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Neurobiological and Psychological Aspects of Brain Recovery

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Preface

If this book had been written 30 or 40 years ago, it could have been titled "Brain recovery? Could it occur?" In fact, the concept that each area of the brain has a rigid network of connections and then a fixed and immutable function was too strongly rooted to accept an alternative idea that an adult brain could modify itself in response to an injury. We used to think that the brain, once damaged, could not repair itself.

If this book had been written 10 years ago, it could have been titled "Neurobiological Aspects of Brain Recovery." In fact, breakthroughs in neuroscience have undoubtedly shown that though individual neurons might be damaged beyond repair, the brain exploits its neuroplasticity properties and tries to repair itself with a powerful efficiency. An ever increasing number of studies have supported the notion that neuronal fibers grow and form new terminals in response to nearby damage and have analyzed the myriad of factors (pre- and post-injury experiences, kind of lesion, drugs, hormones, neurotrophic factors, aging, diet, stress, state of immune system,…) influencing recovery or sparing of function following brain damage.

Today, it is fully rigorous studying brain recovery by addressing the double neurobiological and psychological component of the functional recovery that follows brain injuries. In fact, the effects of a brain damage are extremely widespread, provoking physiological, cognitive, emotional, and behavioral changes and impacting all areas of a person's life. It is now clear that a combination of factors will be required to make as full a recovery as possible. Psychological factors can inhibit recovery of brain function. In many cases, these aspects of the injury may be the most difficult for the affected person to deal with, due to personality changes and social difficulties faced trying to cope with the change. For example, depression and sleep disturbances not only may cause troubles in concentration, memory, and mood but also may cause a negative outlook on life. Current theories suggest that neurobiological and psychological aspects of brain recovery are reciprocally related, so that the psychological aspects may be due to, or a cause of, diminished brain plasticity.

Despite the huge bulk of clinical and experimental data on brain recovery processes, the functional recovery of each subject can hardly be predicted due to the complex variety of mechanisms involved and the possibility to continue recovery over time. No two brain injuries are alike and the course and the degree of functional recovery are different for each subject. So, individuals progress through brain recovery phases at their own pace. There is a first period of spontaneous recovery that takes weeks or months beyond the date of the injury, when the brain attempts to recover the damaged neurons and to redesign the networks controlling communication among neurons. In this first phase, the rehabilitative focus has to be on maximizing the spontaneous recovery processes and improving function within the areas of the specific deficits. Subsequently, the focus may shift toward retraining skills and functions that have been lost and learning adaptive strategies. In neurobiological terms, during the unique window of opportunity in which neural plasticity peaks (one to three months after injury), neurorehabilitative strategies are most effective. However, significant improvements can occur even at later stages, especially when the rehabilitative strategies combine task-specific training with therapies that activate neural plasticity.

In the attempt to work around the damage, the brain uses its greater abilities to adapt function rather than to regenerate structure and this significant adaptive aptitude is based on widespread plastic properties. By understanding molecular and neuronal substrates and interactions that lead to injury-dependent plasticity, we may be able to devise more effective treatment strategies for repair. However, it has to be taken into account that while the synergistic combination (in the correct temporal order) of interventions on sensory or sensory-motor input with molecular interventions may enhance plasticity and thereby promote recovery of function after injury, unfortunately in other cases the combination of drug treatments with behavioral training may reduce the effectiveness of either treatment alone. Thus, it is crucial to elucidate the substrates of injury-induced neuronal plasticity and to understand how the complex interactions between structure (molecules, synapses, neuronal networks) and function (activity, learning, injury) affect persistent changes in the brain. Plasticity substrates likely overlay across developmental processes, adult tissue homeostasis, various types of brain injury, and activity paradigms. How the plastic changes interact with, are influenced by, and directly affect the injury has profound effects on the development of efficient strategies for recovery. One critical feature of brain recovery is that activity facilitates appropriate rewiring after injury and may prevent maladaptive patterns of connections. Activity shapes connections by inducing the expression of promoting or inhibiting growth factors, neutralizing or enhancing either subset to drive structural changes.

The mechanisms of functional recovery can be grouped into two general classes, restitution, and substitution of function. While restitution of function suggests that neuronal pathways are reactivated and functions are restored, substitution of function refers to transfer or reorganization of functions from the damaged tissue to healthy areas. Both kinds of mechanisms are related to synaptic plasticity that modulates density and efficiency of neurotransmitter receptors through protein phosphorylation and regulation of gene expression. Although the changes mediated

by protein phosphorylation have rapid onset and short duration compared with plastic phenomena mediated by gene expression, both plastic processes alter function and efficacy of synapses and finely tune the functional state of neurons in response to varied synaptic inputs. It is known that post-synaptic neurons, once deprived of their characteristic synaptic inputs, develop increased sensitivity to neurotransmitter via the emergence of new receptors and larger surface areas, thus facilitating post-lesional activation of pathways and restitution of function.

The most recent approaches to the "neuroscience of rehabilitation" try to understand the links between motor activity, cognitive functions, and emotional behavior with dendritic structure and cytoskeletal dynamics to reveal the molecular and cellular bases of recovery following brain diseases. Therefore, comprehension of neural architecture appears to be a necessary step toward greater understanding of computation in the nervous system. A strong correlation exists between dendritic abnormalities and motor, cognitive, and emotional behaviors in a variety of neurological diseases including Down, Rett, and Fragile-X syndromes; Autism; Schizophrenia; Alzheimer's, Parkinson's, and Huntington's diseases; and Duchenne/Becker muscular dystrophies. Thus, elucidating the molecular genetic mechanisms by which multiple local interactions of cytoskeleton elements direct the growth of dendrite arbors has direct clinical relevance. Learning to manipulate arbor growth mechanisms appears to be important to develop efficient neuroregenerative strategies. Chapter 1 of the present book (*Structural Plasticity in Dendrites: Developmental Neurogenetics, Morphological Reconstructions, and Computational Modeling* by Nanda, Das, Cox, and Ascoli) reviews the significance of proper dendritic development and neurogenetic mechanisms governing the brain plasticity with an emphasis on transcriptional-mediated cytoskeletal regulation; then it discusses the techniques used to identify the molecules and pathways responsible for arbor development; next, it describes the digital reconstructions of neuronal morphology; it discusses the modeling methodologies to generate artificial neurons in simulations; and finally, it proposes how novel advances on these three fronts can achieve the objective of a systems level understanding of dendritic growth.

Among the processes that maintain cellular metabolism and homeostasis and guarantee regulation of protein synthesis and organelle, the turnover autophagic activation plays important roles in neuronal survival and function under both physiological and pathological conditions. Although autophagic dysfunction has been implicated in the pathogenesis of several neurological pathologies, the cellular factors underlying homeostatic versus pathogenic activation of autophagy have not yet been identified, nor it is fully clarified how the loss of basal autophagy or imbalance of autophagic flux leads to neuronal death and why autophagosomes accumulate abnormally in damaged neurons in the presence of several neurodegenerative diseases as well as brain and spinal cord trauma. Chapter 2 (*Autophagy Mechanisms for Brain Recovery. Keep It Clean, Keep It Alive* by Viscomi, D'Amelio, Nobili, Cavallucci, Latini, Bisicchia, Sasso, and Molinari) reports the current state of knowledge on the relationship between autophagy impairment and pathophysiological mechanisms in several neurological pathologies; describes how molecular mechanisms of autophagy affect neuronal function and contribute to

neurodegeneration in chronic and acute brain pathologies; and discusses the implications of autophagy processes in neurological recovery.

A bulk of research has evidenced the dramatic effects of experience on structure and function of the brain and it is well known that all activity-dependent processes are based on plastic synaptic rearrangements maintaining and refining active synapses and discarding inefficient connections. Multisensory, cognitive, and social stimulations are the crucial incentives that shape the brain patterns to adapt to environment both in physiological and pathological conditions. The importance of environmental stimuli in shaping brain structure and function has led to the development of an experimental setting in which the housing condition is improved to provide a combination of cognitive, motor and social stimulation relative to standard housing, the environmental enrichment. Such a model has a protective and therapeutic potential in reducing symptoms of a variety of neurological diseases with reduced side effects. The structural modifications induced by the prolonged exposure to an enriched environment have been described in widespread brain areas, from neocortical to cerebellar cortical regions. Since the most remarkable functional outcomes of enrichment are related to learning and memory functions, many researches have been focused on the hippocampus. Chapter 3 (*Environmental Enrichment Repairs Structural and Functional Plasticity in the Hippocampus* by Ghiglieri and Calabresi) provides the most recent evidence that environmental enrichment stimulates the endogenous potential of hippocampus for plasticity and repair. It examines the role of environmental enrichment as a trigger for intrinsic resilience mechanisms that preserve synaptic integrity in distinct hippocampal neuronal populations against aging and neurodegeneration. According to the potential of the environmental enrichment to boost proliferation and survival of neuronal and glial cells, the analysis of how the environmental enrichment may reopen the critical periods in which the potential to tune a brain function is maximal, can provide support for efficient therapeutic interventions on loss of function due to a variety of neurological diseases.

The experience-dependent increase in neuronal connectivity may represent the neurobiological substrate not only for the efficient therapeutic interventions but also for the neuroprotective capability to cope with an injury as proposed in the theory of "brain and cognitive reserve." In fact, some individuals maintain high levels of cognitive function despite having pathophysiological signs of what would otherwise be considered debilitating brain damage. The theory of the brain and cognitive reserve has been advanced to provide a mechanistic framework that explains such a discrepancy between behavior and pathology. As described in Chap. 4 (*Translatable Models of Brain and Cognitive Reserve* by Zeleznikow-Johnston, Burrows, Renoir and Hannan), the theory on brain and cognitive reserve posits that individuals have a certain level of capacity for a certain amount of damage they can sustain before showing behavioral symptoms (brain reserve) and that they differ in the ability to maintain cognitive performance despite equivalent levels of neurological insult (cognitive reserve). The individual differences in reserves may be due to different levels of neuronal redundancy for performing a particular task, ability to recruit brain regions to compensate for the loss of others, and ability to adopt

alternative cognitive strategies for performing the same task. The reserve construct emerged by epidemiological evidence showing that environmental factors, such as education, mental and physical activity, and social engagement, are associated with different rate of cognitive decline and onset of dementia suggesting that reserves are not static and could be influenced by environmental and genetic factors. Enhancers of reserves, such as environmental enrichment, voluntary exercise, and antioxidants, have powerful neuroprotective and pro-cognitive effects in experimental models of traumatic brain injury, aging, and neurodegenerative diseases. These improvements appear to be mediated by a combination of factors such as increased synaptogenesis; synaptic plasticity and hippocampal neurogenesis; glial and vascular modifications; elevated neurotrophic factors; and enhanced molecular regulators related to gene expression, epigenetic, and chromatin changes. The full understanding of the molecular mechanisms through which the reserves confer their beneficial effects allowed developing novel drugs called "enviromimetics" capable of acting upon molecular targets, in that they mimic or augment the natural enhancement that comes from positive environmental influences.

The model of brain and cognitive reserve is closely related to the concept of brain plasticity, the ability of the brain to rearrange structure and neural connections, allowing it to change with learning, to repair, and to compensate. Neural plasticity is central to memory and learning processes because it provides the brain with a lifelong possibility to change and adjust when facing environmental demands and stimuli. The focus on lifelong development is important for the cognitive reserve construct in particular, which, as an active process, is likely formed as a combination of baseline capacity, which is then subjected to modulation by multiple experiences and exposures throughout the entire life course. Through this process, an individual develops a level of cognitive reserve which in turn can mitigate the effects of pathology on the clinical diagnosis later in life. Chapter 5 (*Cognitive Reserve: A Life-Course Perspective* by Dekhtyar and Wang) discusses the contributors to cognitive reserve from various stages of the life course, including childhood, early adulthood, middle age, and late life and explores the life-course perspective to cognitive reserve in the framework of cognitive decline and dementia. Baseline cognitive abilities lay the foundation of reserve formation, which is subsequently enhanced by intellectual stimulation provided by educational attainment. By exerting continued demands on the brain, occupational tasks preserve this acquired buffer, much the same way as late-life social engagement and rewarding leisure activities. Ultimately, cognitive reserve can be conceived as a sum of mental, physical, and lifestyle inputs over the entire life course, and the brain ability to withstand the changes associated with aging will to a large extent reflect the gradual accumulation of these inputs. Although most of the neuropathology most likely applies to the older ages, the factors allowing the toleration of this pathology occur throughout the entire life course. In conclusion, it is becoming increasingly clear that variations among individuals in their ability to withstand age-related brain changes are ultimately dependent on their lifetime accumulation of mental, physical, and lifestyle inputs into cognitive reserve.

Chapter 6 (*Neural Correlates of Brain Reserve: The Neuroimaging Perspective* by Serra and Bozzali) describes how environmental factors have significant effects on brain resilience. Years of formal education, occupational attainment, cognitive, social, and physical activities, intelligence quotient, and memory performance represent the most relevant proxies of brain and cognitive reserves so that lifestyle acts on brain plasticity modulating the impact of neurological insults. Although interactive or additive effects among levels of reserves, biomarkers of neurodegeneration, and the risk to develop the clinical symptoms of neurodegenerative disease have been shown, investigating the relationship between cognitive enrichment and brain resilience may provide new therapeutic insights and interventions to prevent the evolution of or treat neurodegenerative disorders.

Studies of brain and cognitive reserves have also addressed the critical issue of the clinical implications of this approach and have indicated the extensibility of the reserve theory to a number of neurological conditions. A critical aspect pertains to the possibility to employ therapeutic interventions aimed at improving reserve in neurological patients as disease progresses. Interestingly, the use of complementary and alternative medicine approaches (from dietary natural products, such as herbals and probiotics, to integrative nondietary approaches, such as meditation and music therapy) is rising among persons with different types of cognitive and health problems who desire a holistic, whole-person-based approach to treatment and a self-control over disease management. Chapter 7 (*Non-pharmacological Approaches Based on Mind-Body Medicine to Enhancement of Cognitive and Brain Reserve in Humans* by Crescentini, Fabbro and Aglioti) discusses the implications of reserves for clinical interventions based on the most practiced form of complementary and alternative medicine, the mind–body medicine. One of the most prevalent practices of mind–body medicine which integrates the mind, brain, body, and behavior with the intent to use the mind to positively influence psychophysical functioning and well-being is mindfulness meditation. Mindfulness is an attribute of consciousness that consists of being aware of and attentive to what is occurring in the present moment with a non-judgmental attitude of openness and receptivity. Mindfulness skills can be developed effectively through the practice in which any arising feeling, thought, emotion, and sensation is not attempted to be changed by the perceiver but is instead observed and accepted. The studies reported in Chap. 7 evidence that meditation may have neuroprotective effects, slow age-related brain degeneration, increase gray matter, and thus improve cognitive performance in healthy older meditators. On such a basis, mindfulness may be now considered an effective mental training strategy able to potentiate individuals' reserve in the conditions of healthy aging and progressive neurological conditions, such as Alzheimer's disease, multiple sclerosis, and Parkinson's disease.

Synaptic plasticity and new synapse formation are assumed to be the basic mechanisms underlying the recovery of sensory-motor function affected by brain damage. Chapter 8 (*Roles of Synaptic Plasticity in Functional Recovery After Brain Injury* by Nagao and Ito) specifically elucidates the roles of synaptic plasticity, i.e., long-term potentiation and depression of synaptic transmission, in brain recovery

addressing at first the characteristics of synaptic plasticity in the intact hippocampus, cerebellum, and red nucleus. Then, in an experimental model of recovery of motor function it addresses the spinal, cerebellar, and cerebral mechanisms underlying the recovery of grasping movement after unilateral spinal cord injury. Furthermore, in an experimental model of recovery of sensory function, Chap. 8 describes the neural mechanisms underlying the recovery of somatosensory and vestibular functions after injury of their central or peripheral pathways. Finally, the chapter by Nagao and Ito reviews the recent progress in neurorehabilitative techniques, emphasizing the following items: The rehabilitation training should start as soon as possible after brain injury to facilitate neural plasticity and to avoid disuse muscular atrophy; the activation of large brain areas should be stimulated, and in addition to the conventional training of locomotion and postural control the training of skilled movement of daily life, as well as the mental (imaginary) training of movements and actions should be promoted; repetition of training with rests of an appropriate duration between training sessions should be performed; and new techniques, such as noninvasive transcranial brain stimulation techniques, neuroprosthesis, and regenerative medicine, including the induced pluripotent stem cell technology, should be developed to provide new tools for neurorehabilitation.

In fact, in the last years the transcranial magnetic stimulation (TMS and rTMS) and transcranial direct current stimulation (tDCS) have shown their ability to modulate brain activity in a noninvasive manner, as described in Chap. 9 (*Integrated Methods of Neuromodulation for Guiding Recovery Following Stroke* by Di Lorenzo and Koch). According to the stimulation parameters it is possible to facilitate or suppress brain activity with variable behavioral effects. While rTMS can create strong currents capable to depolarize neurons, tDCS modulates neuronal activity by weaker electric currents by influencing ion channels and gradients and hereafter the resting membrane potential. In particular, anodal tDCS leads to brain depolarization (facilitation) whereas cathodal tDCS results in brain hyperpolarization (inhibition). Notably, rTMS is employed for therapeutic purposes or as part of a neurorehabilitative strategy for stroke recovery. Cortical stimulation in stroke is meant either to correct maladaptive brain plasticity induced by the cerebrovascular accident or to enhance adaptive brain plasticity during rehabilitation. This aim may be realized by modifying locally cortical excitability or by changing connectivity in neuronal networks. Three types of post-stroke disorders (motor deficit, aphasia, and hemineglect) appear to benefit from cortical stimulation techniques. The therapeutic trials in these three conditions are commonly aimed at rebalancing interhemispheric dynamics, directly increasing the excitability of the ipsilesional hemisphere or decreasing the excitability of the contralesional hemisphere, which results in a reduction of its inhibitory influence onto the lesioned hemisphere (model of interhemispheric competition). The application of an excitability-decreasing paradigm to the contralesional left posterior parietal cortex may represent a putative therapeutic intervention in the treatment of post-stroke neglect in the post-acute phase.

How do brain networks anticipate, endure, respond, and adapt to limit the consequences of a stroke? As described in Chap. 10 (*Resilience of Brain Networks*

After Stroke by Dirren and Carrera), a focal brain lesion triggers widespread alterations of connectivity between even distant brain regions. The study of changes in connectivity distant to the lesion has led to a new approach in the understanding of the neural correlates of brain function and recovery. In fact, brain connectivity architecture is organized not only to maximize functional performances but also to limit the potential consequences of a lesion. In healthy subjects brain networks are built with a limited number of highly connected nodes to promote an optimal balance between specialization and integration of information. Prelesional organization may limit the impact of a lesion on brain networks and its subsequent clinical consequences, and genetic and environmental factors modulate the organization of the human connectome and possibly its resilience to focal insults. Indeed, the anatomical location and the position of strategic nodes in the connectome prevent major neurological deficits, even when these hubs suffer from a targeted attack. Widespread changes in the organization of brain networks are triggered by the lesion and modulation of network organization is clinically relevant during the whole process of recovery, reflecting the mechanisms of plasticity and repair. This effect can be understood as "connectional" diaschisis or "connectomal" diaschisis defined, respectively, as the changes in coupling between the two nodes of a specific network or in the totality of brain connections. Clinically, the reduction in interhemispheric coupling after stroke seems to be particularly relevant. Furthermore, the process of resilience includes response and adaptation to the lesion. Although recent evidence points to the importance of changes in networks configuration during recovery, the changes of brain networks in a reorganized architecture not necessarily will lead to favorable outcome. Understanding how these changes are associated with restoration of function may open new therapeutic options to improve clinical outcome.

Depression has a multifactorial etiology arising from environmental, psychological, genetic, and biological factors. In recent decades, the advent of computerization and the progressive urbanization have led to a strong reduction of the levels of physical activity so that the consequent sedentary lifestyle combined with other factors such as alterations of the sleep/wake cycle, abuse of psychotropic substances, and chronic stress favors the onset of mood disorders and depressive syndromes. Furthermore, even a poor diet impacting on brain plasticity may be a risk factor for the onset of depression. Research has indicated that the main factors involved in the pathogenesis of depression may be neurotransmitter and neurotrophic factors imbalance, hypothalamic-pituitary-adrenal axis disturbance, deregulated inflammatory pathways, increased oxidative damage, neurogenesis dysfunction, and mitochondrial disturbance. In addressing the several hypotheses on the pathogenetic mechanisms of depression, Chap. 11 (*Functional Role of Physical Exercise and Omega-3 Fatty Acids on Depression and Mood Disorders* by Farioli-Vecchioli and Cutuli) focuses the effects of physical exercise and nutritional factors, such as omega-3 fatty acids, on neurotransmitters, neurotrophins, hippocampal neurogenesis, and neuroinflammation. The reported findings emphasize the capacity of omega-3 fatty acids and exercise to elevate the capacity of the adult brain for axonal growth, BDNF-related synaptic plasticity, neurogenesis, and

cognitive functions either under normal and challenging conditions. Given the noninvasiveness and safety of diet and exercise, nutritional and physical interventions represent treatments of choice to enhance cognition, mood, and brain plasticity in depressed patients.

Interestingly, a large number of neurological functions are deeply influenced by the gonadal hormones. Sex steroids prime irreversible life long-lasting changes, referred as "brain masculinization" of specific hypothalamic nuclei, which directly regulate sex functions, and other brain areas involved in the regulation of the endocrine system but also in behavior and, possibly, selected cognitive capacities. In the course of life, the changes in circulating or locally produced sex steroids connote reversible neurophysiological functions and contribute to sex differences in behavior, endocrine functions, and responses to pathological events. In fact, the manifestation of several neurological disorders correlates with specific changes of the synthesis of estrogens. These changes impact the metabolism of neurotransmitters, regulate the activity of glial cells, modulate microglia immune functions, and are involved in brain ability to recover after insult. Chapter 12 (*Estrogen Neuroprotective Activity After Stroke and Spinal Cord Injury* by Maggi) reviews the current knowledge on the mechanistic determinants of the brain sexual dimorphism and on the role of sex hormones in the modulation of brain recovery after stroke and injury in which the sex determines a differential incidence. Chapter 12 describes the well-established relationship between endogenous and exogenous sex hormones and many neurological disorders, such as epilepsy, chorea, and neurodegenerative diseases and emphasizes that the appreciation of the sexually dimorphic functions of the brain may facilitate the development of efficacious therapies for sex-prevalent disorders. Furthermore, a better understanding of the molecular mechanisms involved in female resistance to injury may shed novel light on their etiology and provide new avenues for more targeted therapeutic interventions.

In addition to biomedical factors, more recent research has begun to examine psychosocial influences and processes promoting functional recovery. Among the most important psychosocial aspects of functional recovery are the meanings that people with brain injuries assign to their situation (e.g., the injury, what recovery requires, what they are capable of) and the coping strategies they use in their efforts to achieve functional recovery. Chapter 13 (*Appraisals of and Coping with Acquired Brain Injury: Resources for Functional Recovery* by Park) presents a model of meaning and coping that highlights the centrality of meaning appraisal and coping in adjusting to adverse events. This model is then applied to adaptation to acquired brain injury by drawing on relevant theories and empirical findings. It is increasingly evident that how individuals manage brain injury and its sequelae influences functional recovery and determines the effects of the injury on productivity, social activity, emotional stability, and quality of life. Chapter 13 addresses the roles of appraised meanings, violations, coping, and meanings made in promoting functional recovery. Coping is driven by efforts to alleviate distress that are produced by violations between survivors' global meaning and their appraisal of the brain injury and its implications. Interestingly, long-term well-being following brain injury may require a mix of restoration-oriented coping, loss-oriented coping,

and meaning-focused coping so that both emotion-focused coping and problem-focused coping may be needed simultaneously to deal with different aspects of recovery. Even the reduction in violations between one's life goals and one's actual performance is central to functional recovery. This reduction in violations will largely be accomplished by letting go of goals that are no longer tenable and developing new, more realistic goals in light of the brain injury. The creation of a new identity and development of new perspective about life and expectations about the future are the basis of long-term adjustment following brain injury. Given the pervasive roles played by meaning making throughout the recovery process, increased efforts should be made to incorporate this perspective into existing rehabilitation programs.

Despite the conceptual utility and broad application, brain and cognitive reserve construct does not account for the variability in traumatic brain injury or stroke outcomes. In the clinical practice, it is assumed that the behavioral changes after traumatic events are most often related to cognitive function impairments due to brain damage, but increasingly data report that these manifestations are underpinned by a variety of mechanisms partially related to personality traits and environmental context of the patient. New multidimensional approaches take into account the complexity and dynamic relation between reserve construct and post-damage neurobehavioral changes associated to negative consequences of neurological damage on functional outcomes, caregiver distress, and social reintegration following the traumatic event. The depression often reported after brain damage has been associated with emotional and cognitive disabilities, reduction of quality of life, time of hospitalization, nonadherence to treatment schedules, repeated use of community health services, and increase of mortality. The attempts made to identify the predictors of depressive symptoms after brain damage have revealed the role of physical disability, damage severity, and cognitive decline. The few studies focusing on psychological aspects as predictors of depressive symptoms have indicated that premorbid personality dimensions may be associated with the development of post-damage depression. In this framework, environmental factors, emotional aspects, and premorbid personality traits have increasingly been considered as potential moderators of traumatic brain damage. Chapter 14 (*Premorbid Personality Traits and Brain Recovery: Another Aspect of Resilience* by Laricchiuta, Markett, Reuter, and Montag) defines the role of premorbid personality and attachment style within the context of resilience against the detrimental effects of traumatic brain damage on adaptive functioning. Premorbid personality features appear to be a relevant factor of resilience that predicts brain recovery efficiency or predisposes to neurodegenerative diseases. The biopsychosocial approach should be encouraged in the management of neurobehavioral difficulties, since this approach apprehends behavioral changes as a result of complex and dynamic interactions among neurobiological (type and severity of injury, time post-injury), social (psychosocial history, family context), personal (medical history, personality traits, and pre- and post-morbid coping strategies), and environmental factors (problematic and anxiogenic situations related to brain injury).

As repeatedly described, the often co-present motor, cognitive and affective symptoms dramatically affect the patient's quality of life and the project for self-realization. Changes may occur suddenly, such as after stroke or traumatic brain injury, representing a highly stressful condition for the affected individuals and their family. Indeed, brain injury may provoke a kind of discontinuity in the feeling of self and requires cognitive reintegration to regain a unitary image of body and of the self. The psychopathological symptoms and maladaptive coping styles frequently observed after brain injuries negatively affect the therapeutic outcome. Psychological reactive mechanisms and premorbid cognitive–affective coping style are reported to play a significant role in the patient's recovery processes. Among the various factors potentially modulating the effects of therapeutic interventions, the study of the possible role of psychic defense mechanisms aroused poor interest. Within the traditional psychoanalytic framework, defense mechanisms are described as psychic operations adopted to keep far from consciousness aspects of emotional experience that may cause severe anxiety and mental sufferance. After brain injury, patients may present stable responses conditioned by the adoption of particular defense mechanisms (regression to maladaptive behavioral schema, repression of emotions, denial…) that significantly affect compliance with treatment. In psychological terms, the tendency to use a particular defense mechanism may rely upon the premorbid cognitive/affective style of functioning. Mechanisms of psychological defense, such as repression/denial, may be active in patients who after brain injury show emotion/affective dysregulation and tend to use poorly efficient coping strategies. Moreover, repression/denial can influence the patient's ability to correctly acknowledge the illness and its consequences, in so way hampering the productive participation to the rehabilitative program and social reintegration.

Chapter 15 (*Psychodynamic Factors of Recovery After Brain Injury: A Role for Defense Mechanisms?* by Costa, Gullo and Caltagirone) discusses the possible role of psychodynamic mechanisms in the recovery after brain injury and provides some clues for the purpose of the clinical intervention. To improve the clinical approach to brain-injured patients, the psychological and psychodynamic processes potentially implied in the adjustment response should be correctly recognized and adequately treated, even if valid and reliable tools to assess defense mechanisms in brain-injured individuals are still scarce.

Even a cursory glance at the chapters makes it obvious that there are different views and approaches to the same topic, an aspect of book with which I'm very pleased. The pluralism linked to multifaceted approaches is a good route to take, given the state of the art, and serious attention needs to be paid to all of these approaches (from the most molecular to the most psychodynamic). The fact that there are so many overlapping themes among very different approaches speaks to the interdisciplinary nature of the studies on brain recovery. I hope that this book might stimulate all of us to be more interdisciplinary and to rise to challenge to try to answer difficult questions. All things considered, it is important to emphasize

how the most effective strategies for brain recovery should combine multifactorial (from molecular to psychological) manipulations to drive the most robust and functionally appropriate plasticity.

I would like to thank all the contributors and Springer Press for working with enthusiasm and dedication on this project. Identifying the most prominent factors that contribute to successful injury-induced neuronal plasticity is the current challenge that has to inform future studies on brain recovery to expose new avenues for neuronal repair strategies.

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Chapter 1
Structural Plasticity in Dendrites: Developmental Neurogenetics, Morphological Reconstructions, and Computational Modeling

Sumit Nanda, Ravi Das, Daniel N. Cox and Giorgio A. Ascoli

Abstract Mature dendritic arbors emerge out of complex growth mechanisms involving intracellular, extracellular, and activity-dependent factors. These interactions converge on cytoskeletal effectors, mainly microtubules and actin filaments, which mediate the structural changes and stabilize the mature structure. The quantitative characterization of developmental dynamics remains challenging because current morphological descriptors are static and without explicit representation of subcellular composition. Large datasets of new time-varying reconstructions with co-registered internal cytoskeletal information are required to build statistically reliable models of dendritic growth and plasticity. Here we review the history and current state of experimental and theoretical approaches, and illustrate the progress of an innovative closed-loop research design using the *Drosophila* larva system. Time-lapse confocal images of the fluorescently labeled cytoskeletal components are digitally reconstructed into a novel file structure, enabling comprehensive statistical analysis and data-driven computational simulations of dendritic growth. These data in turn guide the most informative genetic manipulations for testing specific hypotheses.

Keywords Neuronal reconstructions · Stochastic models of dendritic growth · *Drosophila* neurogenetics · Dendrite development · Multispectral fluorescent confocal imaging · Dentritic arborization of sensory neurons · Cytoskeletal regulation · Multichannel reconstruction · Time-lapse reconstruction

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1.1 Introduction

Cognition and behavior emerge from circuits of neurons in the brain. Therefore, comprehension of neural architecture is a necessary step toward understanding computation in the nervous system (Helmstaedter and Mitra 2012; Chiang et al. 2011; Oberlaender et al. 2012). Two distinct tree-shaped neuronal components, differing in both structure and function, are responsible for wiring the circuitry: dendrites and axons. Dendrites receive, integrate, transform, and propagate to the soma signals from other neurons, thus largely defining the computational properties of a neuron. In contrast, axons transmit signals to other neurons, often spanning long distances to connect the network. Since dendrites do not travel as far as axons, it is easier to image and reconstruct their complete arbors. Dendrites and axons grow under multiple constraints, and their internal cytoskeletal structures are also distinct.

Dendritic trees remain, to a certain extent, plastic even after reaching a steady mature shape, thereby continuously adjusting their existing structure. However, overall stability of mature dendrites is necessary for proper functioning of adult circuits and destabilizing dendritic morphology may cause neurodegeneration and functional impairment. One can thus divide structural plasticity of dendrites into two temporal phases: plasticity during development and plasticity after reaching a steady mature shape. During development, dendrites undergo frequent, dynamic changes. In contrast, mature arbor shape is stable over long periods of time. The mechanisms upstream to the emergent changes are different during the two phases. The early developmental growth is, by and large, intrinsically constrained and genetically encoded (Van Pelt et al. 2003). After the initial outgrowth of short neurites from the lamellipodia, one of the neurites elongates rapidly with simultaneous inhibition of the other neurites. This dominant neurite becomes the axon, and develops distinct molecular characteristics (Dehmelt and Halpain 2004). This axonal differentiation is followed by the elongation and branching of the other neurites, forming elaborate dendritic arbors. This phase of initial growth is rapid, with fast elongation and retraction of short branches. As the arbor attains a mature shape, the rate of structural changes slows down (Cline 2001). During the adult phase, external constraints as well as overall neural activity have a greater effect on structural plasticity (Deitch and Rubel 1984). Nevertheless, in both of these phases, all upstream pathways converge onto cytoskeletal dynamics to mediate structural plasticity.

The cytoskeleton is a defining component of eukaryotic cells and constitutes the foundation of their inner architecture. The cytoskeleton is comprised of three primary types of fibers: F-actin filaments, microtubules, and intermediate filaments/neurofilaments. These cytoskeletal fiber systems perform various essential functions including formation of cell morphology (for cells without cell wall), facilitation of cell movement, structural support for polarized intracellular trafficking and positioning of subcellular organelles, and organization of spindle fibers to enable cell division (Kandel et al. 2000; Rodriguez et al. 2003; Lamprecht and LeDoux 2004). Cytoskeletal structures are highly dynamic during early

development, but become relatively stable during adult phase (Koleske 2013). In neurons, as in other cell types, the subcellular organization and dynamic modulation of these cytoskeletal fiber systems is tightly controlled by a vast array of regulatory proteins, including those involved in assembly, disassembly, stabilization, bundling, severing, and molecular motor-based transport (Donohue and Ascoli 2005a; Coles and Bradke 2015; Kapitein and Hoogenraad 2015). F-actin and microtubule polymer assembly is achieved by asymmetrical addition of ATP-bound G-actin monomers and GTP-bound α-β-tubulin heterodimers, respectively, to one end preferentially (barbed or plus end), thereby generating polarized structures that facilitate directional trafficking within cells (Conde and Cáceres 2009; Campellone and Welch 2010). The remarkable self-assembly of cytoskeletal proteins into complex structures is organized by numerous cytoskeleton-associated factors (Karsenti et al. 2006).

In the case of F-actin polymerization, actin nucleators such as Arp2/3, Spire and Formins are able to bind multiple G-actin monomers and as a result modulate the actin nucleation and polymerization processes. For instance, if Arp2/3 activity is high, a dendritic network of short, branched F-actin pushes out a broad lamellipodium, and if Formin activity is high then long F-actin bundles push out filopodia (Letourneau 2009; Baum and Kunda 2005; Breitsprecher and Goode 2013). Similarly, the Rho family of small GTPases, including Rac1, Rho, and Cdc42, as well as certain downstream effectors, have been demonstrated to play pivotal roles in regulating actin dynamics during dendrite and dendritic spine morphogenesis (Redmond and Ghosh 2001; Luo 2002). Activation of Rac1 and Cdc42 functions to promote dendritic branching (Luo et al. 1996; Scott et al. 2003; Murakoshi et al. 2011; Sin et al. 2002), whereas RhoA/Rho1 activation restrains branching (Nakayama et al. 2000; Lee et al. 2000). Moreover, dendritic branch points and termini in *Drosophila* sensory neurons are primarily actin-rich and subject to regulation by Rac1 (Lee et al. 2003; Anderson et al. 2005). Furthermore, coordinated regulation of Rac1 and Rho1 by the multifunctional guanine nucleotide exchange factor Trio plays an important role in sculpting cell-type specific dendritic arborization (Iyer et al. 2012; Shivalkar and Giniger 2012).

In the case of microtubules, which are nucleated at their minus end, either the γ-tubulin ring complex or microtubule fragments act as templates for the assembly of α-β-tubulin heterodimers into the plus end of microtubules (Conde and Cáceres 2009). The importance of microtubule nucleation to dendritic growth and branching has been revealed by a number of studies. Loss of γ-tubulin disrupts nucleation resulting in reduced dendritic branching (Ori-McKenney et al. 2012). Moreover, the microtubule-severing proteins Spastin and Katanin-p60-like1, have been shown to promote dendritic branching in *Drosophila* sensory neurons suggesting that severed microtubules may provide new templates for de novo microtubule assembly and elongation (Jinushi-Nakao et al. 2007; Stewart et al. 2012). In dendrites, large bundles of discontinuous microtubules are linked by microtubule-associated proteins (MAPs) and unlike axons, where microtubules exhibit uniform anterograde polarity, dendritic microtubules have mixed polarity projecting in both the anterograde and retrograde directions facilitating directional transport of vesicular

cargo and organelles via Kinesin and Dynein motor protein complexes, respectively (Baas et al. 1988; Stone et al. 2008; Kollins et al. 2009; Kapitein et al. 2010). Such directional transport is required for proper dendritogenesis as disruptions in this process can result in a loss of dendritic identity (Yu et al. 2000; Hoogenraad et al. 2005) and severe defects in dendritic branch distribution and extension (Zheng et al. 2008; Satoh et al. 2008; Rolls 2011). Another unique feature of dendrites is the presence of satellite endoplasmic reticulum and Golgi outposts, which are primarily localized to dendritic branch points and required for dendritic polarization and branch elongation (Horton and Ehlers 2003; Horton et al. 2005; Ye et al. 2007; Iyer et al. 2013a). Interestingly, a recent study revealed that Golgi outposts can nucleate microtubules with the plus end extending from the dendrite toward the soma, contributing to the generation of mixed microtubule polarity (Ori-McKenney et al. 2012).

Alterations in dendritic cytoskeletal dynamics during development can have important effects on final arbor shape. Rapid turnover of both F-actin filaments and microtubules is dynamically regulated by local availability of actin and tubulin subunits whose concentration may vary between cell regions (Carlier and Pantaloni 2007; Nogales and Wang 2006; Gregoretti et al. 2006; Janulevicius et al. 2006; Graham and van Ooyen 2006). Furthermore, emerging evidence highlights the importance of cytoskeletal cross-linking proteins that contribute to coordinating actin–microtubule dynamics in neuronal development and morphogenesis (Coles and Bradke 2015). Despite these significant advances, it is not yet clear how genetically encoded growth rules are dynamically expressed through the local molecular interactions of cytoskeletal components driving cell-type specific dendritic arborization.

Both experimental and computational approaches are useful to elucidate the mechanisms of dendritic growth. Following classic reductionism, experiments can tease apart the role of specific molecules within the biochemical pathways that causally affect dendritic development. Complementarily, "constructionist" computational models can identify the emergent rules out of the multitude of molecular interactions.

More specifically, two key experimental tasks must be accomplished to gain a proper understanding of dendritic growth. First, the subcellular mediators of dendritic growth must be visualized using advanced genetic expression and microscopy. Second, the molecular pathways associated with dendritic growth need to be perturbed, and the resultant neuronal arbors visualized. The generated experimental data need to be complemented with a 3-step computational strategy. First, both neuronal morphology and cytoskeletal composition must be reconstructed from microscopic images of dendritic arbors in a format suitable to quantitatively describe their changes over time. Second, the dendritic morphology of various neuron types need to be synthetically reproduced by stochastic simulations of dynamic growth built upon branch elongation, bifurcation, termination, and retraction. This step can reveal the optimal combinations of growth parameters for different neuron types. Third, the upstream processes need to be elucidated by

building mechanistic models to inform the stochastic simulation and to connect their computational parameters with meaningful biological counterparts.

This book chapter reviews the experimental and computational approaches used in the study of dendritic growth and structural plasticity. We first review the biomedical significance of proper dendritic development and neurogenetic mechanisms governing this process with an emphasis on transcriptional-mediated cytoskeletal regulation. We then discuss techniques used to identify the molecules and pathways responsible for arbor development, focusing on the fruit fly system. Next we describe the central technique bridging experimental and computational approaches, namely digital reconstructions of neuronal morphology. Penultimately, we discuss the modeling methodologies to generate artificial neurons in simulations. Finally, we propose how novel advances on these three fronts can achieve the objective of a systems level understanding of dendritic growth.

1.2 Biomedical Relevance

Disrupted arbor development is a common feature in a diverse variety of neuropathological disease states including Down, Rett, and Fragile-X Syndromes; Autism; Alzheimer, Parkinson, and Huntington diseases; schizophrenia, and Duchenne/Becker muscular dystrophies (Belmonte et al. 2004; Anderton et al. 1998; Sheetz et al. 1998; Dickson et al. 1999; Garey et al. 1998; Jagadha and Becker 1988; Fiala et al. 2002; Kaufmann and Moser 2000; Ramocki and Zoghbi 2008; Kulkarni and Firestein 2012; Gates et al. 1998). In all of these cases, a strong neuroanatomical correlation exists between dendritic abnormalities and cognitive impairments. Thus elucidating the molecular genetic mechanisms by which multiple local interactions of cytoskeleton elements direct the growth of dendrite arbors have direct clinical relevance. Learning to manipulate arbor growth mechanisms will be important to develop neuroregenerative strategies. Dendrites are the chief site of signal input into a neuron, receiving up to tens of thousands of inputs on each single arbor. In addition, correct dendrite arbor and spine morphology are central to the proper establishment of synapses, and in turn, neuronal circuits. In humans, defects in dendrite arbor developmental processes lead to mental retardation, and pathological alterations in dendritic morphology and spine structure are consistent features in these patients. Disruption of pathways controlling the actin cytoskeleton have been linked to retardation diseases. For example, mutations in several genes that encode components of Rho GTPase signaling pathways, which directly regulate actin dynamics, are causative of Non-Specific X-linked Mental Retardations (Fiala et al. 2002; Newey et al. 2005; Linseman and Loucks 2008). Similarly, a variety of neurological and neurodegenerative diseases are linked to disruptions in microtubule cytoskeletal architecture and intracellular transport. Disruptions in the Dynein–Dynactin microtubule motor based transport system is linked to neurodegenerative disorders including Lissencephaly, Charcot–Marie–Tooth disease, and amyotrophic lateral sclerosis (ALS) (Franker and Hoogenraad 2013). Defects in

microtubule cytoskeleton regulatory molecules, such as the microtubule severing AAA ATPase SPG4/Spastin, have likewise been linked to hereditary spastic paraplegia (Roll-Mecak and Vale 2005; Solowska and Baas 2015), while disruptions in the microtubule associated protein, Tau, have been directly linked to various neurodegenerative Tauopathies and Alzheimer disease (Zempel and Mandelkow 2014). Clearly, proper regulatory control of cytoskeletal dynamics is essential for normal dendritic arbor development and function. Achieving a mechanistic understanding of the links between cytoskeletal dynamics and functional dendritic structure will aid in understanding the cellular and molecular bases of pathologies underlying human neurological disease.

1.3 Developmental Neurogenetics

Uncovering the cellular and molecular mechanisms directing dendritic morphogenesis relies upon neurogenetic dissection of the molecules and signaling pathways that mediate this important developmental process. Model organisms including yeast (*Saccharomyces cerevisiae*), nematodes (*Caenorhabditis elegans*), fruit fly (*Drosophila melanogaster*), zebrafish (*Danio rerio*) and mouse (*Mus musculus*), among others, have proven indispensable in unraveling the complex biological processes governing cytoskeletal and neuronal development. Among these, the fruit fly has emerged as one of the most powerful and genetically tractable models for investigating neural development and function. The rich history and deep knowledge base of *Drosophila* biology, with over 100 years of study, coupled with the powerful genetic toolkit and evolutionary conservation with vertebrates, including human, have made the fruit fly one of the premier model systems for investigating cellular, molecular, and behavioral underpinnings of nervous system development and function. Studies in fruit flies have had tremendous influence on vertebrate neuroscience in a wide array of areas including neural development, the molecular bases of behavior, nervous system function and circuit organization, synaptic transmission and neurodegenerative disorders (Bellen et al. 2010).

Research in *Drosophila* has yielded significant insight into the cellular and molecular processes driving cell-type specific dendritogenesis and neural circuit construction (Jan and Jan 2010; Couton et al. 2015). Here, we focus on one of the most widely studied models for investigating dendritic development in the fruit fly, namely the dendritic arborization (da) sensory neurons of the larval peripheral nervous system. *Drosophila* da neurons constitute an attractive model to investigate the molecular mechanisms underlying the regulation of dendritic morphology for several reasons: (1) the powerful genetic tools available in the fruit fly for investigating gene function; (2) the dendritic arbor lies immediately below a translucent, thin larval epithelium facilitating in vivo live cell and time-lapse imaging; and (3) the class-specific diversity in tree morphology within this group of neurons facilitates comparative analyses to find the key elements controlling the acquisition and maintenance of cell-type specific dendritic arborization and the promotion of

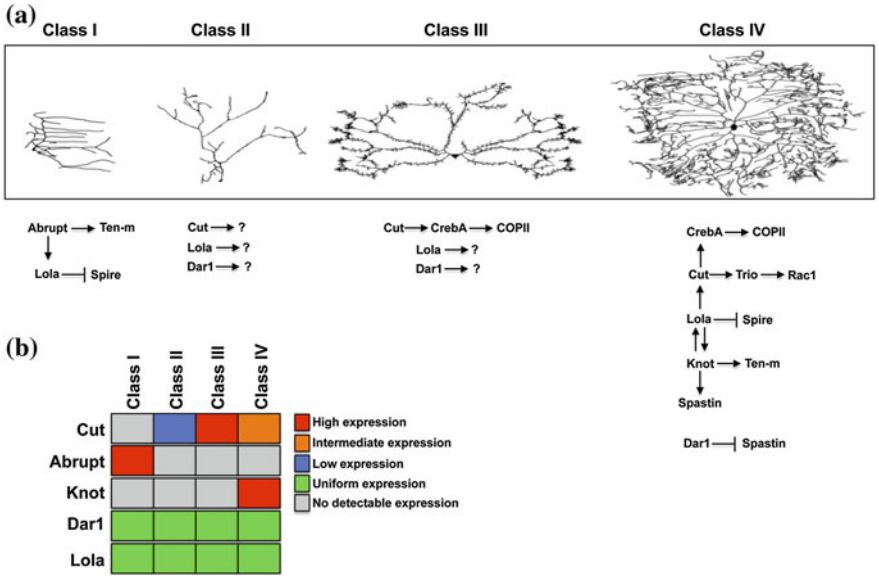

Fig. 1.1 Transcriptional regulation of da sensory neuron dendritic architecture. **a** Shown at *top* are representative tracings of dendritic architecture among class I–IV *Drosophila* da sensory neurons. Shown *below* are known transcriptional regulatory programs that operate in individual da neuron subclasses to mediate class-specific dendritogenesis. **b** Summary of transcription factor protein expression levels and differential expression by da neuron subclass

dendritic diversity. Morphological phenomena including dendritic growth, branching, scaling, tiling, and remodeling have all been characterized using da neurons (reviewed in Parrish et al. 2007a; Corty et al. 2009; Jan and Jan 2010; Tavosanis 2014; Singhania and Grueber 2014). These da neurons are grouped into four distinct morphological classes (Class I–IV) based on increasing complexity of their dendritic arbors (Grueber et al. 2002) (Fig. 1.1a). Studies over the past fifteen years have revealed numerous genetic and cellular programs that govern cell-type specific dendrite development including transcriptional regulation, intrinsic and extrinsic cell signaling pathways, secretory and endocytic pathway function, cytoskeletal modulation, cell adhesion, RNA targeting and local translation, chromatin remodeling, and activity-dependent modulation of dendritic arborization (Jan and Jan 2010; Tavosanis 2014).

