al. 1987c), the hippocampus (Cross et al. 1984), the hypothalamus (Sparks et al. 1988), the basal nucleus of Meynert (Sparks et al. 1992) and the basal ganglia (Sparks et al. 1988).

Changes in the dopaminergic systems in AD are more variable from those seen in the cholinergic and noradrenergic systems, and whether there is a role for dopamine in the etiopathogenesis of AD remains unclear (Martorana and Koch 2014; Attems et al. 2007; Portet et al. 2009; Trillo et al. 2013).

It is well established that GABA neurons are spared in AD (Nagga et al. 1999; Howell et al. 2000), but it seems that the α1 subunit-containing GABA-A receptors appear to be vulnerable as the disease progresses (Mizukami et al. 1998a, b). The roles of these variable responses of selected GABA subunits in the process of the disease are not clear (Li et al. 2016), but it is possible they are implicated in the development of behavioural symptoms in AD patients (Solas et al. 2015).

Glutamatergic neurons are probably those most vulnerable to degeneration in AD. Loss of such neurons is observed in the entorhinal cortex and the hippocampus (Braak and Braak 1991; Hyman et al. 1984; Pearson et al. 1985; Greenamyre et al. 1985, 1987), with a subsequent decrease in glutamic acid levels and loss of glutamate terminals in these regions (Cowburn et al. 1990; Hyman et al. 1987; Procter et al. 1989), whereas a minority of studies report stable levels (Geddes et al. 1986; Monaghan et al. 1987). Thus, it is believed that the specific loss of glutamatergic neurons plays a significant role in the pathological manifestations of AD (Greenamyre and Young 1989; Myhrer et al. 2003; Myhrer 1993; Palmer and Gershon 1990; Danysz and Parsons 2012); however it is well known that glutamate plays a role in neuronal death in general, due to excitotoxicity, through a cascade involving increased calcium entry into the cell (Blass and Gibson 1991; Gooch and Stennett 1996; Kornhuber and Weller 1997). Therefore, such a role might not be exclusive to AD (Choi 1988).

The reduction of NMDA receptors could be the cause behind the memory decline in AD, since glutamatergic hypoactivity in AD patients postmortem correlated well with the severity of cognitive deficits (Greenamyre and Maragos 1993; Sumpter et al. 1986). Additionally, βPP plays an important role in regulating glutamate levels in the synapse, and Aβ protein can enhance the neurotoxicity of glutamate (Mattson et al. 1999; Blanchard et al. 1997; Fernandez-Tome et al. 2004).

There is a number of genetic markers, with some data in support of their involvement in the development of AD. They include fully penetrant mutations in βPP (Mann 1988; Ponte et al. 1988; Tanzi et al. 1987; Wisniewski et al. 1985), Presenilin 1 (Doan et al. 1996; Lehmann et al. 1997; Li and Greenwald 1998), Presenilin 2 (Citron et al. 1997; Levy-Lahad et al. 1995a, b) and the varepsilon4 allele of Apolipoprotein E (Namba et al. 1991; Saunders et al. 1993; Strittmatter et al. 1993a). There are more than 20 additional genetic risk loci identified in genome-wide association studies and massive parallel resequencing efforts (Van Cauwenberghe et al. 2016).

### 13.2.5 Contemporary Neurobiological Understanding of Substance Abuse

The positive reinforcing properties of substances in nondependent subjects are well known (Di Chiara and Imperato 1988; Fibiger 1978; Robinson and Berridge 1993; Wise 1978, 1988; Wise and Bozarth 1987), and it is also known that the compulsive craving of substances comes from changes in the reward circuitry (Dackis and Gold 1985; Frank et al. 1992; Kokkinidis and McCarter 1990; Kokkinidis et al. 1980; Koob and Bloom 1988; Leith and Barrett 1976; Solomon and Corbit 1973), which concern probably a desensitization of the mechanisms of reward and a potentiation of the rewarding effects of lateral hypothalamic and related brain stimulation (Frank et al. 1992, 1988; Kokkinidis and McCarter 1990; Kokkinidis et al. 1980; Leith and Barrett 1976; Schulteis et al. 1995; Wise 1996; Wise and Munn 1995).

Sensitization refers to the phenomenon that after repeated abuse of an addictive substance, the brain function is biased in the opposite direction from that of the acute substance state (Koob et al. 1989; Solomon and Corbit 1973). This is especially well documented for psychostimulants. Such phenomena are the reward-specific effects of alcohol and nicotine (George et al. 1998; Nurmi et al. 1996), amphetamine (Lett 1989; Lorrain et al. 2000; Piazza et al. 1990), cocaine (Horger et al. 1990; Lett 1989; Shippenberg and Heidbreder 1995) and morphine (Lett 1989; Shippenberg and Heidbreder 1995).

While tolerance usually lasts only a few days and gradually disappears after cessation of substance administration, sensitization is very long lasting. It is for these reasons that this specific between-session sensitization constitutes the strongest and longer-lasting positive reinforcement feature of addiction (Robinson and Berridge 1993). A phenomenon of cross-sensitization among different substances also exists (Horger et al. 1992; Itzhak and Martin 1999)

Trigger zones are areas of specific importance for each substance to act and produce its abusive potential. The nucleus accumbens (NAc) is the primary trigger zone for amphetamine (Carr and White 1983; Hoebel et al. 1983) and one of the two sites for nicotine (Pontieri et al. 1996; Reid et al. 2000; Toth et al. 1993; Vidal 1994; Shoaib et al. 1997), cocaine (de Wit and Wise 1977; Risner and Jones 1980), phencyclidine and opiates (Goeders et al. 1984; Olds 1982; Ettenberg et al. 1982; Pettit et al. 1984). Amphetamine and cocaine act via their effect on the dopamine transporter (Pierce and Kalivas 1997; Reith et al. 1986; Heikkila et al. 1975; Hurd et al. 1989; Pettit and Justice 1989; Wise et al. 1995), while phencyclidine (PCP) and morphine act on glutamate or opioid receptors (Chaudieu et al. 1989; Ohmori et al. 1992). Tetrahydrocannabinol (THC) which is the major psychoactive component of marijuana and hashish elevates NAc dopamine levels (Chen et al. 1990; 1993; Tanda 1997; Ton et al. 1988) and so does ethanol (Weiss et al. 1993; Gonzales and Weiss 1998; Imperato and Di Chiara 1986).

A second trigger zone for opiates is the ventral tegmental area (VTA) (Bozarth and Wise 1981; Welzl et al. 1989) where $\mu$-opioid receptors increase the mesocorticolimbic dopamine output by inhibiting GABAergic activity (Dilts and Kalivas 1989; Gysling and Wang 1983; Westfall et al. 1989; Clarke and Pert 1985; Nisell

et al. 1994b; Johnson and North 1992; Johnson and Pillai 1990). THC has also actions in VTA (Chen et al. 1990; French 1997; Melis et al. 2000; Tanda 1997) and the same holds true for alcohol (Gessa et al. 1985; Brodie et al. 1990; Gatto et al. 1994; Rodd-Henricks et al. 2000). Alcohol modulates GABA-gated chloride and glutamate-gated sodium and calcium conductances (Fadda and Rossetti 1998; Lovinger 1997) leading to the inhibition of GABAergic interneurons activity and subsequently to an increase in the dopamine cell firing and dopamine release within the VTA (Bailey et al. 1998; Brodie et al. 1999; Yim et al. 1998). Phencyclidine has an action similar to alcohol (French and Ceci 1990). Nicotine acts in the VTA directly to acetylcholine nicotinic receptors on dopamine cells to increase their firing frequency (Mereu et al. 1987; Clarke and Pert 1985; Benwell et al. 1993; Grenhoff et al. 1986; Nisell et al. 1994a).