1.3.1 Transcriptional Control of Dendritic Development and Cytoskeletal Modulation

Cell-type specific dendritic morphologies emerge via complex growth mechanisms modulated by intrinsic signaling involving transcription factors that mediate

neuronal identity, as well as functional and morphological properties of the neuron subtype (Jan and Jan 2010; Singhania and Grueber 2014; Tavosanis 2014). Moreover, dendrite development is modulated by extrinsic signaling, influenced by external factors such as peripheral glial cells (Yamamoto et al. 2006), and coupled with activity-dependent regulation (Jan and Jan 2010; Tavosanis 2014). Combined, these processes converge on a broad spectrum of cellular pathways, including the cytoskeleton, to direct cell-type specific dendritic arbor development, stabilize mature architecture, and facilitate structural plasticity.

Here, we focus on transcriptional programs that direct cell-type specific dendritic development with an emphasis on discoveries in *Drosophila*. Transcription factors have been demonstrated to exert their effects on dendrite morphogenesis by several different mechanisms. Distinct cell fates and morphologies can be achieved by the presence or absence of a transcription factor, by varying the levels of an individual transcription factor, or by a combinatorial mechanism of action that can involve many transcription factors (Jan and Jan 2010; Puram and Bonni 2013; Santiago and Bashaw 2014). Furthermore, recent evidence reveals that transcription factors involved in cell fate specification may also exhibit independent post-mitotic roles in directing cell-type specific neural differentiation, e.g., dendrite morphogenesis (de la Torre-Ubieta and Bonni 2011; Iyer et al. 2013b).

As cell intrinsic mechanisms for dendritic development, including transcriptional regulation, have been extensively reviewed elsewhere (Puram and Bonni 2013; Santiago and Bashaw 2014), here we focus on emerging evidence demonstrating how cell-type specific transcription factor regulation converges on cytoskeletal modulation to drive dendrite arborization and homeostasis. Comprehensive studies, including genome-wide analyses, in *Drosophila* da sensory neurons have provided substantial insight into individual and combinatorial roles for transcription factors in driving class-specific dendritogenesis (Gao et al. 1999; Moore et al. 2002; Grueber et al. 2003; Sugimura et al. 2004; Li et al. 2004; Kim et al. 2006; Parrish et al. 2006, 2007b; Hattori et al. 2007; Jinushi-Nakao et al. 2007; Crozatier and Vincent 2008; Ye et al. 2011; Sulkowski et al. 2011; Iyer et al. 2013a; b). However, the molecular mechanisms via which these transcription factors govern arbor development and dynamics remains incompletely understood (Santiago and Bashaw 2014). An ensemble of transcription factors, including Cut, Abrupt, Knot (also known as Collier), Dar1 and Lola, are required as major regulators of cell-type specific da sensory neuron dendritic morphogenesis. While recent studies have begun to link cell-type specific transcription factor activity to cytoskeletal regulation and other pathways (Jinushi-Nakao et al. 2007; Iyer et al. 2012, 2013a; Ye et al. 2011; Nagel et al. 2012; Hattori et al. 2013; Ferreira et al. 2014), much remains unknown regarding the molecular mechanisms via which transcription factors direct final arbor shape through spatiotemporal modulation of cytoskeletal dynamics. Here we summarize the current state of knowledge regarding the mechanisms by which these transcription factors functionally converge on the cytoskeleton in specifying differential patterns of dendrite arborization (Fig. 1.1a).

Cut, a member of the evolutionarily conserved CUX family of transcription factors, is a homeodomain containing molecule with functional roles in external

sensory organ cell fate specification (Bodmer et al. 1987; Blochlinger et al. 1988, 1990), class-specific da neuron dendrite morphogenesis (Grueber et al. 2003), and dendritic targeting of olfactory projection neurons (Komiyama and Luo 2007). Cut regulates dendritic diversity among da sensory neurons in an expression level dependent manner (Grueber et al. 2003). Cut protein expression in da neurons is highest in class III da neurons, followed by medium and low expression levels in class IV and class II neurons, respectively, and undetectable in class I neurons (Grueber et al. 2003) (Fig. 1.1b). Genetic depletion of *cut* leads to severe reductions in dendritic arbor complexity, particularly the formation of actin-rich structures such as short, unbranched dendritic filopodia. Conversely, ectopic misexpression of Cut in class I neurons results in supernumerary branching and the de novo formation of dendritic filopodia converting typical class I dendritic morphology toward the characteristic features of class III neurons (Grueber et al. 2003). Cux1/Cux2, the vertebrate homologs of Cut, also function in regulating dendritic branching, spine morphology and synaptogenesis in the mammalian cortex revealing the Cut/Cux molecules have evolutionarily conserved roles in dendritic development and maturation (Cubelos et al. 2010; Li et al. 2010). In contrast to Cut, the BTB/POZ-zinc finger protein Abrupt (Ab) is uniquely expressed in class I da neurons (Fig. 1.1b) and ectopic misexpression in other da neuron classes results in reductions in arbor size and complexity suggesting a role for Ab in restricting dendritic growth and branching in class I neurons (Sugimura et al. 2004; Li et al. 2004). Similarly, the Collier/Olf1/EBF(COE) family transcription factor Knot (Kn) exhibits specific expression in class IV da neurons (Fig. 1.1b) where it functions in combination with Cut to orchestrate class IV specific dendritic arborization (Jinushi-Nakao et al. 2007; Hattori et al. 2007; Crozatier and Vincent 2008). Moreover, ectopic misexpression of Kn is sufficient to promote excessive dendritic branch elongation in class I neurons that otherwise have simple arbors. The combinatorial action of Cut and Kn in specifying class-specific arbor shapes is achieved, at least in part, by differential regulatory effects on the F-actin and microtubule cytoskeletons (Jinushi-Nakao et al. 2007). Furthermore, Kn and Cut regulate the dendritic arbor cytoskeleton through primarily parallel pathways. Cut, acting via Rac1, promotes the formation of actin-rich dendritic filopodia, whereas Kn promotes the expression of the microtubule severing protein Spastin which is believed to generate new sites for microtubule polymerization thereby promoting branch initiation, elongation, and arbor complexity (Jinushi-Nakao et al. 2007). Interestingly, the Krüppel-like transcription factor Dar1, which is expressed in all da neuron subclasses (Fig. 1.1b), is required for Kn-mediated dendritogenesis and appears to restrict Spastin expression to achieve proper levels of this molecule in promoting dendritic growth (Ye et al. 2011). In class IV neurons, Kn suppresses Cut-induced actin-rich dendritic filopodial formation contributing to cell-type specific arborization, whereas in class III da neurons, Cut promotes the formation of these structures (Jinushi-Nakao et al. 2007). Moreover, Kn does not function in regulating Cut protein levels, however Cut controls the amplitude of Kn expression (Jinushi-Nakao et al. 2007). Thus, the regulatory relationships and the class-specific expression patterns of Cut and Kn coordinate the specification of distinct patterns of

arborization among class III and IV da neurons and raises the question of whether these transcription factors may combinatorially converge on common putative downstream effectors that orchestrate F-actin and microtubule cytoskeletal architectures and dynamics.

Recent studies have begun dissecting the molecular mechanisms and downstream effectors via which these class-specific transcription factor codes contribute to different patterns of dendritic arborization (Santiago and Bashaw 2014). Turtle, an evolutionarily conserved member of the Turtle/Dasm1/IgSF9 subfamily of immunoglobulin superfamily molecules, functions as a downstream effector of Cut in directing class-specific dendrite morphogenesis (Sulkowski et al. 2011). Turtle is differentially expressed among da neuron subclasses in a pattern that mirrors that observed for Cut, although Turtle expression is not absolutely dependent upon Cut since low levels of Turtle are detectable in Cut-negative class I neurons (Sulkowski et al. 2011). Loss-of-function and overexpression studies reveal Turtle functions in promoting dendritic branching, particularly filopodial branches, in a manner similar to that observed for Cut. Moreover, genetic and biochemical evidence reveals that Cut specifically binds to the Turtle promoter and positively regulates its expression (Sulkowski et al. 2011). The guanine nucleotide exchange factor (GEF) Trio also functions downstream of Cut. Disruptions in *trio* function reduce dendritic branching complexity in da neurons, whereas overexpression of Trio and the Rac1-specific GEF1 domain leads to increased dendritic complexity and de novo formation of actin-rich dendritic filopodia as seen in Cut overexpression (Iyer et al. 2012). Cox and colleagues demonstrate that *trio* knockdown suppresses Cut-induced dendritic branching and that Trio overexpression can partially rescue *cut* mutant dendritic branching defects (Iyer et al. 2012). Similarly, the conserved actin-bundling protein Fascin functions as a downstream effector of Cut where it promotes the formation of actin-rich filopodial branchlets (Nagel et al. 2012). Class III neurons require Fascin function to specify terminal branches, whereas class IV neurons do not, and Cut-mediated formation of these branches is dependent upon Fascin, although it is unknown whether Fascin is a direct or indirect target of Cut (Nagel et al. 2012). The secretory pathway plays an important role in specifying dendritic shape and dendrites exhibit a unique spatial organization of the ER and Golgi as compared to non-neuronal cells where neurons have somatic and satellite dendritic ER and Golgi (Horton et al. 2005; Ye et al. 2007; Iyer et al. 2013a). A recent study demonstrated that Cut transcriptionally regulates the expression of the COPII secretory pathway genes (*sec31/sec13/sec23/sec24/Sar1*) via the intermediate transcription factor CrebA and that this transcriptional cascade is required for Cut-mediated dendritic arborization (Iyer et al. 2013a). Moreover, Cut regulated expression of the COPII secretory machinery also translates into a concomitant increase in the number of satellite secretory outposts (ER/Golgi) that colocalize with branch initiation sites and mediate terminal dendritic branching (Iyer et al. 2013a) (Fig. 1.1a).

To investigate putative target genes of Ab and Kn, Hattori et al. (2013) conducted genome-wide DAM-ID analyses for Ab and Kn transcription factor binding sites and performed parallel transcriptional profiling analyses in larvae

overexpressing Kn or Ab in da neurons. Comparative analyses of these datasets identified genes that are bound by either, or both, transcription factors, as well as those genes that were altered in response to changes in Ab or Kn expression levels. These analyses identified more than 400 Ab and/or Kn target genes, among which 56 were common to both Ab and Kn revealing both overlapping and unique target genes (Hattori et al. 2013). Given the specific roles of Ab and Kn in directing class I or class IV dendritic development, respectively, it is intriguing that all of the 56 common genes exhibited either upregulation or downregulation by Ab and Kn, as opposed to opposite effects on gene expression (Hattori et al. 2013). One of the common upregulated target genes was the homophilic cell adhesion molecule Teneurin-m (Ten-m) which, however, displayed differential expression with high levels in class I versus low expression in class IV neurons (Hattori et al. 2013). *Ten-m* mutant class I neurons have defects in dendritic branch directionality, similar to defects reporter for *ab* mutants, whereas *Ten-m* disruption in class IV neurons led to defects in dendrite positioning (Hattori et al. 2013). The differential effects and expression of Ten-m suggest a model whereby Ab promotes high Ten-m expression in class I, whereas Kn mediates low levels in class IV and that these quantitatively distinct control mechanisms of two class-specific transcription factors on a common target function to promote dendritic diversity between cell types (Hattori et al. 2013) (Fig. 1.1a). Ab functions to repress dendritic branching in class I neurons, however, until recently the effector pathway via which Ab achieves this function was unknown. Yalgin et al. (2015) have identified Centrosomin (Cnn), a centrosome-associated protein involved in mitotic spindle maturation, as a downstream effector of Ab. Ab positively regulates Cnn expression, which functions to repress dendrite branch formation. Cnn is targeted to the cis face of dendritic Golgi outposts during dendritic branching and is required to recruit microtubule nucleation to these outposts leading to net retrograde microtubule polymerization away from nascent dendrite branching and thereby represses branch formation (Yalgin et al. 2015) (Fig. 1.1a). Another common Ab/Kn upregulated target identified by Hattori et al. (2013) is the BTB/POZ transcription factor *longitudinals lacking* (*lola*) which functions in promoting class-specific dendritic growth and branching. Previous studies demonstrated that *lola* is required to regulate axon guidance in the CNS and PNS (Crowner et al. 2002; Giniger et al. 1994), and genome-wide analyses revealed that Lola negatively regulates the expression of the actin nucleator Spire to promote motor neuron axon growth (Gates et al. 2011). Spire is a conserved member of the WASP homology 2 (WH2)-domain family of actin nucleation factors that functions in nucleation, severing, and capping of actin filaments to regulate their assembly (Quinlan et al. 2005). In a recent study, Ferreira et al. (2014) demonstrated that Lola regulates class-specific dendritic morphogenesis by negatively regulating Spire expression and that Lola promotes the expression of both Cut and Kn in class IV neurons. Lola-mediated suppression of Spire expression inhibits the formation of actin-rich filopodia in class I and class IV neurons thereby contributing to their cell-type specific dendritic architectures (Ferreira et al. 2014) (Fig. 1.1).

1.4 Neurogenetic and Neurogenomic Techniques

The identification of the genetic factors crucial in dendritic morphogenesis has been facilitated by advancements in in vivo and time-lapse imaging techniques and the genetic toolkit that allows manipulation of genes at the level of single neurons in *Drosophila.* For instance, the *GAL4/UAS* binary expression system (Brand and Perrimon 1993) allows for targeted spatiotemporal manipulation of genes via cell-type specific RNA interference (RNAi) mediated knockdown or overexpression studies. Another extensively used technique is the mosaic analysis with a repressible cell marker (MARCM), which allows resolution of dendrites at a single-cell level and genetic manipulation of individual neurons to assess gene function in a cell-autonomous condition during dendritic morphogenesis (Lee and Luo 1999). As we move forward in elucidating the mechanism of dendritic morphogenesis, it has become apparent that a detailed map of the spatial organization of polymerized F-actin- and microtubule-based cytoskeletons at sequential stages of dendrite arbor development are key in investigating how multiple local interactions among cytoskeletal regulators drive cell-type specific dendrite morphogenesis. In vivo visualization of the cytoskeletal components is achieved by implementing multi-fluor labeling of genetically engineered cytoskeletal and membrane reporters. Using this approach, it is possible to reveal distinct subcellular organizations of F-actin and microtubule cytoskeletons across da neuron subtypes and facilitate in vivo time-lapse dissection of genetic programs that govern cytoskeletal modulation in both normal and mutant backgrounds (Fig. 1.2). At a neurogenetic level, dissection of transcriptional programs that modulate cell-type specific dendritogenesis has been greatly enhanced through the use of neurogenomic strategies for profiling cell-type specific gene expression profiles under normal and mutant

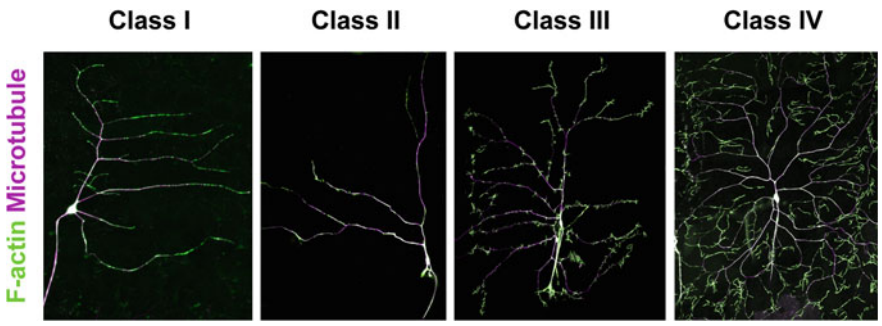

Fig. 1.2 Class-specific da neuron F-actin and microtubule dendritic cytoskeletal organization. Representative images of class I–IV da neurons labeled by class-specific *GAL4* expression of *UAS-GMA* and *UAS-mCherry::Jupiter*. *UAS-GMA* is a GFP-tagged Moesin actin binding domain which labels the F-actin cytoskeleton and *UAS-mCherry::Jupiter* is a mCherry tagged microtubule associated protein (MAP, Jupiter) which labels the microtubule cytoskeleton. Class-specific *GAL4* drivers are: Class I (*GAL4[221]*); Class II (*GMR37B02-GAL4*); Class III (*19-12-GAL4*); Class IV (*GAL4[477];ppk-GAL4*)

genetic backgrounds. Cell-type specific neurogenomic analysis is afforded by novel techniques, such as magnetic bead based cell sorting (Iyer et al. 2009) and laser capture microdissection (Iyer and Cox 2010), that allow for the isolation and purification of genetically tagged neuron subtypes. Neurogenomic studies incorporating cell-type specific isolations and genetic manipulations have been efficiently utilized in dissecting neural function and dendritic development by integrating sophisticated bioinformatics analyses of genome-wide expression datasets including microarray, ChIP-seq, DamID and RNA-seq transcriptomics (Iyer et al. 2013b; Hattori et al. 2013; Parrish et al. 2014; Bhattacharya et al. 2014). Finally, a major step in elucidating how genetic programs drive dendritic morphogenesis is the quantification of mutant effects on dendritic arbor morphology. There are numerous morphometric parameters that are used in quantitatively describing dendritic morphology and these parameters can be calculated using open platform as well as licensed software packages (discussed in detail in Sect. 1.5).

1.5 Dendritic Reconstructions: Data Acquisition, File Formats, and Morphological Databases

Neuronal morphology has always been recognized as fundamental in neuroscience. Ramón y Cajal's first series of manual drawings from Golgi stained neurons in the microscope established three basic steps of neuronal reconstruction: tissue labeling, microscopic imaging, and arbor tracing (Ramón y Cajal 1909). Methods of reconstructing morphology have continuously progressed in all these three areas (Parekh and Ascoli 2013, 2015).

1.5.1 History and Progress in Tissue Labeling

Although Golgi stain is still in use, many new methods of preparing neuron specimens for imaging have been developed that are easier to use and are more sensitive. Other bulk-loaded dyes include horseradish peroxidase (HRP; Trojanowski et al. 1982), biotinylated dextran amines (Reiner et al. 2000), and Fluoro-Gold (Lanciego and Wouterlood 2011). Certain dyes are directly injected intracellularly during electrophysiological recording, such as biocytin, biotinamide, and Lucifer yellow (Kita and Armstrong 1991). Immunohistochemical techniques are also used to tag specific proteins within neurons with labeled antibodies. Through repeated immunostaining, array tomography can serially label multiple proteins within a single cell (Micheva and Smith 2007). The most rapidly developing methods of labeling neurons utilize genetic engineering. Neurons are labeled intrinsically with fluorescent proteins e.g. green fluorescent protein (GFP) or red fluorescent protein

(RFP; Lavis 2011; Hadjieconomou et al. 2011). With consistent progress in fluorophore technology, the signal-to-noise ratio of images is increasing.

1.5.2 Advancements in Microscopy

Progress in microscopy has been driven by continuous attempts of overcoming two primary limitations: resolution and field of view. A large quantity of dendritic reconstructions have been generated from transmitted light microscopic images (Halavi et al. 2012), where the background is bright, and the stained neuron is dark due to light absorption. The contrast of dark neuron against a bright background can be easily inverted by image processing for reconstruction purposes. Bright field microcopy is mostly used for neurons stained with bulk loading dye (e.g. Golgi stain) or with intracellular dye (e.g. Biocytin).

Point illumination is used in both confocal and two-photon microscopy. In confocal microscopy, emanated light from the tissue is filtered spatially with a pinhole aperture. Light coming from a specific z-plane creates a single image, and a sequence of images is produced across the depth of the tissue (Wilson 1989). Moreover, an ever-expanding arsenal of genetically encoded fluorescent proteins and dyes have enabled simultaneous visualization of multi-fluor labeled molecules or subcellular organelles/structures. One limitation of standard confocal microscopy is the spectral properties exhibited by available fluorescent proteins and dyes where significant overlaps in excitation and emission spectra complicate multi-fluorescence imaging which thereby limits the number of molecules that can be simultaneously imaged without spectral cross talk. Recent advancements in confocal microscopy directly address this challenge by implementing spectral imaging techniques with mathematical linear unmixing enabling the discrimination of distinct fluorophores with overlapping spectra. Spectral confocal microscopy thereby facilitates fast, multi-fluorescent time-lapse imaging in living samples with multiplexing up to 34 channels (Zimmermann et al. 2003). Two-photon microscopy generates relatively higher resolution than confocal, with the concurrent emission of two photons, followed by convergence and absorption by the fluorophores at the point of focus (Denk et al. 1990). Reduced photobleaching is another advantage of two-photon microscopy as fluorophores exterior to the focal point are not excited (Denk and Svoboda 1997).

Electron microscopy (EM) has increased the resolution of biological images manyfold by overcoming the limitations enforced by the properties of natural light. However, conventional EM techniques require tissue fixing and dehydration, which affects the cellular composition of the specimen. Advanced cryo-EM technique can sustain the natural hydrated state of the tissue, but in vivo imaging is not possible with electron microscopy (Castón 2013).

The invention of super-resolution microcopy has allowed researchers to achieve high-resolution images of live and fixed tissues that surpass the diffraction limit of light. Techniques like stochastic optical reconstruction microscopy or STORM

(Rust et al. 2006), and fluorescence photo-activated localization microscopy or PALM (Betzig et al. 2006) use successive and random excitation and inhibition of fluorophores to activate only a small number of fluophores at a given time point. The process is repeated multiple times to capture all fluorophores. Increased planar resolution can also be achieved by either preventing emission from excited fluorophores by negative patterning via stimulation emission depletion (STED) microscopy (Klar and Hell 1999) or by creating a positive sinusoidal pattern with the combination of two light beams via structured illumination microscopy (SIM) (Gustafsson 2005). Reconstructions of axons generated using 3D STORM images have been shown to be relatively more accurate than confocal images (Lakadamyali et al. 2012). For example, super-resolution microscopy analyses have recently identified previously unknown subcellular organizations of the actin cytoskeleton into cortical rings and localized patches on both axons and dendrites; these new insights into the periodicity of cytoskeletal organization on neurites have important implications for proper subcellular localization of ion channels and pre-synaptic markers (Xu et al. 2013; D'Este et al. 2015).

1.5.3 Advancements in Reconstruction Systems

Following visualization, faithful reconstructions from stained images are needed for morphological analysis. Although hand tracings of neurons are still used for simple characterizations, digital reconstructions are necessary for highly detailed morphometric quantification. The first steps towards digital reconstruction were taken by controlling and registering the microscope's planar movement and fine focus through an electric stepper connected to a computer (Glaser and Vanderloos 1965). Further advancements in computer controlled microscopes were made to register the locations where the neurites originate, bifurcate and terminate (Wann et al. 1973), as well as to measure the thickness of the neurites and order the traced nodes (Capowski 1977). Film strips (Levinthal and Ware 1972) and micrographs (Macagno et al. 1979) were used to generate similar neuronal reconstruction from tissue serial sections at the EM level. Most of the developments in the last 40 years have been an attempt to automate the process of reconstruction, as the manual hours required to trace single neurons is the major bottleneck in large-scale morphological analysis.

Currently, several manual, semi-manual and automated reconstruction tools are used to trace images and produce digital reconstructions of neurons (Parekh and Ascoli 2013). Neurolucida is a commercial reconstructions system that is extensively used in the neuroscience community. However, many alternative free reconstruction tools are available, including NeuronStudio (Wearne et al. 2005), Trees Toolbox (Cuntz et al. 2010), FIJI neurite tracer (Longair et al. 2011), Neuromantic (Myatt et al. 2012), Neutube (Feng et al. 2014), and more (detailed list of tracing tools at http://neuromorpho.org/neuroMorpho/toolsTable.jsp). Most

reconstruction tools have been developed for light microscopy, but systems also exist for tracing from EM images (Helmstaedter et al. 2013).

Major headways in computational neuroscience and machine vision have facilitated multiple generations of automated reconstruction algorithms especially for confocal image stacks (Jungblut et al. 2012). Fully automated reconstructions tools include Vaa3d (Peng et al. 2010) with all path pruning algorithm (Peng et al. 2011) and Farsight (Wang et al. 2011), but manual reconstructions are still considered the gold standard. Transition to full automation is necessary for large-scale data acquisition (Svoboda 2011). The 2010 DIgital reconstructions of Axonal and DEndritic Morphology (DIADEM) challenge kick started a joint effort to reach this goal by testing several automated reconstructions tools developed (Liu 2011) with a unique metric developed for automated comparison against manual reconstructions (Gillette et al. 2011). A new global scale community effort called Big Neuron (Peng et al. 2015) is currently ongoing to bench-test several automated tracing tools on the Vaa3d platform and to identify an optimal consensus reconstruction among all variants generated by the available algorithms.

1.5.4 Large-Scale Databases

Relative to electron microscopy, light microscopy provides the right balance between resolution and field of view, allowing to image whole neuronal arbors at the detailed level of individual spines. Improvements in light microscopy have increased both the acquisition speed and the resolution of neuronal images, with more detailed morphological attributes being revealed. The combination of sparse and stochastic genetic expression techniques, confocal microscopy, and image registration has enabled automated embedding of neuronal images in anatomical templates to produce digital 3D atlases, which include detailed brain regions or even whole brains (Jefferis et al. 2007; Lin et al. 2007; El Jundi et al. 2009). Continuous growth in the number of digital reconstructions from various species, brain regions, and experimental conditions have created a need to store and curate this huge volume of morphological data, and NeuroMorpho.Org has emerged as the central database to serve this functions (Halavi et al. 2008). Informatics resources like Flybase.org (St. Pierre et al. 2014), providing extensive searchable genetic information on various fly strains, and VirtualFlybrain.Org (Milyaev et al. 2012), containing neuroanatomy and connectivity based query tools, are guiding the process of combining genomics and connectomics. The parallel progress of experimental science and informatics has enabled the reconstruction of a brain-wide neuronal network of more than 16,000 neurons within a 3-dimensional framework of male and female fly brain templates (Chiang et al. 2011). NeuroMorpho.org has mirrored this large dataset and computed additional metadata including brain region and cell-type (Nanda et al. 2015).

1.5.5 File Formats and SWC

Various mathematical representations can be used to describe neuronal morphology. The dendritic (or axonal) arbor can be represented volumetrically by listing all the voxels it occupies or as a contour outlining the surface boundaries. Neuron morphology can also be described by a series of vertices connected to polygons. This highly detailed mesh representation is used to describe EM-level reconstructions and in simulations requiring high levels of volume accuracy, like diffusion of molecules across the membrane (Hepburn et al. 2012). For most applications in quantitative morphometry or computational modeling, however, these representations are too computationally intensive. A more effective way to capture the morphology is to represent the arbor as a series of interconnected cylinders (or truncated cones) with a varying radius, approximating the branching structure at the resolution level of light microscopy.

The de facto file standard used to describe neuronal morphologies reconstructed from light microscopy is the SWC format (Cannon et al. 1998). In SWC, neurites are represented as a set of connected nodes, each with a radius value, generating a tree of connected frustums. Every node has a parent node, except the root node (typically the soma) where the tree originates. The ending radius of the parent frustum is the starting radius of the child frustum. SWC files are simple text files with seven values describing each node: (1) Node ID; (2) Node type (Soma, dendrite, axon or apical dendrite); (3–5) 3D coordinates of the node in X, Y and Z; (6) Radius at the location of the node; (7) Parent node ID. The representation of neuronal morphology via SWC files enable researchers to accomplish systematic morphometric explorations, effective comparative analysis, and the implementation of anatomically plausible computational models (Pyapali and Turner 1996; Bulinski et al. 1998; Cannon et al. 1999; Ascoli 2002; Migliore et al. 2005). Other representation formats include proprietary Neurolucida .asc and .dat format, proprietary Imaris .ims format, and open-source formats like morphML (Gleeson et al. 2010).

Morphometric features can be conceptually divided into local (measurement at single branch or node point level) vs global (measurements at the whole arbor level), or topological vs geometrical. Topological parameters are size-independent features that describe the branching pattern of dendrites. Geometrical parameters provide information on size and spatial embedding. The morphometric analysis tool L-Measure is widely used to analyze SWC files by extracting hundreds of morphometric parameters from each neuronal reconstruction (Scorcioni et al. 2008). L-Measure is used in the NeuroMorpho.org data processing pipeline to batch process thousands of SWC files from a great variety of species, cell types, brain regions, experimental conditions, and reconstruction method at every data release.

1.6 Computational Modeling of Dendritic Growth

All subfields of neuroscience use formal or informal modeling. Informal modeling is frequently used by experimentalists to describe biological phenomena in natural language. Formal models are needed to describe highly complicated systems and are built by using mathematical equations and algorithmic instructions. They allow researchers to simulate the outcomes of hypothesized interactions amongst the components of a system after integrating existing experimental data (Van Ooyen 2011). Generation of artificial dendritic trees in silico is a powerful formal modeling approach for understanding developmental mechanisms. Synthetic dendritic arbors can be generated using local and global rule-based simulations. Comparison between simulated and real trees reveals the reliability of the underlying rules used in the computational models. These rules can then be modified to generate more accurate artificial trees, and the knowledge can be transferred to build new experimental designs.

Artificial neurons can be generated in silico by randomly sampling from distributions of morphometric parameters measured from real neurons. This type of phenomenological models can generate groups of neurons that are statistically equivalent to real neurons in terms of morphometry (Ascoli 1999). The local rule-based models are completely constrained by the set of "basic parameters" that define the amount of elongation and the probability of bifurcation (and of termination) at each iterative step. These measurements are obtained directly from the reconstruction of real neurons and then stochastically resampled to simulate the generation of artificial dendrites. One example of such a model is L-Neuron (Ascoli and Krichmar 2000), which followed earlier theoretical and experimental breakthroughs (Hillman 1979). Another simulator that uses a similar approach is NeuGen (Eberhard et al. 2006).

Later versions of L-Neuron further controlled simulations by binning each measured basic parameters by "fundamental determinants" (Donohue and Ascoli 2005b). For example, if branch radius is used as a fundamental determinant, all basic parameters (elongation rate, bifurcation probability etc.) of a virtual branch with a given radius will be randomly sampled from real branches that have similar radius values. Other fundamental determinants like Path distance from the soma and branch order can also be used as fundamental determinants (Donohue and Ascoli 2008). Generated groups of artificial dendrites are then statistically compared with real dendrites using emergent parameters, such as the total size and asymmetry of the arbor. Certain emergent parameters (e.g. total surface area) may be better reproduced by a given fundamental determinant (e.g. path distance from soma), or a specific cell class may be better predicted than another. These comparative results give insights about the underlying growth rules (Fig. 1.3).

An effective alternative is based on "hidden Markov" models (Samsonovich and Ascoli 2005a, b). This approach is based on the assumed existence of a hidden biophysical constraint, such as the number of terminals in a tree, which is only observable in the emergent arbor and is able to predict the growth mechanism. In

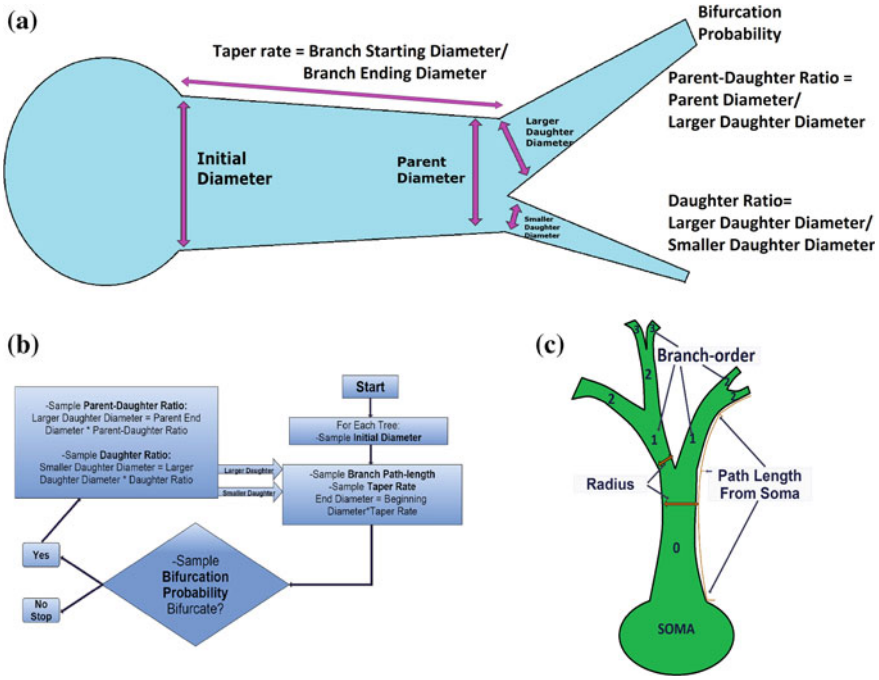

Fig. 1.3 Local rule-based simulation of dendritic growth (Donohue and Ascoli 2008). **a** Description of the basic parameters used for the simulation, **b** A flow chart describing how the basic parameters are stochastically sampled to generate the artificial arbors, **c** Description of the three statistical determinants that fundamentally define the sampling of the basic parameters

both models based on fundamental determinants and hidden Markov models the parameters are biologically relevant. Radius corresponds to microtubule density, path distance from soma relates to time required to transfer resources, and branch order determines the distribution of resources. In the hidden Markov model, the number of terminals reflects a predetermined amount of metabolic resources (e.g. microtubule and F-actin monomers) that acts as a limit of final growth.

A more recent global rule-based model (Fig. 1.4) constrained dendritic structure by the global density matrix of the (desired) dendritic field and a balancing factor, which weighs the costs of wiring length and conduction time (Cuntz et al. 2010). Different balancing factors are optimal for different classes of neurons, providing insight about the connectivity rules of each neuronal class. Another phenomenological simulation of dendritic growth uses three factors to determine the branching probability of each growth cone in a growing tree. Probability decreases with developmental time and with the number of growth cone at a given time-point, and also changes based on Euclidian distance from root or centrifugal order (Van Pelt and Uylings 2002). Inspired by this work, a simulation system called NetMorph was developed to generate large collection of interconnected artificial neurons

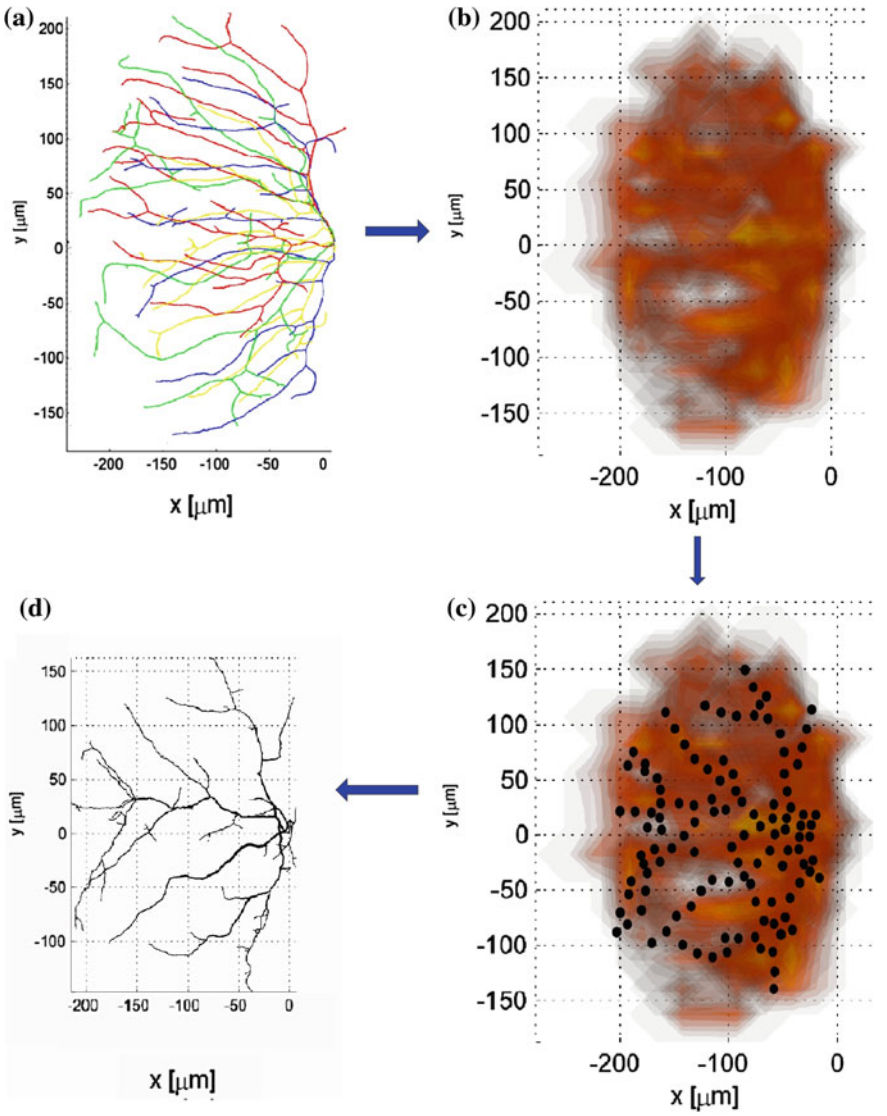

Fig. 1.4 Example of global rule-based simulation of dendritic growth. **a** A group of real Class I da neurons, **b** An average density matrix generated from the group of real cells, **c** Distribution of random points based on the density matrix, **d** An artificial dendritic arbor generated by connecting the points with BF of 0.55 using the minimum spanning tree algorithm (Cuntz et al. 2010)

(Koene et al. 2009). Another algorithm named KDE-Neuron can generate artificial arbors with real neurons as input, using nonparametric statistical distributions (Torben-Nielsen et al. 2008). Arbor morphology can also be effectively constrained by the desired (or hypothesized) computational property of the neuron using evolutionary algorithm to optimize the distribution of the sampling parameters (Torben-Nielsen and Stiefel 2010). Yet a different simulator called CX3D combines stochastic and mechanistic growth rules at the single neuron level, and simulates the development of cortex in a realistic space, with actions like cell division and cell migration also included within the framework (Zubler and Douglas 2009).

Mechanistic models attempt to capture biological phenomenon like dendrite outgrowth, elongation, and bifurcation (Kiddie et al. 2005). In a mechanistic model of dendritic growth, tubulin made in the soma moves towards the growth cones by active transport and diffusion; there it is assembled to form microtubules that lengthen the dendritic branches. The growth and branching of dendrites is also controlled by the phosphorylation state of microtubule-associated proteins (MAPs), as they affect microtubule crosslinking. Dephosphorylated MAP2 boosts branch elongation by increasing crosslinking, while phosphorylated MAP2 increases branching probability by decreasing crosslinking. Because many kinases and phosphatases are calcium-dependent, MAP2 phosphorylation and dephosphorylation are further modulated by intracellular calcium concentration (Fig. 1.5). Several cell types with characteristic dendritic morphology can be generated in this model by altering intracellular calcium dynamics (Hely et al. 2001). Another mechanistic

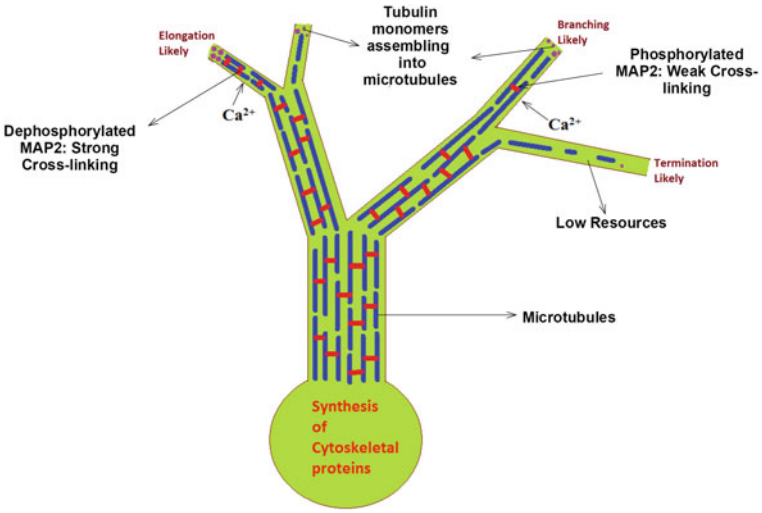

Fig. 1.5 Schematic description of microtubule movement and assembly in a developing dendritic arbor

model can reproduce experimental growth dynamics where the outgrowth of few dendritic growth cones is coupled with the retraction of the other growth cones. This multicompartmental model is based on competition among growth cones for tubulin. Competition increases with the increase in distance between growth cones, and decreases with faster active transport of tubulin. This model can generate various morphologies, both simple and complex, and exemplifies the need to quantify tubulin concentration across the dendritic arbor in order to build data-driven models that can directly test the resource-dependent growth hypothesis (Hjorth et al. 2014).

1.7 Future Directions

The current toolsets of neurogenetics, semiautomated digital reconstructions, and computational modeling support the design of a closed-loop experimental and computational approach. Simulation of neuronal morphology is first constrained by the basic parameters measured from real tracings of fly neurons already available in NeuroMorpho.Org. The simulated neurons are then validated against the real counterparts using a complementary set of emergent parameters. This preliminary iteration of modeling results will guide the design of the next set of experiments, aimed at testing the growth rules suggested by the simulations. Moreover, the initial set of simulations will also reveal the limitations of the existing experimental data and computational tools, thus suggesting the needed advances in the following iterations.

Advancements in and integration of imaging, tracing, and the digital representation of neuronal morphology may catalyze considerable progress in our understanding of dendritic development. Current reconstructions only represent the overall morphology of dendrites at one point in time (Fig. 1.6). A new form of digital reconstruction is required to represent the internal cytoskeletal structures together with the overall morphology as they both change dynamically in time. This will allow us to directly test various theoretical models of dendritic growth by building data-driven mechanistic simulations. The fly larva constitutes an ideal experimental model because it enables time-lapse live imaging in the developing animal.

Nevertheless, manual reconstruction of complex arbors is considerably labor-intensive and time-consuming, which limits the sample size thus reducing the statistical power of the models. Recent advances in genetic engineering and confocal microscopy now allows researchers to acquire low-noise, high-resolution images of dendritic arbors while simultaneously tagging the putative molecular effector of growth, F-actin and microtubules (Fig. 1.7). Expected and ongoing

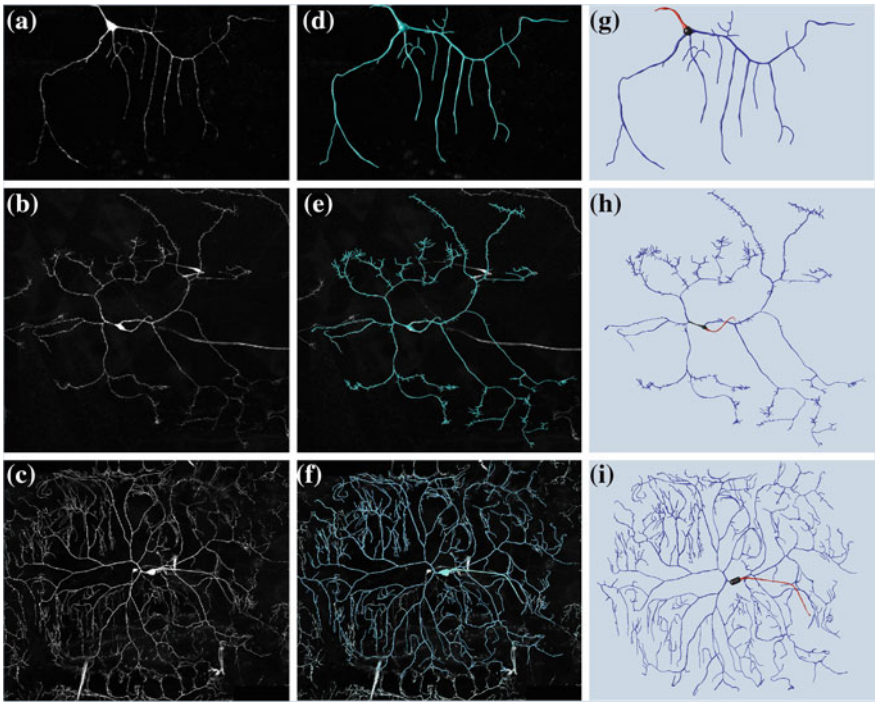

Fig. 1.6 Reconstructions of da neurons. **a–c** Confocal image stacks of Class I, Class III, and Class IV da neurons. **d–f** Edited, intermediate reconstruction of Class I, Class III and Class IV da neurons. **g–i** Final reconstructions of Class I, Class III and Class IV da neurons with assigned dendrite, soma and axon

progress in automated tracing will enable the acquisition of large number of neuronal reconstructions from these multichannel, time-lapse image stacks, adding much needed statistical strength to the models. The local concentration of microtubules and actin filaments (in both monomer and polymer forms) can be used directly in the simulations as statistical determinants of growth.

Successful completion of this modeling strategy will enable the design of even more sophisticated interaction between experiments and simulations to bear down on the causative forces controlling cytoskeletal dynamics. Dynamic time-lapse reconstructions will allow one to computationally simulate structural and molecular changes in time, not only in wild types, but also in advanced genetic constructs. Normal arbor growth can then be perturbed by turning off a specific transcription factor. The effects of these alterations on cytoskeletal dynamics and arbor morphology can be investigated both experimentally by imaging and reconstruction, and computationally by simulations and modeling.