An additional trigger zone for cocaine and phencyclidine is the medial prefrontal cortex (PFC), where addictive substances exert their effect through the NMDA receptor and probably on dopamine through the blockade of the noradrenaline transporter (Carlezon Jr. et al. 1996; Goeders et al. 1986; Goeders and Smith 1986). It has been shown that drug craving is associated with metabolic activation of the anterior cingulate gyrus and the amygdala (Childress et al. 1999; Grant et al. 1996; Kilts et al. 2001). This probably suggests the presence of a transition from dopamine- to glutamate-dependent behaviours with the amygdala mediating the communication between the PFC and the NAc during the conditioning of behaviour (Brown and Fibiger 1993; Everitt et al. 1991; Grimm and See 2000; Berke and Hyman 2000; Robinson and Becker 1986; Wise and Rompre 1989).

Dopamine release and cell firing in the trigger zones are increased by the presentation of novel and motivationally relevant common environmental stimuli (Schultz 1997; Berridge and Robinson 1998), leading to the recruitment of cortically derived memories, cognitive strategies and motor output. In this way, dopamine mediates the initiating and establishing of neuroplastic changes coupled with developing behavioural strategies and habit formation, which are all necessary to adapt to novel stimuli. One characteristic of the activation of dopamine transmission by common environmental stimuli is that dopamine release diminishes with repeated exposure to the same stimulus as the organism establishes an adaptive behavioural response (Cabib and Puglisi-Allegra 1996; Deutch et al. 1985). According to this model, while dopamine contributes and is probably necessary for the establishment of neuroplastic changes that mediate behavioural adaptation and habit formation, it might not have a role in the expression of those behaviours after the habit has been established. After this, it seems that the stimulus elicits the behaviour via interactions among the limbic cortex, thalamus and basal ganglia, with less or not at all involvement of the regional dopaminergic neurotransmission (Graybiel 1998; Jog et al. 1999). It is interesting to note that studies in animal models have confirmed the role of increasing dopamine release in the trigger zones after natural rewarding or aversive stimuli (Berridge and Robinson 1998; Cabib and Puglisi-Allegra 1996; Doherty and Gratton 1997; Kalivas and Duffy 1995; Mermelstein and Becker 1995; Mitchell and Gratton 1991; Taber and Fibiger 1997). The important observation from these studies is that common environmental stimuli cause a dopamine release which is of

substantially less magnitude and duration than the pharmacologic release elicited by most substances of abuse (supernatural stimuli) (Kalivas et al. 1998; Kuczenski and Segal 1999; Marshall et al. 2002; Tanda 1997; Yim et al. 1998).

Relapse often occurs on re-exposure to substances of abuse but also to cues associated with substance administration. This points to the important role for associative learning (O'Brien et al. 1992) which represents enduring or permanent alterations in patterns of synaptic connectivity and function (Berke and Hyman 2000; Quinn and Harden 2013). It seems that associative learning mechanisms interact with neurobiological mechanisms, and therefore the expression of tolerance may be context-dependent (Cepeda-Benito et al. 1999), while the threshold of learning could be modified by homeostatic responses.

Clinical data suggest that in addicted humans, late relapses appear to involve associative learning, as they often occur after encounters with cues previously associated with substance use (Shiffman 1996). These conditioned responses persist far longer than withdrawal symptoms (O'Brien et al. 1992; Berke and Hyman 2000). Thus, the persistence of substance addiction reflects the persistence of the memory for this learned experience, involving a variety of brain areas and neurochemical mechanisms (Hyman 1996; Bourtchuladze et al. 1994; Frey et al. 1996; Nguyen et al. 1994; Nguyen et al. 1992; Castellanos-Ryan et al. 2011) including genetic ones (Berke and Hyman 2000; Cole et al. 1992; Fosnaugh et al. 2002; Brakeman et al. 1997; Cole et al. 1989; Lyford et al. 1995).