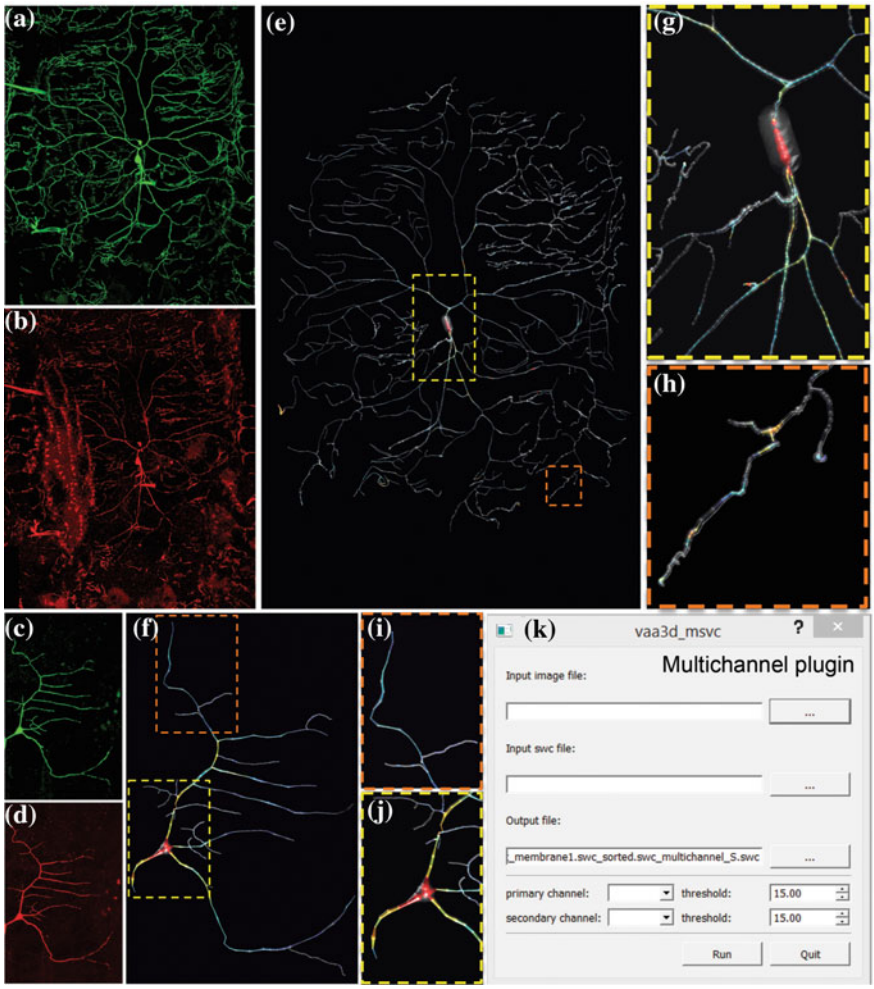

Fig. 1.7 Next generation multichannel reconstruction of da neurons. **a** GFP-tagged membrane of Class IV da neuron. **b** RFP-tagged F-actin of Class IV da neuron. **c** GFP-tagged membrane of Class I da neuron. **d** RFP-tagged microtubule of Class I da neuron. **e**, **f** Two-channel next generation reconstruction of Class IV and Class I da neurons. The overall membrane structure is represented in transparent black, allowing the visualization of the internal cytoskeletal component (F-actin in Class IV, microtubule in Class I). The radius of the internal arbor represents the ratio of the area occupied by the cytoskeletal protein relative to the external structure. Color of the arbor represents quantity of the protein (red is high quantity, blue is low quantity). **g**, **h** Zoomed-in view of soma region and a terminal of the Class IV reconstruction, **i**, **j** Zoomed-in view of soma region and a terminal of the Class I reconstruction, **k** Multichannel plugin toolbox built in the Vaa3D system

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Chapter 2
Autophagy Mechanisms for Brain Recovery. Keep It Clean, Keep It Alive

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Abstract Most neurological pathologies that afflict humans are associated with the abnormal accumulation and aggregation of specific proteins into the cytoplasm and with mitochondrial dysfunction. Neuronal health is sustained by the fine regulation of protein synthesis and organelle biogenesis and their degradation to ensure efficient turnover. Autophagy is a powerful process for removing such proteins and for maintaining mitochondrial homeostasis. Thus, the autophagic activation may play important roles in neuronal cell survival and neuronal function under both physiological and pathological conditions. It is well accepted that the loss of basal autophagy or imbalance of autophagic flux leads to neuronal death. Autophagosomes accumulate abnormally in affected neurons of several neurodegenerative diseases such as AD, HD, PD, as well as in brain and spinal cord trauma. Thus, knowledge of cross-talk between autophagy impairment and pathophysiological mechanisms is a prerequisite for successful therapeutic interventions in neurological disorders. This chapter summarizes current understanding of how autophagy perturbations may affect neuronal function contributing to neurodegeneration in chronic and acute brain pathologies.

Keywords Neurodegeneration · Apoptosis · Neuroprotection · Brain damage · Functional recovery

Abbreviations List

AD	Alzheimer's disease
AVs	Autophagic vacuoles
Atg	Autophagy-related proteins

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CNS	Central nervous system
ER	Endoplasmic reticulum
HCb	Hemicerebellectomy
HD	Huntington's disease
Ko	Knockout
mTOR	Mammalian target of rapamycin
mTORC1	MTOR complex 1
3-MA	3-methyladenine
PD	Parkinson's disease
SCI	Spinal cord injury
SVZ	Subventricular zone
TBI	Traumatic brain injury

2.1 Introduction

Although autophagy is a cellular process described more than 50 years ago, most of the research on its involvement in health and disease has occurred within the past decade.

Autophagy is a catabolic process that involves degradation of dysfunctional cellular components and recycling of cellular constituents, delivering portion of cytoplasm to the lysosomes. Autophagy is considered to be important in the maintenance of cellular metabolism and homeostasis, especially in conditions such as nutrient deprivation or stress, and to guarantee proteins' quality control and organelles' turnover. Moreover, autophagy has been implicated in various cellular processes, including development, differentiation, aging, and immunity (Levine and Klionsky 2004; Mizushima 2005; Mizushima and Klionsky 2007). In order to maintain cellular homeostasis, autophagy is constitutively activated at a basal level, but it can also be induced by several input signals, such as nutrient deprivation, change of intracellular levels of Ca^{2+}, ATP and cAMP, hormones, and accumulation of damaged proteins and organelles (Sarkar 2013). The mTORC1 complex, which contains mTOR, Raptor, mLST8/GßL, Deptor, and PRAS40 (Efeyan and Sabatini 2010), is the main regulator of autophagy. However, autophagy can be also regulated by mTOR-independent pathways, even though the effectors involved in the autophagosome biogenesis are not clear (Sarkar 2013). Several findings have demonstrated that autophagy is involved in several neurodegenerative disorders, such as Alzheimer disease (AD), Parkinson disease (PD), and Huntington disease (HD), as well as in brain and spinal cord trauma. We review the recent progress in our understanding of the molecular mechanisms of autophagy in mammalian brain and discuss the implications of autophagy in neurological recovery in several neurological pathologies.

2.2 The Autophagy Machinery

At present, a number of autophagy-related (Atg) proteins have been identified and characterized in yeast (Klionsky et al. 2003; Klionsky 2005a, b) and evolutionarily conserved in mammals, where additional Atg proteins have been recognized. However, only a part of Atg proteins, defined as the "core Atg" (Xie and Klionsky 2007; Nakatogawa et al. 2009), are involved in autophagosome formation. These proteins can be subdivided into three functional groups: (1) two kinase complexes, ULK complex (consisting of ULK1, Atg13, FIP200, and Atg101) and the class III phosphatidylinositol 3-kinase complex (or Beclin1 complex, comprising PI3 K or hVps34, Beclin1, and p150); (2) two ubiquitin-like protein conjugation systems, ATG16L1 complex (Atg12–Atg5–Atg16L) and LC3; and (3) two transmembrane proteins, Atg9 (and associated proteins involved in its movement such as WIPI-1) and VMP1.

ULK complex mediates the induction step of autophagy and is negatively regulated by mTORC1, which phosphorylates ULK1 and Atg13. After autophagy induction, mTORC1 is inactivated and ULK1 and Atg13 are dephosphorylated, leading to their activation and to the consequent phosphorylation of FIP200 by ULK1. Atg101 is an ULK complex interactor important for both the stability of Atg13 and basal phosphorylation of Atg13 and ULK1 (Mercer et al. 2009; Hosokawa et al. 2009) (Fig. 2.1).

The second complex involved in autophagy is Beclin1–CIII PI3 K that is required for the nucleation of isolation membrane and generation of a pool of phosphatidylinositol 3-phosphate, which acts as platform for other Atg proteins' recruitment. Many interactors of Beclin1 modulate the complex activity: Atg14L, UVRAG, Ambra1, and Bif-1 enhance Beclin1 complex activity; the transmembrane protein VMP1 has a pivotal role in the nucleation step, recruiting Beclin1 and other components of the Beclin1 complex to the phagophore; on the contrary, Rubicon, the anti-apoptotic proteins Bcl-2 and Bcl-XL and the pro-apoptotic protein Bim negatively regulate autophagy (Sarkar 2013) (Fig. 2.1).

The activation of ULK1 is responsible for the phosphorylation of Ambra1, which in turn leads to the activation of Beclin1 and the translocation of the Beclin1–CIII PI3 K complex from the microtubule network to the endoplasmic reticulum (ER), which is the major membrane source for the biogenesis of phagophore (Axe et al. 2008; Hayashi-Nishino et al. 2009). Also Atg9 has a central role in the biogenesis and elongation of the phagophore (Yamamoto et al. 2012).

After the autophagy induction, the isolation membrane is extended by two ubiquitin-like protein conjugation systems. First, the ubiquitin-activating E1-like enzyme Atg7 conjugates Atg5 and Atg12. In particular, Atg7 activates Atg12, which is then transferred to Atg10 and linked covalently with Atg5 (Mizushima et al. 1998). The conjugated Atg12–Atg5 bind Atg16L forming a multimeric complex required for phagophore elongation (Mizushima et al. 2003) and for the efficient function of LC3 (Fig. 2.1). The second system mediates the conjugation of LC3 to phosphatidylethanolamine (PE) (Hanada et al. 2007; Mizushima et al. 2003). Atg4

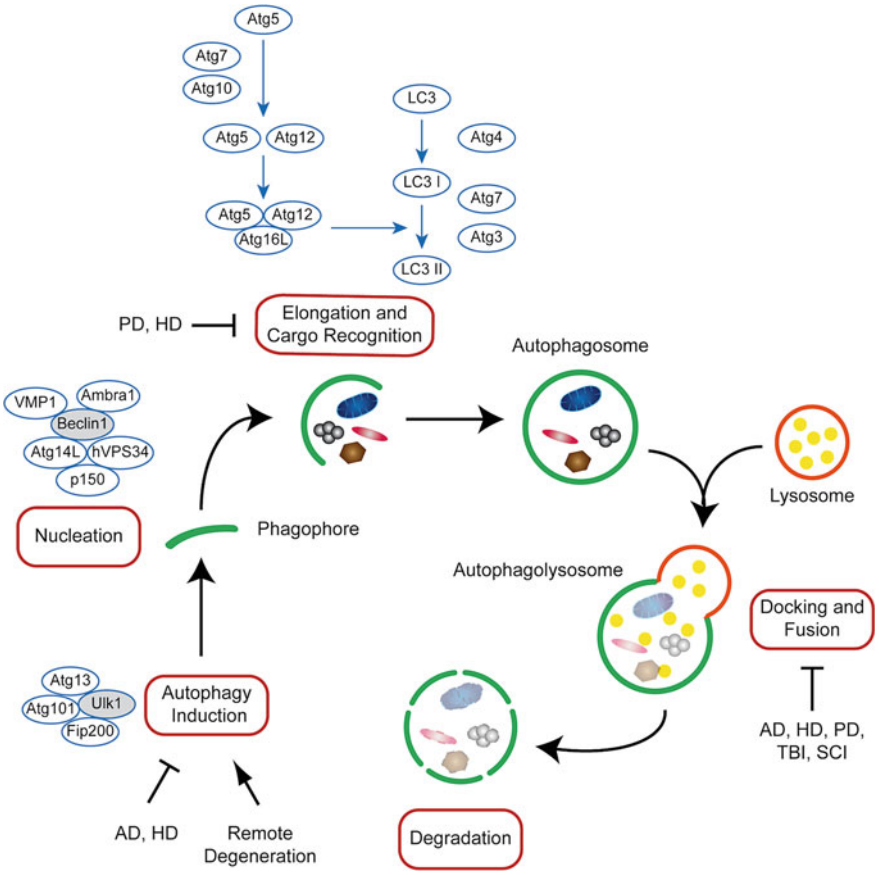

Fig. 2.1 Schematic representation of mammalian autophagy pathway. Following autophagy induction, ULK complex, composed of ULK1, Atg13, FIP200, and Atg101, is activated and starts the autophagosome nucleation. ULK1 also phosphorylates Ambra1, leading to the activation of Beclin1, a component of CIII PI3 K complex (or Beclin1 complex), which consists of PI3 K or hVPS34, Beclin1, and p150. In this step, VMP1 recruits Beclin1 to the phagophore where the complex is required for generating a pool of phosphatidylinositol 3-phosphate (PI3P). Beclin1 activity is positively regulated by several interactors, such as Atg14L. To expand the autophagosome membrane, Atg12–Atg5–Atg16L complex and LC3 ubiquitin-like conjugation systems are required. The Atg12–Atg5–Atg16L multimeric complex is formed by subsequent steps involving Atg7 and Atg10 and is also required for the efficient function of LC3. The second system mediates the conjugation of LC3 to phosphatidylethanolamine (PE). LC3 is processed by Atg4, forming the cytosolic LC3 I. Atg7 binds LC3 I and transfers it to Atg3, which catalyses the conjunction to the lipid PE and the conversion of LC3 I in LC3 II. The complete autophagosome fuses with the lysosome, forming autophagolysosome, and cargo molecules engulfed by autophagosomes are degraded by lysosomal hydrolases and recycled back to the cytoplasm. The specificity of cargo degradation is mediated by selective adaptor proteins, such as p62 that binds ubiquitinated residues of the target proteins or organelles. The steps affected in neurodegenerative diseases and in CNS trauma are indicated. *AD* Alzheimer disease; *HD* Huntington disease; *PD* Parkinson Disease; *TBI* traumatic brain injury; *SCI* spinal cord injury

processes LC3 leading to the generation of cytosolic LC3 I. Then, Atg7 binds and transfers LC3 I to the E2-like enzyme Atg3, which catalyses the conjunction to the lipid PE and the conversion of LC3 I in LC3 II. LC3 II is required during the expansion of autophagosome and decorates both the inner and outer membrane of this structure. However, until the fusion with the lysosome LC3 II is removed from the outer membrane, whereas the inner membrane-attached LC3 II is degraded with the autophagosome cargo (Kabeya et al. 2000; Kirisako et al. 2000) (Fig. 2.1).

Although autophagy was initially considered as a nonselective mechanism, recent evidences underline its implication in selective processes, especially in the quality control of proteins and organelles. Several post-translational modifications have been implicated in the regulation of autophagy, one of which is the ubiquitination. The residues of ubiquitin, in fact, facilitate the recruitment of autophagic receptors and selective adaptor proteins, such as p62 (also called SQSTM1), NBR1, HDAC6, Nix, and Ndp52, which tether the targeted substrate to the core of Atg proteins, such LC3 (Shaid et al. 2013).

2.3 Basal Autophagy in Neurons

The neuron is the basic working unit of the brain, a highly specialized cell designed to transmit information to other nerve cells, muscle, or gland cells and is composed by specific compartments including axons, dendrites synapses, and soma, in which the synthesis, transport, and degradation processes are finely regulated. Autophagy is of particular importance in the synaptic compartments, characterized by high-energy demand and where a fine control of proteins' and organelles' turnover is necessary to ensure the activity. Moreover, autophagy has a key role for the survival and homeostasis of postmitotic cells like neurons, because these cells are not able to dilute misfolded or aggregated proteins and damaged organelles, such as mitochondria, through cell division.

A number of studies in different organisms have demonstrated that autophagy impairment results in intraneuronal protein aggregates and neuronal degeneration (Simonsen et al. 2008; Juhasz et al. 2007).

These studies provide strong evidence that autophagy plays a crucial role in the brain, in which it is normally responsible for clearing abnormal intracytoplasmic contents, which otherwise form protein aggregates and disrupt neuronal function, leading severe functional impairment.

2.4 The Role of Autophagy in Neurodevelopment and Neurogenesis

The importance of autophagy in development has long been suggested by several studies in which autophagic structures were analyzed during embryogenesis (Clarke 1990; Lockshin and Zakeri 2004) and by analyzing mutant mice for several Atg

genes, which have different roles in the regulation of development. The role of Atg genes was investigated using knock out (KO) mice for Atg3, Atg5, Atg7, Atg9, and Atg16L1, which complete the embryonic development, but die shortly after birth, indicating that the proteins encoded by these genes are not indispensable for embryogenesis but have a critical role in the regulation of perinatal starvation (Kuma et al. 2004; Sou et al. 2008; Komatsu et al. 2005; 2008, Saitoh et al. 2009). Instead, Beclin1, Ambra1, or FIP200 deficient mice are died during embrional development at the stage E7.5, E10-E14, and E13.5-E16, respectively (Yue et al. 2003; Fimia et al. 2007). The differences observed among Atg genes are not well understood. It seems possible that the role of these proteins may be related to other function; alternatively, the different lethalities may depend on the step in which each factor is involved (Mizushima and Levine 2010). In the latter case, Atg9 constitutes an exception because it acts in early phase of autophagy process but its loss causes a less severe phenotype (Suzuki and Ohsumi 2007).

The generation of conditional KO mice allowed understanding the function of Atg proteins in specific tissues. Brain-specific deletion of Atg5 and Atg7 results in the development of progressive motor and behavioral deficits, suggesting that these proteins are involved in motor function. The histological analysis of Atg5 conditional KO mice revealed a partial loss of Purkinje cells and the deposition of intraneuronal aggregates of ubiquitinated proteins, which accumulate in a time-dependent manner starting at embryonic day E15.5. These evidences suggest that basal autophagy in Purkinje neurons is necessary to ensure the correct proteins' turnover, avoiding aggregates' formation (Hara and Mizushima 2006). Atg5 KO embryos also display defects in apoptotic corpse engulfment in photoreceptor and ganglion cell layers of the retina at E18.5 (Qu et al. 2007). Moreover, recently it has been proposed that Atg5 plays a crucial role in developing embryonic cortex to ensure the formation of correct multiple-layer architecture. In fact, conditional KO of Atg5 in cortical neural progenitor cells (NPCs) leads to unbalanced cortical NPCs' differentiation and proliferation causing an abnormal morphology of cortical neurons. It has also been shown that Atg5 exerts its function in cooperation with β-Catenin and both are required to regulate cortical NPCs' proliferation and differentiation (Lv et al. 2014).

Also conditional KO of Atg7 affects Purkinje cells causing axonal swellings, with accumulation of aberrant membrane structures and progressive dystrophy and degeneration of the axon terminals. To note, these events take place long before neuronal death, suggesting that basal autophagy is not only involved in cellular quality control but it is also required to regulate membrane homeostasis in the axonal terminals (Komatsu et al. 2007).

ULK1 protein is expressed in different neuronal populations during development and is particularly abundant in developing cerebellar granular cells, which regulates axon outgrowth. The critical role of ULK1 in neurite extension/parallel fiber formation has been demonstrated inhibiting its activity by means the expression of its dominant negative form (Tomoda et al. 1999). It was also suggested that ULK1 regulates endocytotic trafficking of growth factors that are necessary during polarized axon elongation. Nevertheless, is not clear whether ULK1 acts

influencing autophagy or has a different function through the interaction with other proteins, for example, in NGF–TrkA endocytosis (Tomoda et al. 2004; Zhou et al. 2007).

A central role for autophagy has recently been proposed also in adult neurogenesis. Ambra1 and Beclin1 are highly expressed in adult subventricular zone (SVZ) of the lateral ventricles, a region where new neurons are generated and then migrate through the rostral migratory stream to the olfactory bulb to become interneurons (Ming and Song 2011). Autophagy seems to be involved in two different mechanisms in SVZ: on the one hand it sustains the pool of stem cell, and on the other hand it increases neuronal precursors' survival. In fact, Beclin1 heterozygous mice (Beclin1$^{+/-}$) present an increase of apoptotic cells and a decrease in cell division in SVZ compared to wild-type mice (Yazdankhah et al. 2014).

Recent evidences support the idea that autophagy can also play an essential role in dendritic spine pruning during postnatal life. Indeed, in layer V pyramidal neurons from postmortem temporal lobe of patients with autism spectrum disorders (ASD) have been observed an increased spine density with reduced developmental spine pruning. These spine alterations correlate with mTOR hyperactivation and autophagy impairment. In fact, Tang and colleagues demonstrated that transgenic Tsc2± mice, with a mutated Tsc2 protein that indirectly inhibits mTOR, show a constitutive activation of mTOR that causes autophagy blockage, postnatal spine pruning defects, and ASD-like behaviors. Moreover, rapamycin is able to revert these phenotypes in Tsc2± mice but not in Tsc2±: Atg7 conditional KO double mutants, indicating that autophagy is required for the correct remodeling of spine architecture (Tang et al. 2014).

2.5 Autophagy and Neurological Pathologies

Mounting evidence has firmly established the importance of neuronal autophagy for brain functioning. Although increasing findings implicate autophagic dysfunction in the pathogenesis of several neurological pathologies, the cellular factors underlying homeostatic vs. pathogenic activation of autophagy have not been identified, nor is it understood how dysfunctional autophagy may lead to neuronal death.

Current opinion suggests that the loss of basal autophagy or imbalance of autophagic flux leads to neurodegeneration. Autophagosomes accumulate abnormally in affected neurons of several neurodegenerative diseases such as AD, HD, and PD (Rubinsztein et al. 2005) as well as after brain and spinal cord trauma (Lipinski et al. 2015).

Although the abnormal accumulation of autophagosomes in neurons constitutes the first clue of deficits in autophagy, the precise mechanisms underlying autophagic dysfunction in neurodegenerative diseases are not fully understood (Nixon 2013). Since the buildup of autophagic vacuoles (AVs) may reflect stimulation of the induction of autophagy, impairment of later digestive steps in the autophagic

pathway, or a slow rate of autophagosome formation combined with insufficient lysosomal fusion and digestion, determining the defective step(s) along the autophagic pathway in neurodegenerative diseases is critical for understanding the pathogenic role of autophagy. Either defect of autophagic flux or excessive activity of autophagy can contribute to neurodegeneration (Chu 2006). Therefore, understanding the exact mechanisms by which autophagy may be compromised in neurodegeneration has a crucial role in the development of therapeutic treatments that act on the pathway.

2.6 Autophagy in Neurodegenerative Diseases

2.6.1 Alzheimer's Disease

AD is the most common cause of dementia, accounting for 50–60% of all cases (Ferri et al. 2005), and is characterized by age-related brain degeneration that leads to progressive cognitive and behavioral impairments.

At the histopathological level the pathogenesis of AD is linked to the accumulation of extracellular plaques including aggregated amyloid-β (Aβ) peptide and intracellular tangles, which cause progressive, selective, and massive neuronal loss. Increasing evidence has implicated autophagic dysfunction in the pathogenesis of AD.

The mechanisms underlying autophagic failure in AD involve several steps, from autophagosome formation to degradation (Liang and Jia 2014; Nixon and Yang 2011). Evidence suggests that abnormalities of autophagy induction or autophagosome formation contribute to the pathogenesis of AD (Nixon and Yang, 2011). In addition to the defects in earlier stages of autophagy, accumulating evidence has suggested a critical role of lysosomal proteolytic failure in the development of AD-related neurodegeneration (Wolfe et al. 2013).

Although autophagic dysfunction at different levels may contribute to the accumulation of proteins in the AD brain, there has been a growing interest in manipulating autophagy as a potential therapeutic target for AD (Zhu et al. 2013; Friedman et al. 2015).

Pharmacological induction of autophagy through the mTOR has proved effective in reducing neuronal aggregates and slowing the progression of neurological symptoms in several mouse models of AD (Maiese et al. 2013; Cai et al. 2015). These findings have led to the reasonable proposition that targeting the induction of autophagy can have potential therapeutic benefits in AD.

However, conflicting data from recent studies in AD models raise caution about the applicability of the induction of autophagy as a generalized treatment strategy for AD (Cai et al. 2012).

For example, inhibition rather than stimulation of autophagy has been suggested to alleviate Aβ42-induced cell death (Ling and Salvaterra 2009; Wang et al. 2010).

These findings demonstrate that enhancement of new autophagosome formation without a parallel increase in autophagic flux results in the harmful accumulation of intermediate AVs (Nixon 2007).

Furthermore, several studies showed that the timing of intervention is crucial in reducing neurodegeneration in AD. At this regard induction of autophagy before the development of AD-like pathology is able to reduce the levels of soluble Aβ and tau and amyloid plaques, whereas induction after the formation of mature plaques and tangles has no effect on AD-like pathology or cognitive deficits (Majumder et al. 2011).

Taken together all these findings indicate that in AD therapeutic interventions modulating autophagy have to take into account nature of the autophagic defect, timing of intervention, and the optimal level and duration of modulation.

2.6.2 Parkinson's Disease

PD is a late-onset neurodegenerative disease that is characterized by progressive degeneration of dopaminergic neurons of substantia nigra and the symptoms are tremor, rigidity, and impaired balance and coordination (Thomas 2009). Accumulation of α- synuclein-containing Lewy bodies in substantia nigra neurons is the hallmark of PD (Lesage and Brice 2009). In recent years, growing evidence obtained from PD patients and animal models of PD has demonstrated that autophagy plays a pivotal role in PD pathogenesis (de Vries and Przedborski 2013).

Mutations that induce the overexpression of α-synuclein, such as gene duplications, are sufficient to cause PD (Singleton et al. 2003; Cavallarin et al. 2010). Overexpression of α-synuclein impairs autophagy by inhibiting the small GTPase Rab-1A (Winslow et al. 2010), which has an important role in autophagosome biogenesis, and an abundance of α- synuclein induces a mislocalization of an early acting part of the autophagy machinery blocking the formation of putative autophagosome precursors known as omegasomes (Winslow et al. 2010). Neurons expressing mutated α-synuclein also show accumulation of autophagosomes, defective dopamine release, and higher susceptibility to autophagic cell death (Spencer et al. 2009). The co-overexpression of Beclin1 and α-synuclein reduced accumulation of α-synuclein in cells and rescued them from lysosomal accumulation and autophagy alterations (Spencer et al. 2009). Introduction of Beclin1 gene into the brain of α-synuclein transgenic mice ameliorated the synaptic and dendritic pathology, enhanced lysosomal activation, and reduced alterations in the autophagy pathway. These results provide evidence that autophagic modulation can be a novel therapeutic target for the treatment of PD (Spencer et al. 2009).

The enhancement of autophagy activation for the efficient turnover of dysfunctional mitochondria has been considered also a possible therapeutic target in PD (de Vries and Przedborski 2013). Recent studies implicate that the defects in mitophagy may be an important pathogenic mechanism of PD (Vives-Bauza et al. 2010; de Vries and Przedborski 2013). Parkin and PINK1—whose mutations cause

autosomal recessive form of PD—are components of a signaling pathway that controls mitophagy, through which the neurons can degrade damaged mitochondria (Youle and Narendra 2011; Narendra and Youle 2011). The selective targeting of parkin to damaged mitochondria during mitophagy is dependent on wild-type PINK1 but not mutant PINK1 suggesting the regulatory role of parkin and PINK1 in mitophagy (Dagda et al. 2009).

2.6.3 Huntington's Disease

HD is one of the most common polyglutamine diseases, which are a group of inherited neurodegenerative diseases caused by CAG trinucleotide repeat expansion (Ross and Tabrizi 2011). This disorder shows neuronal loss in striatum and cortex leading to progressive impairment of voluntary movement coordination (Tellez-Nagel et al. 1974). Protein aggregates and inclusion caused by mutant huntingtin protein have been shown to induce autophagy (Ravikumar et al. 2002) and that mutant huntingtin is *di* per se an autophagy substrate (Ravikumar et al. 2002). A growing body of evidence suggests that further stimulation and activation of autophagy are beneficial for HD (Martin et al. 2015). Inhibition of autophagosome formation by 3-methyladenine (3-MA) or inhibition of autophagosome–lysosome fusion prevents the clearance of mutant huntingtin and raises the levels of soluble and aggregate mutant huntingtin in experimental models of HD (Williams et al. 2008). Conversely, rapamycin treatment, which stimulates autophagy, increases mutant huntingtin clearance and decreases the levels of soluble proteins, aggregates and decreases neurodegeneration in cell models of polyglutamine disease, and reduces neurological deficits in a mouse model of HD (Williams et al. 2008). Notably, autophagy clears only mutant huntingtin; by contrast, clearance of wild-type huntingtin is unaltered in cells treated with autophagy modulators (Sarkar et al. 2007). Collectively, these data suggest that autophagy is specifically involved in the clearance of only aggregate-prone mutant forms of huntingtin.

2.7 Autophagy in CNS Trauma

CNS trauma, including TBI and SCI, is one of the primary causes of death and long-term disability among people worldwide (Hyder et al. 2007). CNS trauma can lead to long-term cognitive, sensorimotor, and psychiatric changes, and in case of SCI, to autonomic changes and chronic pain.

Brain and spinal cord trauma cause both direct mechanical tissue damage (primary injury) and biochemical changes that cause more delayed and progressive cell loss (secondary injury) (McAllister 2011). The primary mechanical damage initiates complex delayed changes that collectively spread the injury to the intact neighboring cells contributing to secondary cell damage and loss. Secondary neuronal

degeneration, in turn, entails destructive downstream events that can affect cells that were unaffected or only marginally affected by the initial damage. Furthermore, additional damage can occur at a distance over days and months after injury spreading along anatomical and functional connections reflecting CNS connectivity. This latest phenomenon has been termed "remote damage" (Block et al. 2005) and can last for days, weeks, or months.

Since primary injury is almost instantaneous and cell damage in the directly injured area is often irreversible, it cannot be treated. Conversely, the secondary injury that occurs in hours, days, and months after the initial impact involves changes in specific biochemical, cellular, and molecular pathways, providing a therapeutic opportunity (Viscomi and Molinari 2014).

Among post-traumatic secondary biochemical responses, signs of autophagy have also been observed (Lai et al. 2008; Liu et al. 2008; Clark et al. 2008). The function of autophagy after CNS damage has long been a source of controversy, with both beneficial and detrimental roles proposed (Erlich et al. 2007). More detailed delineation of changes in autophagy flux over time after CNS damage is needed. In this chapter, we detail recent advances in the study of autophagy after CNS trauma, which have begun to clarify how autophagy levels and flux are affected by injury and how their manipulation may represent a potential novel neuroprotective target.

2.8 Traumatic Brain Injury

Autophagic activity is significantly altered after TBI, but its mechanisms and functions remain controversial (Smith et al. 2011). Accumulation of autophagosomes begins to rise several hours after the injury (Lai et al. 2008). This has been observed in both rat and mouse models of TBI and SCI, as well as in human TBI autopsy samples (Liu et al. 2008) suggesting that TBI is a powerful inducer of autophagy. Although autophagosomes appearance after CNS injury is well established—mainly through electron microscope studies and/or accumulation of the autophagosome marker protein LC3-II—less certain is whether accumulation of autophagosomes is due to increased autophagosome biosynthesis and elevation of autophagy flux or to impaired autophagosome degradation and inhibition of flux.

More recently, autophagy flux has been assessed in several models of TBI by monitoring the levels of the autophagic substrate p62 (Sarkar et al. 2014). After TBI it has been demonstrated that accumulation of autophagosomes was not due to increased initiation of autophagy but rather to a decrease in clearance of autophagosomes, as reflected by accumulation of the autophagic substrate p62. Furthermore, autophagy impairment after TBI—caused at least in part by lysosomal dysfunction—may contribute to cell death in neuronal cells proximal to the injury site (Sarkar et al. 2014).

Although much evidence has implicated the autophagy in the responses to TBI, the function of autophagy in TBI remains controversial. Several studies suggest that pharmacological modification of the mTOR-dependent pathway by rapamycin increases neuronal survival in the injured region and improves functional recovery after injury (Erlich et al. 2007). Conversely, recent evidence has demonstrated that autophagy is part of the complex mechanism of the cellular response to TBI and can mediate neuronal death (Luo et al. 2011). Pre-treatment with 3-MA, a nonselective inhibitor of autophagy, attenuates TBI-induced cell death, lesion volume, and neurological deficits, implying that inhibition of autophagy is an efficacious therapeutic goal for the treatment of TBI.

These findings suggest that autophagy mediates neuronal response to TBI and that its modulation may represent an attractive strategy with regard to drug design in mitigating the neuronal damage that is associated with TBI.

2.9 Spinal Cord Injury

Increased markers of autophagy have been observed after SCI (Kanno et al. 2009a, b) but its function remained controversial, with both beneficial and detrimental roles proposed (Lipinski et al. 2015).

Accumulation of autophagosomes begins to rise within 24 h after SCI (Liu et al. 2015). However, recent findings demonstrate that the accumulation of autophagosomes after SCI is not due to increased initiation of autophagy, but rather to inhibition of autophagy flux, which has been correlated to impairment of lysosomal function contributing to defects in autophagic clearance (Liu et al. 2015). Furthermore, authors demonstrated that motor neurons with blocked autophagy displayed markers of ER stress and ER stress-induced apoptosis (Liu et al. 2015). All together these data identify for the first time the cellular mechanism leading to accumulation of autophagosomes after SCI and suggest that restoration of autophagy flux may be a potential neuroprotective strategy after SCI.

Interestingly, after SCI the inhibition of the autophagy flux is transient (Liu et al. 2015) and at later time points after damage autophagic flux is restored. However, although it is not clear how autophagy flux may be restored after damage, it has been hypothesized that the increase in lysosomal biogenesis could compensate for the initial damage increasing the autophagy flux.

Despite the interest on the autophagy activation after SCI has been growing, still evidences are scant on the function of autophagy in SCI pathophysiology. Few data exist at regard. Recently, pharmacological modulation of the mTOR-dependent pathway by rapamycin was shown to reduce neuronal tissue damage and cell death and improve neurological recovery after SCI (Sekiguchi et al. 2012). Although this study supported rapamycin-enhanced autophagy-mediated neurological recovery in the acute phase after SCI, the molecular and biochemical mechanisms by which autophagy is protective after spinal cord injury remain unknown.

2.10 Remote Degeneration After Focal CNS Damage

In the chapter on the CNS trauma, a separate section deserves the topic of remote degeneration after focal brain trauma. If until several decades ago, the mechanism of remote degeneration was considered irrelevant; today there is mounting evidence that remote damage may have a crucial role in accounting for clinical findings that cannot be explained by local changes occurring in many acute CNS pathologies, such as stroke, and spinal and brain trauma (Carrera and Tononi 2014; Viscomi and Molinari 2014). Yet, the network vision of brain malfunctioning after trauma highlights the potential of remote damage to act as a decisional node in functional outcomes after brain damage. Remote degeneration after focal brain damage is a complex phenomenon, many aspects of which are unknown. Secondary damage can occur next to an area that has experienced irreversible primary damage and in distal areas that are functionally related to the primary site of injury (Block et al. 2005). Among post-injury biochemical responses, signs of autophagy have also been observed in a paradigm of "remote cell death" induced by focal cerebellar lesion (Viscomi et al. 2012). In this experimental model, neuronal cell death of precerebellar neurons is caused by target deprivation and axonal damage (Fig. 2.2). Moreover, the accumulation of autophagosomes and autophagolysosomes in damaged neurons appears early after injury (Viscomi et al. 2012) due to increased autophagosome biosynthesis and elevation of autophagy flux and not to decreased autophagosome degradation and inhibition of flux (Viscomi et al. 2012).

The function of autophagy in the secondary damage after brain trauma has long been a source of controversy, with both beneficial and detrimental roles proposed (Viscomi and D'Amelio 2012). This may reflect the fact that the function of autophagy can change drastically depending on flux, with unobstructed flux usually contributing to neuroprotection and flux inhibition promoting cell death. This hypothesis was confirmed by findings of enhanced autophagy by rapamycin, which was associated with a significant increase in survival of axotomized neurons and greater functional recovery, consistent with the neuroprotective role of enhancement of autophagy flux (Fig. 2.2) (Viscomi et al. 2012; Viscomi and D'Amelio 2012). The mechanisms by which increased autophagy flux contributes to neuroprotection after injury have yet to be investigated. Brain and spinal cord damage can lead to generation of damaged cellular components such as mitochondria, lysosomes, and peroxisomes, which are both vulnerable to and a source of oxidative stress. Increased autophagy flux could help eliminate these injured organelles to protect the cells from further damage, as suggested by Viscomi et al. (2012).

All together these findings may have therapeutic significance for several acute brain pathologies, such as stroke and spinal trauma, which would benefit tremendously if early autophagy events can be targeted. In fact, because remote cell death mechanisms are long-lasting, they are a suitable target for pharmacological intervention to halt neuronal death and improve functional recovery and autophagy may be a good candidate for promoting neuroprotection.

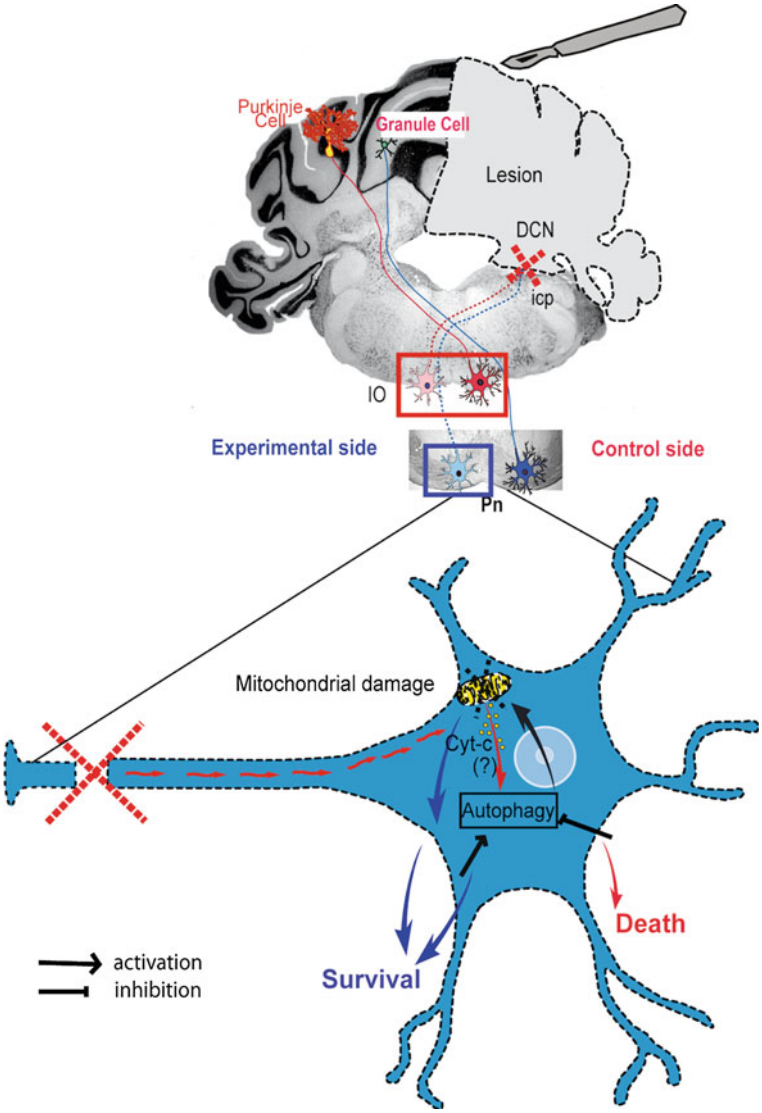

Fig. 2.2 Schematic diagram of the function of autophagy in remote cell death mechanism. Due to the crossover of the cerebellar input–output organization, HCb induces axonal lesions and subsequent degeneration of the contralateral inferior olive (IO) and pontine nuclei (Pn), with sparing of the IO and Pn on the ipsilateral side. After damage, retrograde signaling reaches the cell body, provoking the activation of different events. Among these lesion activates autophagy in precerebellar axotomized neurons. It has been hypothesized that the autophagy machinery is activated in response to mitochondria sufferance. When damaged mitochondria release cytochrome-c (Cyt-c) into the cytosol (1), autophagy is activated possibly to engulf the suffering mitochondria (2), neutralizing pro-apoptotic factors release. By enhancing autophagy, it is possible to support neuronal survival while a reduction in autophagic activation is associated with increased cell death. *DCN* deep cerebellar nuclei, *icp* inferior cerebellar peduncle

2.11 Conclusions

In the last years there has been considerable progress in demonstrating a pathogenic role for autophagy impairment in several neurological pathologies. Although this evidence provides a strong rationale for developing therapeutics to modulate autophagy in these disorders, much work remains to be done. Since that emerging data suggest that autophagy flux may be either increased or decreased after CNS trauma, and this event depends on the brain area and severity of the injury, more detailed monitoring of changes in autophagy flux over time is needed. Furthermore, evaluating the in vivo efficacy of autophagy drugs in the brain overcoming all the obstacles created by the blood–brain barrier, it is a primary challenge. Yet, how neurons and glia contribute differentially to the overall autophagy activity in brain and the possibility that different, or even reciprocal, responses to a drug may occur in different neural cell types are a few of the issues that will need to be considered in these in vivo evaluations. Last but not least, functional studies, which are rather weak in brain studies, should be implemented in transgenic animals with defects in autophagy machinery. Greater investigation of these aspects might provide insight into the complex mechanism of autophagy in the brain that will ultimately aid the future development of therapeutic interventions in chronic and acute neuronal disorders.

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Chapter 3
Environmental Enrichment Repairs Structural and Functional Plasticity in the Hippocampus

Veronica Ghiglieri and Paolo Calabresi

Abstract In the developing brain, gene-environment interactions shape structure and function in response to experience. In mammals, brain development has been programmed to reach complete maturation after birth to take maximum advantage of appropriate stimulations. In this context, an enriched environment is the best incentive for activity-dependent synaptic plasticity and neurogenesis. The present chapter provides an appraisal of seminal and most recent evidences that environmental enrichment (EE) stimulates the endogenous potential of hippocampus for plasticity and repair. After discussing structural and functional changes induced by EE, we examined the evidence in support to the role of EE as a trigger for intrinsic resilience mechanisms that preserve synaptic integrity in distinct hippocampal neuronal population against aging and neurodegeneration. Finally, according to the potential of EE to boost proliferation and survival of neuronal and glial cells, we explored the hypothesis that the strict temporal organization of critical periods can be challenged by appropriate EE protocols, providing support for sustainable therapeutic interventions on neurological diseases characterized by permanent loss of function.

Keywords Synaptic plasticity · Resilience · Hippocampus · Memory · Neurogenesis

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3.1 Effects of Experience in the Developing Brain

In the evolution of the vertebrate central nervous system, gene expression and environmental inputs act synergistically to determine developmental trajectories. In mammals, brain development has been programmed to reach complete maturation after birth. The strategy of being born immature has been conserved by natural selection to allow newborns to take maximum advantage of appropriate stimuli. Thus, multisensory, nutritional and social stimulations typical of an animal's community are the first incentives that shape the correct behavioral patterns to adapt to its respective environment. In such context, external and internal stimuli act as fuel for the plethora of processes that take place in the development of neuronal connections to guide their growing and rearrangement.

In the developing brain, genes are important intrinsic factors that interact with experience to guide brain organization. During development, cell communication plays an important role in determining the fate of a neuron. Once cell proliferation processes lead to production of new cells, these migrate and differentiate into neurons or glial cells, guided by chemical signals that promote axons and dendrites extensive growing to form synaptic connections. Here, an active synapse rearrangement is based on activity-dependent processes, in order to maintain and refine active synapses and discard inefficient connections. Synapse rearrangement is critically influenced by external stimuli and therefore by experience.

Seminal studies performed in the early 1960s by Hubel and Wiesel, demonstrated that the pattern of visual stimulation affects the development of visual perception and that animals, deprived of vision in early developmental stage, are not able to see later when exposed to light. In these animals the retinal cells and the geniculate nucleus responded well to visual stimuli but the visual cortex was not able to respond to the input, suggesting that, in a specific time window, proper visual stimulation was necessary for the maturation and strengthening of the connections from the lateral geniculate nucleus to the visual cortex (Hubel and Wiesel 1963, 1964; Wiesel and Hubel 1963).

Like the correct assembly and tuning of sensory system apparatus depends on sensory experience at specific critical stages, also improvement of social skills depends on social experience at specific time point of development. An example is provided by the process of *imprinting*, a form of learning observed and studied by Konrad Lorenz, by which birds become indelibly attached to a prominent moving object in their immediate environment during few hours after birth. This object is generally the mother or the caregiver, and the attachment, acquired rapidly, is persistent although the critical period for building this habit lasts just a few hours (Vicedo 2009).

These results led to the concept of critical periods as time windows in which the potential to develop and tune a brain function is maximal. After the first experiments in which critical periods were described in the maturation of the cortical connections that control visual perception, many studies on other aspects of

behavior followed, leading to the general concept that environment and cognitive challenges may promote specific capabilities by changing functional and structural interactions within existing pathways.

3.2 Environmental Enrichment as Testable Scientific Concept

The modern concept of environmental enrichment (EE) consists in an experimental setting in which the animal housing condition is improved to provide a combination of cognitive, motor and social stimulations relative to standard housing. To date it is generally accepted that EE improves hippocampal-dependent functions (Laviola et al. 2008; Nithianantharajah and Hannan 2006) and has a therapeutic potential in reducing symptoms of a variety of neurological diseases with reduced side effects.

The importance of environmental stimuli in shaping cerebral functions dates back to the 1800s when Johann Spurzheim perceived that the brain, as other organs, could be increased in size by exercise (Fischer 1984). In 1874 Charles Darwin was the first to propose that the brains of domestic rabbits were reduced in comparison with those from the wild, because captivity did not allow breeding animals to improve their instincts and senses as much as did wild animals (Diamond 2001). Following these first observations the impact of enriched environments on the brain functions started to become a basic concept in ethology. However, only in the late 1940s Donald Hebb was the first to propose EE as a research topic, following observation that some of the laboratory rats brought at home and allowed to live as pet in more stimulating conditions showed improvements in behavioural skills compared to laboratory littermates (Hebb 1947).

In the early 1960s, Hubel and Wiesel studies on sensory deprived animals brought the first experimental evidence that during development adequate stimuli are necessary for building an appropriate anatomy and physiology of cortical areas (Hubel and Wiesel 1970; van Praag et al. 2000; Wiesel and Hubel 1965). At the same time Rosenzweig and colleagues introduced EE as a testable behavioral paradigm to study the impact of experience on the brain (Rosenzweig 1966; Rosenzweig and Bennett 1996; Rosenzweig et al. 1962).

In these first studies the structural correlates of behavioral improvement were mostly restricted to increases of total brain weight and total brain proteins in cortical areas. However, beneficial effects do not only bring to more content of brain material but also to improved functional connectivity and intrinsic capability to repair brain circuits and respond to excitotoxic insults.