There are strong data from twin and adoption studies suggesting that genetic factors explain a significant proportion of the variability of substance use disorders (Bierut et al. 1998; Bolos et al. 1990; Cadoret et al. 1986, 1995, 1996; Kendler et al. 2000; 2007; Kendler and Prescott 1998a, b; Lin et al. 1996; Merikangas et al. 1998; Sabol et al. 1999; Uhl et al. 2001; Haile et al. 2007). They play a stronger role for substance dependence and problematic use rather than substance use per se and probably with a significant interaction with malleable environmental risk factors (Boomsma et al. 1994; Cutrona et al. 1994; Grove et al. 1990; McGue et al. 2000; True et al. 1997; Demers et al. 2014; Volkow and Muenke 2012).

## 13.3 Psychopharmacology

### 13.3.1 Lithium

Lithium is a rather rare chemical element with atomic number 3 and its symbol is 'Li'. It belongs to the alkali metal group; it is the lightest metal and the least dense solid element. Two stable lithium isotopes can be found in nature. It is soft, silver-white and highly reactive and inflammable.

Although trace amounts exist in all organisms, there are no known physiological functions for lithium and live organisms can survive without it. In spite of this, lithium has been used as medication already since the late nineteenth century to cure a variety of diseases but especially uric arthritis. It was also widely used in beverages in the late nineteenth and early twentieth century. However it was proven to be

toxic if taken in high dosages, and its use was abandoned in the early twentieth century (Marmol 2008; Shorter 2009; Johnson and Amdisen 1983; Strobusch and Jefferson 1980).

After the WWII, in 1949 the Australian John Cade (1912–1980) reported positive results from the treatment of ten acutely manic patients (Cade 1949, 2000); however 2 years later, he reported the first death because of lithium toxicity in a patient whose bipolar illness otherwise responded extremely well to treatment. During the 1950s several researchers studied lithium and its usefulness in BD (Noack and Trautner 1951). However the important contribution that made the difference came from Mogens Schou (1918–2005) who randomized acutely manic patients to lithium or placebo, and in 1954 he published the results which made a significant impact to undertake a randomized controlled trial of lithium in acute mania (Bech 2006; Schou et al. 1954). Poul Christian Baastrup (1918–2002) demonstrated in 1964 the efficacy of lithium for the maintenance phase of bipolar disorder (Baastrup 1964). In the US, in 1960 Samuel Gershon published the first North American paper on lithium (Gershon and Yuwiler 1960). Further studies established lithium and robustly linked it to the treatment of all phases of (Schou et al. 1970; Angst et al. 1969, 1970; Baastrup et al. 1970; Baastrup and Schou 1967; Bech 2006; Schioldann 1999, 2006, 2011; Johnstone et al. 1988; Mitchell and Hadzi-Pavlovic 2000). Latter Fred Goodwin suggested it could be also useful in the treatment of depression as add-on to antidepressants (Goodwin et al. 1969a, b, 1972, 2003; Goodwin 2002; Goodwin and Zis 1979). The recommended serum lithium levels were determined with certainty in 1976 (Bech et al. 1976).

The specific biochemical mechanism of lithium action in bipolar disorder is unknown. Treatment with lithium demands regular serum level tests and monitoring of thyroid and kidney function. Dehydration can result in increasing lithium levels. Serum lithium concentrations are recommended to be in the 0.4–1.2 mmol/l range (lower end of the range for maintenance therapy and the elderly, higher end for children) on samples taken 12 h after the preceding dose (Amdisen 1977; Chen et al. 2004; Solomon et al. 1996; Perlis et al. 2002).

The adverse effects of lithium include leukocytosis, polyuria and polydipsia, dry mouth, hand tremor, headache, neurocognitive problems, confusion, muscle weakness, ECG changes, nausea, vomiting, diarrhoea or constipation, muscle twitch, vertigo, EPS, euthyroid goitre, hypothyroidism, acne, hair loss and hair thinning, renal toxicity and renal interstitial fibrosis, seizures, coma, hallucinations, erythema multiforme, Brugada syndrome, sinus node dysfunction, pseudotumour cerebri, increased intracranial pressure and papilledema and weight gain or loss. Lithium is also a teratogen, causing birth defects in a small number of newborn babies, including Ebstein's anomaly (Shepard et al. 2002). Most adverse effects are dose-dependent.