Indeed, these observations gave tremendous inputs to studies on synaptic plasticity that begun to be extensively analyzed in terms of morphological, molecular and electrophysiological aspects of a behaviorally relevant response to a given stimulus. Many studies have then shown that environmental stimulation elicits various plastic responses in the adult brain, ranging from biochemical changes to

increased complexity of dendritic arborization, gliogenesis, neurogenesis as well as improved learning (Altman and Das 1964; Cummins et al. 1973; Diamond et al. 1966, 1976; Greenough et al. 1973, 1978; Holloway 1966; Kempermann et al. 1997; Walsh et al. 1969; Walsh and Cummins 1979).

By the time the existence of effects of environment on the brain reached a general consensus among scientists, animal models and measurement techniques were rapidly developing into precise and sophisticated approaches. As a result, environmental influences became even more critical and subtle effects that may have previously been part of the experimental noise turned out to be an issue (Burrows and Hannan 2013; Olsson and Sherwin 2006; Toth 2015; Wurbel 2001). A first concern that concurred to limit the translational significance of most of these studies regarded the acknowledged evidence that an environment for laboratory animals was considered enriched relative to a standard housing condition. Standard cages, in fact, provide food, shelter and some degree of social stimulation but surely not sufficient to properly mimic a natural environment in which animals or individuals are familiar with dynamic and active situations. Thus, the first criticism that had a tremendous impact in the building of EE protocols was that laboratory animals lived, in fact, in a deprived environment that prevented them from performing instinctive behaviors for which they are motivated and that is poor of adequate sensory, motor and social stimulations. This becomes a critical issue when animal models of disease are used to exploit the therapeutic potential of enrichment protocols, limiting the clinical impact of a basic research study.

A possible way to overcome this primary artifact was to replicate quantifiable functional or structural markers of human disease in animal models in which symptoms could be prevented, reduced or even reversed by enriching the context with adequate stimulations and for a sufficient time during a given critical period.

3.3 Structural Changes

3.3.1 Neurogenesis

In the early sixties of the twentieth century, at the beginning of the research on EE, it was still unclear whether the brain could regenerate damaged or injured tissues. The brain was considered by scientists to be immutable, subject only to control of genes and it was known that in most brain regions, the generation of neurons was generally confined to a discrete developmental period (Eriksson et al. 1998). Therefore, the increase in brain volume was a provocative discovery, soliciting more insights into possible mechanisms of such response. However, the same discoveries that helped to define the existence of critical periods were also bringing valuable information on the capability of experience to change the brain structure and chemistry and, therefore, to change its developmental patterns.

The initial report of an increase in brain weight was soon followed by the demonstration that this effect was mostly restricted to posterior regions of the cortex (Bennett et al. 1964) that was later associated to increases in cell volume, dendritic branching, spine density, and synapses per neuron rather than to an increase in the number of neurons (Globus et al. 1973; Turner and Greenough 1985; Volkmar and Greenough 1972).

In the first studies EE-induced anatomical changes in the hippocampus were less obvious than those observed in the neocortex. At the same time Altman's seminal studies were providing the first anatomical evidence for the presence of dentate granule cells newly generated by multipotent neural stem cells in the postnatal hippocampus (Altman and Das 1964), able to functionally integrate into the adult central nervous system (Paton and Nottebohm 1984). However, it was only 30 years later that adult neurogenesis was demonstrated in the hippocampus with the advent of bromodeoxyuridine (BrdU) (Kuhn et al. 1996), a synthetic analogue of thymidine used to mark replicating cells in living tissues with immunoistochemical techniques.

Soon after, the existence of another niche of adult neurogenesis was revealed in the subventricular zone of the lateral ventricles where newly generated neurons migrate to the olfactory bulb (Gage 2000). As the discovery of adult neurogenesis generated a tremendous interest in neuroscientists from any specific field, remarkable advances has been made over the past decade in the study of almost every aspects of neuron proliferation in the mammalian central nervous system. Several innovative approaches, such as BrdU labeled samples from patients (Eriksson et al. 1998) and ^{14}C labeling from nuclear weapon testing (Spalding et al. 2005), have provided new insights into adult neurogenesis in humans. Two recognized foci of continuous neuronal proliferations were found and a recent work proposed the existence of continuous neurogenesis in human striatum (Ernst et al. 2014).

Given the variety of effects that environmental stimulation exerts on behavior, different components of enrichment protocols have been analyzed for distinct effects they may generate in healthy and pathological brains (van Praag et al. 2000). Although a conclusive opinion cannot be easily reached due to the variability in the protocols employed to test its efficacy, enrichments that include voluntary exercise and motor activity seem to have a critical role in determining the most remarkable effects on cellular functions. This conclusion has been corroborated by the observation that voluntary exercise was repeatedly associated to both increases in neurogenesis and cell survival in exposed animals, while enriching protocols without a specific motor stimulation were mostly able to promote survival pathways in adult cells (Olson et al. 2006). These contributions produce additive effects, with enhanced neurogenesis compared to either treatment alone (Fabel et al. 2009).

3.3.2 Postsynaptic Changes

Among the postsynaptic changes observed following EE, dendritic spine density increases have been the most frequently observed modifications in the cortex and hippocampus (Moser et al. 1994; Turner and Greenough 1985). Although enhanced dendritic proliferation and spine number is found across species, including primates, variability exists due to subtle differences in housing conditions and the effects may depend on the branch type (i.e. apical vs. basal dendrites), age and gender (Juraska et al. 1985; Kolb et al. 2003). In fact, first reports indicated an EE-induced increase in CA1 spine density, which was limited to basal dendrites (Moser et al. 1994, 1997), but more recent evidence point to effects also on apical dendrites (Malik and Chattarji 2012; Rampon et al. 2000b). Relevant to the age of exposure to enriched housing conditions, enhanced dendritic tree complexity of dentate granule cells were found only when EE was started at weaning, and not if it was started in adulthood (Fiala et al. 1978). However, this result may vary depending on the gender.

In a chronic imaging study, Yang et al. (2009) have shown that, in addition to spine formation, spine elimination is enhanced in the somatosensory cortex in a sensory-enriched standard-sized housing condition, suggesting that enriched experience promotes a general increase in spine turnover (Yang et al. 2009). In rodent hippocampus, while studies reported spine density increases after EE (Kondo et al. 2012; Malik and Chattarji 2012; Moser et al. 1994), another elegant study has shown only volume increases (Li et al. 2013), supporting the view that hippocampal principal neurons have more intricate dendritic arborizations after EE (Faherty et al. 2003). This apparent discrepancy might depend on the fact that in specific layers of CA1, profound modifications of spine density rely on the hemispheric laterality (Shinohara et al. 2013). Thus, the measure of pulled data from left and right hippocampal tissue preparations would underestimate the effects of EE. Another aspect that may be a confounding factor is that spines of CA1 pyramidal cells in animals exposed to EE, displayed more frequently non-perforated synapses (Rampon et al. 2000a), which suggests that the new spines may form smaller and possibly weaker synapses. These synapses are very active but might not be detected accurately with a commonly used method like Golgi-staining. If spine size is increased one may consider this parameter as a realistic index of morphological plasticity in response to EE. However, the distribution of postsynaptic density size, was similar to the one observed in control mice (Shinohara et al. 2013), suggesting that compensatory mechanisms are in act to renormalize the synaptic strength in order to keep the excitability of neurons under control. Accordingly, in CA1 neurons, firing rates are renormalized after a certain time from exposure to novel environments (Hirase et al. 2001).

Beside its actions on pyramidal neurons and granule cells, EE also increases inhibitory synapses in innervated spines, arising from various subclasses of interneurons (Kubota et al. 2007). Caroni and coworkers have shown that crosstalk between parvalbumin-positive and vasoactive intestinal peptide (VIP)-positive

interneurons in CA3 is critically changed after 3 weeks of EE, even though it is not clear whether specific subclasses of interneurons exhibit distinct innervation patterns after EE (Donato et al. 2013).

3.3.3 Presynaptic Changes

Presynaptic structural alterations were also reported after EE, although less consistently than postsynaptic changes. Nithianantharajah et al. (2004) found increases in synaptophysin, a glycoprotein involved in turnover of synaptic vesicles, as a marker of presynaptic plastic changes, after 30 days of EE exposure of young rats in multiple brain areas including cortex, hippocampus, thalamus and hypothalamus (Nithianantharajah et al. 2004). These data were a clear demonstration that an increased number of functional synapses are built after EE in these areas.

The cortex of mature rats living in enriched conditions displays a higher amount of synaptophysin than the age-matched control (Saito et al. 1994), accompanied by a concomitant increase of the packing density of synaptic vesicles (Nakamura et al. 1999). In frontoparietal cortex and hippocampus, increases in synaptophysin have been observed also in aged EE mice (Frick and Fernandez 2003). Recently, more detailed morphological analyses of the mossy fiber projection by dentate gyrus (DG) granule cells onto hippocampal CA3 were conducted at different stages of EE exposure and can be found discussed in a recent comprehensive review (Caroni et al. 2012). The authors first demonstrated that age-dependent volume increase of mossy terminals is observed in animals kept in EE (Galimberti et al. 2006). In a subsequent elegant chacterization, it was shown that giant boutons formed by the mossy fibers of dentate granule cells onto CA3 pyramidal cells appeared larger in volume and more intricate in morphology after as early as one month of EE. Such morphological changes of mossy terminals are found to be dependent on beta adducin binding protein and include rearrangement of the cytomatrix at the active zone and postsynaptic structural changes, also observed at CA1 synapses (Bednarek and Caroni 2011). A determinant role in the formation of stable synapses (Salinas and Zou 2008) is played by a finely regulated dynamic interaction between pre and post synaptic elements provided, among other factors, by beta adducin and wingless-related integration site (Wnt) proteins. These lipid-modified secreted peptides can be postsynaptically released from CA3 neurons and manage presynaptic activity during maturation of hippocampal synapses where they facilitate LTP (Ahmad-Annuar et al. 2006; Ataman et al. 2008; Cerpa et al. 2008; Chen et al. 2006; Hall et al. 2000; Packard et al. 2002). In particular, their action is necessary to promote the increase of mossy fiber-CA3 synapse number (Gogolla et al. 2009), making Wnt signaling pathways critically sensitive to experience, an ideal molecular support of changes in connectivity in the plastic brain.

Among presynaptic changes, axonal transport is also an aspect that can be affected by EE, which may upregulate KIF1A, a kinesin superfamily motor protein expressed in axons (Kondo et al. 2012), which is necessary for EE-induced learning

and spine density increases. Moreover, brain-derived neurotrophic factor (BDNF), a neurotrophin, whose increase is precociously observed in a variety of brain areas after EE, was shown to upregulate KIF1A expression and its activity in axonal transport (Kondo et al. 2012). In turn, KIF1A is directly implicated in transporting BDNF-containing dense-core vesicles to presynaptic terminals (Lo et al. 2011), bringing to the concept of a BDNF–KIF1-positive feedback loop.

3.3.4 Gliogenesis

Aside from neurons, increases in gliogenesis and glial nucleus volume have been also reported in pioneering and recent studies in cortical (Diamond et al. 1966; Ehninger and Kempermann 2003; Jones and Greenough 1996) and hippocampal areas (Steiner et al. 2004; Ziv et al. 2006) as a possible effect of EE. As for neurogenesis, voluntary exercise seems to have an enhanced effect on gliogenesis compared to other enriching components (Ehninger and Kempermann 2003; Steiner et al. 2004). Astrocyte-neuron contact activity is key to synaptogenesis (Hama et al. 2004) and maturation of dendritic spines (Haber et al. 2006; Nishida and Okabe 2007). Furthermore, calcium-dependent gliotransmission is able to enhance experience-dependent synaptic plasticity both in vitro (Henneberger et al. 2010) and in vivo (Takata et al. 2011). Interestingly, the astrocytic gap junction proteins connexin 30 that modulate perisynaptic astrocytic microprocess morphology (Pannasch et al. 2014) depends on astrocyte calcium signaling. This protein has been shown to be elevated after 2 weeks of EE (Rampon et al. 2000b), to be positively regulated by neural activity (Roux et al. 2011).

Hippocampal astrocytes in animals exposed to EE have higher levels of glial acidic fibrillary protein (GFAP), the main intermediate filament protein expressed by these cells (Sampedro-Piquero et al. 2014; Viola et al. 2009). GFAP modifications were associated to structural changes in the dorsal dentate gyrus after 2 h of a spatial memory task in rats, as detected using diffusion tensor magnetic resonance imaging. These changes were also accompanied by enhanced immunolabeling of synapsin and BDNF (Sagi et al. 2012). EE-induced changes include more complex ramifications in astrocytes and can be considered as an index of trafficking of molecules for neuron-glia interactions (Hirase and Shinohara 2014).

3.4 Functional Changes

Most of the remarkable functional outcomes of EE in laboratory animals falls in the field of learning and memory. For this reason, following initial findings of experience-dependent morphological changes in the neocortex, most of the research devoted to understanding the mechanisms underlying EE effects shifted the focus to the hippocampus, because of the easy assessment of hippocampal-dependent

behavioral functions in rodents and for its well conserved trisynaptic circuitry in the vertebrate nervous systems.

Despite these promising characteristics, studies investigating the effect of EE on hippocampal function have produced mixed results, mostly due to the variability in the samples analyzed (genetic background, age and sex of animals) as well as in duration and distinct features of behavioral protocols employed to test its efficacy. However, a general consensus has been reached in validating the evidence that animals exposed to EE show increased synaptic density (Faherty et al. 2003; Nithianantharajah and Hannan 2006) and augmented synaptic strength in the CA1 hippocampal region (Foster and Dumas 2001; Foster et al. 1996; Green and Greenough 1986).

This enhancement on synaptic function was expected from the enhanced morphological organization of the neuropil and the increased expression of nerve growth factor (NGF) (Falkenberg et al. 1992; Mohammed et al. 1993; Pham et al. 1999) as well as of glial-cell-derived neurotrophic factor (*GDNF*) (Yang et al. 2009).

The hippocampus plays a pivotal role in higher cognitive processes as it functionally interacts with cortical processing, receiving inputs from multiple association areas of the neocortex, and sending efferent projections back to cortical areas (Swanson and Kohler 1986; Van Hoesen 1982).

After the demonstration of hippocampal long-term potentiation (Bliss and Lomo 1973), electrophysiological studies in this area gained significant popularity because synaptic plasticity soon appeared to represent a good functional index against which behavioral and morphological studies could be compared. Since plasticity is increased in newborn cells, the discovery of adult neurogenesis encouraged the first studies hypothesizing that synaptic plasticity could be changed in response to EE during adulthood (Saxe et al. 2006; Snyder et al. 2001). However, characterizing plasticity might be difficult in typical EE experiments and changes in basal transmission of CA3-CA1 synapses are still controversial with studies reporting enhancement (Artola et al. 2006; Duffy et al. 2001; Foster and Dumas 2001; Li et al. 2006) or mixed results (Irvine and Abraham 2005). The field of synaptic plasticity, however, offers more clear indications of the effect that EE may exert in hippocampus and other brain areas in which activity-dependent plasticity is high. It is an established fact that EE enhances LTP at the Schaffer collaterals (Artola et al. 2006; Buschler and Manahan-Vaughan 2012; Duffy et al. 2001; Huang et al. 2006; Li et al. 2006, 2013, Malik and Chattarji 2012). Initial studies using intracellular sharp electrode recordings showed that single cell excitatory postsynaptic potentials in CA1 are not significantly changed in EE rats (Foster and Dumas 2001). More recent whole-cell patch clamp studies show that the frequency but not the amplitude of miniature EPSCs is elevated in CA1 pyramidal cells recorded from animals exposed to EE (Li et al. 2013; Malik and Chattarji 2012). Relevant to LTD, one study reported that amplitude of this form of plasticity in CA1 subfield is also enhanced after EE exposure (Artola et al. 2006). However, in the perforant path, which consists of the main afferent signal into the dentate gyrus, the basal synaptic transmission is increased in control conditions in

enriched animals (Foster et al. 1996; Green and Greenough 1986), although LTP induction is unaltered (Feng et al. 2001; Irvine and Abraham 2005), or occluded (Foster et al. 1996). Interestingly, prolonged long-term exposure to either EE or impoverished condition has less influence on basal synaptic transmission or LTP (Eckert et al. 2010), suggesting that compensative mechanisms take place after long lasting environmental simulations. Also the excitability of neurons increases with EE probably due to changes in potassium conductances. An interesting study has shown that response to EE is compartmentalized in the dendritic arbor of CA1 pyramidal cells and that even a short exposure to an enriched environment induces an increased propagation of dendritic sodium spikes in a subset of CA1 pyramidal individual branches (Makara et al. 2009). CA1 pyramidal cells of EE-exposed rats also show a lower spike threshold that increases their responsivity to current injections (Malik and Chattarji 2012). Action potential properties may also change with EE, with CA1 pyramidal cells exhibiting a reduced after-hyperpolarization potential (Kumar and Foster 2007; Malik and Chattarji 2012). In a recent review Hirase and Shinohara (2014) addressed the question whether anatomical and behavioral changes are associate to changes in neuronal population activity (Hirase and Shinohara 2014). To date, few recent studies have investigated this aspect with mixed conclusions of the effect of EE on cross correlation coupling between synaptically connected areas, and none of these regards hippocampus. However, the search for an enhanced functional connectivity represents an important avenue of investigation as cortical and hippocampal neuronal discharge activities are modulated with gamma oscillations during cognitive processing (Buzsaki and Wang 2012; Engel et al. 2001) and the gamma oscillation power increases during theta states in animals exposed to EE (Shinohara et al. 2013) as well as the interhemispheric coherence of gamma oscillations. Although the mechanisms underlying these network modifications are not clear, activation of NMDAR seems to have a role since chronic administration of ketamine, a NMDA receptor antagonist, is able to counteract such increase.

3.5 Hippocampus, EE and Disease

Why enrichment has such strong effect in the hippocampus and why it is able, by restoring neurogenesis and increasing dendritic branching, to induce recovery in diseases conditions?

The hippocampus is part of the limbic system and it is connected with the ventral tegmental area, the ventral striatum and the amygdala. Its dopaminergic innervation supports a role for hippocampus as important player for the regulation of motivation. Many neurotransmitters that can be deregulated in disease conditions strongly modulate hippocampal physiology. In a review of Kemp and Manahan-Vaughan a complete description of neurotransmitters involved in hippocampal plasticity and their implications for behavior can be found (Kemp and Manahan-Vaughan 2007). For its greater ability to respond to multiple stimuli,

hippocampus is also connected to structures known to control habit formation and motor control as striatum, in particular dorsomedial and ventral portions (Calabresi et al. 2016), and cerebellum (Yu and Krook-Magnuson 2015), with whom it engages an active interaction to regulate motor behavior (Krook-Magnuson et al. 2014; Onuki et al. 2015; Rochefort et al. 2011). Therefore, it is not surprising that, by acting on hippocampus, EE may increase the intrinsic ability of the brain to compensate for damaged pathways and sustain repair processes.

3.5.1 Ischemia/Stroke

Ischemia is characterized by episodes of oxygen and glucose deprivation that may last seconds to minutes. In vitro and in vivo models have been developed to study the vulnerability of specific subclasses of neurons and hippocampal neurons together with striatal cells have been found particularly sensitive. After ischemia, excitotoxic processes activate cell death pathways that may result in aberrant forms of plasticity to end with neuronal death. Strikingly, one week exposure to EE after ischemia enhances gliogenesis with increased astrocytes and NG2-positive glial cells proliferation (Komitova et al. 2006). Newborn NG2-positive cells also express BDNF suggesting that an increased number of this neuronal subtype might be associated to beneficial effects of EE in rescuing physiological plasticity in post-stroke brain responses. When a focal ischemia or a traumatic brain injury are followed by EE, environmental stimuli are able to improve behavioral outcomes on several sensorimotor tasks (Nudo et al. 1996; Passineau et al. 2001; Xerri and Zennou-Azogui 2003) but also to ameliorate postural reflexes and limb placement deficit elicited by the lesion (Johansson 1996; Nudo et al. 1996; Passineau et al. 2001; Xerri and Zennou-Azogui 2003). EE effects in odor discrimination and object exploration tasks and a slight improvement in performance in the Morris Water Maze can also be observed when animals are exposed to enriched housing conditions before transient global cerebral ischemia (Gobbo and O'Mara 2004). Interestingly, voluntary wheel running has also been shown to provide protection against ischaemia. In gerbils presurgical housing with running wheels significantly reduced mortality induced by global ischemia. In addition, hippocampal cell damage was attenuated (Stummer et al. 1994, 1995). These beneficial effects were associated to recovery of expression of NGF-induced gene A and glucocorticoid receptors (Dahlqvist et al. 1999).

3.5.2 Movement Disorders

In movement disorders the brain structures mostly studied are the basal ganglia and relevant cortices that interact with them, as well as the cerebellum and its related cortical networks. However, in a recent study the role of hippocampus in movement control has been revisited after the demonstration of a bidirectional cerebellum-hippocampal functional connectivity that explains why cerebellum

becomes critical to hippocampal functioning on a hippocampal-dependent task (spatial navigation) and the hippocampus can become a key structure in a cerebellar-dependent task (Yu and Krook-Magnuson 2015). Moreover, the importance of investigating the relationship between basal ganglia and limbic system, in particular the hippocampus, emerged from recent papers that include the hippocampus as a target area for therapeutic interventions in diseases classically characterized by impairment of motor control (Calabresi et al. 2013, 2016). In the last years, non-motor aspects of movement disorders like Parkinson's disease (PD), Huntington's disease (HD) and multiple sclerosis (MS) have gained increasing attention for their impact on the quality of life of the patients and for the emergence of cognitive, emotional and psychiatric complications linked to current therapies. Studies on experimental models provided a general agreement that besides specific cortical areas that may variably be affected in each disorder, cognitive impairments are also repeatedly associated with hippocampal plastic abnormalities (Costa et al. 2012; Di Filippo et al. 2016; Hodgson et al. 1999; Murphy et al. 2000; Pendolino et al. 2014; Usdin et al. 1999). Among neurodegenerative diseases that may gain therapeutic benefit from EE exposure the most studied is HD. In fact, although less attention has been paid to hippocampal changes in this typical basal ganglia disorder, cognitive symptoms and loss of behavioral flexibility are associated with hippocampal dysfunctions in both rodent models and in clinical studies conducted in HD patients (Giralt et al. 2012).

The first observation of a consistent cell loss in the hippocampus in HD was shown in patients, in which these changes primarily occur in the CA1 area (Spargo et al. 1993). In experimental HD, morphological alterations occur as early as 3 weeks of age in CA1 and then gradually progress in DG and CA3 by 10 weeks (Morton et al. 2000). These abnormalities are associated with deficit in hippocampal LTP (Hodgson et al. 1999; Morton et al. 2000; Murphy et al. 2000; Usdin et al. 1999) and with loss of mossy fiber potentiation (Gibson et al. 2005) and depression (Milnerwood et al. 2006).

Interestingly, relevant to the effects of EE, two studies suggest that in HD mice actin polymerization in dendritic spines, which normally stabilizes LTP, is defective and up-regulates endogenous levels of BDNF. This trophic factor, indeed, has been shown to stimulate actin polymerization in neurons, rescue plasticity and reduce learning deficit (Lynch et al. 2007; Simmons et al. 2009).

Although the hippocampus is recognized as a reliable environmental sensor that hosts multiple forms of experience-driven plasticity, EE-induced dendritic spine increase, was also found in the motor cortex (Hirase and Shinohara 2014). Accordingly, voluntary exercise is a common component of EE paradigms associated to increase in neurogenesis and cell survival. This feature is not surprising if one considers that increases in the expression of BDNF, a neurotrophic factor strongly associated to cell proliferation, are observed early in cortex and hippocampus of animals exposed to EE with motor components, and that physical activity itself is able to elevate the expression of this neurotrophin (Neeper et al. 1995; Widenfalk et al. 1999), which has also been suggested to function in learning and synaptic plasticity (Figurov et al. 1996; Kang and Schuman 1995). The

modification of BDNF levels in response to different behavioral paradigms such as general enrichment, voluntary motor activity, as well as in learning and in neurogenesis confirms a central role for trophic support in sustaining experience-dependent structural and functional plasticity.

3.5.3 *Inflammation and Stress*

The hippocampal formation is known to be particularly vulnerable to damage from epileptic seizures, excitotoxicity and to the effects of pathological increases of adrenal steroids levels during chronic stress. Hippocampal neurons are sensitive to chronic inflammation, thus enabling neurodegenerative diseases with inflammatory components to potentially affect the variety of hippocampal functions over the course of the disease. The hippocampus is also implicated in the perception of pain (Pham et al. 2010) and in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis in response to stress (McEwen 1999). EE also seems to decrease the effect of stress experienced early in life (Francis et al. 2002) and to decrease the levels of adrenal glucocorticoids secreted during the diurnal rhythm and the chronic stress. Hippocampus is particularly enriched in glucocorticoids receptors and when the adrenal steroids levels increases hippocampal neurons promptly exerts their action on hypothalamic neurons via the bed nucleus of stria terminalis, inhibiting hypothalamic release of corticotrophin releasing factor (Herman and Cullinan 1997). The cost of this response is the suppression of neuronal activity necessary for short term memory in hippocampus and temporal lobe (Kirschbaum et al. 1996; McEwen and Sapolsky 1995) and the atrophy of dendrites of pyramidal neurons in the CA3 region of the hippocampus due to a deregulated management of glutamatergic tone. Interestingly, EE is associated to recovery of hippocampal dendritic arborization, increase in cell survival and in total volume of hippocampus. These effects may help hippocampus to exert its functions on HPA axis and counteract chronic stress-induced failures in synaptic plasticity.

3.5.4 *Autism Spectrum Disorders*

An intact and functional neuronal activity in the hippocampus is classically considered necessary for declarative and episodic memory as well as for spatial learning. However, hippocampus is also required for a correct processing of olfactory stimuli, for social transmission of relevant information and it is a major regulator of stress response. Thus, the hippocampus is essential to flexible cognitive processes by which we are able to elaborate contextual aspects and thus construct, manipulate, and update representations of outer world in order to respond to a given task or situation (Rubin et al. 2014).

The aspects of behavior that mostly depend on this hippocampal feature are the social interaction and the motor control. For example, successfully navigating a new context would require making appropriate responses to both novel and familiar stimuli and updating representations of ongoing interactions (Rubin et al. 2014). In autism spectrum disorder behavioral flexibility and sociability are impaired. In experimental models of developmental disorders, EE is able to promote recovery of behavioral skills and morphological features in hippocampal neurons (Restivo et al. 2005; Kondo et al. 2008; Reynolds et al. 2013).

It has been recently shown that in a model of early onset epilepsy associated with hippocampal dysfunction and cognitive and social impairment (Sgobio et al. 2010), EE is able to reduce seizure severity and rescue dendritic branching when animals are exposed to enriching conditions at weaning (Morelli et al. 2014). These results have a translational relevance as the model consists in transgenic mice lacking Basson, a presynaptic protein of the cytomatrix at the active zone that orchestrates neurotransmitter release and maturation of synapses. Thus, this model recapitulates features that mimic human neurodevelopmental disorders characterized by epilepsy, mental retardation, and sensory deficit (Tavyev Asher and Scaglia 2012). Recent clinical evidence pointed to the importance of tailoring EE protocols for patients showing distinct degree of functioning alterations. In fact, sensorimotor enrichment therapy in autistic children, even at an age in which current treatments are considered not anymore effective (Woo and Leon 2013), can be successful in reducing symptoms and improving cognitive functions if an in-home EE protocol is employed.

3.6 Reopening of Critical Periods by EE: Therapeutic Implications

The present chapter provides seminal and most recent evidences that EE stimulates the endogenous potential of hippocampus for plasticity and repair. An enriched environment with motor and multisensorial stimulations might constitute a trigger for intrinsic resilience mechanisms that preserve synaptic plasticity and morphology in distinct hippocampal neuronal population against aging and neurodegeneration. The experience-dependent increase in neuronal connectivity in healthy subjects might represent a neurobiological substrate for the capability to cope with brain injury and disease proposed in the theory of ‘cognitive reserve’ or ‘brain reserve’ (Stern 2002). This construct emerged by epidemiological evidence showing that environmental factors, such as the levels of education and of mental and physical activity, are associated with different rate of cognitive decline and onset of dementia and that EE in adult age is also effective in improving specific behavioral patterns (Caporali et al. 2014, 2015; Cutuli et al. 2015).

According to the enormous potential of EE to boost proliferation and survival of neuronal and glial cells, the responses to multiple combined stimulation protocols

have also been recently studied in relation to the possibility to challenge the strict temporal organization of critical periods. Two recent studies have brought evidence that critical periods can be reopened by EE, providing support for sustainable therapeutic interventions on neurological diseases characterized by permanent loss of function (Wang et al. 2013; Zhu et al. 2014). Possible approaches might be oriented at enhancing signaling between neuronal ensembles and strengthening neuronal circuits in order to allow the brain to efficiently utilize existing neuronal circuits and recruit alternative networks when required by multiple challenges (Nithianantharajah and Hannan 2006).

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Chapter 4
Translatable Models of Brain and Cognitive Reserve

Ariel M. Zeleznikow-Johnston, Emma L. Burrows, Thibault Renoir and Anthony J. Hannan

Abstract The observation of variation in levels of neuropathology required for individuals to develop cognitive deficits led to the theory of 'brain and cognitive reserve' (BCR). This theory posits that there are intrinsic and environmental factors that modify the probability that an individual will develop a neurological disorder in response to a given insult. The development of animal models has allowed this theory to be tested, with rodent experiments demonstrating how environmental factors such as environmental enrichment and exercise levels can ameliorate models of ageing, neurodegeneration and brain injury. Physiological studies in these animal models have identified putative neurobiological mediators of improved BCR from the molecular to anatomical level. Improvements in the development of these models will enable improved testing of the BCR theory and further aid in the quest for developing enviromimetic drugs.

Keywords Environmental enrichment · Exercise · Neurological diseases · Psychiatric disorders · Dementia · Alzheimer's disease · Huntington's disease · Adult neurogenesis · Synaptic plasticity · Experience-dependent plasticity

4.1 The Theory of Brain and Cognitive Reserve and Supporting Evidence in Humans

Naively, one would expect a clear positive relationship between neuropathology and behavioural deficits. Yet, as is described below, some individuals maintain high levels of cognitive function despite having physiological signs of what would

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otherwise be considered debilitating brain damage. The theory of 'brain and cognitive reserve' (BCR) is an attempt to provide a mechanistic framework that explains the common discrepancy between behaviour and pathology.

BCR posits a mixture of two hypotheses. First, that individuals have a certain level of 'brain reserve', i.e. a particular capacity for an amount of damage they can sustain before showing behavioural symptoms. Second, that individuals differ in their ability to maintain cognitive performance despite equivalent levels of neurological insult, termed 'cognitive reserve'. Inter-individual differences in cognitive reserve may be due to differing levels of redundancy available for performing a particular task, ability to compensate for the loss of brain regions by recruiting others, and/or the ability to adopt alternative cognitive strategies for performing the same task.

The two hypotheses are theoretically overlapping and practically difficult to disambiguate, so this chapter will consider the combined concept of BCR. This will be broadly categorised as neuroprotective resistance to brain damage and associated neurological and psychiatric disorders. It will also be demonstrated that BCR can be mediated and modulated by genetics, environment and experience.

The first evidence for BCR was found in the variation in levels of neuropathology found in the brains of individuals with Alzheimer's disease. Accumulation of β-amyloid plaques and neurofibrillary tangles, hallmarks of Alzheimer's disease (AD), can be detected in the brains of healthy subjects (Crystal et al. 1988), including at levels that exceed the usual criteria for AD at autopsy (Katzman et al. 1988; Mortimer 1997). Additionally, evidence for BCR in Huntington's disease exists, as environmental factors have been shown to influence the onset and symptom severity in mice and men (van Dellen et al. 2000; Wexler et al. 2004; Trembath et al. 2010). In standard ageing, the magnitude and rate of cognitive decline can vary highly between individuals (Deary et al. 2009). This variance is interesting and as-yet unexplained, though it may be due to environmental factors that have been linked to variance in cognitive performance in healthy adults (Foubert-Samier et al. 2012). Furthermore, there is no clear relationship between mild-cognitive impairment and development of dementia, with 44% of patients showing this impairment returning to normal levels of cognition (Gauthier et al. 2006).

In response to these findings, both environmental and physiological factors have been identified that modify the probability that an individual will develop a neurodegenerative disease. Individuals with higher levels of fitness (Barnes et al. 2003), education (Katzman 1993; Satz et al. 1993), intelligence (Schmand et al. 1997), work history (Stern et al. 1995) and social engagement (Wang et al. 2002; Saczynski et al. 2006) are less likely to suffer from various neurodegenerative diseases and show neural markers indicative of brain reserve (Foubert-Samier et al. 2012). Physiologically, individuals with greater brain size and larger pyramidal neurons are less likely to develop dementia despite neuropathology (Katzman et al. 1988; Graves et al. 1996). This work has led to intense efforts to identify potential factors involved with BCR; efforts which have been systematically reviewed (Valenzuela and Sachdev 2006; Valenzuela 2008; Stern 2012). Differing levels of

BCR could account for this variation, altering the timepoint at which individuals transition between normal cognition, mild-cognitive impairment and dementia in both normal ageing and pathological states.

4.2 Necessity and Design of Animal Models

While observational epidemiological studies have been critical for developing the concept of BCR, they are limited by their inability to show causal links between factors which may modulate BCR and clinical outcomes. Animal models provide a means to study both the aetiology of neurological diseases and their modulation by BCR. From a basic science perspective they enable investigation of the genetic, molecular, cellular and systems neurophysiology that underlies BCR. From a preclinical perspective, they are able to model a variety of natural processes, diseases and disorders; including traumatic brain injury (TBI), normal ageing and neurodegeneration. Much work has already been done in phenotypic characterisation and mechanistic exploration of disease development in these animals, providing a context in which to examine theories of BCR. Importantly, animal models also enable testing of putative therapeutics to enhance BCR. Studies that have examined the effects of physical activity and cognitive stimulation on animals are most directly relatable to human epidemiological studies. Efforts have also been made to develop and understand pharmacological enhancers of BCR, such as antioxidants and antidepressants. These experimental paradigms have greatly broadened our understanding of the role of BCR in attenuating neurological insults.

Animal models of human diseases attempt to capture the aetiological and symptomatic aspects of the disease while ignoring species-specific biology and discarding the ethical and practical constraints of working on humans. For aetiologically 'simple' diseases, such as monogenic disorders, this can be done by creating a complete model. However, for diseases with more complex origins and symptoms, animal models typically only encapsulate part of the disease (Burrows and Hannan 2015).

Conceptual parameters are critical to designing good animal models, of which construct validity, face validity and predictive validity have been discussed in detail (Burrows et al. 2011). Construct validity is a measure of how accurately the development of a disease in an animal model recapitulates that which occurs in a human. For example, construct validity for genetic disorders requires that the patient-specific mutations/polymorphisms are re-created as closely as possible. Inducing Huntington's disease in transgenic mice through insertion of a pathological human huntingtin transgene is an example of good construct validity (Mangiarini et al. 1996). Construct validity may also be achieved by replicating a well-validated environmental factor, such as the physical injury incurred in traumatic brain injury or cerebral artery occlusion in stroke (Xiong et al. 2013). Face validity describes how well the phenotype of an animal model of a human disease resembles the symptoms and signs of that disease in humans. Models of

Alzheimer's disease aim to recapitulate progressively developing β-amyloid plaques and neurofibrillary tangles seen in the disease, along with other molecular and cellular pathogenic processes (Hsiao et al. 1996; Jankowsky et al. 2001). In the absence of overt biomarkers or pathological changes, behavioural features representative of those seen in the human disease/disorder are required to achieve face validity. This is challenging, as the correlates (e.g. specific cognitive deficits or affective states) may only be approximate and methods of assessment used in animals are unlike those used in the clinic. Predictive validity indicates whether previously identified therapeutics for a disease can alleviate the disease in a particular model and also whether insights gained from interventions trialled on animal models can be used to develop therapeutics for human diseases. For example, rodent models of anxiety disorders can typically have their anxiety-like phenotypes alleviated by administration of anxiolytic drugs (Belzung and Griebel 2001; Petit-Demouliere et al. 2005). Predictive validity is the most directly translatable aspect of animal models, yet it is also the area in which models most frequently fail.

4.3 Experimental Paradigms to Study BCR

4.3.1 Animal Models of Brain Ageing

BCR theory is predicated on the notion of variance in cognitive performance between individuals and the existence of factors which can influence this variance. Ageing is typically associated with cognitive decline in humans, but both the rate and magnitude of decline can vary widely between people. In addition, environmental factors are known to impact upon age-related cognitive impairment.

Laboratory rodents display decreased performance on a variety of cognitive tasks with increasing age in a manner akin to humans. Despite the caveats that rodents have a greatly reduced average lifespan compared to humans (2–3 years for laboratory mice and rats as opposed to >70 years for humans in developed countries), and that neuroanatomical differences limit direct comparison between human and rodent neuropathology, they can serve as a useful model of ageing. Efforts have been made to standardise the strains and tests used such that age-related cognitive impairment can be investigated in rodent models (LaSarge and Nicolle 2009). In particular, The National Institute of Ageing provides dedicated rat and mouse strains for performing ageing research, with the F344 rat strain having been extensively tested (https://www.nia.nih.gov/research/).

Aged rats (Gage et al. 1988; Gallagher et al. 1993; LaSarge and Nicolle 2009; Ménard and Quirion 2012) and mice (Bennett et al. 2006; Gil-Mohapel et al. 2013) consistently develop impairments of spatial long-term memory. Studies have shown that impairments also become apparent in other cognitive domains. Working memory declines in rats (Segovia et al. 2008) and mice (Bennett et al. 2006). Executive function is also impaired in aged rats (Barense et al. 2002; Nicolle and

Baxter 2003); and mice (Young et al. 2010). Interestingly though, there is typically a large degree of variability visible within the aged cohorts, with some studies attempting to dichotomise animals into age-impaired and age-unimpaired animals (Gage et al. 1988; Young et al. 2010; Ménard and Quirion 2012).

Systematic efforts to describe and explain the cause of this variance have not been performed. Individual studies examining physiological correlates, such as synaptic and downstream protein levels (Ménard and Quirion 2012) or modulatory neurotransmitters (Gage et al. 1988), have been conducted. However, more studies to identify these physiological correlates and then experimentally manipulate them are required in order to show a causal link between particular mechanisms and age-related cognitive impairment variance. Nevertheless, the consistent variation in cognitive performance observed in aged rodents is suggestive of a role of BCR in ageing and provides reason to interrogate ageing models to further our understanding of neural markers of BCR.

4.3.2 Environmental Enrichment (EE)

Environmental enrichment (EE) is an environmental modification that seeks to provide an 'enriched' environment compared to the 'standard' environmental conditions of an animal (Nithianantharajah and Hannan 2006). EE was originally investigated by Donald Hebb, who found that rats allowed to roam his house performed better on cognitive tasks than those kept in laboratory housing (Hebb 1947). The effects of EE are often compared with those of increased educational, physical and social activity in humans, although scientists must be careful to avoid anthropomorphising animal experiences and conditions.

In scientific rodent housing facilities, standard conditions typically comprise a bland container with bedding, *ad libitum* food and water, nesting material and single-sex social groups of 2+ animals. EE comprises a non-standardised set of modifications that often include: a larger cage (perhaps with multiple levels); increased social group size; running wheels; toys (which may or may not be changed on a regular basis); olfactory stimuli; weekly alteration of food/water location; or any other environmental modification.

Placing animals into an enriched environment has been shown to have dramatic and wide-ranging procognitive and neuroprotective effects (Nithianantharajah and Hannan 2006; Baroncelli et al. 2010). Developmentally, EE encourages increased maternal care and accelerates the development of visual acuity in young mice (Sale et al. 2009). In young adult mice, EE has been shown to improve performance on a wide range of cognitive behavioural tasks, including long-term memory (Kempermann et al. 1997; Rampon et al. 2000a, b; Tang et al. 2001; Schrijver et al. 2002; Garthe et al. 2015), though not without some exception (Schrijver et al. 2002; Simpson and Kelly 2011). The difference in cognitive abilities between standard housed and enriched animals becomes starker in aged mice (Bennett et al. 2006; Harburger et al. 2007), which is in keeping with the theory that EE improves BCR.

In animal models of neurodegenerative diseases, EE increases the level of neuropathology required for a given level of behavioural deficit (van Dellen et al. 2000; Richards and Deary 2005; Fischer et al. 2007; Petrosini et al. 2009). A key example of this can be seen in a study demonstrating that EE could substantially delay neurodegeneration and onset of motor impairments in the R6/1 mouse model of Huntington's disease, the epitome of a genetic disorder (van Dellen et al. 2000). Reductions in pathology in other mouse models of neurodegeneration have been seen following EE. Reductions in both Aβ accumulation and plaque deposits (Lazarov et al. 2005) and tauopathy in mouse models of Alzheimer's disease have been reported following EE (Lahiani-Cohen et al. 2011).

These EE-induced reductions in pathology are accompanied by improvements in cognition (Jankowsky et al. 2005; Valero et al. 2011). In models of TBI, post-injury EE significantly improves long-term memory performance (Passineau et al. 2001; Maegele et al. 2005; Hoffman et al. 2008; Sozda et al. 2010), though not necessarily with a concomitant rescue of their anxiety-like phenotype (Kovesdi et al. 2011). While EE paradigms involve an increase in voluntary motor behaviour or exercise, access to running wheels in isolation can test this independent of the cognitive and sensory stimulation aspects of EE. Interestingly, one study using a mouse model of AD showed dissociation between EE and wheel running, with selective beneficial effects of enrichment on spatial memory performance (Wolf et al. 2006). Further work has been done to show the timing of EE contributes to its procognitive effects, as early life exposure (10 weeks of EE housing commencing at 3 months of age) had an improved ability to reduce the severity of impairments in a mouse AD-model compared to EE later in life (Verret et al. 2013). This work suggests that EE may be more effective at enhancing BCR when animals are exposed to it during critical periods of development (Verret et al. 2013).

In addition, EE-induced improvements are also reported in psychiatric symptoms seen in animal models of neurodegeneration. For instance, EE has been shown to ameliorate depressive-like behaviours in a mouse model of Huntington's disease (Pang et al. 2009; Blázquez et al. 2014).

4.3.3 Voluntary Exercise

Exercise, even in the absence of other elements of EE, has been shown to have a major impact on BCR. Exercise is normally administered to rodents by the placement of running wheels or discs within their home-cage. Implementation of this can differ, as number of animals per cage or time of running wheel accessibility can determine how much running an individual rodent will perform. Mice will typically run 6–12 km per dark cycle, but this varies with background strain and exact housing conditions (Swallow et al. 1998).

Although less work has been done than in EE models, some studies have looked at the effects of exercise alone at ameliorating TBI. Rats subject to brain injuries (Griesbach et al. 2004; Kim et al. 2010) have shown improved long-term memory

when given voluntary or forced exercise post-injury. Interestingly, these effects seem to occur only when exercise is commenced after a post-injury delay, with immediate exercise potentially being counterproductive (Griesbach 2011). In addition, exercise can also alter propensity to develop epilepsy, which can be acquired post-TBI. Rats subjected to fluid-percussion injury and subsequent subeffective doses of the convulsant had their latency to first seizure and duration of seizures attenuated by forced treadmill running (Silva et al. 2013).

Exercise in the absence of other EE parameters has also been found to have beneficial effects in AD models. Five months of wheel running decreased the amyloid plaque burden and improved the acquisition of long-term spatial memory in AD mice, although it did not improve long-term memory retention performance (Adlard et al. 2005). Improvements due to exercise can occur even after the onset of AD pathology, as aged AD mice given three weeks of wheel running show decreased working and long-term memory errors compared to their sedentary controls (Nichol et al. 2007).

Similarly, exercise has also shown positive effects on delaying disease onset in R6/1 (Pang et al. 2006; Van Dellen et al. 2008; Renoir et al. 2012; Harrison et al. 2013) and R6/2 HD mice (Wood et al. 2011). However, it should be noted that one study using singly housed N171-81Q mice failed to find a therapeutic effect of running (Potter et al. 2010), suggesting that the positive exercise studies may have been confounded by social housing effects (Mo et al. 2015a, b). It should also be noted though that N171-81Q mice use a non-HTT (prion) promoter to express the transgene, so have weaker construct validity than the other HD mouse models (e.g. R6/1 and R6/2) which incorporate the HTT promoter.

4.3.4 Antioxidants

Oxidative stress occurs when reactive oxygen or nitrogen species (ROS/RON) are produced at a rate that exceeds a cell's ability to clear them, resulting in oxidation of biomacromolecules. ROS are produced naturally as a by-product of cellular metabolism and can play physiological roles in cell signalling and immune responses. However, disruption of the cell's redox state can lead to toxic protein and lipid alterations as well as DNA strand breaks.

ROS are cleared by a combination of enzymatic and non-enzymatic factors (Rahman 2007). Catalase, superoxide dismutase (SOD) and glutathione peroxidase (GPx) are among the enzymes that catalyse the removal of ROS into less toxic species. They do so in combination with non-enzymatic factors such as vitamin E, vitamin C, thiols and melatonin. Artificially elevating the levels of non-enzymatic antioxidant factors as a way of increasing brain reserve has now been extensively explored in animals.

Abnormal levels of β-amyloid in rodent models of AD have been consistently associated with oxidative stress in the brain (Smith et al. 1998; Praticò 2008). Logically then, attempts have been made to assess whether antioxidant treatments

are capable of preventing or delaying the physiological and behavioural markers of AD pathology in animal models of the disease. This work has mainly occurred in the transgenic rodent models described previously.

In AD mouse models, an age-related linear relationship exists between increased free radical production and cognitive impairment (Bruce-Keller et al. 2011). However, studies assessing potential therapeutic effects of antioxidants have shown mixed results. Melatonin has been shown to decrease β-amyloid burden, abnormal nitration of biomolecules, oxidative stress, mitochondrial dysfunction and increase survival time in some studies (Matsubara et al. 2003; García-Mesa et al. 2012), but no effects were found in another (Quinn et al. 2005). In the same model, curcurmin was able to lower abnormal protein oxidation and reduce inflammatory markers (Lim et al. 2001), while α-lipoic acid improved cognitive function relative to untreated control mice (Quinn et al. 2007). In another model, mice treated with NAC or pioglitazone for 6 weeks showed improvements in cerebrovascular activity without concomitant improvement in cognition or β-amyloid burden (Nicolakakis et al. 2008). Similarly, pioglitazone showed no ability to prevent cognitive impairment in another AD mouse model (Masciopinto et al. 2012).

These results, while broadly showing positive effects, are inconsistent, varying with which strain of mouse and which antioxidant was used. Unfortunately, there has been no coherent approach to standardise the administration and dosage of the antioxidants, the length of administration, or strains of mouse used. This lessens our ability to determine whether particular antioxidants are definitively beneficial in animal models of AD (Pérez-Severiano et al. 2000; Wright et al. 2015).

Similarly, pre-motor symptomatic HD patients have elevated ROS and lowered circulating antioxidant levels than age-matched controls (Klepac et al. 2007), suggesting that impairments in oxidative stress regulation may contribute to pathology in HD (Gil-Mohapel et al. 2014). Correspondingly, elevated levels of oxidative stress and mitochondrial dysfunction are observed in animal models of HD. Several antioxidants have shown efficacy in treating preclinical HD animal models, including nordihydroguaiaretic acid (Lee et al. 2011), XJB-5-131 (Xun et al. 2012), curcumin (Hickey et al. 2012) and N-acetylcysteine (Wright et al. 2015, 2016); but not resveratrol (Ho et al. 2010).

4.4 Putative Neurobiological Mechanisms of BCR

4.4.1 Overview

Given the broadly neuroprotective and procognitive nature of treatments that enhance BCR, one would expect underlying mechanisms that are correspondingly generic in their ability to protect against brain damage and augment compensatory plasticity. For antioxidants the proposed mechanism is one of increasing tolerance for oxidative stress, a relatively straightforward mechanism. However, the plethora

of studies attempting to describe a diversity of underlying causes for EE and exercise suggest not just one or two discrete mechanisms but an orchestra of physiological contributors, each acting in concert with the others.

Unfortunately, this presents problems for scientists in isolating particular mechanisms and excluding confounding factors. Which proteins are acting in partnership to protect neurons, which neurons are modifying their plasticity to compensate for network damage and which genes are altering their expression levels as non-causal downstream effects?

As an example, EE induces physiological alterations on every level of the biological scale. Alterations in gene expression (Rampon et al. 2000b) and epigenetics (Fischer et al. 2007; Arai and Feig 2011), increases in neurotrophin levels (Baroncelli et al. 2010), increases in adult hippocampal neurogenesis (Garthe et al. 2015), modifications to monoaminergic neurotransmitter levels (Rasmuson et al. 1998; Del Arco et al. 2007), structural alterations in synapses (Nithianantharajah et al. 2004; Bednarek and Caroni 2011), electrophysiological alterations of synapses (Buschler and Manahan-Vaughan 2012; Alwis and Rajan 2014; Novkovic et al. 2015b) and even modifications of gross morphology (Juraska and Kopcik 1988; Alwis and Rajan 2014) are seen following exposure to EE.

The inclusion of multiple variables makes elucidating the causal path from an enriched environment to procognitive behavioural observations extremely difficult. Nonetheless, we will examine a subset of those most plausibly linked to BCR in animal models.

4.4.2 Synaptic, Cellular and Physiological Mediators

4.4.2.1 Synaptogenesis and Synaptic Plasticity

BCR posits the dual idea of increased brain reserve and increased cognitive compensatory capacity. EE-induced alterations in synaptogenesis and synaptic plasticity are amongst the most plausible mechanistic underlying candidates. Animals in EE conditions have increased neocortical and hippocampal synapses (Greenough et al. 1985; Turner and Greenough 1985; Rampon et al. 2000a; Galimberti et al. 2006), synapse proteins (Nithianantharajah et al. 2004) and dendritic branching (Connor et al. 1982; Faherty et al. 2003; Leggio et al. 2005).

These alterations are accompanied by corresponding shifts in the electrophysiological properties of the neurons. Animals housed in EE conditions have enhanced hippocampal long-term potentiation (LTP) (Duffy et al. 2001; Mainardi et al. 2010; Hullinger et al. 2015) and metaplasticity (Buschler and Manahan-Vaughan 2012).

Accompanying these electrophysiological changes are alterations in spine morphogenesis and dynamics. Large mossy terminals on CA3 neurons in the hippocampus are enlarged in mice housed in EE conditions (Galimberti et al. 2006). EE conditions increase the turnover frequency of cytoskeletal proteins in synapses

(Bednarek and Caroni 2011), presumably a physical substrate of increased plasticity (Caroni et al. 2014).

4.4.2.2 Adult Hippocampal Neurogenesis

Adult hippocampal neurogenesis (AHN) in humans and rodents occurs in the subgranular zone of the hippocampus, which produces neurons that integrate into the inner granular zone of the dentate gyrus and form functional synapses with local neurons (Deng et al. 2010). These young neurons have particular properties, such as heightened excitability and integration into a sparse network, which make their influence disproportionate to their numbers within the hippocampus (Aimone et al. 2011). Relevant to BCR theory, the rate of granule cell proliferation, functional integration and survival can be influenced by both internal signals (e.g. growth factors, hormones and neurotransmitters) and external factors (e.g. stress, EE and drugs).

AHN has been implicated in both spatial learning and memory and in maintaining a healthy affective state. AHN is required for long-term allocentric spatial memory (Garthe et al. 2009) and is thought to be necessary for 'pattern separation'—the ability to disambiguate similar memories (Clelland et al. 2009; Aimone et al. 2011). Interestingly, AHN is also implicated in depression, as reduction in AHN is seen in depressive-like animal models (Mineur et al. 2007) and therapies that treat depressive symptoms tend to boost neurogenesis (Santarelli et al. 2003; Miller and Hen 2015).

Numerous studies have shown that EE and exercise can positively impact AHN in animals (Kempermann et al. 1997; Fabel et al. 2009; Simpson and Kelly 2011). In particular, exercise is thought to particularly promote proliferation while EE supports functional integration and survival (Olson et al. 2006; Zhao et al. 2008; Fabel et al. 2009), though some studies find effects only in exercise (Kobilo et al. 2011; Mustroph et al. 2012). Also intriguing is the fact that the effects of exercise and EE have been shown to be additive (Fabel et al. 2009). Conversely, stress and treatment with stress hormones inhibits AHN (Gould et al. 1997; Mirescu and Gould 2006; Schoenfeld and Gould 2013). This suggests multiple mechanisms at play in regulating AHN.

Positive and negative environmental regulation of AHN has contributed to the theory of "neurogenic reserve" (Kempermann 2008, 2015). Derived from the more general theory of BCR, the neurogenic reserve hypothesis holds that positive influences of exercise and cognitive stimulation are pitted against negative regulators like stress and social isolation and that maintaining a higher level of AHN can allow for maintenance of memory function in the face of neurological insult. As the rate of neurogenesis decreases dramatically over the course of an animal's lifespan (Seki and Arai 1995; Kuhn et al. 1996), lifelong maintenance of AHN and its contribution to BCR may have particularly beneficial effects when commenced early.

It should be noted that a few studies have found beneficial effects of EE in the absence of AHN (Meshi et al. 2006; Kerr et al. 2010), which may occur through some of the other mechanisms listed in this section.

4.4.2.3 Glial Contributions

Glia are the support cells of the brain, roughly equal in number to neurons across an average of the human brain (Herculano-Houzel 2014). The number, morphology and activity of glial cells vary widely over different brain regions and is dynamically subject to environmental modulation. In that they play a role in supporting neuronal function and survival, glia are proposed to be a contributor to BCR.

Ageing rodent brains show hypertrophy of astrocytes that correlates with cognitive impairments, with both hypertrophy and working memory deficits being rescued by EE (Soffié et al. 1999). In contrast, other studies have shown mice under EE conditions developing increased astrogenesis (Kronenberg et al. 2007) and morphological alterations (Viola et al. 2009). Perhaps more important than total increase or decrease is astrocyte activity. For example, rats subject to cortical ischaemia and housed in EE conditions show increased astrocytes in glial scars, where they may be involved in repair or compensatory plasticity mechanisms (Komitova et al. 2006).

Other cell types have been shown to influence BCR, as well as associated cognitive processes including learning and memory. Exercise can increase oligodendrocyte numbers in the central nervous system (Krityakiarana et al. 2010), which one study has shown to be necessary for acquiring novel motor skills (McKenzie et al. 2014). Even microglia, the brain's immune regulatory cells, have been shown to play a role in learning and neurogenesis regulation (Ziv et al. 2006).

4.4.2.4 Vascular Alterations

Both EE (Ekstrand et al. 2008; Herring et al. 2008) and exercise (Black et al. 1990; Isaacs et al. 1992; Swain et al. 2003) have been shown to induce vasculature alterations in various brain regions of healthy and AD-model rodents. In particular, hippocampal and striatal vasculature is responsive to exercise in mice (Clark et al. 2009; Van der Borght et al. 2009) and rats (Palmer et al. 2000; Ding et al. 2004, 2006), though there are species-specific differences in magnitude of angiogenesis. Intriguingly, exercise-induced angiogenesis in rats has been implicated in increased MWM performance even in the absence of neurogenesis (Kerr et al. 2010).

Increased angiogenesis remodelling could be supporting BCR through a variety of means. Increased availability of nutrients or neurotrophic factors through increased brain perfusion could be beneficial in keeping neurons alive in cases of stroke and ischaemia. Alteration of vasculature may enable improved neuroimmune surveillance. Alternatively, vascular alterations may not play a causal role in BCR, instead being merely secondary to increased neuronal or glial metabolic demands in animals subject to exercise or EE conditions.

4.4.3 Molecular Regulators

4.4.3.1 Gene Expression, Epigenetic and Chromatin Modifications

For the above physiological processes to be altered under different environmental conditions they must somehow interact with genetic regulators of transcription and translation. Interestingly, this process seems to occur extremely quickly after exposure to EE (Ali et al. 2009), with robust changes in gene transcription related to transcription factors, synapse function and epigenetics observable from as early as 3–6 h (Rampon et al. 2000b).

Epigenetics refers to the process of long-term gene expression regulation in the absence of changes to the genome. Regulation of DNA methylation is one such epigenetic process, in which DNA methyltransferases (DNMTs) methylate cytosine side-chains on DNA in processes associated with gene suppression (Okano et al. 1998), while ten-eleven translocation (TET) proteins promote demethylation (Ito et al. 2011). Histones, proteins that DNA is wrapped around to form chromatin, also aid in gene expression regulation. Histone N-tail terminals can be acetylated, methylated, ubiquitinated or phosphorylated in order to modify DNA packaging and hence gene expression (Strahl and Allis 2000). With regards to environmental impacts on neuronal function, DNA methylation and histone acetylation have been the most studied thus far.

Long-term memory processes are associated with hippocampal histone 3 (H3) acetylation increases (Levenson et al. 2004) and alteration in DNA methylation (Sweatt 2009). In contrast, imbalance between histone acetylation and deacetylation are implicated in neurodegeneration (Saha and Pahan 2006), with global histone acetylation decreases over an animal's lifespan associated with transcriptional dysregulation (Lovatel et al. 2013).

EE (Fischer et al. 2007) and exercise (Gomez-Pinilla et al. 2011; Abel and Rissman 2013; Lovatel et al. 2013) have both been shown to increase histone acetylation in association with rescue of cognitive impairments. Indeed, a recent study has even shown EE-induced upregulation of histone acetylation to be involved in restoring visual cortex plasticity in adulthood (Baroncelli et al. 2016).

Exercise and EE have also been shown to be associated with DNMT and TET activity in the hippocampus (Elsner et al. 2013; Irier et al. 2014). One particular focus has been that of brain-derived neurotrophic factor (BDNF), a protein whose role is described in the next section. Hippocampal BDNF gene expression has been shown to be affected by the methylation of BDNF promoters (Gomez-Pinilla et al. 2011; Kuzumaki et al. 2011). This regulation of BDNF may be in association with epigenetic control of AHN (Covic et al. 2010), though much work remains to be done in understanding the environmental regulation of epigenetics with regards to BCR.

4.4.3.2 Neurotrophins

EE and exercise have been shown to affect multiple neurotrophic proteins including: BDNF, nerve growth factor, glial cell-derived neurotrophic factor, and vascular endothelial growth factor (Nithianantharajah and Hannan 2009). Of these, BDNF has been most studied in relation to BCR and neurodegenerative diseases (Zuccato and Cattaneo 2009).

BDNF is a widely distributed neurotrophic protein that is required for neuronal proliferation and survival both developmentally and in adulthood. In addition, it is implicated in learning and memory processes in animals and humans (Bekinschtein et al. 2007; Heldt et al. 2007; Minichiello 2009; Bekinschtein et al. 2014). The synaptic plasticity (Novkovic et al. 2015a) and activity-dependent synaptic maintenance (Kellner et al. 2015) that underlie these processes have both been shown to utilise BDNF. In addition, BDNF is a known regulator of AHN (Scharfman et al. 2005).

Moreover, BDNF gene and protein expression is increased in the hippocampus and neocortex of rodents placed in EE or exercise-conducive housing conditions (Nithianantharajah and Hannan 2009). Exercise in aged mice is associated with increased hippocampal BDNF concomitant to improvements in cognitive performance and increases in AHN (Zajac et al. 2010; Marlatt et al. 2012), while EE has been demonstrated to induce AHN through BDNF-dependent mechanisms (Rossi et al. 2006).

However, whether BDNF is a key mediator of enhanced physiological and hence cognitive function in animals, or whether there are additional causal variables that play a greater role in AHN and learning and memory, remains to be determined (Bekinschtein et al. 2011).

4.4.3.3 Neurotransmitter and Neuromodulator Dynamics

Given the dramatic effects that EE has on behaviour and physiology, one would expect to see alterations in neurotransmitters, neuromodulators and their receptors. Indeed, EE has been found to affect the glutamatergic, GABAergic, cholinergic, serotonergic and dopaminergic systems, as reviewed in (Mora et al. 2007). These signalling pathways are complex and overlapping, making it difficult to draw conclusions about the role of neurotransmitters in mediating enhancement of BCR.

4.5 Conclusion

4.5.1 Enviromimetics

Our ultimate goal is to understand BCR well enough to develop therapeutics that can enhance it and decrease the burden of neurological disorders. Initially this was achieved by using epidemiological studies to identify natural enhancers of BCR:

exercise, education, cognitive stimulation, etc. Through studying homologues of these natural activities in animals, scientists seek to find the molecular mechanistic systems through which they confer their beneficial effects. Drugs capable of acting upon such targets are labelled 'enviromimetics', in that they mimic or augment the natural enhancement that comes from positive environmental influences (Hannan 2004; McOmish and Hannan 2007; Sale et al. 2014). Such drugs are theorised to work by interacting with one or more of the mechanisms identified above.

Selective serotonin reuptake inhibitors (SSRIs), commonly prescribed as antidepressants, are a potential candidate. SSRIs boost hippocampal BDNF (De Foubert et al. 2004) and increase AHN (Malberg et al. 2000). Additionally, they have shown some potential in treating physiological and behavioural symptoms in animal models of AD (Nelson et al. 2007) and HD (Duan et al. 2004; Grote et al. 2005; Peng et al. 2008).

More recently, histone deacetylase (HDAC) inhibitors have been explored in enhancing BCR in neurodegenerative disease (Abel and Zukin 2008; Chuang et al. 2009). As previously noted, global histone acetylation levels decrease over an animal's lifespan, with histone acetylation:deacetylation imbalance thought to contribute to cognitive decline. HDAC inhibitors improve cognitive and motor deficits in HD (Ferrante et al. 2003; Hockly et al. 2003; Gardian et al. 2005), AD (Qing et al. 2008; Ricobaraza et al. 2009; Kilgore et al. 2010; Benito et al. 2015) and ageing (Benito et al. 2015) models in a manner reminiscent of EE, suggesting that they may be candidate enviromimetics.

4.5.2 Room for Improvement

Despite a wealth of preclinical research, therapeutics trialled in animal models translate to the clinic with an extremely low success rate. Success rates for drugs to treat neurological disorders stands at about 8% (DiMasi et al. 2010), while putative AD therapeutics have an abysmal 0.4% success rate (Cummings et al. 2014). There exist no pharmaceuticals for treating the cognitive impairments that come with TBI, neurodegenerative diseases or normal ageing. While developing such treatments is a fundamentally challenging task, this problem may be exacerbated by imperfect animal experimentation.

For optimal animal models, many issues need to be considered. Issues of underpowered studies, lack of clear hypotheses, a priori observation criteria and publication bias occur in behavioural neuroscience as elsewhere in science. Construct, face and predictive validity need to be carefully evaluated (Burrows and Hannan 2013). When considering the overwhelming failure of preclinical AD trials to translate, many have noted the discrepancy between a disease which takes decades to develop in humans yet only months in rodent models. Different behavioural results can be observed in different rodent strains, or even the same strain tested in different laboratories, lessening generalizability of findings (Crabbe et al.

1999). Lack of standardisation of animal handling, housing and testing undoubtedly contribute to inter-lab variability.

Some attempt to address these issues is made through the use of touchscreen testing chambers (Clark et al. 2006; Bussey et al. 2008; Horner et al. 2013). Derived from computerised human cognitive testing batteries, touchscreens combine standardised equipment and testing protocols with automated observational recordings in an approach that improves standardisation and reproducibility. While not appropriate for all behavioural tests, touchscreens are representative of an attempt to increase translatability of preclinical animal modelling.

4.5.3 Summary

Inter-individual differences in the level of neuropathology required to develop cognitive impairments initially led to the theory of BCR. Epidemiological evidence showing that environmental factors such as education, physical activity and social engagement could influence the likelihood of developing dementia suggested that BCR is not static and could be influenced by environmental and genetic factors.

Animal models are crucial for both basic and preclinical neuroscience research in that they allow the linkage of physiological manipulations with behavioural outcomes. Decreases in BCR—such as through TBI, ageing and neurodegenerative diseases—can be modelled in rodents with various degrees of success. Enhancers of BCR, such as EE, exercise and antioxidants, have been consistently found to have neuroprotective and procognitive effects in these models. These improvements are probably mediated by a combination of factors such as increased synaptic plasticity, AHN, elevated neurotrophic factors and enhanced molecular and genetic regulation.

We hope that the work that has already been done in understanding BCR will continue to be built upon and that improvements in animal experimentation will enhance our ability to develop novel enviromimetic drugs for treating neurological disorders and cognitive impairments.

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Chapter 5
Cognitive Reserve: A Life-Course Perspective

Serhiy Dekhtyar and Hui-Xin Wang

Abstract The concept of reserve has been developed to account for the discontinuity between the extent of brain damage at its clinical manifestation in the form of cognitive decline or dementia. In this chapter, we discuss contributors to cognitive reserve from various stages of the life-course, including childhood, early adulthood, middle age, and late life. Evidence from observational, as well as intervention trials is presented and assessed. We conclude by arguing that reserve formation in dementia risk is a life-course process whereby baseline cognitive abilities are subjected to modulation by subsequent experiences at diverse stages over the entire life-course. Variations among individuals in their ability to withstand age-related brain changes is ultimately dependent on their life-time accumulation of mental, physical, and lifestyle inputs into cognitive reserve.

Keywords Reserve · Cognitive reserve · Brain reserve · Dementia · Life-course · Education · Occupational attainment · Childhood cognitive ability · Social networks · Leisure activities

5.1 Introduction

It has been reported that about a quarter to two-thirds of people characterized as cognitively intact throughout longitudinal assessments in fact fulfil pathological criteria for dementia at autopsy (Neuropathology Group 2001; Steffener and Stern 2012; Crystal et al. 1988; Morris et al. 1996; Price and Morris 1999; Mortimer et al.

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2003). These findings provided an empirical underpinning for the well-established regularity in clinical practice that the same degree of head injury, or stroke, often leads to drastically different levels of cognitive impairment across individuals. As a result, the concept of reserve was developed to account for the discontinuity between the extent of brain damage and its clinical manifestation (Stern 2002, 2009). Reserve hypothesis postulates that functioning may be maintained in the presence of brain changes or insults due to the aspects of brain structure and function that can buffer the effects of neuropathology. Therefore, the greater the reserve, the more severe is the pathology required to manifest as functional impairment (Richards et al. 2004). The distinction between brain structure and function in the definition of reserve has led to the subdivision of the concept into two components: brain reserve and cognitive reserve, each emphasizing distinctive aspects of protection against the mounting pathology.

Brain reserve encompasses protection from cognitive impairment or dementia due to anatomical features of the brain, such as size, neural count, or synaptic connectivity (Katzman 1993). The brain reserve hypothesis argues for a critical point of pathology, beyond which any further deterioration will invariably lead to functional impairment (Satz 1993). Individuals with larger brains, more neurons, or better-connected synapses should be able to sustain more insults prior to the clinical manifestation. The brain reserve hypothesis is also known as the passive model because it assumes that the effects of a given insult will lead to identical effects across individuals and that the eventual differences are only due to the brain reserve capacity—the damage is either sufficient or insufficient to deplete this capacity beyond a fixed critical level. This model, therefore, does not account for individual differences in brain network efficiency or flexibility, which might exist even at identical levels of brain size or synaptic count.

Cognitive reserve is a concept related to brain reserve, in a way that it is also meant to help cope with underlying brain damage. The difference is that cognitive reserve emphasizes efficiency and resilience of the brain networks rather than the biological characteristics of these networks (Stern 2009). Efficiency—brain network's ability to operate effectively despite sustained disruption, and flexibility—recruitment of alternate networks when faced with disruption to the standard approaches, are the centrepieces of the cognitive reserve model. In contrast to the brain reserve model, a fixed threshold for functional impairment is not assumed in the framework of cognitive reserve—instead, the critical threshold varies across individuals as a function of how efficient or resilient the brain networks are at utilizing the remaining neuron connections. Therefore, the effects of brain damage might vary across individuals depending on their ability to cope with the damage, even if the underlying brain reserve capacity is held constant.

The concept of reserve has been called upon to account for a well-established finding in epidemiological literature that high educational (Katzman 1993; Meng and D'Arcy 2012) and occupational attainment (Qiu et al. 2003; Stern et al. 1994) appear to protect against cognitive decline and dementia. Explaining this finding using the predictions of the brain reserve hypothesis would imply a conclusion that the brains of highly educated individuals are considerably different in terms of

anatomical features than the brains of individuals with less advanced education. The cognitive reserve explanation provides a more plausible explanation: people with higher educational or occupational attainment are able to process tasks in a more efficient manner because their brains actively attempt to cope with brain damage by using pre-existing cognitive processing approaches, or by activating compensatory mechanisms (Fratiglioni and Wang 2007)—and high education or occupational attainment might indicate the extent to which these strategies will be successfully used across individuals.

Both brain reserve and cognitive reserve models are closely related to the general concept of brain plasticity (Mahncke et al. 2006)—the ability of the brain to re-arrange structure as well as neural connections, allowing it to change with learning, to repair, and to compensate. Plasticity is central to memory foundation and learning processes because it provides the brain with a life-long possibility to change and adjust when facing environmental demands and stimuli. The focus on life-long development is important for the cognitive reserve construct in particular, which, as an active process, is likely formed as a combination of baseline capacity, which is then subjected to modulation by multiple experiences and exposures throughout the entire life-course. Through this life-long process an individual develops a level of cognitive reserve which in turn can mitigate the effects of pathology on the clinical diagnosis later in life.

In this chapter, we will explore the life-course perspective to cognitive reserve in the framework of cognitive decline and dementia in greater detail. We start out by laying out some well-established epidemiological evidence in favour of the cognitive reserve hypothesis, with particular emphasis on reserve contributors from various stages of the life-course, including childhood. For each reserve contributor, we also discuss potential neural and cellular mechanisms that could account for the reported findings. We proceed by presenting a tentative model of cognitive reserve over the life-course, which emphasizes various reserve components and contributors from different points throughout the life-span. Conclusions are offered at the end of the chapter.

5.2 Early Adulthood: Educational Attainment

Evidence of an elevated risk of dementia in people with low educational attainment is cited most often in support of a cognitive reserve hypothesis for late-life dementia and cognitive decline. The evidence is so abundant and consistent that the recently discovered decline in dementia prevalence in the West has been in part attributed to expanding educational opportunities in rich industrialized societies (Langa 2015). A recent meta-analysis (Meng and D'Arcy 2012) has found more than 100 studies reporting either protective effects of high education or detrimental effects of low attainment on the risk of dementia from a wide variety of contexts. Most often, an explanation of these effects involves a reference to the general cognitive reserve hypothesis, emphasizing brain networks efficiencies and flexibilities, whereby

individuals with high attainment are suspected to have more efficient brain networks which remain operational even under the burden of pathology, or are able to re-distribute tasks away from the damaged areas in favour of the networks unaffected by the pathology (Herlitz and Dekhtyar 2013).

An alternative to the cognitive reserve explanation behind the association between education and late-life cognitive decline or dementia is the so-called brain-battering hypothesis (Del Ser et al. 1999). It builds on the notion that well-educated individuals are more prone to engage in healthier lifestyles associated with a lower burden of vascular and behavioural risks (Gottfredson 2004), which are then implicated in late-life dementia risk (Norton et al. 2014). Therefore, any eventual association between education and cognitive decline or dementia is not due to education mitigating the impact of pathology on the clinical expression of the disease, but rather due to education protecting individuals from developing vascular neuropathology which, ultimately, is the cause of dementia. The brain-battering hypothesis was first used to account for a peculiar finding that individuals with low education were both diagnosed as demented and eventually died earlier than the highly educated ones, although they did not differ in the rate of cognitive decline or the neurodegenerative burden; the only difference between the two groups was in terms of cerebrovascular pathology (Del Ser et al. 1999). Further, lifestyle factors, such as smoking, were found to alter the association between education and non-Alzheimer disease dementia (Cobb et al. 1995), suggesting mediation by vascular factors. Finally, mixed findings have been reported between education and measures of brain pathology or structure, casting doubt on the model of cognitive reserve (Roe et al. 2008; Christensen et al. 2007; Koepsell et al. 2008), although there have been issues with representativeness, sample size, and selection of pathological measures in these studies. Another possibility for the association between education and dementia is the so-called detection bias, suggesting that subjects with dementia who are less-educated would be diagnosed at an earlier pathological stage of the disease as compared to those with higher education. This is especially relevant since some studies have found that low education has been associated with an elevated incidence of dementia, whereas at the same time no association has been established between low education and the rate of memory decline or mortality of dementia patients (Qiu et al. 2001; Tuokko et al. 2003).

Although detection bias and the earlier-discussed brain-battering hypothesis are both legitimate alternatives to the general theory of cognitive reserve in explaining the link between education and cognitive decline, increasing evidence is pointing to the existence of a neural basis for cognitive reserve in dementia risk. The risk of Alzheimer's disease was more than halved in the group with higher educational level, even after adjustment for demographic, socioeconomic, lifestyle, and vascular characteristics in a large Finnish study (Ngandu et al. 2007). Similarly, a large study based on harmonization of longitudinal clinical data and neuropathology from three long-standing population-based studies that included post-mortem donation of 872 brains (Brayne et al. 2010) has shown that education did not protect against the accumulation of neurodegenerative or vascular pathologies in the brain at death. It did, however, mitigate the association between pathology burden and cognitive

decline, so that for a specific pathological burden, those with more education were at a lower risk of dementia in late life. Considering the fact that evidence has been derived from relatively large sample size, population-based nature of the data, and longitudinal assessments, it is becoming increasingly likely that that the association between low education and increased incidence of dementia is not due to an increased burden of neuropathology, but rather due to increased vulnerability of less-educated individuals to cognitive deterioration due to neuropathological insults (Brayne 2010).

5.3 Mid-Life: Occupational Attainment and Mental Activity

While education is viewed as a contributor to cognitive reserve from early adulthood, there has also been considerable interest in epidemiological literature in reserve contributors from mid-life, of which occupational attainment has been one of the most prominent (Karp et al. 2009; Andel et al. 2005). It is believed that demanding occupational roles enhance cognitive reserve by maintaining intellectual flexibility even into the ages when cognitive function is otherwise expected to decline (Schooler 2004). Furthermore, prolonged mental stimulation at work prevents disuse and subsequent atrophy of cognitive processes and skills (Fratiglioni et al. 2004), as predicted by the "use it or lose it" hypothesis (Salthouse 1991).

A number of epidemiological studies have found that individuals in manual occupations are at an elevated risk of poor cognitive performance (Dartigues et al. 1992) and dementia (Qiu et al. 2003; Smyth et al. 2004). One of the explanations offered to account for these findings concerns differences between occupations in the extent of complexity of tasks an individual performs daily, with substantively complex occupational roles expected to provide the most demanding practice and exercise (Schooler et al. 1999). The work complexity aspect has been subsequently assessed in a number of epidemiological studies, with occupational tasks graded along the broad dimensions of complexity with data, people, and things (Karp et al. 2009; Andel et al. 2006; Kröger et al. 2008). Results from these studies have indicated that individuals in occupational roles requiring expertise in tasks dealing with people and data are at a reduced risk of poor cognitive functioning (Smart et al. 2014) and dementia in late life (Dekhtyar et al. 2015a). These effects are not explained by shared genetic- or early-life environmental confounding as demonstrated in a co-twin study (Andel et al. 2005).

Similarly to the effects of education, several imaging and autopsy-verified studies have generally corroborated the findings reported in epidemiological literature, suggesting the existence of a neural basis for the relationship between occupational attainment and cognitive decline and dementia. For instance, it has been shown that higher occupational attainment was associated with a greater pathologic burden (lower regional cerebral blood flow in medial frontal cortex and left

dorsolateral frontal cortex) in patients with frontotemporal dementia (FTD), suggesting a reserve pathway because increased pathologic load must have been initially present for clinical symptoms to appear (Borroni et al. 2009). Furthermore, FTD patients with occupations requiring advanced verbal abilities also had reduced regional glucose utilization in the left inferior frontal gyrus, whereas those with more physically demanding roles at work displayed reduced metabolic rate of glucose utilization in the supplementary motor area (Spreng et al. 2011), further indicating that a neural basis might underlie the effects. A recent study has also shown that survival was prolonged in autopsy-confirmed FTD patients with higher occupational attainment (Massimo et al. 2015). Finally, in the context of AD, controlling for clinical dementia severity, less relative perfusion has been found in the parietal region in individuals whose occupations were characterized by higher interpersonal skills (Stern et al. 1995).

Whereas the association between occupational complexity and dementia has mostly been attributed to cognitive reserve pathways emphasizing neural efficiency or neural compensation, it is also possible that other mechanisms are also implicated. Some studies have suggested the detrimental effects of work stress could also be at play. A study from Sweden found that low job control (in both demanding and non-demanding jobs) was associated with an elevated risk of dementia, even after accounting for vascular factors (Wang et al. 2012b).

5.4 Late Life: Social Networks and Leisure Activities

Although the effects of mid-life cognitive stimulation through complex occupational demands is well-established, a number of studies have suggested that late-life stimulating activities can serve as an additional line of defence against cognitive decline and dementia. Of these stimulating activities, the effects of social networks and leisure activities have been particularly emphasized. Living alone and having limited social contacts have been found to be associated with more than a 50% increase in the risk of dementia in later life in a community-based cohort of 1203 non-demented individuals aged 75 or more from Stockholm, Sweden (Fratiglioni et al. 2004). Interestingly, infrequent social contacts with network resources have not been found to elevate the risk of dementia, provided those contacts were deemed as satisfying. A later study using a more detailed assessment of social networks based on the validated Lubben Social Network Scale reported largely comparative findings, albeit in an exclusively female study population (Crooks et al. 2008). Several pathways have been suggested to account for the findings, including the possible precipitating effects of limited social contacts in situations when pathological alterations are already in place, akin to the reserve model predictions (Fratiglioni et al. 2000). A biological mechanism could also be at work, with previous literature suggesting a link between social integration and immune system (Seeman 1996), whereas both degenerative and vascular dementia also exhibit considerable inflammatory components.

More recent studies into the relationship between social networks and dementia have explored specific activity dimensions, with leisure activities receiving considerable interest. A systematic review has found that 52 original articles linking leisure activities (mental, physical, and social components) and dementia have been published between 1991 and 2011 (Wang et al. 2012a). Observational studies are mostly consistent in indicating beneficial effects of physical (Tolppanen et al. 2015), mental (Karp et al. 2006), and social leisure activities (Paillard-Borg et al. 2009; Verghese et al. 2003) on dementia. Importantly, various leisure activities could have a different effect on the pattern of cognitive decline in old age. Thus, a recent study using detailed data from China has reported that in almost 1500 men and women aged 65 and older, higher levels of mental ability were associated with slower decline in global cognition, language, and executive function. In contrast, higher levels of physical leisure activities were related with less decline in episodic memory and language, with a clear dose-response pattern observable across both mental and physical leisure types (Wang et al. 2013). While observational studies are mostly consistent at indicating protective effects of physical and mental abilities on dementia, randomized control trials have so far lacked similar consistency (Wang et al. 2012a), although some promising findings been reported in a trial of a multi-domain intervention consisting of diet, exercise, cognitive training, and vascular monitoring (Ngandu et al. 2015). Similarly, transitioning from a sedentary lifestyle to moderate physical activity has been shown to have a beneficial effect on cognitive functioning and dementia (Lovden et al. 2013). In general, more research is required to unequivocally conclude that stimulating (socially, physically, and mentally) lifestyles in old age provide an additional line of defence, over and above of that already developed through educational or occupational stimulation.

5.5 Early Life: Childhood Cognitive Ability

Although education, a contributor to cognitive reserve from early adulthood, occupational attainment, a contributor from mid-life, and social networks/leisure activities from late life have all been implicated, to various degrees, in late-life cognitive decline and dementia, a number of questions have remained. One of the most pertinent issues concerns the directionality of the effects of education and occupational attainment: are mentally stimulating lifestyles true risk factors for cognitive decline and dementia, or are their effects simply a consequence of differences in prior cognitive ability? The former possibility, known in the literature as the *differential preservation* hypothesis, suggests that intellectual stimulation and development of mental abilities can in fact delay age-related decline—therefore the extent to which either factor (higher education or occupation) is present, differentially affects the trajectory of cognitive change and decline (Salthouse 2006; Gow et al. 2014). In contrast, the *preserved differentiation hypothesis* argues that educational and occupational effects on cognitive functioning in late life are ultimately confounded by differences in baseline cognitive abilities (Smart et al. 2014).

The possibility that early-life cognitive abilities might be implicated in late-life cognitive decline and dementia has been suggested in the literature previously, although testing the hypothesis proved difficult due to considerable data limitations. For instance, an investigation of autobiographies written by 22-year old nuns has revealed that those nuns who would later develop also had lower linguistic ability, which served as a marker of intelligence, as opposed to the nuns who would not develop the disease (Snowdon et al. 1996). A later study based on the same data indicated that low early-life linguistic ability was also related to lower brain weight, higher degree of cerebral atrophy, more advanced neurofibrillary pathology, and neuropathologic criteria for AD (Riley et al. 2005). Although a seminal study that provided tentative support for the hypothesis that early-life cognitive ability might underlie the risk of late-life decline and dementia, the Nun study had limitations: its population was not representative and the sample size was small (especially in the neuropathological study), which means that the issue of preserved differentiation versus differential preservation of cognitive abilities throughout the life-course remained unaddressed.

Some of the more comprehensive investigations of the effects of early cognitive ability on late-life cognitive ageing have come from the data on Scottish children (known as the *Lothian cohorts*), born in the 1920–1930s who took an identical cognitive test at the age of 11, and were subsequently enrolled in a study of cognitive ageing after the age of 70 (Deary et al. 1921). It has been reported that childhood intelligence was not associated with early-onset dementia, whereas differences by early-life intelligence did exist in the case of late-onset dementia (Whalley et al. 2000). A subsequent study on the same material revealed that lower childhood IQ was a risk factor for vascular dementia, but not Alzheimer disease, suggesting potential mechanisms via the vascular pathology, akin to the brain-battering hypothesis (McGurn et al. 2008). A recent study has explicitly examined the relative importance of the preserved differentiation vs. the differential preservation hypotheses using the Lothian cohorts' data, although in the context of cognitive ageing and not dementia. It was shown that complex occupational roles in mid-life were associated with improved cognitive performance in later life, even after controlling for IQ at age 11 (Smart et al. 2014). On the one hand, these results confirmed the differential preservation hypothesis, suggesting that engagement in complex environments in later life may help preserve cognitive function in advanced ages. On the other hand, since the effect size of occupational complexity was reduced by more than half once childhood intelligence was accounted for, it appears that engagement in complex activities is also partly a consequence of earlier cognitive abilities, as would be predicted by the preserved differentiation hypothesis.

It is, however, important to note that early-life cognitive ability may be associated with cognitive ageing not only by virtue of life-long stability of cognitive abilities, i.e. by affecting the level of functioning in old age, but also by influencing the rate of decline. Longitudinal assessments of cognitive ageing are not uncommon, although only a handful of studies also managed to collect early-life ability measures, and contradictory findings have been reported thus far. For instance, the

latent growth curve analysis of the Lothian cohort data has shown that intelligence at age 11 was associated with the baseline level of cognitive ability at age 79, but not with the rate of decline 8 years later (Gow et al. 2011). On the other hand, childhood cognitive ability was associated with both the level as well as the change in cognitive abilities between ages 43–53 in the National Survey of Health and Development data (Gow et al. 2012). Although more studies are needed to clarify the issue, it appears that early-life ability can affect late-life cognitive declines, and not just the levels of ability, although this may not happen uniformly across all stages of the ageing process.

One way of contributing to the debate about the relative importance of preserved differentiation versus differential preservation in the context of cognitive ageing over the entire life-course would be by examining whether the late-life risk of dementia is reduced in individuals with high education or in complex occupation, after childhood cognitive ability is taken into account. Only two studies so far has been able to combine information on childhood cognitive ability, educational attainment from early adulthood, and life-time occupational complexity in a life-course model of cognitive reserve in dementia (Dekhtyar et al. 2015a).

A large population-based study from Uppsala, Sweden has followed more than 7500 individuals aged 65 for 29 years to detect their incident dementia. To capture childhood cognitive ability, school grades from the third year of elementary school (age 10) were extracted from the school archives, while information was also collected on formal education, and life-time occupational attainment. It was reported that participants with the lowest 20% of school grades from age 10 were at an elevated risk of dementia, relative to the rest of the population (HR: 1.21, $p < 0.05$). Effects of education on dementia disappeared once early-life school performance was accounted for, whereas higher occupational complexity with data preserved its association with a reduced risk of dementia (Dekhtyar et al. 2015a). These findings were later confirmed in a study of about 450 men and women aged 75 or more who underwent detailed neuropsychological assessment, as opposed to the inpatient diagnosis which was used in the study from Uppsala. An even greater risk of dementia (HR: 1.5; $p < 0.05$) was found in individuals with the lowest childhood school grades. These findings indicate that baseline cognitive abilities have a long-term effect on the risk of dementia; this risk can be somewhat modulated by subsequent stimulating work environments, although initial abilities appear more decisive for the late-life risk of dementia.

5.6 Life-Course Model of Reserve

An earlier discussion has indicated that factors influencing the development of reserve are located at various stages of individual's life-course. In the case of dementia risk in old age, pre-morbid cognitive ability is of outmost importance, since it modifies the clinical expression of pathology (Richards and Deary 2005). The fundamentals of pre-morbid cognitive abilities are the current elements of brain

structure (brain reserve) and function (cognitive reserve), with the former emphasizing inputs based on structural neural network complexity, while the latter targeting the functional processing efficiency and flexibility. Ultimately, both structural and functional inputs are in turn influenced by a variety of factors originating as early as childhood, if not before, considering a wealth of literature of genetic (Deary et al. 2004) and early-environmental influences on adult functioning (Dekhtyar et al. 2015b). We have identified childhood cognitive ability, education, occupational complexity, and late-life leisure activity here as some of the most pertinent inputs into the model of reserve over the life-course, but other influencing factors clearly contribute, including health behaviours, socioeconomic environment, and lifestyles (Richards and Deary 2005). Therefore, although most of neuropathology most likely applies to the older ages, the factors allowing the toleration of this pathology occur throughout the entire life-course.

In conclusion, based on the evidence presented in this chapter, it is becoming increasingly clear that the development of reserve that can mitigate the impact of pathology on the clinical expression of disease occurs at various stages throughout the life-course. Baseline cognitive abilities lay the foundation of reserve formation, which is subsequently enhanced by intellectual stimulation provided by educational attainment. By exerting continued demands on the brain, occupational tasks preserve this acquired buffer, much the same way as late-life social engagement and rewarding leisure activities. Ultimately, cognitive reserve can be conceived as a sum of its mental, physical, and lifestyle inputs over the entire life course, and the brain's ability to withstand the changes associated with ageing will to a large extent reflect the gradual accumulation of these inputs.

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Chapter 6
Neural Correlates of Brain Reserve: A Neuroimaging Perspective

Laura Serra and Marco Bozzali

Abstract Brain (BR) and Cognitive reserve (CR) are known to modulate the clinical features of Alzheimer's disease (AD). This is a critical issue especially in the absence of diseasemodifying treatments, but with non-pharmacological interventions available which might delay patients' cognitive disabilities. We reported here a selection of studies investigating the neurobiological substrate of BR and CR in patients with AD at different clinical stages.

Keywords Brain reserve · Cognitive reserve · Alzheimer disease · Mild cognitive impairment · Quantitative magnetic resonance imaging

6.1 Introduction

The concept of reserve was introduced by Stern to account for individual differences in brain susceptibility to age-related and pathological changes (Stern et al. 1992). The reserve's hypothesis has been demonstrated in several neurological disorders such as Alzheimer's disease (AD) (Serra et al. 2011, 2015; Bozzali et al. 2014), vascular injury (Elkins et al. 2006; Dufouil et al. 2003), Parkinson's disease (Glatt et al. 1996), traumatic brain injury (Kesler et al. 2003), HIV (Farinpour et al. 2003) and multiple sclerosis (Sumowski and Leavitt 2013). However AD remains the prototypical model to explain the effect of CR on neuropathology.

Originally, a brain and cognitive classification of reserve was postulated. Brain reserve (BR) refers to differences in brain size and other quantitative aspects of the brain (e.g. amount of neurons or synapses) that explain differential susceptibility to functional impairment in presence of pathology or neurological insult (Stern 2012).

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This concept arose by the observation that prevalence of dementia is lower in individuals with larger brains (Katzman et al. 1988; Schofield et al. 1997; Mortimer et al. 2005). The BR implies a passive model of reserve, suggesting that the brain tolerates more accumulation of neuropathology before it reaches a critical threshold for the appearance of clinical symptoms (Stern 2012). Conversely, the cognitive reserve (CR) posits the differences in cognitive processes as a function of lifetime intellectual activities and other environmental factors that explain the nonlinear relationship between the severity of patients' brain damage and the correspondent clinical symptoms. The CR suggests that the brain actively copes with brain damage using the preexisting cognitive processes or by enlisting compensatory mechanisms (Stern 2002, 2009). The CR model hypothesises that cognitive processes are crucial for explaining individual' differences despite equal brain changes or pathology (Barulli and Stern 2013). Cognitive processes consist of differences in cognitive efficiency, capacity or flexibility resulting from life experiences. CR relies on current neural activity to explain functional differences much more than BR does, suggesting that neuronal activity is modelled by cognitive (social and physical) activities experienced during life. Therefore, recently, together with the CR also the "neural reserve" concept has been proposed (Stern 2012). Neural reserve involves cognitive networks' efficiency and it provides the neural basis of CR. Individual differences in networks' efficiency, or the use of alternative strategies, may provide reserve against the impact of brain damage. The introduction of the neural reserve concept reduces the distance between BR and CR hypotheses, and it makes differences more nuanced (Stern 2012).

Stern et al. (1994) addressed the concept of CR in a study on AD incidence. Analyzing data from a large cohort of non-demented individuals, the authors assumed that AD pathology slowly develops over time independently of CR, and that the pathology begins many years before the onset of clinically diagnosed AD. Individuals with greater reserves should be able to tolerate AD pathology better than those with lower CR levels. As a consequence, AD onset should be delayed in subjects with high reserve. Stern hypothesised that environmental factors, such as years of formal education, occupational attainment and leisure activities, may be considered as proxy measures of CR (Stern 2012) (see Fig. 6.1).

6.2 Proxy Measure of CR

Several studies demonstrated that environmental factors have a significant effect on brain resilience (see Stern 2012 for a review). In particular, years of formal education (Valenzuela et al. 2011), occupational attainment (Valenzuela et al. 2011), lifetime cognitive (Sattler et al. 2012), social (Sattler et al. 2012) and physical activities (Rydwik et al. 2013), intelligence quotient (Rentz et al. 2010), and memory performance (Stern 2012) have been considered the most relevant proxies of CR. However, among all these CR measures, education is considered the most relevant factor impacting on brain resilience (Stern 2012). Indeed, it has been stated

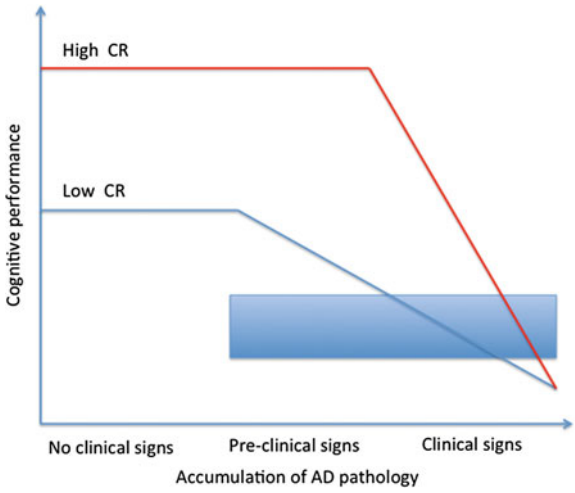

Fig. 6.1 This figure illustrates the different clinical AD onset according with low and high CR levels. In particular, in patients with high CR the onset of dementia is postponed compared to those with low CR (figure modified from Stern 2009)

that education may influence the development of AD in several ways. Education may induce an increase of synaptic density in the neocortex, causing a delay in the AD onset (Katzman 1993). Obviously, the deterioration occurs independently of education, but the educational level may reflect cognitive capacity that allow to delay the clinical symptoms of AD, which does not become evident until the deterioration reaches a more severe degree. As a consequence, more AD pathology is needed to cause dementia in patients with higher educational level (Stern 2012). In addition, education could also be considered as a socializing process, promoting learning strategies, encouraging the development of divergent thinking and enabling the individual to perform more competently on cognitive demand (Gilleard 1997). Moreover, education appears to be an important environmental experience that may enhance neural connectivity as well as the propensity to engage in mentally stimulating activities throughout life (Vance and Crowe 2006). Finally, education may improve the intellectual approach to life events (Friedland 1993), which can lead to lifelong mental stimulation and an enhanced activation of the brain regions involved in cognitive processing (Friedland 1993).