Lithium toxicity manifestations include nausea, vomiting, diarrhoea, asthenia, ataxia, confusion, lethargy, polyuria, seizures and coma, coarse tremor, muscle twitching, convulsions and renal failure. Several authors have described 'syndrome of irreversible lithium-effectuated neurotoxicity' (SILENT), associated with episodes of acute lithium toxicity or long-term treatment within the appropriate dosage range. Symptoms are said to include cerebellar dysfunction (Ikeda et al. 2010; Porto

et al. 2009; Adityanjee et al. 2005; Adityanjee 1989, 1987). Unfortunately, in long-term use, toxic effects might be induced even at therapeutic plasma levels (Fountoulakis et al. 2008b).

### 13.3.2 Antipsychotics

Antipsychotics or neuroleptics (also called previously major tranquilizers) were developed initially for the treatment of schizophrenia and psychotic symptoms, but today their usefulness has been proved in the treatment among others of bipolar disorder and refractory unipolar depression (Fountoulakis 2015b).

Chlorpromazine was the first to be discovered in 1952 and initially was developed as an anaesthetic agent for general surgical use. The French Henri Laborit (1914–1995) reported that chlorpromazine was inducing indifference towards traumatic events in otherwise mentally healthy persons. Jean Delay (1907–1987) and Pierre Deniker (1917–1998) were the first to use it as monotherapy in agitated psychosis (Delay and Deniker 1955, 1956; Delay et al. 1952, 1956).

Antipsychotics are grouped into the first-generation antipsychotics (FGAs), also called typical antipsychotics, and the second-generation agents (SGAs), also called atypical antipsychotics. The common pharmacodynamics property of all antipsychotic agents is dopamine D2 receptors blockade, and it is believed that they act their therapeutic effect through this pathway. Most antipsychotics also affect a number of other neurotransmitters.

The most frequent adverse events for FGAs are extrapyramidal symptoms (EPS) and hyperprolactinaemia, while weight gain and metabolic abnormalities are caused mainly by SGAs. Other adverse effects include sedation, headaches, dizziness, diarrhoea, sexual dysfunction, osteoporosis, orthostatic hypotension, anticholinergic side effects, memory problems, angle-closure glaucoma, blurred vision, constipation, dry mouth or hypersalivation, agranulocytosis, leukopenia and neutropenia and QT prolongation. Tardive dyskinesia and neuroleptic malignant syndrome are the most severe adverse events.

### 13.3.3 Antidepressants

Antidepressants are agents used for the treatment of depression but also of anxiety disorders, obsessive compulsive disorder, eating disorders, chronic pain, neuropathic pain and other neurological and psychiatric conditions.

In 1951, research on the two new antituberculosis agents, isoniazid and iproniazid, suggested the two agents also possessed some psychotropic properties (Selikoff and Robitzek 1952; Robitzek et al. 1952; Selifoff et al. 1952). Following these reports, in 1952 Max Lurie (born 1920) and Harry Salzer (born 1906) reported that isoniazid improved depression in two thirds of their patients. They also introduced the term antidepressant (Salzer and Lurie 1953). A year before, in France, Jean Delay with the resident Jean-Francois Buisson reported the positive effect of

isoniazid on depressed patients, but they published these results years later (Delay and Buisson 1958). Nathan Kline supported the use of iproniazid as an antidepressant, but eventually in 1961, it was withdrawn from the market because of lethal hepatotoxicity (Lopez-Munoz et al. 2007).

In 1957 the Swiss psychiatrist Roland Kuhn (1912–2005) discovered the first tricyclic antidepressant in the process of improvement of the efficacy of chlorpromazine in conjunction with the Geigy Pharmaceutical Company. He also coined the term 'thymoleptic' (Kuhn 1958, 1957). In 1988, fluoxetine, the first SSRI, was introduced. It was developed at Eli Lilly and Company in the early 1970s by Bryan Molloy, Klaus Schmiegel, David Wong and others. In spite of a long-lasting recent debate, the efficacy of antidepressants in the treatment of unipolar depression is no longer a matter of dispute (Fountoulakis et al. 2013; Fountoulakis and Moller 2012; Sartorius et al. 2007).