Consistently, previous studies showed a significant reduction of AD risk in patients with mild cognitive impairment (MCI), or in healthy elderly with different levels of CR, measured as educational level, (Stern 2012). Specifically, reduced risk to develop AD was observed in patients with MCI and high CR, 12 years before the clinical assessment (Sattler et al. 2012).

Some studies indicate that not only reaching a high educational level, but also being employed in highly mentally demanding occupation is related to a decreased risk of developing AD (Evans et al. 1997; Stern et al. 1994; Qiu et al. 2003). For instance, individuals without a lifetime occupation showed an increased risk of AD (Anttila et al. 2002). Evans et al. (1997) showed that subjects with lower socioeconomic status, computed considering education, occupational attainment and income, had a higher risk of developing AD. Also Stern et al. (1994) suggested that

the risk of developing AD was stronger in subjects with both low education and low lifetime attainment, supporting a synergic effect of education and occupation. Therefore, education and occupational attainment can influence the development of AD supporting the idea that engaging in mentally stimulating activities can be beneficial for coping with AD neuropathology (Stern 2012). Moreover, several articles showed that patients with AD usually had few hobbies and were less involved in psychosocial activities during their lifetime (Friedland et al. 2001; Crowe et al. 2003; Wilson et al. 2002; Verghese et al. 2003). In particular Wilson et al. (2002) found that subjects engaged in frequent cognitive activities such as reading, watching television or card playing were less likely to develop AD than subjects with infrequent activities. More recently, using a comprehensive questionnaire investigating cognitive, social, physical leisure activities, education and occupation, an increased risk to develop AD in amnesic MCI (a-MCI) patients with low CR level was found (Serra et al. 2015). In addition, this study revealed that a-MCI patients with high CR and high baseline general cognitive efficiency (as measured by MMSE), showed a significant difference in the survival's time compared to patients with high CR but low baseline MMSE. Specifically, patients with high CR and high baseline MMSE remained AD-free for 21 months respect to those high CR and low baseline MMSE (see Fig. 6.2). Conversely, no difference in the survival's time was found in a-MCI patients with low CR and different level of baseline cognitive efficiency (see Fig. 6.3).

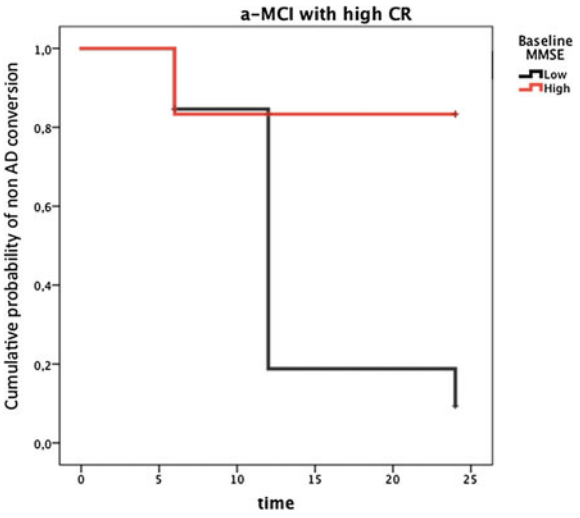

Fig. 6.2 This figure illustrates the Kaplan-Meier curves obtained in a-MCI patients with high CR level and modelled according to their baseline cognitive efficiency, as measured by Mini Mental State Examination (MMSE). In *red*, there is shown the survival time for patients with high MMSE scores at baseline, while in *grey* there is reported the survival time for patients with low MMSE scores at baseline. Patients with high CR and high MMSE scores at baseline (in *red*) converted to Alzheimer Disease significantly later than those with baseline low MMSE scores (in *grey*) at baseline. Figure modified from Serra et al. (2015)

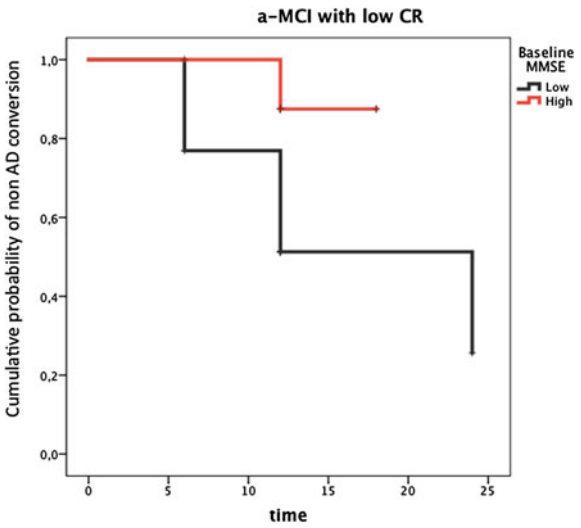

Fig. 6.3 This figure illustrates the Kaplan-Meier curves obtained in a-MCI patients with low CR and modelled according with their baseline cognitive efficiency, as measured by Mini Mental State Examination (MMSE). In *red* is shown the survival time for patients with high baseline MMSE while in *grey* is reported the survival time for patients with low baseline MMSE. No difference in the time of conversion to Alzheimer's disease was detected between patients with low (in *grey*) or high (in *red*) MMSE score at baseline. Figure modified from Serra et al. (2015)

Moreover, a longitudinal study in a large cohort of elderly showed that enriched cognitive life styles both reduced the risk of cognitive decline and improved the recovery of cognitive functions in the early stage of neurodegenerative diseases (Marioni et al. 2012). More recently, Smart et al. (2014), showed an association between complexity of occupation and successful ageing, supporting the hypothesis that more stimulating environments preserve cognitive ability later in life. However, a combination of different measures of CR (such as education, occupation and cognitive lifestyle) was found more sensitive to reduce the AD risk, with respect to the different CR proxies separately (Valenzuela et al. 2011).

6.3 Reserves and AD-Related Biomarkers

Several studies showed an interaction effect between levels of CR, AD biomarkers (e.g. APOE, β-amyloid levels, brain atrophy, etc.) and the risk to develop the clinical symptoms of AD (Jack et al. 2013; Serra et al. 2011, 2015; Soldan et al. 2013; Bozzali et al. 2014).

In particular, Jack et al. (2013) showed that people with a high risk of cognitive impairment due to AD pathophysiological processes, have both $APOE_4$ and low CR levels. On the contrary, individuals with low genetic AD risk and high CR levels better withstand AD pathology and, therefore, maintain longer normal

cognitive functions. Recently, an interaction between CR, tau and phosphorylated tau (p-tau), but not β-amyloid levels, was demonstrated (Soldan et al. 2013). However, also an additive, rather than interacting, effect was reported for CR levels and AD biomarkers (Vemuri et al. 2011).

Several neuroimaging studies have provided in vivo evidences that lifestyle acts on brain organization, confirming both BR and CR concepts. For instance, Garibotto et al. (2013), using FDG-PET, showed positive correlation between CR measures (as education and occupation) and cholinergic activity in the bilateral hippocampus and in the right posterior cingulate gyrus, both in AD and MCI patients. The authors affirmed that the significant correlation found between cholinergic activity, in structures traditionally involved in memory, and CR proxies, suggests that BR in AD is associated with a preserved/stimulated cholinergic neurotransmission (Garibotto et al. 2013).

Recently, other studies showed a significant association between CR proxy, β-amyloid levels measured in CSF, and FDG-PET metabolism, in patients with preclinical AD (Garibotto et al. 2012; Ewers et al. 2013). In AD patients Aβ-carriers, higher education was associated with an altered metabolism, as measured by FDG-PET, suggesting that CR plays a compensatory function to sustain cognitive ability in presence of early AD pathology (Garibotto et al. 2012; Ewers et al. 2013). An association between FDG-PET metabolism in the temporoparietal cortex and high CR levels was observed also in MCI patients converters compared to MCI non-converters and controls (Garibotto et al. 2008). Similar results were found also in prodromal AD (Morbelli et al. 2013).

Using resting-state functional MRI (RS-fMRI) Bozzali et al. (2014) showed that CR modulated the functional connectivity in the posterior cingulate cortex, whose disconnection with the temporal lobes is known to be critical for the conversion from MCI to AD (Fig. 6.4). This effect was highly significant in AD patients, less evident in patients with MCI, and totally absent in healthy subjects (Bozzali et al. 2014). The authors hypothesised that CR effects observed in patients were primarily the result of neural compensation (i.e. compensatory resources recruited to cope with brain change) rather than neural reserve (i.e. preexisting resources determining individual performance in the absence of pathology) (see Stern 2012 for a review) (Bozzali et al. 2014).

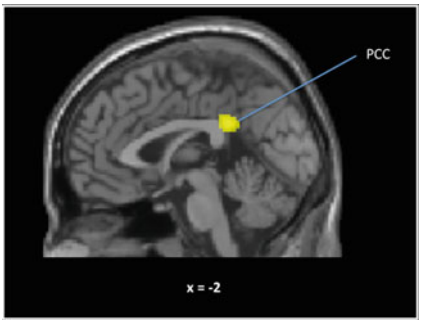

Fig. 6.4 This figure shows positive association between DMN functional connectivity (into the Posterior Cingulate cortex) and CR level across AD and a-MCI patients. Figure modified from Bozzali et al. (2014)

Several structural neuroimaging studies provided strong evidence of the relationship between CR levels and brain resilience. In particular, using voxel-based morphometry (VBM), AD patients with high CR (measured as years of formal education) showed significant grey matter atrophy in the entorhinal cortex and in the temporal pole (see Fig. 6.5, panel A), while less educated AD patients showed widespread atrophy in the supramarginal gyrus, posterior cingulate cortex and precuneus (Serra et al. 2011) (see Fig. 6.5, panel B). Another study (Murray et al. 2011) showed that education counteracts the effect of hippocampal atrophy, but of cerebrovascular disease as well in patients with AD. Similarly, Brickman et al. (2011) provided evidence that healthy elderly with high CR suffered from a severe white matter damage compared with those low CR, suggesting that they were more able to cope with neurodegeneration. More recently, a significant higher risk for AD conversion was shown in a-MCI patients with higher CR levels (compared to those with low CR level) and white matter lesions in associative fasciculi (Serra et al. 2015). Brain structural damage measured in terms of cortical thickness has been correlated to different levels of CR (Querbes et al. 2009; Arenaza-Urquijo et al. 2013). In particular, MCI patients that could convert to AD 6–12 months later,

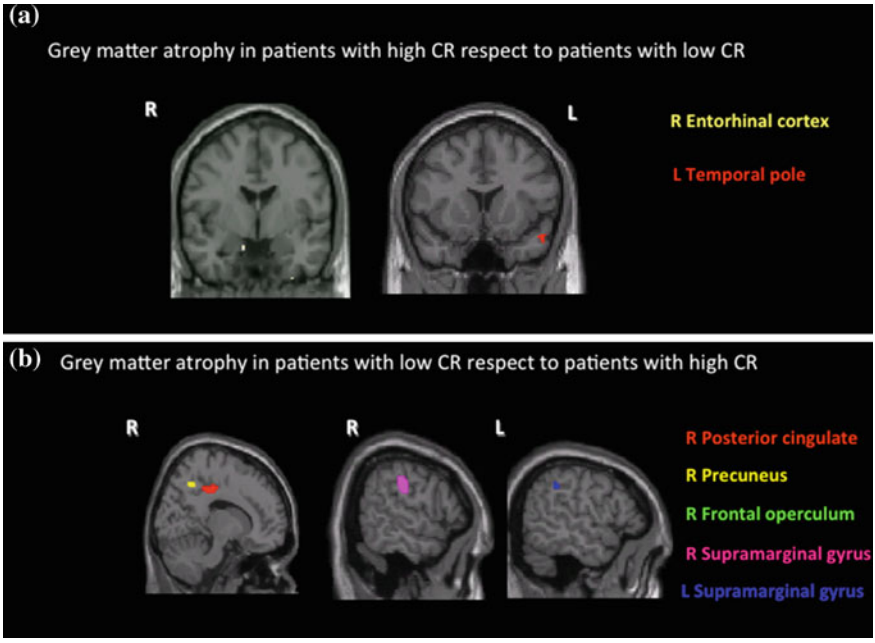

Fig. 6.5 *Panel A* shows regional grey matter changes in patients with high compared to those with low CR. Patients with high CR accumulated more atrophy in the entorhinal cortex and temporal pole, regions traditionally involved in the memory functions. Conversely, *panel B* shows grey matter density loss in patients with low CR compared to patients with high CR. In particular, patients with low CR suffered from a widespread brain atrophy involving, mainly, the supramarginal gyrus, the precuneus and the posterior cingulate cortex. Figure modified from Serra et al. (2011)

showed low CR levels and significant reduced cortical thickness at baseline, as compared to non-converter MCI (Querbes et al. 2009). Moreover, an inverse relationship between high CR, hippocampal atrophy and decrease cortical thickness was demonstrated in the supramarginal gyrus also healthy elderly Aβ-42 carriers (Arenaza-Urquijo et al. 2013).

6.4 Conclusion

CR concept is a theoretical general framework introduced to explain individual differences to withstand brain damages. Several behavioural and neuroimaging studies support the evidence that lifestyles act on brain plasticity modulating the impact of neurological insults. However, once that AD is clinically evident, the protective benefits of premorbid experience are assumed to be substantially decreased, and since AD is more advanced in those with higher premorbid skill levels they decline more rapidly (Stern 2012). In addition, the relationship between cognitive enrichment and brain resilience in the human being needs to be further investigated, in order to provide new therapeutic insights and interventions to treat or prevent the evolution of neurodegenerative disorders. However, further studies assessing relationship between different CR levels and non-pharmacological treatments seem to be necessary and desirable in the immediate future.

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Chapter 7
Non-pharmacological Approaches Based on Mind-Body Medicine to Enhancement of Cognitive and Brain Reserve in Humans

Cristiano Crescentini, Franco Fabbro and Salvatore M. Aglioti

Abstract In recent years, the concepts of cognitive reserve (CR) and brain reserve (BR) have been used to take account of the interindividual variability between cognitive impairment and degree of brain damage occurring in a variety of neurological disorders. These studies, however, have typically not addressed the critical issue of the clinical implications of this research for the clinical care of the patients. After an introduction to CR and BR theory, the present chapter will review studies exploring CR and BR in healthy aging and in a series of progressive and relatively common neurological conditions such as Alzheimer's disease (AD), multiple sclerosis (MS), and Parkinson's disease (PD). In the second part of the chapter, we will discuss the implications of CR and BR for clinical interventions based on mind-body medicine (in particular meditation), as possible approaches aimed at potentiating individuals' reserve in the conditions of healthy aging, AD, MS, and PD.

Keywords Cognitive reserve · Brain reserve · Alzheimer's disease · Multiple sclerosis · Parkinson's disease · Mind-body medicine · Mindfulness meditation

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7.1 Introduction: What Are Cognitive Reserve and Brain Reserve?

The theory of reserve derives from research on Alzheimer's disease (AD) and was argued to account for the discrepancy between degree of brain damage and clinical manifestation (Barulli and Stern 2013; Stern 2002, 2009; Steffener and Stern 2012). More in particular, it was advocated that individual differences in leisure life experiences, educational level, or general intelligence as well as differences in brain size, number of synapses, or neuronal count can protect some people better than others against manifestation of cognitive decline. Among these factors, an operational distinction has been made between proxies associated to Cognitive Reserve (CR) and proxies associated to Brain Reserve (BR) (Stern 2009; Steffener and Stern 2012), which in turn reflects a distinction between functional and structural measures of brain networks, respectively.

CR is expressed by flexible and efficient activation of cognitive strategies and brain networks while handling cognitive tasks. What makes some people maintaining their functioning and coping better than others with brain damage is their way of using flexibly and efficiently such neurofunctional processes. Common cognitive or behavioral proxies of CR are educational level, vocabulary knowledge, participation in leisure/recreational activities, occupational attainment, and general intelligence (IQ) (Stern 2009; Steffener and Stern 2012). CR may also be derived from networks of task-related neural activity that might mediate the effects of CR proxies on performance. Stern (2002, 2009) has proposed that CR is neurally implemented into the forms of neural compensation and neural reserve. Neural compensation refers to the process whereby individuals vary in the use of neurofunctional processes not generally engaged by a task in normal situations in order to compensate for pathology-related disruption of normal networks. Neural reserve relies on the concepts of *efficiency* and *capacity* to explain the interindividual differences in the activation of task-related cognitive strategies and brain networks during task performance. Individuals with more efficient and greater capacity networks may withstand brain damage in case of pathology better than subjects with less efficient and lower capacity networks. To summarize, CR is not conceptualized as a purely passive cumulative product of lifetime intellectual enrichment but rather as a set of cognitive processing strategies and functional brain networks that may enhance neural efficiency; on this view CR may be shaped by life experiences throughout the lifespan (Stern 2002, 2009; Barulli and Stern 2013).

By contrast, anthropometric proxies such as the maximal lifetime brain volume (MLBV) (estimated with head size or intracranial volume) or synaptic density are considered to be effective measures of BR (e.g., Sumowski and Leavitt 2013). Specific cognitive or clinical deficits will occur when BR capacity will be depleted beyond some critical threshold (Katzman 1993; Satz 1993; Stern 2009; Steffener and Stern 2012). The higher BR, the later the occurrence of cognitive deficits in the presence of disease.

Thus, on the one hand BR is conceptualized as a passive model, in that the threshold for functional decline is fixed by quantitative brain measures. However, on the other hand, CR is considered to be an active model in that the same threshold is not fixed but can be dynamically altered by experience (Barulli and Stern 2013). Having said this, it is worth mentioning that the boundaries between the two models are nuanced given that they may be intercorrelated (see Steffener and Stern 2012).

In the next two main sections we will: (i) briefly review studies exploring CR and BR in healthy aging and in critical chronic, progressive and relatively common neurological conditions such as AD, multiple sclerosis (MS), and Parkinson's disease (PD); and (ii) we will discuss the implications of CR and BR for clinical interventions based on mind-body medicine (in particular mindfulness meditation, MM), as possible approaches aimed at potentiating individuals' reserve.

7.2 Application of the Reserve Theory in Neurology

7.2.1 Healthy Aging and Alzheimer's Disease

The discrepancy between clinical phenotype of AD and its pathological severity has been discussed for about 30 years. For example, in a prospective study Katzman et al. (1989) observed advanced AD pathology from brains of 10 cognitively preserved individuals in a postmortem examination. These results are in line with more recent findings showing that individuals who are more inclined to suffer from clinical dementia may have less severe AD pathology while others with no manifestation of clinical dementia may have more neuropathological signs (Riley et al. 2002). As mentioned in Introduction, the reserve theory has been proposed to explain these apparently counterintuitive findings. More generally, a large number of studies have investigated the potential impact of CR indexes such as educational level, occupational attainment, and participation in leisure activities (e.g., playing or listening to music, visiting friends, reading, doing physical activities, playing games or card, doing charity work, being involved in spiritual/religious activities, etc.) on the risk of developing dementia (for reviews see Stern 2012; Xu et al. 2015).

In a series of seminal epidemiological studies, Stern and colleagues have reported significant protective effects of the above-mentioned CR indexes against manifestation of clinical dementia (see in Stern 2012). Briefly, in a first longitudinal study carried out on a large sample (n = 593) of non-demented older individuals (from 60 years of age), Stern et al. (1994) found that those with less than 8 years of education or with low occupational levels (e.g., unskilled, skilled trade, or craft) had respectively 2.2 times and 2.25 times greater risk of developing dementia relative to those with more education or with higher lifetime occupational attainment. More recently, Stern and colleagues (Scarmeas et al. 2001) have extended these findings to participation to leisure activities in non-demented elders: it was shown that individuals engaged in more leisure activities had 38% less risk of developing

dementia than those engaged in less leisure activities. These data are in line with a more recent review by Valenzuela and Sachdev (2006a; see also Valenzuela and Sachdev 2006b) who globally quantified the protective effects of higher CR (measured with the three indexes discussed above plus pre-morbid IQ) in a reduction of 46% of the risk of developing dementia. This striking result was found over a median of 7.1 years follow-up and involved data from 29,279 individuals from 22 studies. In line with the reserve theory, other studies have documented that people with greater reserve are able to withstand more severe AD pathology, with the effect that the onset of clinical dementia may be delayed; however, disease pathology progresses over time independently of an individual's reserve (see in Stern 2012; Stern et al. 1995, 1999).

These data globally show that high CR among healthy elders reduce risk for incident dementia in the future, thus suggesting that taking into consideration stimulating activities in elders, such as reading and hobbies, may usefully help predicting their future cognitive decline (Wilson et al. 2002; Verghese et al. 2003). These findings complement results of other studies on normal aging showing that higher CR (e.g., higher educational, occupational attainment, participation in leisure activities) is associated with slower cognitive decline (see in Steffener and Stern 2012) and with less hippocampal atrophy (Valenzuela et al. 2008). Overall, the protective effects of CR against cognitive decline, both during the course of neurodegeneration and in healthy aging, have been ascribed to individual differences in the ability to maintain cognitive performance through use of alternate brain networks (i.e., neural compensation) or differential recruitment of brain resources, for example in frontal and parietal regions (i.e., neural reserve) (Stern 2009; Wook Yoo et al. 2015; Bartrés-Faz et al. 2009).

With regards to BR, anthropometric indicators such as head circumference have often been used as proxy for brain size and BR. Head circumference has been shown to mitigate risk for dementia in a number of studies (Schofield et al. 1997; Borenstein Graves et al. 2001; Mortimer et al. 2003; but see Espinosa et al. 2006). As a recent example, Perneczky et al. (2010) have shown that head circumference altered the relationship between brain atrophy and cognitive decline in 270 AD patients. It was found that larger values of this BR index were associated with less cognitive impairment in the face of brain atrophy; in other words, for a given level of atrophy, patients with a larger head circumference showed better cognitive performance. Moreover, as evidence of the interdependence of BR and CR proxies, in the study of Mortimer et al. (2003) it was found an interaction between head circumference and educational attainment in the risk for AD: increases in risk due to small head circumference could be overcome by high education.

More recently, a considerable research effort is being directed at exploring more specific structural markers of BR. A number of key brain structures primarily involved in neurodegenerative processes such as the lateral ventricles, the hippocampus and white matter lesion volume have been identified. Abnormalities in these brain regions have indeed proved predictive of subsequent development of dementia and AD or disability in cognitively intact individuals (see in Cavedo et al. 2012). For example, Cavedo et al. (2012) have recently provided normative data for

the three mentioned structural markers of BR in a sample of 158 cognitively intact people ranging from 40 to 90 years of age. Low and high BR were identified for each marker (respectively indicated by the 5th and 95th percentiles threshold), thus making it possible to effectively use these data to estimate the brain's resilience to neurodegeneration in both cognitively intact and AD individuals.

7.2.2 Multiple Sclerosis

Multiple Sclerosis (MS) is a chronic inflammatory, demyelinating and degenerative disease of the central nervous system (CNS) (Noseworthy et al. 2000). It is the most common nontraumatic neurologic disease among young adults. Cognitive disturbances occur at various degrees in 40–65% of patients affected by MS (Rao et al. 1991; Chiaravalloti and DeLuca 2008; Jongen et al. 2012; Guimarães and Sá 2012) and are considered as one of the most disabling symptoms of the disease. Especially when coupled with other disabling symptoms such as depression, fatigue, or anxiety, cognitive changes can profoundly impair patients' health-related quality of life (HRQOL) (Chiaravalloti and DeLuca 2008). These changes affect in particular speed of information processing, attention/working memory and learning and memory.

In the last ten years, more than 20 studies drew on the reserve theory to account for the interindividual discrepancy between cognitive impairment and MS-related brain structural damage. Overall, these studies have used a variety of proxies of CR and have investigated how each of these is able to buffer the effects of MS disease. Thus, a series of cross-sectional studies have shown that educational level and pre-morbid IQ (estimated through word-reading tests or vocabulary knowledge) protect against MS-related cognitive inefficiency and memory problems. In more detail, it was shown that MS patients with low CR, but not with high CR, perform poorer than healthy controls on measures of complex information processing efficiency and verbal learning and memory (Sumowski et al. 2009a; see also in Sumowski and Leavitt 2013; Crescentini et al. 2014; Sumowski 2015). Another series of cross-sectional studies also showed the critical role of intellectual enrichment in mitigating the effect of disease burden on cognition. For instance, it was shown that the detrimental effect of MS-related brain atrophy (estimated from computations of third ventricle width) on cognitive status (information processing efficiency and memory performance) was reduced in MS patients with high versus low pre-morbid IQ (Sumowski et al. 2009b, 2010a). The MS patients with high CR could withstand better than the MS patients with low CR the brain damage associated to MS without manifesting cognitive impairment.

Of importance, other cross-sectional studies have also underlined the critical role of cognitive leisure activities performed during early adulthood (e.g., hobbies, playing a musical instrument, reading, producing art, and nonartistic writing and playing structured games) in protecting against disease-related cognitive impairment and in attenuating the negative effect of MS disease burden (e.g., T2 lesion

volume) on current cognitive status of MS patients. Thus, taking part in more early-life cognitive leisure activities was positively correlated with better cognitive outcome (e.g., processing speed and memory) after controlling for pre-morbid IQ, education, and brain atrophy (see in Crescentini et al. 2014; Sumowski 2015). Overall, the reviewed data of cross-sectional studies on reserve against cognitive impairment in MS have recently been corroborated by longitudinal research. A protective effect of intellectual enrichment (e.g., educational level and vocabulary knowledge) against decline in cognitive efficiency and memory over up to 5 years has indeed been reported (Benedict et al. 2010; Sumowski et al. 2014; see also Amato et al. 2013). With regards to other CR proxies such as occupational attainment, the findings seem more mixed with some studies finding a benefit against cognitive impairment (Ghaffar et al. 2012) while others failing to report such positive influences (Scarpazza et al. 2013). Of critical importance, a more limited number of studies has recently started to take into account measures of current, active CR of patients already diagnosed with MS (i.e., leisure/recreational activities concurrent with the comorbidity): positive relationships with MS patients' health, well-being, and cognition have been reported (Schwartz et al. 2013a, b, c, d; see also Crescentini et al. 2014).

The studies reviewed above suggest that intellectual enrichment mitigates the negative effects of MS neuropathology on cognitive status due to greater efficiency and capacity of neural networks. Sumowski et al. (2010b) have recently showed that this is the case in a functional and structural imaging study of CR in MS. In particular it was found that during the execution of a demanding working memory task, CR (vocabulary knowledge) was positively associated with default network activity (anterior and posterior cingulate cortex) but negatively associated with prefrontal recruitment. In other terms, MS patients with high CR required less deactivation of the default network and less activation of the prefrontal cortex (a finding reflecting less use of cerebral resources in general), in order to perform the working memory task as accurately as MS patients with low CR. Moreover, MS patients with high CR, who showed more default network and less prefrontal cortex activation during the working memory task, could withstand more severe brain atrophy before showing cognitive status similar to patients with low CR.

Finally, with regards to BR, two recent studies by Sumowski and colleagues showed that larger MLBV reduces risk for cognitive impairment in MS. In particular, in a cross-sectional study (Sumowski et al. 2013) it was found that larger MLBV attenuates the impact of brain pathology on cognitive efficiency, while in a longitudinal sample (Sumowski et al. 2014) the same BR proxy was shown to soften decline in cognitive efficiency over 4.5 years.

7.2.3 Parkinson's Disease

Parkinson's disease affects 1% of people over 60 years of age and 4% of those aged over 80 (Dorsey et al. 2007; De Lau and Breteler 2006), and is the second

commonest neurodegenerative disorder in developed countries. PD has been traditionally considered as a motor disorder characterized by behavioral manifestations (i.e., tremor, rigidity, bradykinesia, and postural instability) reflecting pathological depletion of dopamine-producing cells in regions of the ventral midbrain such as the substantia nigra pars compacta. However, the neuropathology of PD also involves non-dopaminergic systems of the nervous system not directly involved in motor control (Olanow et al. 2009). Accordingly, there is a growing consensus that PD, even in its earliest stages, also affects cognitive functions, up to the point that, with PD progression, non-motor symptoms can be more disabling than the motor symptoms (Chaudhuri et al. 2006). The most frequently affected neurocognitive domains in PD are working memory, problem-solving, planning, attentional shifting, and inhibitory control (Cools et al. 2001; Owen 2004; Braver and Cohen 2000; Crescentini et al. 2008). Neuropsychiatric symptoms such as depression, anxiety, fatigue, apathy, and psychotic symptoms are also common in PD and have serious consequences for daily functioning and quality of life (Aarsland et al. 2009). Several symptomatic therapies such as deep brain stimulation as well as dopamine replacement have proven effective in providing considerable benefit to PD patients. However, no treatment has yet been shown to definitively delay or stop the disease progression or to effectively treat non-motor symptoms.

As with MS, a considerable number of studies have investigated whether CR affects the development of cognitive deficits and dementia in PD. However, the protective effects of only a restricted type of CR proxies have been tested in PD. In particular in a recent review and meta-analysis, Hindle et al. (2014; see also Muslimovic et al. 2007; Poletti et al. 2011 for other reviews on CR in PD) have identified 34 studies that tested the effects of educational level (a proxy of passive, pre-morbid CR) against manifestation of cognitive decline in PD. Most of these studies were cross-sectional investigations, while a more restricted number involved longitudinal cognitive decline and long-term dementia diagnosis. The meta-analysis showed that higher education has beneficial effects on cross-sectional performance of cognitive tests tapping global cognition (e.g., Mini Mental State Examination, MMSE), executive function, attention, memory, and visuospatial functions (see Table 1 in Hindle et al. 2014, for a list of neuropsychological tests included in each cognitive domain). Furthermore, higher education was also associated with a reduced rate of cognitive decline but there was no evidence of a protective effect of this CR index against long-term diagnosis of dementia in PD. Two more recent cross-sectional studies not included in the meta-analysis have further investigated the CR theory in PD by employing educational attainment as a proxy for CR. Kotagal et al. (2015) have shown the protective effect of educational level against manifestation of motor impairment in PD: higher education level associates with lower severity of PD-related motor burden than lower years of education. In the second study, Lucero et al. (2015) have tested whether educational attainment can influence the correlation existing between cognitive impairment and cortical β-amyloid accumulation, which is generally associated with cognitive decline and dementia in PD. In particular, it was found that for PD patients with less than

16 years of education, higher fibrillar β-amyloid deposition in the brain correlated with worse global cognitive function (e.g., MMSE). However, for patients with at least 16 years of education this correlation was absent, with the patients maintaining better cognitive function despite the presence of neuropathology. Considering that low and high educated PD patients had comparable levels of fibrillar β-amyloid deposition, these findings suggest a protective role of education not against the development of neuropathology but against the negative effects of cortical β-amyloid pathology on PD patients' cognition.

Turning back to the meta-analysis of Hindle et al. (2014), it also highlighted the absence of studies that took into consideration proxies of CR other than education, such as occupation, lifestyle, or leisure activity. Nonetheless, two out of the 34 original studies involved in the meta-analysis also considered, as proxy of CR, a measure of pre-morbid general intelligence in addition to education (i.e., Armstrong et al. 2012; Koerts et al. 2013). Positive effects of pre-morbid IQ were found in relation with reduced odds of mild cognitive impairment diagnosis in PD (Armstrong et al. 2012), and with better performance on cognitive tests tapping executive functioning, memory and psychomotor speed (Koerts et al. 2013; see also Liozidou et al. 2012 for related findings).

More recently, a few studies have tried to further extend the theory of reserve to PD by studying other proxies of CR. In a cross-sectional imaging study, Lee et al. (2014) have shown, for example, that olfactory performance, which is commonly diminished in PD, acted as CR in non-demented PD patients. First of all, it was observed that deficits in verbal memory function were more severe in the PD patients who showed poor performance in an olfactory identification test relative to patients with higher olfactory performance. However, it was critically found that PD patients with high olfactory performance (relative to patients with low score in the olfactory test) had decreased gray matter (GM) density in a key set of brain regions related to olfaction (temporal, orbitofrontal, mesiofrontal, anterior and middle cingulate and prefrontal). Olfactory performance was furthermore negatively correlated with intracerebral volume and brain GM volume, which are markers of BR. These data thus globally suggest that higher olfactory performance in PD may compensate GM volume loss in order to reduce the manifestation of cognitive dysfunction. However, the exact reserve mechanism of olfactory performance against PD pathologies remains unclear. Finally, in a longitudinal cohort study with 4-year follow-up, Hindle et al. (2015) have documented for the first time an effect of cognitive lifestyle (i.e., current social engagement given by the number of people that PD patients know well and visit and amount of telephone use in the last week) on measures of global cognition (MMSE as well as measures of attention, memory, language and visuospatial function) and dementia severity (Clinical Dementia Rating, CDR) in PD. Beside a positive effect of higher educational level and recent social engagement on cross-sectional global cognition, it was found that low levels of social engagement (telephone use in particular) were associated with an increased risk of dementia.

7.3 Non-pharmacological Approaches Based on Mind-Body Medicine to Enhancement of Cognitive and Brain Reserve in Neurological Conditions

7.3.1 Mind-Body Medicine and Interventions

The set of reviewed studies indicate the extensibility of the reserve theory to a number of neurological conditions. Consequently, an issue emerges about the implications of this research for clinical care of the patients. A critical aspect pertains to the possibility to employ therapeutic interventions aimed at improving reserve in newly diagnosed neurological patients. In other words, it appears important to empirically test whether changes in intellectual enrichment and leisure activities can moderate cognitive decline in different neurological conditions while disease progresses.

Surveys indicate that the interest and use of complementary and alternative medicine (CAM) approaches is rising among aging persons with different types of cognitive and health problems (Lavretsky 2009). For example, it was shown that approximately 40% of PD patients (Rajendran et al. 2001; Ghaffari and Kluger 2014; Bega et al. 2014) and 60% of MS patients (Barnes et al. 2004; Apel et al. 2006; Esmonde and Long 2008; Crescentini et al. 2014) have tried one or more forms of CAM therapies in addition to traditional treatments. Common reasons for using CAM are patients' desire for a more holistic, whole-person based approach to treatment, patients' interest into taking more self-control over disease management and their dissatisfaction with conventional medicine. Common types of CAM include dietary natural products such as herbals, vitamins, minerals, and probiotics as well as integrative nondietary approaches such as acupuncture, massage, meditation, movement therapies, relaxation techniques, Tai chi, Yoga, cannabis, music therapy, hypnotherapy, magnetic field therapy, biofeedback, and neuromuscular electrical stimulation (Horowitz 2011; Ghaffari and Kluger 2014; Bega et al. 2014). For the vast majority of CAM, there are only few controlled trials (CT) and randomized controlled trials (RCT) evaluating their effectiveness or mechanisms of action in different neurological conditions; this thus makes it difficult to recommend any specific modality or therapy.

Nevertheless, recent evidence is beginning to show that the most commonly practiced form of CAM, namely mind-body medicine, may be a helpful therapeutic option for cognitive and psychological symptoms occurring in certain neurologic diseases (e.g., Wahbeh et al. 2008). Mind-body medicine (Vitetta et al. 2005) integrates the mind, brain, body, and behavior with the intent to use the mind to positively influence psychophysical functioning and well-being. One of the most prevalent practices of mind-body medicine is meditation, including in particular mindfulness meditation (MM).

The most common forms of meditation derive from healing and spiritual traditions originated in India several centuries BCE. The term meditation globally refers to the complex attentional and emotional regulatory training procedures that

are generally followed by people for the promotion of well-being (Lutz et al. 2008; Fabbro 2010). In the past three decades there has been an increase in scientific interest in the psychological and neurocognitive benefits of meditation, in particular of MM. Mindfulness is an attribute of consciousness that consists of being aware of and attentive to what is occurring in the present moment with a non-judgmental attitude of openness and receptivity (Baer 2003; Brown and Ryan 2003; Kabat-Zinn 1990, 1994, 2003). Mindfulness skills can be developed effectively through the practice of MM in which any arising feeling, thought, emotion, and sensation is not attempted to be changed by the perceiver but is instead observed and accepted. Popular formalizations of MM for clinical interventions are the mindfulness-based stress reduction (MBSR), a program in which several mind-body techniques are amalgamated such as MM, yoga postures, breathing exercises, and relaxation techniques, and the mindfulness-based cognitive therapy (MBCT) (see in Baer 2003, 2010). There is increasing evidence in healthy young and old individuals suggesting a role of MM interventions in potentiating cognitive and brain reserve. For example, several research lines have demonstrated that MM interventions can promote improvements in cognitive function, especially memory, attentional regulation and executive control, and changes in the brain structure (Cahn and Polich 2006; Newberg et al. 2014; Lutz et al. 2008; Malinowski 2013; Tomasino et al. 2013). Moreover, positive clinical outcomes for depression, anxiety, pain, immune function, substance abuse, and stress-related disorders have been reported in clinical studies employing MM trainings (e.g., Baer 2003; Brown and Ryan 2003; Didonna 2009; Chiesa and Serretti 2011).

In the sections below we will specify how meditation and MM interventions may be relevant for building patients' reserve in the neurological conditions of AD, MS, and PD.

7.3.2 *Meditation in Healthy Aging and Alzheimer's Disease*

Despite empirical evidence for the effect of meditation and MM interventions in healthy older adults being limited, recent cross-sectional studies indicate that meditation and MM may have the potential to preserve brain function and to counteract or prevent age-related brain degeneration (for empirical and conceptual reviews see Xiong and Doraiswamy 2009; Crescentini et al. 2014; Gard et al. 2014; Luders 2014). A few studies have shown that meditation can bring about enduring structural changes in the brain. Lazar et al. (2005) provided the first evidence of the effect of meditation experience on cortical thickness. The authors examined structural brain images of participants with extensive insight meditation experience (n = 20 with 9.1 $\pm$ 7.1 years of experience) (Insight meditation typically involves training of present moment awareness and mindfulness). Regional cortical thickness in areas such as the right insula and right prefrontal cortex (that are involved in interoception and attention), was greater in the practitioners compared to non-meditators controls (n = 15). Tellingly, between groups differences in

prefrontal cortex thickness were most evident in older individuals, suggesting that meditation may help to attenuate the aging process by preserving cortical thickness.

Another important cross-sectional study further suggested that engagement in meditation may positively modulate neural and cognitive reserve in attention-related brain regions (Pagnoni and Cekic 2007). It was found that regular Zen meditation (a practice focused on attentional and postural self-regulation) positively affects normal age-related decline of cerebral gray matter volume and attentional performance. More in particular, this study documented gray matter differences (particularly in the putamen, a basal ganglia region crucially involved in attention) between expert meditators (n = 13 with >3 years of experience) and controls (n = 13) with only the latter displaying the expected negative correlation of both attentional performance and gray matter volume with age. More recent cross-sectional studies by Luders et al. (2009, 2011, 2012, 2015; see also Luders 2014) have further revealed larger brain regions, thicker or more complex cerebral cortices, and enhanced brain connectivity in long-term meditators (with >20 years of experience) compared to healthy control subjects, for example in hippocampal and frontal regions.

Overall, these studies provide preliminary evidence that meditation may have neuroprotection and neuroplasticity effects, slowing age-related brain degeneration. Of note, MM-related increases in gray matter may result in improved cognitive performance in older meditators. Indeed, a few recent studies have documented findings in this direction, for example showing improved efficiency in attentional resources and functions (van Leeuwen et al. 2009; McHugh et al. 2010; see also Pagnoni and Cekic 2007). These results are significant with regards to elderly subjects' CR.

A major limitation of the reviewed studies on meditation in older individuals is that the investigations are mostly cross-sectional and involve expert meditators. Nevertheless, a more limited longitudinal evidence exists in the form of RCT (see review of Gard et al. 2014). For example, Moynihan et al. (2013) have conducted the largest RCT on the effects of MBSR on executive function, frontal alpha asymmetry, and immune function in a large sample of healthy older adults (n = 201, mean age = 73.4 years). Briefly, relatively to a wait list control group, MBSR participants reported a lower Trails B/A ratio (a measure indicating improved executive function) and a reduced shift to rightward frontal alpha activation (an indicator of positive emotions) after the intervention. Furthermore, the MBSR group had improved mindfulness (assessed with the Mindful Attention Awareness Scale, MAAS; Brown and Ryan 2003) both after the intervention and at 24 weeks of follow-up.

On the basis of the findings on the effects of meditation in older people, there is increasing consensus in considering meditation and MM as effective mental training strategies that may positively influence cognition (e.g., attention and memory functions) and risk factors (e.g., high levels of cholesterol, hypertension, chronic stress, inflammation) in neurodegenerative diseases such as AD (see empirical and conceptual reviews of Newberg et al. 2014; Marciniak et al. 2014; Innes and Selfe 2014; Larouche et al. 2015; Khalsa 2015). In a first longitudinal, non-randomized

pilot study, Newberg et al. (2010) tested the effect of an 8 week yoga/meditation program based on the practice of *Kirtan Kriya* (a form of mantra meditation derived from the Kundalini yoga tradition), on the memory functions of a group of older individuals with memory problems ranging from age-related memory difficulties (n = 7), mild cognitive impairment (the prodromal phase of AD encompassing a wide range of cognitive deficits, especially memory impairment; Peters et al. 2014) (n = 5), and early AD (n = 3) (overall mean age: 64 years). It was found that the yoga/meditation practice (vs. listening to music performed by a group of control subjects) led to improvements on neuropsychological tests of logical memory and verbal fluency and in the Trail Making Test (part B) measuring working memory and attention. Moreover, improvements in practitioners' attention were correlated with increases in cerebral blood flow in attention- and memory-related prefrontal regions, a finding suggestive of yoga/meditation-related increases in brain network efficiency/capacity (namely CR).

More recently, with the same technique of *Kirtan Kriya* applied to individuals with age-related impaired memory (n = 7), mild cognitive impairment (n = 5) and AD (n = 3) (overall mean age: 62 years), Moss et al. (2012) showed improvements in participants' depression, anxiety, and fatigue symptoms. These improvements correlated with changes in cerebral perfusion observed in frontal and parietal regions; of note, this study reported no effect of meditation on cognitive functions. Another study by Innes et al. (2012) also reported positive effects of 8-week meditation based on *Kirtan Kriya* on blood pressure, stress, mood and memory functions in adults with mild cognitive impairment/early-stage AD and their caregivers (n = 12; mean age: 73 years).

Finally, with regards to MM interventions, in a "proof of concept" clinical trial, an MBSR program was offered to 14 subjects with mild cognitive impairment (mean age: 73 years) (Wells et al. 2013a, b). A first set of fMRI data has reported interesting results in regards to the prevention of advancement to dementia (Wells et al. 2013a). In particular, MBSR participants versus usual care controls showed reduced hippocampal atrophy and increased functional connectivity between the posterior cingulate cortex and bilateral medial prefrontal cortex and left hippocampus (i.e., critical nodes of the default mode network). Moreover, in a series of qualitative interviews (Wells et al. 2013b), MBSR participants reported to have enjoyed the program and to have better: (i) mindfulness skills, (ii) well-being, (iii) inter-personal skills, (iv) acceptance/awareness of cognitive impairment, and (v) decreased stress reactivity. Nevertheless, there were no significant differences between the MBSR and control groups on most measures of neuropsychological functioning. Thus, besides showing that MBSR may have a positive impact on key brain regions crucially affected in mild cognitive impairment and AD, this clinical trial suggests that adults with mild cognitive impairment can safely participate to a MM program (see Paller et al. 2015 for related findings and arguments).

To conclude, any generalization of the reviewed results is made very difficult by the insufficient amount of research carried out on the effect of meditation on age-related cognitive decline and neurodegenerative conditions such as AD. For example, conclusions from these studies are limited due to their methodological

problems (e.g., scarce use of active control conditions), small sample size and differences among meditation techniques. However, the reviewed studies appear to motivate further longitudinal investigations to test the efficacy of meditation programs for the prevention and management of individuals' cerebral and cognitive decline. The findings reviewed in this section suggest that the practice of meditation may produce structural and functional brain changes indicative of increases in subjects' BR and CR; this may occur in particular in brain regions associated with attentional and memory functions.

7.3.3 Meditation in Multiple Sclerosis

The strongest evidence for the efficacy of meditation and in particular MM on MS morbidity outcomes comes from a recent randomized, single-blind, controlled trial by Grossman et al. (2010). These authors have investigated the effects of an 8-week MM program (based on MBSR) compared to usual care on a series of common MS symptoms known to affect cognitive processing, such as depression, fatigue, anxiety, and quality of life in 150 patients with MS (predominantly relapsing-remitting MS, RR-MS). After the 8-week MM training, improvements were found across all outcome measures, with the benefits remaining present at 6-month follow-up. This important study has rigorously extended the findings obtained 10 years before in the first RCT of MM in MS which was conducted in a much smaller sample of patients (n = 16) (Mills and Allen 2000).

More recent evidence to support the use of meditation as an effective management adjunct for MS has been collected as additional CT and RCT. For example, in two CT Tavee et al. (2011) and Burschka et al. (2014) have tested the effects of MM interventions (vs. standard care) on small samples of MS patients (n = 17 with any diagnosis of MS in Tavee et al. 2011 and n = 32 with a predominant diagnosis of RR-MS in Burschka et al. 2014). The MM interventions included mindful breathing, mindful movement (Tai chi), and walking meditation over a 2-month period (Tavee et al.) and a 6-month period (Burschka et al.). Tavee et al. (2011) reported improvements in MS patients who practiced MM in perceived physical and mental health, pain, and in cognitive and psychosocial components of fatigue but not in mobility. Nonetheless, with a 6-month MM intervention, Burschka et al. (2014) were able to confirm positive effects on fatigue, life satisfaction, and depression, observing also significant improvements in balance and coordination.

Finally, in a very recent RCT, Bogosian et al. (2015) reported an innovative approach to deliver an 8-week MM intervention, not including mindful movement, to patients with progressive (primary and secondary) MS and with any level of disease severity and disability (n = 40 randomly assigned to MM or waiting-list control). The authors employed a virtual classroom approach to deliver the MM intervention via Skype video conferences. This type of approach appeared to be feasible and effective for MS patients with significant physical disability as the participants showed improvements in distress, anxiety, and depression scores.

Other pieces of the literature that support the use of meditation in MS have been proposed in the forms of cohort or pre- and postinterventional studies, surveys, and cross-sectional studies (for a review see Levin et al. 2014a; see also Simpson et al. 2014; Levin et al. 2014b). Overall, these studies highlight a positive association between meditation and HRQOL in MS although some of them are limited by small sample size, use of non-validated instrument and unclear MS diagnosis. Finally, two recent cross-sectional studies took into consideration the effects of trait mindfulness (globally reflecting the disposition to persist in mindful states over time irrespective of meditation practice; see Crescentini and Capurso 2015), rather than MM, on MS patients' health. In the first of these two studies, Senders et al. (2014) found that greater trait mindfulness measured in 119 MS patients (predominantly with RR-MS) was associated with decreased perceived stress and maladaptive coping and with increased resilience and adaptive coping, as well as with higher (mental health) quality of life. A more recent study by Schirda et al. (2015) showed that reduced emotion dysregulation partially mediated the positive association between trait mindfulness and quality of life in individuals with MS.

Overall, the reviewed studies have provided preliminary evidence that MM is a helpful therapeutic option for managing cognitive/psychosocial symptoms in individuals with MS, and in this sense, it is interesting to note that the UK National Institute for Clinical Excellence (NICE) now includes the recommendation of MM interventions as one potential treatment for fatigue in MS (Simpson et al. 2015).

7.3.4 Meditation in Parkinson's Disease

Fitzpatrick et al. (2010) performed the first qualitative, phenomenological analysis of 12 PD patients participating in an 8-week mindfulness-based cognitive therapy (MBCT). A semi-structured interview schedule suggested that PD patients may benefit from MM interventions by changing patterns of coping with the stress and worrying of PD and establishing group support after the intervention. Shortly thereafter, a number of more rigorous empirical studies testing the effects of MM in PD have been put forward. A recent study used brain MRI voxel-based morphometry to make quantitative analyses of the neurobiological effects of an 8-week MM intervention in 14 PD patients compared to a usual care group of 13 PD patients (Pickut et al. 2013). In particular, increases in gray matter density were found in the meditator versus control group in the right amygdala, bilateral hippocampus, temporoparietal junction, and caudate nucleus, and in the left cuneus, left lingual gyrus, and left thalamus. The structural changes were thus seen to occur in this study in brain networks playing important roles in PD.

More generally, some of the nodes of these functional networks have been suggested to mediate compensatory neuroplasticity phenomena in PD that contribute to maintain behavioral performance in the face of network deficits. For example, recent fMRI evidence suggests that increased task-related neural activity (i.e., a sign of neural inefficiency) in regions such as dorsolateral prefrontal cortex,

caudate nucleus, and inferior parietal cortex during working memory tasks, may be compensatory to maintain PD patients' behavioral performance at similar levels of healthy controls (Trujillo et al. 2015). Of interest, the authors of this fMRI study have speculated that the relatively high educational level of the involved PD patients (reflecting the highest level of completed education; see in Trujillo et al. 2015) could have served as a protective factor against cognitive decline, possibly via increased cognitive reserve.

A very recent pilot study and one RCT have further investigated the psychological effects of MM in PD patients. Pickut et al. (2015) performed a randomized controlled longitudinal trial on 14 PD patients participating in an 8-week MM intervention based on the MBSR and on 13 PD patients receiving usual care. The authors reported significant and specific changes after the MM training in terms of reduction on the motor scores of the Unified Parkinson's Disease Rating Scale (UPDRS), which indicated improvements in patients' motor function. They also found increased scores for the "observe" facet of the Five-Facet Mindfulness Questionnaire (Baer et al. 2006), a very well-known self-report rating scale that proved adept to measure mindfulness skills before or after a MM training. This latter result indicates a better ability of PD patients of noticing or attending to internal and external experiences after the MM training. Attendance rate at the training sessions of the MM course was 97.3% in the study of Pickut et al. (2015), while PD patients reported to have spent on average 55 min performing home meditation practices over the 8-week training period. Overall, the data suggest the feasibility and adherence to a MM program for PD patients.

Cash et al. (2015) performed a pilot study of an 8-week MM intervention for PD patients ($n = 29$) and their caregivers ($n = 10$). From pre- to immediate-post-intervention, PD patients showed increased mindfulness levels, improvements of depressive symptoms, and better cognitive performance on measures related to language functioning, mental flexibility, and attention/working memory. The patients also reported fewer cognitive and emotional symptoms associated with PD. Moreover, the level of self-reported engagement with home practice averaged 20 min per day, 6 days per week, and the patients attended on average six classes. Homework compliance was seen to correlate with improvements observed in mental flexibility and working memory tasks, as well as with anxiety symptoms and mindfulness levels. Increased mindfulness was also associated with better PD-related quality of life.

As with other neurodegenerative illness such as AD and MS, the effects of mind-body therapies on PD patients' mental and physical health have also been investigated in the forms of Tai chi and Yoga programs, which combine multiple physical elements with mindfulness of breathing and relaxation (for a review see Ghaffari and Kluger 2014). Tai chi in particular is one of the most widely accepted forms of alternative therapy in PD (for reviews see Lee et al. 2008; Ni et al. 2014). In this context, in a recent review and meta-analysis of 9 RCT on the topic (Ni et al. 2014), it was found that Tai chi performed with medication (vs. medication alone or other exercises plus medication) had positive influences on PD patients' HRQOL and on mobility and balance outcomes. Finally, with regards to Yoga, a very recent randomized controlled pilot study tested the effects of a 12-week yoga therapy in a

group of 8 PD patients compared with a non-intervention control group of five patients (Sharma et al. 2015). Significant improvements in physical function (UPDRS), diastolic blood pressure, and HRQOL was found in Yoga participants. These data complemented other earlier findings from the same group showing a positive effect of yoga on motor function, balance, and posture in PD patients (Colgrove et al. 2012; see also Ghaffari and Kluger 2014).

Overall, although based on small samples of PD patients with no intervention control groups, the latter set of studies suggest that MM (likely also in the contexts of yoga and Tai chi) may be an acceptable and useful form of group intervention benefiting people with PD. The positive effects appear to occur in a variety of ways, which are also relevant for CR: from reduction of symptoms frequently observed in PD such as anxiety and depression, to better motor, cognitive, and emotional functioning and to structural changes in key brain regions involved in PD.

7.4 Conclusions

We discussed data obtained from neuroscience and psychology studies about the complex issue of the health effects of mind-body interventions based on meditation in healthy aging and in the neurological conditions of AD, MS, and PD. The implications of these clinical interventions were discussed in terms of their potential contribution in improving patients' reserve. The research on the effects of mind-body approaches on neurodegenerative disorders is still in its infancy, with most knowledge coming from either cross-sectional studies or longitudinal studies carried out on small samples of patients with no active control groups. Despite these limitations, the reviewed literature on meditation, MM and, to a lesser extent, Yoga and Tai chi interventions suggests that these techniques may represent mental enriching activities that may help AD, MS, and PD patients cultivating a cognitive reserve to protect as much as possible against cognitive (and psychosocial) decline.

The reviewed evidence may thus suggest that there is adequate justification to encourage more systematical examination of the effects of mind-body medicine on cognitive decline in AD, MS, and PD. Randomized longitudinal controlled trials focusing on research methods adopted in MM research (e.g., MBSR and behavioral and MRI functional/morphometric testing) should continue to be designed for exploring the beneficial effects on improving cognitive function in these neurological conditions, either directly or indirectly through the effects on other psychosocial symptoms (e.g., anxiety, fatigue, depression).

Mind-body interventions in individuals with neurodegenerative disorders could be conceptualized as forms of intensive training aimed at complementing disease-modifying effects of medical therapies by increasing patients' reserve. Indeed, rather than protecting from the progression of disease pathology, the interventions could attenuate the relationship between the disease progression and cognitive decline, allowing the patients to withstand better brain pathology while

disease progresses and coping more effectively with the disease burden at the cognitive and psychosocial levels.

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Chapter 8
Roles of Synaptic Plasticity in Functional Recovery After Brain Injury

Soichi Nagao and Masao Ito

Abstract Patients with brain injury or stroke suffer from sensory-motor disorder caused by the loss of function of damaged brain tissues. The goal of neurorehabilitation is to facilitate the recovery of the impaired sensory-motor function through new learning in the remaining intact brain tissues. Synaptic plasticity, i.e., long-term potentiation and depression of synaptic transmission, and new synapse formation through axonal sprouting, are assumed to underlie such new learning. To further elucidate the roles of synaptic plasticity in neurorehabilitation, four items are addressed in this chapter. First, the characteristics of synaptic plasticity in the intact hippocampus, cerebellum, and red nucleus are reviewed. Second, the spinal, cerebellar, and cerebral mechanisms underlying the recovery of grasping or gripping movement after unilateral spinal cord injury are discussed as an experimental model of neurorehabilitation of motor function. Third, the neural mechanisms underlying the recovery of somatosensory and vestibular functions are discussed as an experimental model of the neurorehabilitation of sensory function after injury of their pathways in the central or peripheral nervous system. Finally, recent progress in neurorehabilitation techniques, noninvasive transcranial brain stimulation, neuroprosthesis, and regenerative medicine, including the induced pluripotent stem cell technology, is reviewed in relation to synaptic plasticity.

Keywords Long-term potentiation (LTP) · Long-term depression (LTD) · Axonal sprouting · Motor learning · Cerebellum · Brain stimulation · Neurorehabilitation

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8.1 Introduction

In the mammalian central nervous system (CNS), stem cells generate neurons from the embryonic period to the juvenile period, but cease to produce neurons in adulthood, except in limited areas of the hippocampus and olfactory bulb. Moreover, unlike the neurons in the peripheral nervous system, the axons of CNS neurons are assumed to never regenerate once they are severed. Therefore, when CNS neurons are damaged, the functions that they originally mediate are lost. However, after months or years of rehabilitation training, partial or sometimes nearly complete recovery of motor, sensory, and even cognitive functions occurs. This is mainly due to the learning of the remaining intact CNS neurons.

Neural signals are relayed from neuron to neuron through synapses, which have both presynaptic and postsynaptic neuronal components. When the action potential reaches an axon terminal and depolarizes the presynaptic membrane, Ca^{2+} enters into the axon terminal through the opening of membrane voltage-gated Ca^{2+} channels, which consequently release neural transmitter molecules, e.g., glutamate, stored in vesicles in presynaptic terminals, to postsynaptic neurons. Then, the released neural transmitter molecules bind to their specific receptors located on the postsynaptic membrane, thereby opening ion channels, which consequently depolarizes the postsynaptic neurons. In some synapses, the efficacy of such signal transmission is not fixed and is modifiable depending on the dynamic characteristics of synaptic inputs. This phenomenon is called "synaptic plasticity" and is assumed to underlie the learning and memory of the brain.

Synaptic plasticity occurs in various time scales. Modifications of synaptic signal transmission efficacy are induced after minutes, hours and days of changes in synaptic inputs. On the other hand, the reorganization of the neural circuitry through the sprouting of axons and new synaptic formation are induced after weeks, months, and years of changes of synaptic inputs. Such synaptic plasticity underlies the recovery of brain functions after brain injury. Here, we will first explain the characteristics of synaptic plasticity, as revealed by in vivo and in vitro experiments, then consider their roles in the recovery of motor and sensory functions after brain injury, and finally describe new tools that may promote synaptic plasticity in neurorehabilitation.

8.2 Synaptic Plasticity

Two different types of plasticity of synaptic transmission efficacy have been found. One is long-term potentiation (LTP) discovered in the hippocampus by Bliss and Lomo in 1973, and the other is long-term depression (LTD) discovered in the cerebellum by Ito and his colleague in 1982. Hippocampal LTP and cerebellar LTD are respectively considered to be the neural basis of declarative and nondeclarative

(motor) memories. To date, their neural and molecular mechanisms have been studied widely using in vitro slice preparations.

8.2.1 Hippocampal LTP

In the

hippocampus, LTP occurs in three major pathways: the perforant pathway in the dentate gyrus, the mossy fiber pathway in conus ammonium 3 (CA3), and the Schaffer collateral pathway in CA1 (Fig. 8.1a). In the dentate gyrus, when the perforant fibers originating from the entorhinal cortex are stimulated by high-frequency (10–15 Hz) electric pulses briefly (2–3 min), the efficacy of synaptic transmission between perforant fibers and granule cells, which is determined from the magnitude of extracellularly evoked field postsynaptic potentials in the granule cell layer with a

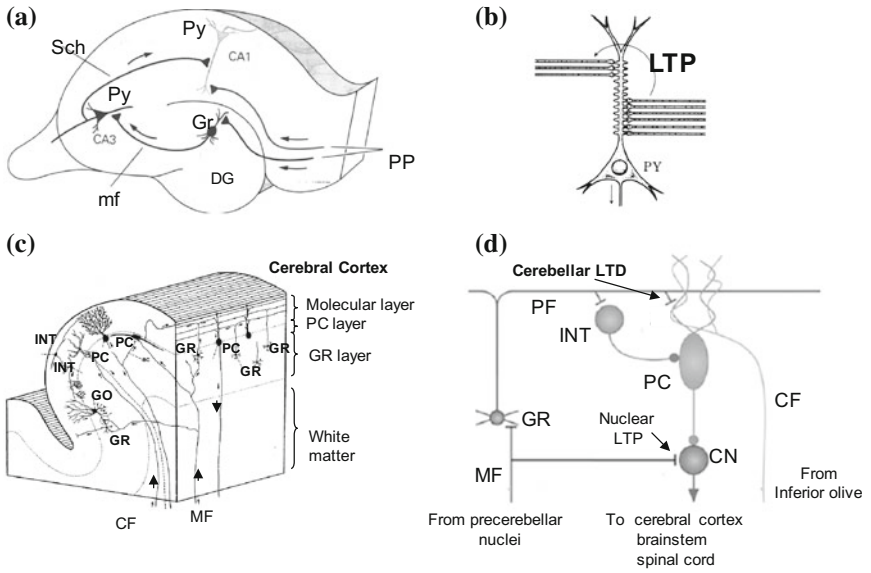

Fig. 8.1 Hippocampal long-term potentiation (LTP) and cerebellar long-term potentiation (LTD). **a** Basic neural network in hippocampal formation. CA cornus ammonis: DG dentate gyrus: Gr granule cell; Mf mossy fiber; Py pyramidal neuron; PP perforant path axonal fiber; Sch Schaffer collateral axonal fiber. **b** Hippocampal associative LTP in CA1. **c** Basic neural network in cerebellum. **d** LTD at parallel fiber-Purkinje cell synapse and LTP at mossy fiber-cerebellar nuclear neuronal synapses. CF climbing fiber; CN cerebellar (vestibular) nuclear neuron; GO Golgi cell; GR granule cell; INT inhibitory interneuron; MF mossy fiber; PC Purkinje cell; PF parallel fiber. Note that, granule cells in the hippocampus indicate neurons of dentate gyrus, whereas those in the cerebellar cortex indicate the small neurons in the granular layer. Similarly, mossy fibers indicate unmyelinated axons of granule cells of dentate gyrus in the hippocampus, while they indicate unmyelinated axons of precerebellar nuclear neurons in the cerebellum

microelectrode, is increased for 2–3 h by LTP. This LTP is assumed to be induced by the increase in the density of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-type glutamate receptors (AMPA-type GluRs) on the postsynaptic membrane, which is triggered by the increase in intracellular Ca^{2+} concentration caused by the strong depolarization after high-frequency stimulation of input perforant fibers.

In CA3, when the mossy fibers originating from the granule cells in the dentate gyrus are stimulated briefly (2–3 min) at 10–20 Hz (tetanus stimulation) or with 3 trains of electrical pulses (50 Hz) repeated at 5 Hz (theta burst stimulation), the transmission efficacy of the synapses between the mossy fibers and CA3 pyramidal neurons are increased by LTP. This LTP is induced mainly by the increase in the amount of glutamate released from mossy fiber terminals.

In CA1, a different type of LTP is induced. The pyramidal neurons in CA1 receive two different types of afferent fiber, the Schaffer collateral fibers of pyramidal neurons in CA3 and perforant fibers. When weak electrical stimulation of perforant fibers is repeatedly combined with strong electrical stimulation of Schaffer collateral fibers, the transmission efficacy between the weakly stimulated perforant fibers and CA1 pyramidal neurons is increased by LTP (Fig. 8.1b). This LTP is associative, because LTP is induced by the coactivation of presynaptic inputs with postsynaptic neurons (spike-timing-dependent LTP). Another important feature of LTP is that it is induced via the activation of postsynaptic *N*-methyl-d-aspartate-type glutamate receptors (NMDA-type GluRs). Activation of NMDA-type GluRs increases the intracellular Ca^{2+} concentration in postsynaptic areas, which consequently increases the density of postsynaptic AMPA-type GluRs.

Behavioral studies of gene-manipulated mice lacking hippocampal LTP have suggested that LTP underlies the acquisition of declarative memory. These mice showed impairment in the spatial navigation task or the acquisition of contextual memory in fear conditioning. LTP accompanies structural changes of synapses, i.e., the increase in the size of spines that contain excitatory synapses. However, whether LTP induces the formation of new synapses or spines in the adult hippocampus is as yet not confirmed.

In hippocampal slices, LTD is often induced by low-frequency (1 Hz) stimulation of input fibers for long time (15 min) or by strong stimulation of postsynaptic neurons followed by weak stimulation of presynaptic neurons (e.g., Stanton and Sejnowski 1989). LTD is assumed to counterbalance LTP and to be involved in the formation of declarative memory with LTP. LTP and LTD demonstrated in the hippocampus occur in some of the neurons in the cerebral cortex.

8.2.2 Cerebellar LTD

The Purkinje cells in the cerebellar cortex receive two inputs: the parallel fibers projected from the granule cells in the granular layer of the cerebellar cortex and the climbing fibers projected from the neurons in the inferior olive (Figs. 8.1c, d). Granule cells receive mossy fiber inputs from the precerebellar nuclei and project

parallel fibers to Purkinje cells. Purkinje cells project their inhibitory outputs to the neurons in the cerebellar nuclei and small portions of the vestibular nuclei.

When parallel and climbing fibers are conjunctively stimulated by electrical pulses, e.g., 1 Hz for 5 min, the transmission efficacy of parallel fiber-Purkinje cell synapses is decreased by LTD, at least for 3–5 h (Ito et al. 1982; Ito and Kano 1982; Ito 1984). On the other hand, by stimulating parallel fibers alone at 1 Hz, the transmission efficacy of the parallel fiber-Purkinje cell synapse increases by LTP (Sakurai 1987; Lev-Ram et al. 2002). Hereafter, we call LTD of parallel fiber-Purkinje cell synapses as cerebellar LTD.

The cerebellum also contains inhibitory interneurons, i.e., stellate cells and basket cells, which show synaptic plasticity. Stellate cells are located in the molecular layer, which is composed of parallel fibers and dendrites of Purkinje cells, whereas basket cells are located near the cell bodies of Purkinje cells. Stellate cells and basket cells receive parallel fiber inputs and in turn supply inhibitory synapses to Purkinje cell dendrites and cell bodies, respectively. Stimulation of parallel fibers induces disynaptic inhibitory postsynaptic currents (IPSCs) in Purkinje cells through the action of these inhibitory interneurons. Combined stimulation of climbing fibers and parallel fibers induces LTP at parallel fiber-stellate cell inhibitory synapses (Jorntell and Ekerot 2002, 2003; Rancillac and Crepel 2004), which is complementary to LTD in Purkinje cells. Another form of synaptic plasticity induced by climbing fiber stimulation is the prolonged increase in IPSCs in Purkinje cells. This phenomenon is called rebound potentiation (Kano et al. 1992) and assumed to cooperate with cerebellar LTD in depressing the parallel fiber-mediated activation of Purkinje cells (Tanaka et al. 2013).

8.2.3 Motor Learning and Cerebellar LTD

The cerebellum is assumed to play an important role in motor learning underlying the recovery of brain function after brain injury (see Sects. 8.3.4, 8.4.4, and 8.6.1). Therefore, we focus on the role of cerebellar LTD in motor learning here.

Many lines of evidence obtained from experiments on the adaptation of reflex eye movement have suggested that cerebellar LTD underlies cerebellar motor learning (Ito 1984, 1989, 2001, 2006, 2011; Ito et al. 2014; also see Honda and Ito 2016). In an area of the cerebellum called the flocculus, Purkinje cells receive signals necessary for eye movement via the parallel fibers and directly inhibit the vestibular nuclear neurons that relay the signals for reflex eye movement (e.g., Ito 1984). To induce the adaptation of reflex eye movement, animals are trained to watch the motion of a stripe- or dot-patterned screen, with or without the motion of animals (e.g., Nagao 1983). The error generated during such eye movement training, i.e., the mismatch between the screen and eye motion, is sensed as retinal slips, which is transmitted to the floccular Purkinje cells via climbing fibers (Maekawa and Simpson 1973) and induces cerebellar LTD at the synapses that mediate the signals related to reflex eye movement to floccular Purkinje cells

(Yamazaki and Nagao 2012). Then, the magnitude of inhibitory outputs of flocculuar Purkinje cells to the vestibular nuclear neurons relaying the signals for the reflex eye movement decreases, which consequently increases the magnitude of the evoked eye movement (Fig. 8.1d).

Importantly, the adaptation induced by cerebellar LTD recovers within 24 h, and repetition of training of watching screen motion induces another synaptic plasticity, i.e., LTP, in the target vestibular nuclear neurons (Pugh and Raman 2006) that lasts up to one month (Shutoh et al. 2006; Okamoto et al. 2011; Wang et al. 2014). Formation of such a long-term motor memory is assumed to be the goal of neurorehabilitation training.

Two recent electron microscopy studies of mice (Wang et al. 2014; Aziz et al. 2014) have suggested that the density of synaptic AMPA-type GluRs on floccular Purkinje cells decreases as the adaptation occurs after 1 h of training, and then recovers after 24 h as the adaptation disappears, suggesting that cerebellar LTD is caused by the down-regulation of postsynaptic AMPA-type GluRs. These two studies also suggested that the repetition of cerebellar LTD may induce the elimination of parallel fiber-Purkinje cell synapses.

Another important feature of cerebellar motor learning is the spacing effect: repetition of training with appropriate rest periods facilitates the formation of long-term memory in the cerebellar or vestibular nuclei. When resting periods were inserted between training sessions, consolidation of the motor memory of adaptation of reflex eye movement in the vestibular nuclei was accelerated in mice (Okamoto et al. 2011; Aziz et al. 2014). A theoretical study (Yamazaki et al. 2015) has suggested that the activity of Purkinje cells modified by cerebellar LTD may induce LTP in synapses of cerebellar or vestibular nuclear neurons (nuclear LTP in Fig. 8.1d) during rest periods. The spacing effect is important for establishing a protocol of neurorehabilitation. The role of cerebellar motor learning in the neurorehabilitation of motor and sensory functions will be discussed later in Sects. 8.3.4 and 8.4.4.

In primates including human beings, the cerebellum is mainly connected to the cerebral cortex. The motor command signals, e.g., the signals for the intention to move the limbs, are generated in the primary motor (M1) cortex and sent to the contralateral cerebellar cortex via the pontine (perhaps also pontine reticular) nuclei. The cerebellar cortex returns its outputs to the contralateral M1 cortex, via the cerebellar nuclei, red nucleus (RN), and thalamus (Ito 1984). Therefore, the cerebellum and cerebral cortex form a closed-loop network. It has been suggested that the cerebellum may acquire an internal model for movement in such a closed-loop network (Ito 1984, 2011). The internal model for movement has two components: one for generating the appropriate signals for driving muscles and joints to realize motor command signals, and the other for predicting the consequence of motor command signals before their execution. Learning of such an internal model for movement plays an important role in the motor control in healthy subjects, in the recovery of sensory-motor function through the remaining intact brain tissue, and in using tools that assist limb movement after brain injury (Sect. 8.6.1).

8.2.4 Synaptic Reorganization Through Sprouting of Axons

LTP and LTD observed in the hippocampus, cerebral cortex, and cerebellum underlie learning and memory in a time scale of hours or days. In contrast, the recovery of brain function after brain injury often takes several months or years of training. Sprouting of axons and new synapse formation may be involved in such a long-term recovery of brain functions.

Sprouting of CNS axons was first demonstrated by the anatomical studies (Raisman and Field 1973; Raisman 1977, 1978), in which the effects of injury were compared between the superior cervical sympathetic ganglion and the septal nuclei of the limbic area in adult rats. After injury, the denervated postsynaptic sites were reinnervated by new synapses in both regions. The severed axons regenerated and formed new synapses in the superior cervical sympathetic ganglion, however, they did not reestablish their original contacts in the septal nuclei. On the other hand, the undamaged local axons sprouted and formed new synapses in the septal nuclei.

The physiology of synapse formation by axonal sprouting was studied in neurons of the red nucleus (RN) of adult cats by Tsukahara and his colleague (Fig. 8.2). RN neurons receive two synaptic inputs: one from the cerebral primary motor (M1) cortex neurons, i.e., the corticospinal tract (CST) and the other from the cerebellar interpositus nucleus (IP) neurons. They project their axons to the spinal cord via the rubrospinal tract (RuST). Tsukahara and his colleagues examined the synaptic responses of RN neurons by using an intracellular microelectrode recording technique. As shown in Fig. 8.2a, electrical stimulation of CST induced excitatory postsynaptic potentials (CST-EPSPs), which are characterized by a long rise time, whereas electrical stimulation of the axons of IP induced short-latency EPSPs (IP-EPSPs), which are characterized by a short rise time. The difference in the rise time of EPSPs indicates that the synapses formed by axons of IP neurons are located in the cell bodies and proximal dendrites of RN neurons, whereas those formed by CST axons are located in the distal dendrites of RN neurons.

Lesions of IP induced the rearrangement of these synapses. At 2 weeks after IP lesioning, the lesioned IP axons degenerated and IP-EPSPs diminished. On the other hand, the rise time of CST-EPSPs decreased compared with that in the intact animals (Fig. 8.2b). These results suggest that CST axons, which originally formed synapses on the distal dendrites of IP neurons, sprouted to their cell bodies or proximal dendrites, and formed new synapses there (Tsukahara et al. 1975). These observations were later confirmed by electron microscopy experiments.

Furthermore, cross-innervation experiments revealed that the new synapse formation through axonal sprouting plays a role in correcting the malfunction of motor control (Tsukahara and Fujito 1976; Murakami et al. 1976; Tsukahara et al. 1982; Fujito et al. 1982). In these experiments, the forelimb extensor and flexor muscles were surgically cross-sutured with flexor and extensor motor nerves, respectively, in cats. After the motor nerves reinnervated their target muscles, the activation of the flexor nerve contracted the extensor muscles, and the activation of the extensor nerve contracted the flexor muscles. Consequently, when the cats tried to flex their

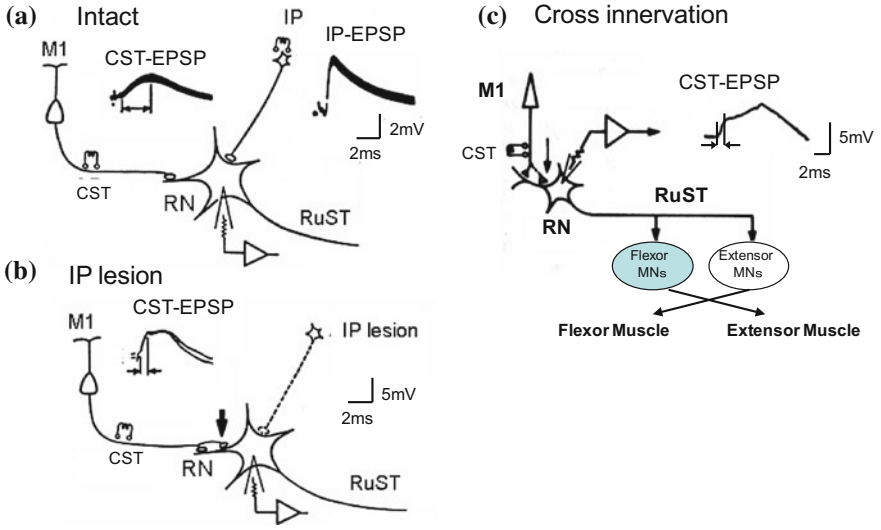

Fig. 8.2 Sprouting of axons of neurons of primary motor (M1) cortex and red nucleus (RN) neurons after experimental lesion of cerebellar interpositus nucleus (IP) in cats. **a** Before lP lesioning. A glass microelectrode was inserted in the cat RN under general anesthesia, and excitatory postsynaptic potentials (EPSPs), which were evoked by electrical stimulation of the corticospinal tract (CST) or IP, were recorded. Examples of EPSPs are shown as CST-EPSP or IP-EPSP. Note that the rise time of EPSPs after stimulation marked by ⟷ or → is long in CST-EPSP and short in IP-EPSP, indicating that CST formed synapses on the distal dendrites, while axons of IP neurons formed synapses on the proximal dendrites on RN neurons. **b** Similar to A, but in cats after IP lesioning. The rise time of CST-EPSP decreased to one-thirds of that in intact cats, indicating that CST sprouted to the proximal dendrites and formed new synapses there. **c** EPSPs obtained several months after the surgery for cross-innervation of flexor and extensor neurons to extensor and flexor muscles. The rise time of CST-EPSPs became much shorter than that of intact cats, indicating that CST axons sprouted to the proximal dendrites and formed synapses with them. M1, primary motor cortex. RuST, rubrospinal tract. Modified from Tsukahara et al. (1975 and 1982)

forelimbs, the forelimbs extended, resulting in a clumsy forelimb motion. However, several months after the surgery, the cats regained their ability to flex and extend their forelimbs smoothly through compensation. At that time, the rise time of CST-EPSPs decreased to one-third of that in control cats (Fig. 8.2c), indicating that CST axons sprouted to the cell bodies and proximate dendrites of RN neurons to compensate for the effects of cross-innervation.

The molecular mechanisms underlying axonal sprouting and new synapse formation have been investigated in relation to the development of neural connections, such as the optic nerve-tectum (superior colliculus) projection. So far, more than one hundred proteins that promote axonal growth, guidance, and adhesion, and cytoskeletal modification have been identified. These proteins are secreted either from the presynaptic axon terminals or their partner postsynaptic neurons, and act to connect or disconnect the presynaptic axons to the postsynaptic neurons, depending

on the site in the brain, the stage of development, and the time after brain injury. Some of them will be mentioned later in Sects. 8.3.5, 8.3.6, and 8.4.3.

8.3 Neural Mechanisms Underlying Recovery of Hand Movement After Spinal Cord Injury

Spinal cord injury or stroke disrupts the spinal descending tracts and induces paralysis of the limbs, i.e., hemiplegia. However, weeks or months later, hemiplegia improves partially or even nearly completely, through the compensatory mechanism of the remaining intact neural tissue. Below, we consider the neural mechanisms underlying the recovery of voluntary hand movement after spinal cord injury.

8.3.1 Spinal Descending Pathways Related to Hand Movement Control

The motoneurons innervating the skeletal muscles of the forelimbs (arms and hands) are located in the anterior horn of the spinal cord, from the fourth cervical segment (C4) to the first thoracic segment (Th1). The motor command signals for forelimb movement are generated in M1 cortical pyramidal cells and transmitted to MNs either directly or indirectly through the following three spinal descending tracts: the corticospinal tract (CST), rubrospinal tract (RuST), and reticulospinal tract (ReST) (Fig. 8.3a, b).

Not only the pyramidal cells in the deep layer of M1 cortex, but also those in the premotor and supplementary motor cortex, and even an area of the parietal cortex, project their axons to the spinal cord via CST (Strick 1988; Dum and Strick 1991). Most of such CST axons cross the midline of the medulla at the pyramidal decussation, and descend within the contralateral dorsolateral funiculus (DF) to MNs at C4–Th12. A small portion of CST axons (10%) do not cross the midline of the medulla, but descend the ipsilateral DF, and cross the midline of the spinal cord near the target MNs (Fig. 8.3b). In primates, CST directly innervates MNs, and controls the individual finger movement. On the other hand, in four-pedal animals, CST does not directly innervate MNs, and controls the spinal reflex and gross forelimb movement. CST is assumed to develop postnatally. A recent study (Kamiyama et al. 2015) has suggested that the reorganization of CST innervation may occur at the cervical level (C7), but not at the lumber level (L4), in the juvenile rats.

The neurons of the magnocellular part of the red nucleus (RN) in the midbrain issue their axons to the spinal cord via RuST. RuST crosses the midline of the brain and descends the medulla and contralateral ventrolateral funiculus (VF) of the spinal cord. RuST preferentially facilitates extensor muscles in monkeys (Mewes and Cheney 1991). Note that RuST is under the control of CST, because CST

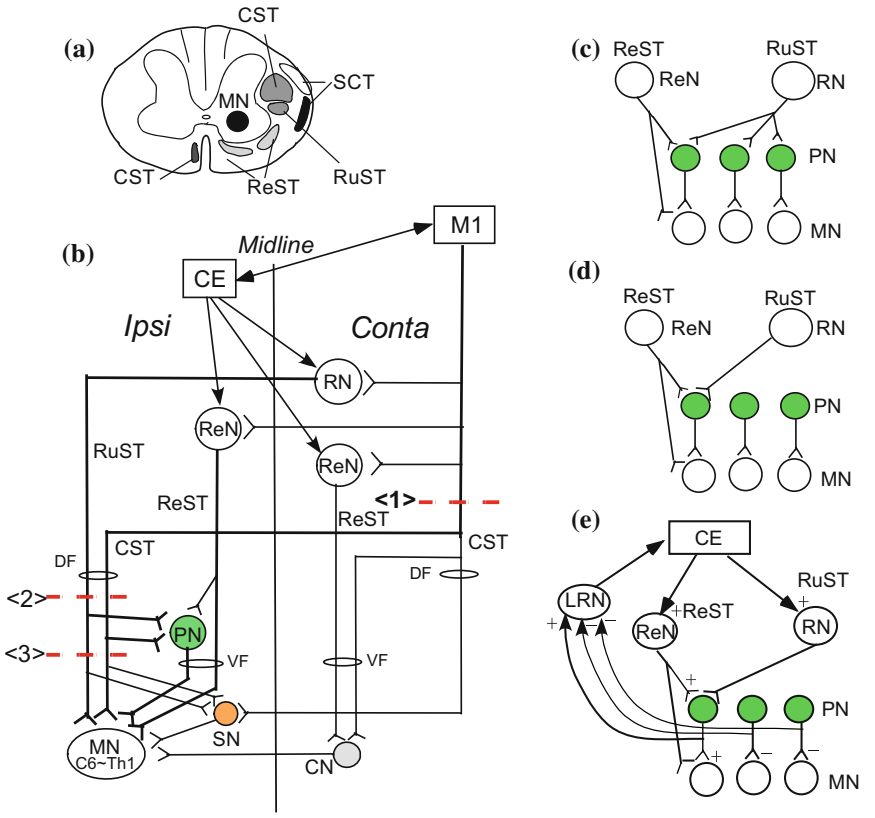

Fig. 8.3 Spinal descending pathway involved in the recovery of gripping and reachingReaching hand functions. **a** Section of spinal cord at cervical level. **b** Descending pathway to neurons of spinal cord at C6–Th1, which control hand movement. Dotted lines marked by <1>, <2>, and <3> indicate the lesioned sites in the studies by Lawrence and Kypers (1968a), Sasaki et al. (2004), and Alstermark et al. (2011), respectively. Only the major corticospinal tract (CST) pathway originating from the contralateral primary motor cortex is shown. **c** and **d** Innervation of propriospinal neurons (PN) by reticulospinal tract (ReST) and rubrospinal tract (RuST) in intact spinal cord (**c**) and after dorsolateral spinal cord lesioning involving CST at C4–5 level (**d**). **e** Neural circuitry involved in recovery of hand movement function after C4–5 spinal cord lesioning postulated by Alstenmak and Pettersson (2014a). + and − respectively indicate facilitation and depression. CE cerebellum; CN commissural interneurons; Contra, contralateral to MN; MN motoneurons; IPSI, ipsilateral to MN; PN propriospinal interneurons; ReN brainstem reticular nuclei; SN segmental interneurons; For other abbreviations, see text Isa et al. 2006

innervates the RN neurons of origin of RuST. Although RuST is well developed in four-pedal animals, it is poorly developed in monkeys and only rudimentary in human beings (Nathan and Smith 1955; Onodera and Hicks 2010). In primates, most of the functions of RuST are mediated by CST.

Some of the neurons in the brainstem reticular formation issue their axons to the spinal cord via ReST. ReST does not cross the midline of the brain, enters the

ipsilateral VF, and descends to MNs. ReST facilitates flexor muscle movement and suppresses extensor muscle movement. ReST mainly controls locomotion, i.e., walking or swimming, in intact animals, and plays an important role in the recovery of hand movement after the injury of CST (Sects. 8.3.2 and 8.3.3). ReST is also under the control of CST, because CST innervates the neurons of origin of ReST.

8.3.2 *Experimental Model of Spinal Paralysis*

Experimental studies of the functions of these spinal descending tracts started 50 years ago. Lawrence and Kypers (1968a) lesioned bilateral CST at the cervical level to disrupt the direct CST-MN connection in monkeys (<1> in Fig. 8.3b). Immediately after the lesioning, the monkeys showed flaccid paralysis of the limbs, but within days or weeks, they recovered their locomotor function considerably, and regained their ability to run and climb in their cages. However, they did not recover their hand movement completely; although they recovered some of their grip function, they never recovered their fine and independent finger movement necessary for precision grip.

To study the neural mechanisms underlying the recovery of hand movement, Lawrence and Kypers (1968b) further lesioned the remaining spinal descending tracts. Lesioning in the lateral part of the spinal cord including RuST (Fig. 8.3a) resulted in the permanent loss of the recovered hand function, but little affected the other locomotor or reaching functions. On the other hand, lesioning in the medial part of the spinal cord including ReST and the vestibulospinal tract severely affected gross hand movement involving reaching, but the animals retained their ability to grasp food when it was placed close to their hands.

Results of these two studies established the basic concept on the role of the spinal descending tracts. The direct CST-MN pathway, which is well developed in primates, controls the dexterous individual digit movement in intact animals. Even in the absence of this direct CST-MN pathway, CST can strongly affect MNs through RuST to recover grip function. On the other hand, ReST mainly controls locomotor activity and reaching.

8.3.3 *Role of Spinal Interneurons in Recovery After Spinal Cord Injury*

There are a large number of interneurons in the spinal cord, which play a role to relay motor command signals to MNs. Propriospinal interneurons (PNs) innervate the ipsilateral MNs in two or three segments below them. Segmental interneurons innervate the ipsilateral MNs in the same segment, and commissural interneurons innervate the contralateral MNs in the same segment (Fig. 8.3b). In monkeys, the

motor command signals from M1 cortex are relayed to MNs of C4–Th12, either directly via the CST-MN pathway or indirectly via the CST-PN-MN pathway (Alstermark et al. 1999). In contrast, in rodents, the direct CST-MN pathway is weak, and motor command signals are relayed to MNs via the CST-PN-MN pathway or ReST. A recent study of Alstermark and Pettersson (2014b) has suggested that ReST plays a major role in grasping in rats.

The role of PNs in the recovery of grip function after spinal cord injury was demonstrated by Sasaki et al. (2004), in which CST was lesioned at DF in C4–C5 (<2> in Fig. 8.3b) in adult monkeys (also see Isa et al. 2006; Alstermark and Isa 2012; Nishimura and Isa 2012). When the grip function recovered 1–28 days after lesioning of spinal cord, the responses of MNs in C6–Th1 were examined by the electrical stimulation of CST at the bottom of medulla (pyramid of medulla) by a microelectrode technique. The results were clear: monosynaptic responses were absent, whereas the disynaptic responses via PNs remained, suggesting that the CST-PN-MN pathway underlies the recovery of grip function (also see Alstermark and Lundberg 1992). This suggestion was later confirmed by the study of Alstermark et al. (2011), in which the recovery of precision grip was delayed markedly and incomplete even 3 months after CST lesioning, when the spinal cord was lesioned at C2, which was above PNs innervating the MNs in C6–Th1 (<3> in Fig. 8.3b).

Furthermore, Zaaimi et al. (2012) demonstrated that ReST plays an important role in the taking over of the damaged direct CST-MN pathway by the indirect CST-PN-MN pathway (also see Baker 2011). They lesioned unilateral CST at the lower brainstem in monkeys. After lesioning, the MN responses induced by electrical stimulation of the ipsilateral intact CST were not altered, but the disynaptic responses induced by electrical stimulation of RuST and ReST in the medial longitudinal fasciculus (MLF) were enhanced in MNs for flexor muscles, but not in MNs for extensor muscles. These findings suggest that ReST plays an important role in PN control after CST lesioning, because RuST preferentially controls extensor muscles (see Sect. 8.3.1). Thus, after CST lesioning, the motor command signals from M1 cortex are assumed to be sent to MNs through the ReST-PN-MN pathway (Fig. 8.3b).

8.3.4 Spinal and Cerebellar Plasticities Underlying Recovery of Grip Function

Then, a question is raised: what is the role of RuST in the recovery of grip function after spinal cord injury demonstrated in the study of Lawrence and Kypers (1968b)? Alstermark and Pettersson (2014a) have proposed that the RuST may facilitate the ReST-PN synaptic connection in an early stage after injury on the basis of their cat study (Alstermark et al. 1987 ; Pettersson et al. 2000). In their study, following the complete unilateral lesioning of CST and RuST at C5 in cats, the grip function of

the cats was impaired markedly even 6 months after surgery. However, even when only a small portion (4%) of RuST was kept intact, the cats recovered their grip function within one week, even after complete CST lesioning. Moreover, such a RuST action was seen only in the early stage after injury, as the recovered grip function was not affected by the second lesioning of the remaining RuST one month after the first spinal cord injury. Thus, the grip function recovery initially mediated by RuST would soon be taken over by ReST.

What is the neural mechanism underlying the recovery of grip function mediated by RuST and ReST? Alstermark and Pettersson (2014a) have proposed that associative LTP, which was observed in the hippocampal CA1 (Sect. 8.2.1, Fig. 8.1b), may occur to facilitate ReST-PN synapses through RuST. In intact monkeys, PNs receive inputs mainly from CST, moderately from RuST, and only partially from ReST. After injury of CST, the PNs that mediate the motor command signals for gripping would be shared by RuST and ReST. Therefore, the concomitant activities of RuST and ReST may induce associative LTP at ReST-PN synapses (Figs. 8.3c, d). This implies that RuST may direct the plasticity of ReST-PN synapses. In human being, the remaining intact CST may play a similar role to monkey RuST (see Sect. 8.3.1).

Moreover, cerebellar motor learning is assumed to play an important role in the successful takeover of damaged CST by ReST (Fig. 8.3e). Importantly, the PNs at C3–C4 send motor command signals for the ipsilateral forelimb movement not only to MNs at C4–Th1, but also to the lateral reticular nucleus (LRN) neurons in the medulla (Alstermark et al. 1981; Ekerot 1990). Because LRN is a member of precerebellar nuclei that project mossy fibers to the cerebellum, LRN may provide the cerebellum with an internal (efference) copy of motor command signals (Alstermark and Ekerot 2013), which is discussed in Sect. 8.2.3. Azim et al. (2014) have demonstrated that selective ablation of a group of PNs (V2a interneurons) impaired reaching movement, and selective activation of the LRN-cerebellar pathway by an optogenetic technique strongly affected reaching movement in mice. Alstermark and Pettersson (2014a) have suggested that the cerebellum detects the decrease in PN activity induced by CST injury and adjusts its inhibitory action on the neurons of the origin of ReST and RuST in the brainstem through learning. Moreover, as the cerebellum is closely connected to the contralateral M1 cortex that projects CST (see Sect. 8.2.3), it may affect the recovery of grip function at the level of the cerebral cortex.

8.3.5 Cerebral and Other Mechanisms Underlying Recovery of Grip Function

Other motor areas may also play a role in the recovery of grip function after spinal cord injury. The role of the cerebral motor cortex was examined in monkeys by positron emission tomography (PET) by Nishimura et al. (2007). They reported that

bilateral M1 cortices were activated in the early stage (1 month) after injury, whereas the contralateral M1 cortex and bilateral ventral premotor (PMv) cortices were activated in the later stages (3–4 months) after injury. Moreover, in the stage in which M1 and PMv cortical activities increased, the expression level of the plasticity-related GAP-43 gene increased in the pyramidal cells of the deeper layers of M1 and PMv cortices (Higo et al. 2009). GAP-43 is phosphorylated during hippocampal LTP (Gianotti et al. 1992; Namgung et al. 1997) and is expressed at high level at the cones of growing axons during development. Thus, LTP or axonal sprouting may occur in M1 and PMv cortices in the early stage after injury.

Because M1 cortex directly innervates the forelimb MNs in the cervical spinal cord, coherence of activities were observed in the electroencephalography (EEG) recording of M1 cortex and the electromyography (EMG) recording of the muscles of the contralateral forelimb in the β-band oscillation range (14–30 Hz) in intact monkeys. After unilateral CST lesioning, such coherence of activities was lost, and instead a different type of coherence of activities in the γ-band oscillation range (30–46 Hz) emerged in the EMG recordings of finger muscles (Nishimura et al. 2009). These coherent activities may represent the coupling among finger muscle MNs, which reflects the reorganization of neural circuitry in the spinal cord.

Ipsilateral M1 cortex controls cervical MNs through the direct CST pathway, which recrosses the midline at the cervical segment level, or through the indirect pathways via ReST (not shown in figures). These pathways are assumed to inhibit the CST originating from contralateral M1 cortex, and to be not functional under intact condition. This is because inactivation of ipsilateral M1 cortex by local injection of muscimol, an agonist of the inhibitory transmitter γ-amino butyric acid (GABA), did not affect the grip function in normal monkeys (Fogassi et al. 2001). However, ipsilateral M1 cortex may play a role in the recovery of grip function after spinal cord injury, because the muscimol-induced inactivation of ipsilateral M1 cortex impaired the recovery of grip function one month after injury, but not 3–4 month after injury (Nishimura et al. 2007). Moreover, in a monkey study by Rosenzweig et al. (2010), the CST fibers originating from ipsilateral M1 cortex massively sprouted and crossed the midline of the spinal cord 6 months after unilateral spinal cord injury at C7. Thus, the effect of ipsilateral M1 cortex on grip function may depend on the stage of recovery after spinal cord injury (Sect. 8.5.3).

A recent monkey study by Sawada et al. (2015) has suggested that the accumbens nucleus in the basal ganglia may be involved in the recovery of grip function after spinal cord injury. Pharmacological inactivation of the accumbens nucleus depressed the activity of the sensory-motor cortex as well as the finger movement during the recovery from injury, but not after the complete recovery.

The role of the cerebral motor cortex in the recovery of grip function was examined in stroke patients by functional magnetic resonance imaging (MRI) (Ward et al. 2003a, b). In these patients, CST was damaged mainly in the territory of the middle cerebral artery, but M1 cortex itself was spared. Compared with the patients with good recovery, those with poor recovery showed stronger activation in the ipsilateral M1, bilateral supplementary, premotor, cingulate, and posterior parietal cortices, and ipsilateral cerebellum, suggesting that relatively wide

areas of the cerebral cortex, including the ipsilateral areas, are recruited for generating the signals for grip control in patients with poor recovery.