Currently there are several classes of antidepressants including the selective serotonin reuptake inhibitors (SSRIs), the serotonin-norepinephrine reuptake inhibitors (SNRIs), the tricyclic antidepressants (TCAs) and the monoamine oxidase inhibitors (MAOIs).

The main neurotransmitter pathway through which antidepressants seem to exert their beneficial effect is that of serotonin. Pure noradrenergic action is unlikely to be sufficient to produce an antidepressant effect; however double-acting agents (which affect both serotonin and noradrenaline pathways) might be more efficacious in comparison with purely serotonergic agents but also with more adverse effects.

The most common adverse effects include nausea, increased appetite and weight gain, loss of sexual desire and other sexual problems (e.g. erectile dysfunction and decreased ability to achieve orgasm), fatigue and drowsiness, insomnia, dry mouth, blurred vision, constipation, dizziness, agitation, irritability, anxiety, sexual problems and hyperprolactinaemia. Serotonergic syndrome is a potentially lethal event. Treatment with antidepressants also might induce suicidal thoughts, but no completed suicide has been attributed to treatment with antidepressants. Some agents after abrupt stop of treatment might cause withdrawal symptoms which persist for no more than 1–2 weeks.

Although the teratogenic risk is low with antidepressants, SSRI use in pregnancy has been associated with an increased risk of spontaneous abortion, preterm birth and low birth weight (Malm 2012; Rahimi et al. 2006).

The usefulness of antipsychotics in the treatment of bipolar depression is a matter of continuous debate (Pacchiarotti et al. 2013). It is interesting that some data suggest that norepinephrine activity is necessary for an antidepressant to act in bipolar depression; still this very activity increases the risk for the patients to switch to mania or hypomania (Fountoulakis et al. 2012).

### 13.3.4 Valproate

Sodium valproate is the sodium salt of valproic acid. It is an anticonvulsant efficacious in the treatment of epilepsy (all partial and generalized seizures including absence seizures) as well as in the prevention of migraine headaches. It was first

synthesized in 1882 by B.S. Burton as an analogue of valeric acid which can be found naturally in valerian and was used in the cosmetics industry. Valeric acid appears similar in structure to GABA but lacks the alcohol and amine functional groups that contribute to the biological activities of the GABA. In 1962 Pierre Eymard accidentally discovered its anticonvulsant properties (Meunier et al. 1963). Valproic acid was approved as an antiepileptic for the first time in 1967 in France. Later it has been proven to be efficacious in the treatment during all phases of bipolar disorder (Fountoulakis et al. 2017a, c)

Its mechanism of action includes weak blocking of sodium ion channels and weak inhibition of enzymes that deactivate GABA (e.g. GABA transaminase). It is unclear whether it also stimulates GABA synthesis.

Adverse effects include tiredness, tremor, nausea, vomiting, sedation and gastrointestinal symptoms as well as reversible hair loss in about 10% of patients. Also some patients experience vision problems, endocrinological disorder (increased testosterone production in females and menstrual irregularities), memory problems, weight gain, infections, drowsiness and headache, liver damage, polycystic ovaries, movement disorders (even hallucinations, anxiety and confusion), swollen pancreas, low body temperature and potentially life-threatening blood abnormalities (e.g. low platelet count). Valproate has the highest risk of birth defects of any of the commonly used antiepileptic drugs during pregnancy (Cummings et al. 2011). Overdose results in tremor, respiratory depression, coma and metabolic acidosis and eventually can result to death. Serum or plasma levels of valproic acid concentrations should be in the range of 50–150 mg/l for the treatment of BD.

### 13.3.5 Carbamazepine

Carbamazepine is an antiepileptic efficacious against partial seizures, generalized tonic-clonic seizures and mixed seizures and also useful for the treatment of trigeminal neuralgia. It was discovered in 1953 and was first marketed as a drug to treat trigeminal neuralgia in 1962 and as an antiepileptic in the UK since 1965 and the USA since 1974. In 1971 the first studies concerning bipolar disorder appeared in Japan (Okuma and Kishimoto 1998), and in the next few years, it has been proven to be efficacious in the treatment of bipolar disorder (Fountoulakis et al. 2017a, c).

The mechanism of action of carbamazepine includes the stabilization of the inactivated state of sodium channels, thus reducing the excitability of the neurons. It has also been shown to bind to GABA receptors (Granger et al. 1995).

The most common adverse effects with carbamazepine treatment may include drowsiness, dizziness, headaches and migraines, motor coordination impairment, nausea, vomiting, constipation, cardiac arrhythmias, blurry or double vision, aplastic anaemia or agranulocytosis and a dangerous or even fatal skin reaction (Stevens-Johnson syndrome and toxic epidermal necrolysis). It can also exacerbate preexisting hypothyroidism. It can cause syndrome of inappropriate antidiuretic hormone, and it can aggravate juvenile myoclonic epilepsy and other types of epilepsy, especially absence seizures (Liu et al. 2006).

Among the agents used in the treatment of BD, carbamazepine is the drug most potent to interactions with other medication. It is a CYP450 inducer, and thus it might increase the metabolism and elimination of many agents, including warfarin, lamotrigine, phenytoin, theophylline, valproic acid, benzodiazepines and some antipsychotics. It also reduces the effectiveness of birth control pills, thus leading to unexpected pregnancies. Other agents, like erythromycin, cimetidine, valproic acid, valnoctamide and calcium channel blockers as well as grapefruit juice, decrease carbamazepine metabolism and increase its serum availability often to toxic levels. As a drug that induces cytochrome P450 enzymes, it accelerates elimination of many benzodiazepines and decreases their action.

Carbamazepine is teratogenic and is associated among others with the development of spina bifida (Jentink et al. 2010), neurodevelopmental problems and delays (Cummings et al. 2011), craniofacial defects, cardiovascular malformations and hypospadias.

### 13.3.6 Lamotrigine

Lamotrigine is an antiepileptic efficacious in the treatment of focal seizures, primary and secondary tonic-clonic seizures and seizures associated with Lennox-Gastaut syndrome. It was marketed for the first time in 1994. It is chemically different to other antiepileptics. It has been proven efficacious in the prevention of depressive episodes during maintenance treatment of bipolar disorder (Fountoulakis et al. 2017a, c)

Lamotrigine is a triazine derivate that inhibits voltage-sensitive sodium channels, leading to stabilization of neuronal membranes. It also blocks calcium channels and has weak 5-HT3 receptor inhibition. Probably other actions also exist since lamotrigine exerts a variety of effects and adverse events which cannot be explained by its above pharmacodynamics properties alone (Rogawski and Loscher 2004a, b; Lees and Leach 1993). It is metabolized by hepatic glucuronidation.

Its adverse effects include life-threatening skin reactions, including Stevens-Johnson syndrome, DRESS syndrome and toxic epidermal necrolysis. Since December 2010, lamotrigine carries an FDA black box warning for aseptic meningitis. Other adverse events include loss of balance or coordination, double vision, blurred vision, dizziness, drowsiness, insomnia, anxiety, vivid dreams or nightmares, dry mouth, mouth ulcers, memory and cognitive problems, runny nose, cough, indigestion, abdominal pain, weight loss, missed or painful menstrual periods, vaginitis and leukopenia.

Certain contraceptives decrease serum levels of lamotrigine (Reimers et al. 2005). It has low teratogenic action; however if used during the first trimester, it may increase the risk for cleft lip and palate malformation in newborns.

Lamotrigine has fewer drug interactions than other antiepileptics; however caution is needed when co-administered with hepatic enzyme-inducing medications (Anderson 1998).

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