8.3.6 *Regeneration of CST May Be Important in Clinical Spinal Cord Injury*

So far, we have discussed the neural mechanism underlying the recovery of function after experimental spinal cord injury induced by a knife cut or electrical coagulation. In these studies, most of the CST axons were severed completely, and only a small number of axons were expected to survive. However, in clinical cases in which the spinal cord is damaged by infarction, hemorrhage, or trauma, all of the CST axons may not be damaged, and a considerable number of axons may survive after injury.

It has long been believed that the axons of adult CNS neurons do not regenerate. However, now, this belief is not necessarily correct, and lines of evidence have suggested that incompletely or partially damaged CNS axons regenerate in adult (e.g., Sane and Jessell 2012). For example, in the study by Bareyre et al. (2004) of rat spinal cord injury at the cervical level, CST axons not only sprouted toward a group of PNs at the cervical level but also grew over the lesioned area and arborized to lumbar MNs three months after injury. The same group suggested that the transcription factor STAT3, which is transiently expressed in M1 cortical neurons (Lang et al. 2013), and the fibroblast growth factor (FGF) family protein (FGF22), which is secreted by PNs (Jacobi et al. 2015), may be involved in the regeneration of CST axons in mice. STAT3 is assumed to promote the sprouting of CST axons, and FGF22 and its receptors (FGFR1 and FGFR2) are assumed to play a role in the formation of new synapses between CST and PNs. Another molecule that is assumed to promote the repair of axons in rats is the hepatocyte growth factor (Kitamura et al. 2007). The regeneration of partially lesioned CST axons promoted by such factors may be involved in the recovery of limb function in patients with spinal cord injury (also see Sects. 8.4.1, 8.4.3, and 8.6.2).

8.4 Reorganization of Neural Network After Injury of Sensory Pathway

Functional recovery occurs in terms of not only motor function but also sensory function after brain injury. We will review the recovery of sensory function after deafferentation of sensory inputs in the peripheral and central somatosensory systems, and after unilateral labyrinthectomy.

8.4.1 *Neural Network Reorganization After Deafferentiation of Somatosensory Pathway*

Cutaneous and proprioceptive afferent inputs enter the spinal cord, ascend through the dorsal column, and project to the cuneate and gracile nuclei in the medulla. Then, the axons of cuneate and gracile neurons cross the midline of the brain, and project to the somatosensory cortex (Broadmann areas 1 and 3) via the thalamus (Fig. 8.4). These somatosensory systems are assumed to be highly plastic (Jenkins et al. 1990; Recanzone et al. 1990; Kaas 1991; Jones 2000).

In patients with syndactyly, a magnetoencephalography (MEG) study demonstrated that the representation of the fingers is not organized as separate fingers in the somatosensory cortex. When the fingers of the patients were separated surgically, each of the newly separate fingers became individually represented in the somatosensory cortex within several weeks (Mogilner et al. 1993).

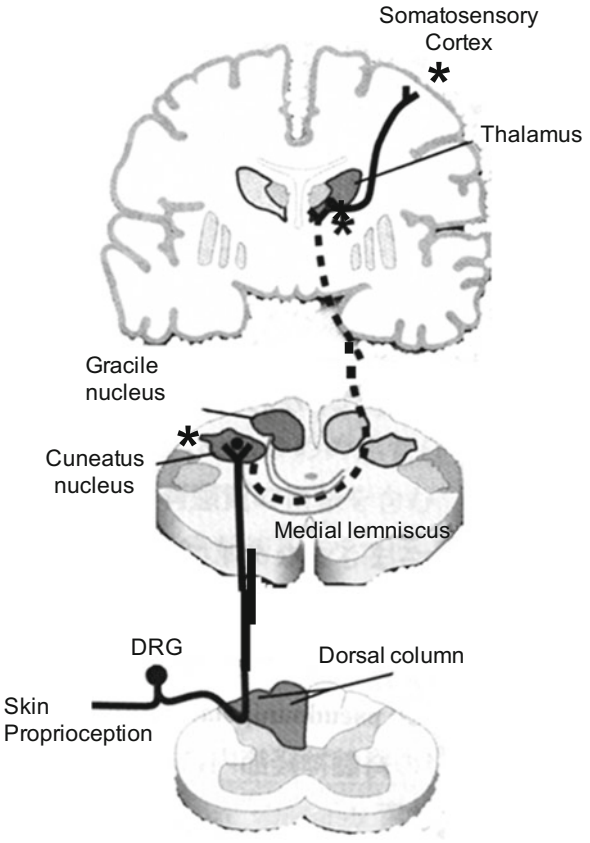

Fig. 8.4 Somatosensory pathway mediating cutaneous and deep sensations. DRG, dorsal root ganglion. * indicates site of synaptic plasticity after amputation of limb

Surgical denervation of the paw induces reorganization of the paw area of the somatosensory cortex in cats, particularly in kittens (Kalaska and Pomeranz 1978). When a digit was amputated in adult monkeys, the cortical representation of the hand was reorganized and the areas representing the adjacent digits expanded slightly (0.5–0.7 mm) into the area representing the amputated digit 2–8 months after amputation (Merzenich et al. 1984). Moreover, Pons et al. (1991) demonstrated that the reorganization of the somatosensory cortex took place in a much wider area than this more than 12 years after the amputation. Such a large change in the area of somatosensory representation (somatotopy) may be induced by the plasticity of not only the somatosensory cortex but also the subcortical sensory system including the spinal cord, brainstem, or thalamus (Fig. 8.4) (also see Florence and Kaas 1995).

Injury of the dorsal column of the spinal cord induces a deficit of tactile sensation on the ipsilateral side below the injury. Cutaneous tactile sensation is necessary for reaching and grasping, as shown by a study in which the monkeys with lesions of the unilateral dorsal column at C4–C6 showed impaired reaching and grasping using their ipsilateral hand (Qi et al. 2013). However, these impairments improved quickly, even when only a small fraction (1%) of the sensory afferent nerve axons remained intact. Thus, the regeneration of the incompletely lesioned nerve axons addressed in 8.3.6 seems to play a role in the recovery of hand function. Qi et al. (2014) also demonstrated that the neuronal activity in the contralateral somatosensory cortex (area 3b) recovered by active hand-use in the first few weeks after dorsal column lesioning. Use-dependent plasticity in the remapping of the somatosensory system through regenerated neural axons may occur at the level of the brainstem, thalamus, or somatosensory cortex, as mentioned above.

Neural plasticity in the somatosensory system that occurs after brain injury is often accompanied by negative effects. Patients with an amputated limb often continue to have a vivid sensation, i.e., pain of the missing limb, which is known as the "phantom limb syndrome." The phantom limb sensation is assumed to originate from the rearrangement of cortical neural circuits after limb amputation. The afferents from the areas representing adjacent limb/body expand to the cortical areas representing the amputated limb. Remapping would occur for the area that represented the limb before amputation through the afferents from the other sites on the skin (Ramachandran 1993).

8.4.2 Compensation for Vestibular Function After Unilateral Labyrinthectomy

Patients with unilateral injury of the vestibular organ or nerve show impaired vestibulo–ocular and vestibulospinal reflexes. They often show spontaneous nystagmus, which is composed of the rhythmic alternation of slow and quick eye movements, and a tendency to fall to the lesioned side. However, these vestibular impairments recover

through compensatory mechanisms. Generally, patients with vestibular organ injury, e.g., Ménière's syndrome, show severe symptoms of vestibular deficits with quick recovery, whereas patients with vestibular nerve injury, e.g., surgical resection of the vestibular nerve along with the tumor in the middle fossa, show mild symptoms of vestibular deficits with slow recovery (Allum 2012). Because these symptoms of vestibular impairments are induced by the decrease in the excitatory drive in the neurons of vestibular nuclei, whether the activity of vestibular nerve is preserved or recovered after lesioning is critical for the improvement of vestibular function. Here, we consider the neural mechanisms underlying compensation after the unilateral labyrinthectomy including both the Vestibular organ and nerve.

Vestibular nuclear neurons (VNs) receive head motion signals sensed by the vestibular semicircular canal organ through the vestibular nerve, and also the non-vestibular signals from neurons in the pontine reticular formation, other brainstem neurons, and the cerebellum (Fig. 8.5a). VNs issue these signals to the brainstem or spinal neurons that control vestibulo–ocular or vestibulospinal reflexes. VNs are composed of excitatory and inhibitory neurons, and some of the inhibitory VNs suppress the VNs on the contralateral side, i.e., commissural inhibition (Fig. 8.5a).

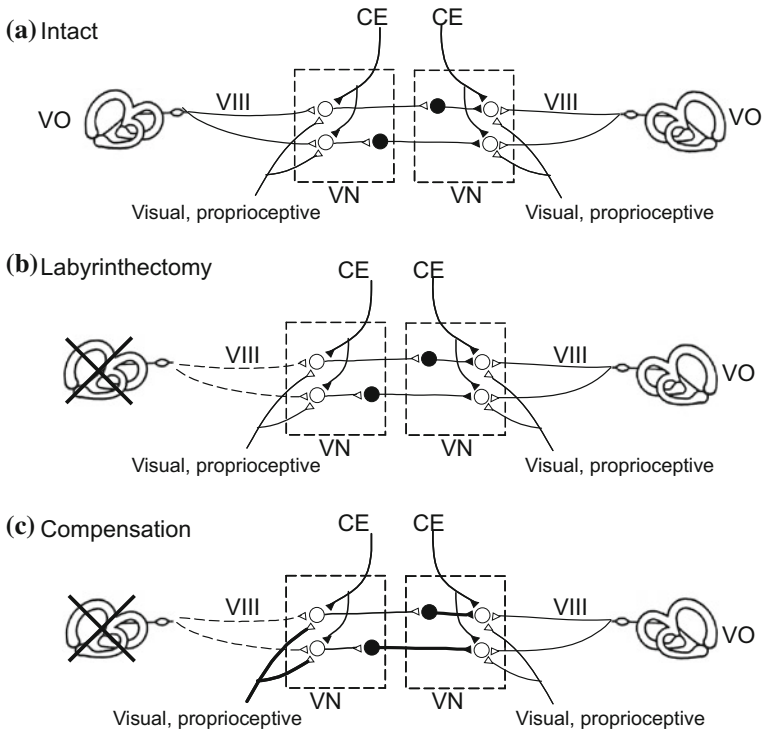

Fig. 8.5 Basic brainstem vestibular circuitry involved in vestibular compensation. **a** Intact state. **b** Immediately after unilateral labyrinthectomy. **c** After vestibular compensation. *Thick lines* in C indicate putatively potentiated pathways. For details, see the text. CE cerebellum; VN vestibular nuclei; VO vestibular organ; VIII vestibular nerve

8.4.3 Brainstem Mechanism Underlying Vestibular Compensation

Then, we consider the neural mechanism underlying the vestibular compensation after unilateral labyrinthectomy. Immediately after unilateral labyrinthectomy, the spontaneous activity of ipsilateral VNs decreased, and concomitantly that of the contralateral VNs increased owing to the diminished commissural inhibition (Fig. 8.5b). Such an imbalance of activity between the labyrinthectomized VNs and intact VNs induces spontaneous nystagmus, which is corrected gradually with the increase in the spontaneous activity of ipsilateral VNs and decrease in the spontaneous activity of contralateral VNs. This may occur through the following four possible mechanisms (Fig. 8.5c): (1) Recovery of the activity of the vestibular nerve axons that survived after labyrinthectomy (see Sect. 8.3.6), (2) LTP of synapses mediating nonvestibular signals to ipsilateral VNs, (3) enhanced commissural inhibition on contralateral VNs, and (4) adjustment of cerebellar inhibition on bilateral VNs (see Sect. 8.4.4).

The major nonvestibular signals for VNs are the visual inputs relayed by the pontine tegmental reticular nucleus (Miyashita et al. 1980; Miyashita and Nagao 1984; Kano et al. 1991), which induce optokinetic response (OKR) eye movement. Because OKR natively cooperates with the vestibulo–ocular reflex (VOR) during head movement, the enhanced OKR after unilateral labyrinthectomy may compensate for the diminished VOR. Such a role of visual inputs in vestibular compensation is exemplified clinically by Romberg's sign: the patients with this disorder after compensation can stand stably with their eyes open, but cannot stand with their eyes closed. Involvement of the proprioceptive inputs is suggested for the compensation of vestibulospinal reflex (e.g., Precht 1977).

The commissural inhibition on the contralateral VNs would be enhanced when LTP occurs in the synapses between inhibitory interneurons and VNs (Fig. 8.5c). Unfortunately, no experimental studies of the plasticity of vestibular inhibitory interneurons have been carried out to date. LTP occurs at inhibitory interneuron-Purkinje cell synapses in the cerebellar cortex (see Sect. 8.2.2) and other brain areas. Studies of adult cats (Tighlet et al. 2007; Dutheil et al. 2009) suggest that inhibitory VNs and glia cells may be newly generated within one week after unilateral labyrinthectomy in the vestibular nuclei where vestibular afferent inputs were lost. If so, the commissural inhibition on contralateral VNs may be enhanced by the newly generated inhibitory interneurons. However, it is not known why the loss of vestibular nerve afferents selectively enhances the neurogenesis of inhibitory VNs.

The period of one week after unilateral labyrinthectomy is assumed to be critical for compensation, because the reorganization of neural circuitry in the vestibular nuclei is assumed to start at that time (Lacour and Bernard-Demanze 2015). Li et al. (2001b) demonstrated that brain-derived neurotrophic factor (BDNF) mRNA was induced in the ipsilateral medial vestibular nucleus 24 h after unilateral labyrinthectomy, and its expression level returned to the basal level within 72 h in rats. BDNF is assumed to play a role in the formation of new synapses by axonal

sprouting, as well as LTP and LTD inductions in the hippocampus (Scharfman et al. 1999) and cerebral cortex (Akaneya et al. 1996, 1997). Thus, it is suggested that the axonal sprouting and new synapse formation might occur in VNs at a relatively early stage of vestibular compensation.

8.4.4 Role of Cerebellum in Vestibular Compensation

The cerebellar flocculus, which is referred in Sect. 8.2.3, is assumed to be involved in vestibular compensation by adjusting its inhibitory drive on VNs (Fig. 8.5c). An early study (Courjon et al. 1982) demonstrated that vestibular compensation was delayed in the cats lesioned in the flocculus before unilateral labyrinthectomy. However, in the same study, the floccular lesioning after the completion of vestibular compensation, i.e., more than two months after unilateral labyrinthectomy, did not affect the recovered function. Beraneck et al. (2008) demonstrated that the vestibular compensation delayed in *lurcher* mutant mice in which the cerebellar cortex is virtually absent. Li et al. (2001a) demonstrated that BDNF mRNA induction occurred specifically in a small area of the inferior olive projecting climbing fibers to the flocculus in rats, when examined 6–30 h after unilateral labyrinthectomy. As has been mentioned in 8.2.3, the floccular Purkinje cells that receive such climbing fiber projections, in turn, inhibit directly the VNs that actually control VOR. Therefore, BDNF produced in a subregion of the inferior olive may play a role in vestibular compensation through the flocculus.

Although the involvement of the cerebellar flocculus in vestibular compensation is well demonstrated, as mentioned above, the role of cerebellar LTD is not yet well clarified. Experiments using the delta 2-type glutamate receptor knockout mice that lack cerebellar LTD demonstrated a delay in compensation (Funabiki et al. 1995; Murai et al. 2004), whereas those using the protein kinase C inhibitor-expressing transgenic mice that also lack cerebellar LTD demonstrated no delay in compensation (Faulstich et al. 2006). However, caution is needed in the interpretation of gene-knockout mouse experiments, because in the mice carrying the mutated AMPA-type GluRs at the C-terminus, the absence of cerebellar LTD was reported by Schonewille et al. (2011), but it has been recently shown that cerebellar LTD is actually inducible under certain stimulating conditions in the same mice (Yamaguchi et al. 2016).

8.5 Noninvasive Brain Stimulation and Neurorehabilitation

Noninvasive methods such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (TDCS) of the cerebral cortex have been used in neurorehabilitation since the mid-2000s.

8.5.1 TMS of Brain

In TMS, application of a magnetic field through the coil attached to the skull induces electrical currents under the cortical tissue in parallel with the plane of the coil, and depolarizes neurons in the tissue. The effects of single TMS applied to the motor cortex can be evaluated from the EMG activity of target limb muscles, when the stimulus strength is over the threshold. Repetitive application of TMS pulses to the motor cortex at low (~1 Hz) and high (~10 Hz) frequencies, respectively, induce a decrease or an increase in EMG activity of target muscles. These changes in EMG activity last 30 min or more after the end of stimulation, depending on the duration of TMS pulses. Furthermore, theta burst TMS, e.g., 3 pulses at 50 Hz at an interval of 5 Hz, similarly increases EMG activity. These phenomena are assumed to be induced by LTD or LTP of neurons in the M1 cortex, similar to hippocampal LTP and LTD discussed in Sect. 8.2.1 (Rothwell 2010).

Paired associative stimulation protocols have been developed for TMS. Low-frequency electrical stimulation of peripheral nerves is combined with TMS of the motor cortex in these protocols. Repetitive pairing of synchronous TMS and peripheral nerve stimulation induces an LTP-like effect on the EMG activity of target muscles, whereas asynchronous TMS and peripheral nerve stimulation induces an LTD-like effect on the activity of them. The underlying mechanism is assumed to be similar to that underlying hippocampal LTP and LTD (see Sect. 8.2.1).

8.5.2 TDCS of Brain

In TDCS, weak (0.5–2 mA) direct electric currents (DC) are applied to the skull using a battery-powered low-current generator via the anode and cathode sponge-enclosed electrodes (20–35 mm^2 in area, for each). The generated currents penetrate the scalp and are expected to change the membrane potentials of cortical neurons underneath only slightly, which would still affect neuronal excitability. Anodal stimulation (positive electrode over the area of interest) for 10 or 15 min increases the excitability of neurons below the positive electrode, whereas cathodal stimulation (negative electrode over the area of interest) for more than 30 min decreases it. How does TDCS induce such a long-term change in excitability of neurons has not been studied by in vivo experiments. A study by Frisch et al. (2010) demonstrated by electrophysiological methods that anodal TDCS induces LTP in M1 cortex in mouse brain slice preparations (also see Rothwell 2010).

8.5.3 Brain Stimulation as a Tool for Neurorehabilitation

A number of pilot clinical studies have suggested that repeated applications of TMS or TDCS temporally facilitate motor learning in stroke patients, as well as in

healthy subjects (Wessel et al. 2015). Repetitive low-frequency (1 Hz) TMS of an intact motor cortex, which temporally reduces the excitability of the motor cortex, combined with high-frequency (20 Hz) stimulation of the motor cortex of the lesioned side, transiently improves finger movement on the ipsilateral side in stroke patients. Likewise, combination of the cathodal TDCS of intact motor cortex and the anodal TDCS of lesioned motor cortex induces similar effects (e.g., Liew et al. 2014; Wessel et al. 2015). These findings suggest that the reduction of inhibitory action of intact motor cortex may additively act with the enhancement of excitatory action of lesioned motor cortex in these stimulation protocols. However, the effects of TMS and TDCS on stroke patients exhibit a considerable interindividual variability, depending on the focus of stroke, the stimulation site, and the time of stimulation after stroke. As described in Sect. 8.3.5, the effect of intact M1 cortex on the recovery of grip function depends on the stage after CST injury. Thus, to develop reliable neurorehabilitation protocols using TMS or TDCS, further comprehensive studies are required.

8.6 Recent Progress in Neurorehabilitation Techniques

Several new techniques or tools have been developed that may be utilized in neurorehabilitation. Some of them may promote neural plasticity and regeneration, and play an important role in neurorehabilitation.

8.6.1 Learning of Use of Instruments to Assist Limb Movement

Patients with spinal cord injury are often forced to use various instruments, e.g., canes, crutches, prosthetic limbs, to assist their movement. Cerebellar motor learning of an internal model of movement discussed in Sect. 8.2.3 would play an essential role in mastering the use of such instruments as a part of patient's limb.

Recent progress in information technology (IT) has produced artificial limbs for neurorehabilitation. For example, the robot suit "HAL (hybrid assistive limb)" has been developed by a group of Tsukuba University for people with the handicap in motor control caused by diseases, traumas, or aging (Yoshimoto et al. 2015; Sczesny-Kaiser et al. 2015). HAL is composed of an artificial forelimb or forelimb-body-leg combination driven by electrical batteries. These instruments are controlled through a personal computer using the signals of EEG or EMG activity. When the subject wearing HAL intend to move its own limb, the motor command signals issued from M1 cortex is detected by the EEG or EMG electrodes attached on the surface of the skull or intact muscles. Then, the motor command signals are decoded by the personal computer and utilized to control the robot limb to assist the

movement of the subject's own limb. The subject masters how to use HAL through motor learning, using its own sensory feedback system by trial and error. Motor learning not only by the cerebellum (Sects. 8.2.3 and 8.3.4) but also by the cerebral cortex, basal ganglia, and spinal cord (Sects. 8.3.4 and 8.3.5) may play their respective roles in operating HAL.

8.6.2 Application of Regenerative Medicine for Brain Injury

Another important progress in neurorehabilitation is the application of regenerative medicine, which started in the mid-2000s (Okano and Yamanaka 2014). As has been discussed in Sects. 8.3.4 and 8.4.1, even with only a small percentage of axons which remain intact or regenerate after brain injury, they will contribute to the restoration of the lost function by other intact brain tissues. Now, it is expected that regenerative medicine will promote the recovery of damaged neural tissues.

Therapies by using the viral vectors containing mRNAs of neurotrophic factors that promote neural growth, e.g., the hepatocyte growth factor, have been developed for experimental spinal cord injury (Kitamura et al. 2011). Transplantation of neural stem/progenitor cells derived from rat fetal CNS restored the motor function after spinal cord injury in adult rats (Ogawa et al. 2002), and that derived from human CNS facilitated the recovery of spinal cord injury in common marmosets (Iwanami et al. 2005). Furthermore, transplantation of neural stem/progenitor cells derived from induced pluripotent stem (iPS) cells of mouse (Tsuji et al. 2010) and human (Kobayashi et al. 2012) origins similarly induced the recovery from spinal cord injury in mice and common marmosets, respectively. It is notable that these studies consistently demonstrated that the transplantation in the subacute stage (2–4 weeks) after spinal cord injury, which corresponds to the period when relatively large brain areas are activated for the recovery of hand function, as described in Sect. 8.3.5, was most effective.

8.7 Conclusions

Studies of experimental brain injury discussed in this chapter have suggested that the synaptic plasticity, including the formation of new synapses through sprouting of axons of the remaining intact neurons, is the basic mechanism underlying the recovery of motor and sensory functions after brain injury. Synaptic plasticity starts in a relatively early stage after injury in rather wide areas of the brain. Learning in the cerebellum and other brain areas plays an important role in the readjustment of the performance of neural circuitry reorganized by synaptic plasticity. To design an effective protocol of neurorehabilitation for patients with brain injury, the following three items are noted. (1) Rehabilitation training should start soon after brain injury to facilitate neural plasticity and to avoid disuse muscular atrophy. (2) Activation of

large brain areas is important: Training of skilled movement that the patient actually perform in daily life, e.g., writing with a pen, or even the mental (imaginary) training should be promoted in addition to the conventional training of locomotion and postural control. (3) Repetition of training with rests of an appropriate duration between training sessions is recommended to enhance the consolidation of memory of cerebellar motor learning.

Finally, it is expected that the development of new techniques, i.e., noninvasive brain stimulation techniques (TMS and TDCS), IT-based machines, and regenerative medicine including iPS cell technology will provide new tools for neurorehabilitation through enhancement of neural plasticity.

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Chapter 9
Integrated Methods of Neuromodulation for Guiding Recovery Following Stroke

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Abstract Stroke is the major cause of disability; nonetheless, cerebral plasticity mechanisms carry out different strategies to compensate the brain damage; therefore, the understanding of these processes are crucial for optimizing clinical and functional recovery. In the last decade, there has been remarkable progress in unraveling the pathophysiological mechanisms leading to altered motor function, speech disorder and visuo-spatial impairment especially by applying neuromodulation techniques such as non-invasive brain stimulation (NIBS). Accordingly, several approaches have been performed in order to directly verify the efficacy of NIBS in improving these altered functions. Here, we summarize the main neurophysiological findings in the field of post-stroke recovery and especially the major results obtained from application of NIBS in the acute and chronic phase of stroke patients.

Keywords rTMS · TDCS · Neuromodulation · Stroke · Aphasia · Neglect

9.1 The Noninvasive Brain Stimulation (NIBS) Techniques

In the last years, transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have shown their ability to modulate brain activity in a noninvasive manner. According to the stimulation parameters, it is possible to facilitate or to suppress brain activity with variable behavioral effects (Hummel and Cohen 2006). TMS uses short-lasting, electric currents conveyed through a copper wire coil to generate a rapidly changing high-intensity magnetic field. By holding the coil over the subject's skull, the magnetic field on its part induces perpendicular currents in the brain strong enough to directly depolarize neuronal elements and

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influence cortical excitability. Repetitive TMS (rTMS) can either enhance (5–20 Hz, high-frequency [HF] stimulation) or suppress (approximately 0.2–1 Hz, low-frequency [LF] stimulation) cortical activity and modulate excitability beyond the duration of the applied trains (Chen et al. 1997; Fregni and Pascual-Leone 2007; Hummel and Cohen 2006). More recently, "theta-burst stimulation" (TBS) has been presented as a novel TMS paradigm. Typically, three short trains of repetitive high-frequency rTMS (50–100 Hz) in theta frequency (5 Hz) are used. The stimulation pattern can be tuned to either enhance (via intermittent theta-bursts, iTBS) or suppress brain activity (via continuous theta-bursts, cTBS) (Di Lazzaro et al. 2005; Huang et al. 2005). While rTMS can create strong currents capable to depolarize neurons, tDCS is able to modulate cortical activity by weaker electric currents by influencing ion channels and gradients and hereafter the resting membrane potential (Nitsche et al. 2008). Briefly, prolonged weak currents (1–2 mA) are delivered into brain tissue transcranially via two large electrodes. The length, strength, and polarity of the stimulation determine the duration and direction of the excitability change. Anodal tDCS leads to brain depolarization (facilitation), whereas cathodal tDCS results in brain hyperpolarization (inhibition) (Nitsche and Paulus 2000). As for TMS, tDCS effects seem to be mainly mediated by the changes of excitability of inhibiting or facilitating interneuronal circuits. The enduring effect of neural excitability shift is thought to be longer than with rTMS (Paulus 2003). tDCS has got several beneficial aspects: low price, transferable from laboratories to home and easiness in practical routine in particular combined with multimodal behavioral tasks. Most commonly reported adverse effects in tDCS have been tingling, itching, headache, and burning sensation, while serious complications can be heat-induced skin lesions. In TMS mild side effects have been headache and neck pain, whereas a rare adverse effect (Rossi et al. 2009) is the induction of seizures. Neurophysiological effects of NIBS are still not clearly understood. An improvement in temporal input–output coupling of neuronal firing rates has been implied to promote synaptic plasticity (Nowak et al. 2009): glutamate driven, it could be considered corresponding to long-term potentiation/depression (LTP/LTD) as seen in hippocampal slices after repeated activation of synaptic pathways (Hallett 2007). Indeed, post-tDCS effects of anodal and cathodal stimulation could be decreased by a NMDA-antagonist (Liebetanz et al. 2002). Accordingly, a partial NMDA-agonist selectively is able to potentiate the duration of motor cortical excitability modulation by anodal tDCS (Nitsche et al. 2004) suggesting a considerable influence of glutamatergic neurotransmission in tDCS. Recently, MR spectroscopy studies revealed that anodal tDCS decreases GABAergic transmission, while cathodal tDCS shows similar effects on glutamate concentrations (Stagg et al. 2009). Hereby, NIBS does not only activate directly the cortical regions stimulated itself but also modulate neurotransmission within or toward remote brain areas (Stagg et al. 2011). NIBS is also able to affect neuronal gene expression (Hausmann et al. 2000). For instance, longer rTMS protocols significantly enhanced brain-derived neurotrophic factor (BDNF) mRNA in the hippocampus, parietal, and piriform cortices (Müller et al. 2000).

9.2 Stroke

In the last fifteen years, it has been proposed the use of rTMS for therapeutic purposes or as part of a neurorehabilitation strategy for stroke recovery (Hummel et al. 2008). Cortical stimulation in stroke is meant to either correct maladaptive brain plasticity induced by the cerebrovascular accident or enhance adaptive brain plasticity during rehabilitation. This aim may be realized by modifying locally cortical excitability or by changing connectivity in neuronal networks. The potential therapeutic value and underlying mechanisms of action depend on the lesion size, site and the time between stroke onset and treatment application. Therefore, recommendations may depend on whether rTMS is applied during the acute, subacute, or chronic period of stroke recovery. In the acute phase, a loss of function occurs within the damaged regions and connected areas, altering modulatory control, especially via transcallosal projections onto homologous regions of the contralesional hemisphere (Floel et al. 2008), whereas the chronic stage is characterized by a marked slowing in the rate of naturally occurring functional recovery. Post-stroke hyperexcitability of the contralesional hemisphere may decrease the excitability of the ipsilesional hemisphere, again via transcallosal projections, representing a poor prognostic factor for clinical outcome (Traversa et al. 1998). However, there is a growing body of literature suggesting that in some patients at least, increased activity within the contralesional hemisphere may be adaptive and promote functional recovery (Lotze et al. 2006). The processes of interhemispheric balance are not just limited to M1: it has been shown that the degree of inhibitory interaction between the hemispheres was highly skewed in the parietal regions involved in visuospatial control (Koch et al. 2011). Three types of post-stroke disorders appear to benefit from cortical stimulation techniques: motor deficit, aphasia, and hemineglect. The therapeutic trials in these three conditions commonly aimed to directly increase the excitability of the ipsilesional hemisphere or to decrease the excitability of the contralesional hemisphere, which results in a reduction in its inhibitory influence onto the lesioned hemisphere. The studies reviewed here include either "conventional" (HF or LF) rTMS protocols or TBS protocols, considering that LF rTMS and cTBS are excitability-decreasing protocols and HF rTMS and iTBS are excitability-increasing protocols.

9.3 Motor Function

After a pioneering study showing that electric stimulation to the ipsilesional M1 had functional benefits in animals (Plautz et al. 2003), several studies followed in stroke patients. Both activating high-frequency rTMS/iTBS (Kim et al. 2006) and anodal tDCS administered to the affected hemisphere (Boggio et al. 2007; Fregni et al. 2005; Hummel and Cohen 2006) demonstrated their potential to promote motor recovery. Also, low-frequency rTMS/cTBS (Fregni et al. 2006; Mansur et al. 2005; Takeuchi et al. 2005, 2008) and cathodal tDCS (Boggio et al. 2007; Kim et al.

2010) were found to suppress the contralesional overactivity, rebalancing the interhemispheric dynamics and therefore improving motor performance mostly in the chronic stage of stroke recovery. High-frequency rTMS over the affected hemisphere showed functional improvement outlasting at least 10 days after stimulation (Khedr et al. 2005) in the earlier stage after stroke. More recently, long-term effects outlasting up to three months were also reported for both activating (Chang et al. 2010) and inhibiting (Conforto et al. 2011) rTMS when combined with motor training in early and even late phases of recovery. Recently, the bilateral stimulation has been investigated by a couple of studies. Simultaneous anodal and cathodal tDCS in combination with occupational therapy (Lindenberg et al. 2010) or constraint-induced movement training (Bolognini et al. 2011) resulted in additional therapeutic gains compared to motor therapy alone. Also, bilateral rTMS showed beneficial effects compared to contralesional stimulation which persisted 1 week (Takeuchi et al. 2009). Summarizing, there is evidence that rTMS and tDCS might help to promote functional recovery in patients with mild-to-severe motor impairment and subcortical strokes, whereas less is known about the efficacy of brain stimulation when the cortex itself is affected. Combining tDCS and robot-assisted arm training, Hesse et al. (2011) did not find additional improvement in patients with severe paresis and extensive cortical lesions in the subacute stage after stroke. More recently, anodal tDCS applied to the lesioned hemisphere in severely affected patients did not observe positive effects in the acute phase after stroke (Rossi et al. 2012). These results highlight two main issues: It is of great importance that (1) NIBS has to be applied simultaneously with specific rehabilitative training to enhance effects and subsequent functional recovery and (2) it has to be determined where NIBS has to be delivered. In this view, fMRI analysis revealed a positive correlation of ipsilesional M1 activity with rTMS response, indicating that cortical plasticity in ipsilesional M1 may serve as a marker for the efficacy of facilitatory rTMS and should be considered when aiming to create an individually tailored treatment protocol (Ameli et al. 2009).

9.4 Aphasia

Recovery of language impairment is often incomplete despite intensive speech therapy (Pedersen et al. 2004). Two different neurostimulation strategies for recovery might be designed to improve language functions after stroke. First, in patients with smaller left-hemispheric lesions, the recruitment predominantly occurs in perilesional brain areas with involvement in right-hemispheric language structures to a variable degree. Since parts of the perilesional language regions are preserved, activating left-hemispheric neurostimulation might improve their recruitment for language recovery. Indeed, increased perilesional activation was found to be associated with better naming performance (Fridriksson et al. 2010). Secondly, homologous right-sided language regions might be potential targets in two different aspects. Based on the above-mentioned model of the interhemispheric

competition, a downregulation might help to suppress an abnormal strong interhemispheric inhibition from right-sided regions to perilesional left-sided language areas. In patients with larger left-sided frontotemporal lesions, predominantly homologous language networks in the right hemisphere are recruited and an activation of contralesional regions might support their recruitment and enhance recovery after stroke (Schlaug et al. 2011). In this view, both the affected and the unaffected language networks might serve as targets for brain stimulation. Application of anodal tDCS to the affected hemisphere over several days reported positive effects persisting up to three weeks after stimulation (Fridriksson et al. 2011). Another report has not found any benefit for anodal but for cathodal tDCS applied to the left Broca's area (Monti et al. 2008). Inhibiting rTMS (Barwood et al. 2011; Weiduschat et al. 2011) and tDCS administered to the unaffected hemisphere also showed improved auditory verbal comprehension in the subacute stage after stroke (You et al. 2011). The aim to rebalance interhemispheric dynamics after stroke should be limited to extensive left-hemispheric lesions, where contralesional language areas are suggested to play a crucial role in language recovery and should not be downregulated via NIBS. Indeed, anodal tDCS applied to the non-language-dominant unaffected hemisphere led to variable language improvement persisting up to 2 weeks after stimulation (Flöel et al. 2011).

9.5 Hemispatial Neglect

Hemispatial neglect is a common and disabling syndrome following unilateral brain damage, particularly to the right hemisphere. In many cases, neglect is associated with hemorrhagic or ischemic stroke to right perisylvian regions, often including the right inferior parietal lobe and/or nearby temporo-parietal junction. It is defined as the inability to respond or move toward novel stimuli presented in the space contralateral to brain damage (Ellison et al. 2004). Though a satisfactory recovery occurs spontaneously in most cases, a third of patients shows clinical signs of neglect even one year after the cerebrovascular lesion (Karnath et al. 2011). Following the pioneering publication by Oliveri (Oliveri et al. 1999), most published work studying rTMS as a putative therapeutic intervention in neglect so far has focused on excitability-decreasing paradigms (LF rTMS or cTBS) applied to the left hemisphere. The effects of excitability-increasing paradigms (HF rTMS or iTBS) over the lesioned cortical regions have not yet been really evaluated. In a first study using brief HF rTMS trains in 7 patients with neglect, a reduction in errors on the bisection line test during a "virtual lesion" of the contralesional posterior parietal cortex was demonstrated (Oliveri et al. 2001a, b). Using a twin-coil approach to measure excitability within the intact left hemisphere of neglect patients, it was observed that a single session of 1 Hz rTMS to the contralesional hemisphere could ameliorate visual neglect and reduce contralesional brain hyperactivity (Koch et al. 2008). Other studies have assessed the effects of a 10-day course of LF rTMS of the contralesional left parietal cortex (Brighina et al. 2003;

Shindo et al. 2006; Song et al. 2009; Lim et al. 2010), reporting various features of clinical improvement. The only sham-controlled study compared the therapeutic effect of 10 LF rTMS sessions of the contralesional left parietal cortex to that of 10 HF rTMS sessions of the ipsilesional right parietal cortex performed in 27 patients with visuospatial neglect in the acute stroke period (Kim et al. 2013). This study showed a better improvement in the right HF rTMS group compared to the left LF rTMS and sham groups. Regarding TBS, there are three studies that assessed the effects of an excitability-decreasing paradigm (cTBS) applied to the contralesional hemisphere (Nyffeler et al. 2009; Cazzoli et al. 2012; Koch et al. 2012). In a first study (Nyffeler et al. 2009), a significant improvement in a visual attention task was observed for more than 24 h after 4 cTBS trains applied to the left posterior parietal cortex in 11 patients with post-stroke neglect. The same group applied 8 trains of cTBS over 2 consecutive days in 24 subacute stroke patients with right-hemispheric stroke in a randomized, double-blind, sham-controlled study (Cazzoli et al. 2012): cTBS but not sham stimulation induced a significant improvement in daily living activities and a better neuropsychological performance, lasting for at least 3 weeks after cTBS. Finally, in another randomized, double-blind, sham-controlled study, another group performed ten sessions over 2 weeks of 2 cTBS trains delivered daily to the left posterior parietal cortex in 20 patients with subacute right-hemispheric stroke, showing that cTBS but not sham stimulation decreased the severity of spatial neglect with after-effects lasting up to 2 weeks after treatment (Koch et al. 2012). Given the consistent results of several studies conducted by different teams, we can consider as possible effective the application of cTBS paradigm to the contralesional left-hemispheric posterior parietal cortex in the treatment of post-stroke neglect in the post-acute phase.

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Chapter 10
Resilience of Brain Networks After Stroke

How the Brain Anticipates, Endures, Responds, and Adapts to Focal Aggressions

Elisabeth Dirren and Emmanuel Carrera

Abstract How do brain networks anticipate, endure, respond, and adapt to limit the consequences of a stroke? Recent studies suggest that understanding the whole process of resilience of brain networks may create new opportunities in the management of patients. The first step of resilience relates to the status of brain networks before the stroke has occurred. In healthy subjects, brain networks seem to be organized to limit the consequences of a lesion. Indeed, the anatomic location and the position of strategic nodes in the network architecture prevent major neurological deficits, even when these hubs suffer from a targeted attack. The second step in the process of resilience reflects how the brain endures the impact of stroke. Widespread changes in the organization of brain networks are triggered by the lesion. This effect can be understood as "connectional" diaschisis or "connectomal" diaschisis defined, respectively, as the changes in coupling between two nodes of a specific network or in the totality of brain connections. Clinically, the reduction in interhemispheric coupling after stroke seems to be particularly relevant. Further steps in the process of resilience include response and adaptation to the lesion. Recent evidence points to the importance of changes in network configuration during recovery. However, it remains debated whether normalization or reorganization of brain networks in a most efficient architecture will lead to a favorable outcome. Based on the concept of resilience, further studies are needed to determine how therapeutic strategies may promote an optimal architecture of brain networks to improve functional outcome.

Keywords Stroke · Brain networks · Diaschisis · Brain graph · Small-world architecture · Connectivity connectome · Recovery

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10.1 Introduction

How do brain networks anticipate, endure, respond, and adapt to limit the consequences of a stroke?

Far beyond the infarct and its surroundings, a stroke produces cataclysmic changes in the organization of brain networks. In fact, a focal lesion triggers widespread alterations of connectivity between distant brain regions (Carrera and Tononi 2014; Grefkes and Fink 2014). Recently, the application of graph theory to neurosciences has open new perspectives in the field. We can now estimate the impact of a lesion on the architecture of a specific network or on the connectome, defined as the comprehensive description of the network of elements and connections forming the human brain (Sporns et al. 2005). Although the clinical relevance of these findings remains largely to be established, the determination of changes in connectivity distant to the lesion has lead to a new approach in the understanding of the neural correlates of brain function (Bullmore and Bassett 2011) (Fig. 10.1).

Nevertheless, it would be too simplistic to consider that the brain is "caught by surprise" and only passively endures the consequences of the stroke. In fact, mounting evidence suggests that brain connectivity architecture is organized not only to maximize functional performances but also to limit the potential consequences of a lesion. It is now demonstrated that brain networks are built with a limited number of highly connected nodes, or hubs, to promote an optimal balance between specialization and integration of information (Hagmann et al. 2008). We are only starting to understand how this "prelesional" organization is key to limit the impact of a lesion on brain networks and its subsequent clinical consequences. Furthermore, recent studies have identified several genetic and environmental factors that modulate the organization of the human connectome and possibly its robustness to focal insults (Thompson et al. 2013).

Immediately after it has endured the first consequences of the lesion, the brain responds and begins to adapt to the focal aggression. Modulation of network organization is clinically relevant during the whole process of recovery, reflecting, in fact, the mechanisms of plasticity and repair (Fornito et al. 2015). Understanding how these changes are associated with restoration of function may open new therapeutic options to improve clinical outcome.

In this chapter, we will describe how the study of brain networks after stroke has led to a better understanding of the process of resilience, defined as the way the

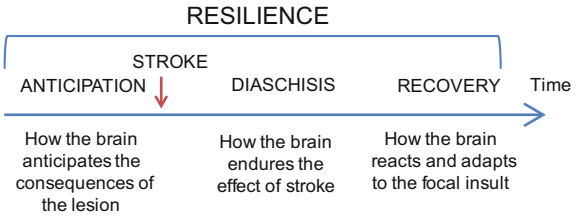

Fig. 10.1 Steps in the process of resilience of brain networks

brain anticipates, endures, responds, and adapts to focal aggressions. We will also discuss the therapeutic relevance of these findings.

10.2 Methodological Aspects

Before reviewing how focal lesions impact brain networks, it is important to summarize the methods that are most commonly used to determine connectivity in the human brain.

Structural connectivity using diffusion tensor estimates the tridimensional orientation of the diffusion of water molecules for each brain voxel (Van Essen and Ugurbil 2012). In human, diffusion tensor imaging (DTI) can be applied to determine white matter connections between gray matter regions, based on the measure of fraction anisotropy (FA) and mean diffusivity (MD) maps. Today, DTI is widely used to assess to fiber bundles but has important limitations in the context of stroke (Griffa et al. 2013). These are mainly related to the distortion of the surrounding tracts caused by the lesion, to the Wallerian degeneration following stroke, and to the issue of crossing fibers in single voxels (Wedeen et al. 2008). The limitation related to crossing fibers is particularly relevant when studying brain networks, since crossing fibers can be detected in at least 70–90% of the white matter voxels. To address this issue, different techniques have been developed using orientation distribution functions. Diffusion spectrum imaging (DSI) and qBall are variants of DTI, whose merits are to allow imaging of multiple fibers orientations in a single voxel (Wedeen et al. 2005; Tuch et al. 2002).

Functional connectivity refers to the temporal correlations between neural, electrical, or haemodynamic signals arising from distinct brain regions. Resting-state fMRI (rs-fMRI) can be used to determine functionally connected regions based on the measure of their spontaneous fluctuations of brain oxygen-level dependant (BOLD) (Raichle 1998; van den Heuvel and Hulshoff Pol 2010). Electroencephalography (EEG) and magnetoencephalography (MEG) are other methods to determine functional connectivity based on the measure of neuronal electrical activity (Schoffelen and Gross 2009). Despite a lower spatial resolution than rs-fMRI, EEG and MEG are useful to capture the changes in coupling over time. Based on these techniques, several resting-state networks can be identified (Damoiseaux et al. 2006). They include the precuneus-dorsal posterior cingulate network, the visual network, the default mode network, the fronto-parietal network, the salience network, the somatosensory motor network, and the dorsal attention network. These functional networks are organized as anticorrelated task-positive and task-negative networks (Fox et al. 2005). From time-series data, the causality between two brain regions can be inferred based on the principle that causes to precede, and help predict, their effects (Seth et al. 2015). Effective connectivity can also be used to determine, in a predefined network, the intrinsic or task-dependent influences that a particular area exerts over another (Friston 2011; Westlake and Nagarajan 2011). Static models include psychophysiological

interactions (PPI) and structural equation modeling (SEM), and dynamic causal modeling (DCM) is an example of a dynamic model (Friston 2011).

Structural and functional connectivity methods do not carry necessarily the same information. Whereas structural connectivity represents anatomic connections, functional connectivity does not necessarily correspond to direct connections between brain regions but may represent indirect, polysynaptic functional connections. As such, and particularly after stroke, differences in methods to assess connectivity have to be considered in detail when interpreting and planning connectivity studies, taking in account the effect of lesion on tracks of interest.

10.2.1 Network Analysis

When applying network theory to brain connectivity, brain regions and their relations can be represented by nodes and edges (Bullmore and Sporns 2009). Graph theory refers to a branch of mathematics that deals with analyzing integrative properties of discrete nodes, interconnected by edges. In neurosciences, it is now possible to determine the importance of brain regions, considered as nodes, in specific networks or in the connectome (Sporns et al. 2005). The most common measure of the importance of a node is its degree, which represents the number of connections it has with other nodes of the network (Rubinov and Sporns 2010). A high-degree node is referred as a "hub." Recently, the notion of "rich club" has been developed to emphasize the tendency for high-degree nodes to be more densely connected among themselves than nodes of a lower degree, providing important information on the higher-level topology of the brain network (van den Heuvel and Sporns 2011). The measures of centrality can also be used to determine the importance of a node reflecting its position in the network of interest (Rubinov and Sporns 2010). Closeness centrality is defined as the inverse of the average shortest path length from one node to all other nodes in the network. The betweenness centrality is defined as the fraction of all shortest paths in the network that pass through a given node (Rubinov and Sporns 2010). Brain graphs may also be used to describe more complex motives (Bullmore and Sporns 2009). When studying brain connections in healthy subjects, a "small-world" architecture can be recognized, consisting of communities of highly connected nodes but with only few connections between nodes of different communities (Watts and Strogatz 1998). This organization promotes functional specialization between communities but preserves their functional integration (Sporns et al. 2007). As such, the small-world organization, with a subtle balance between economy and efficiency, maximizes local and global information processing between nodes of the network, reducing its wiring costs (Achard and Bullmore 2007; Tononi et al. 1994). Recent studies have suggested that the hierarchical modularity of the small-world organization may be particularly relevant for higher functions (Carrera 2015; Park and Friston 2013). However, as we will discuss later in this chapter, the clinical relevance of a disorganization of the

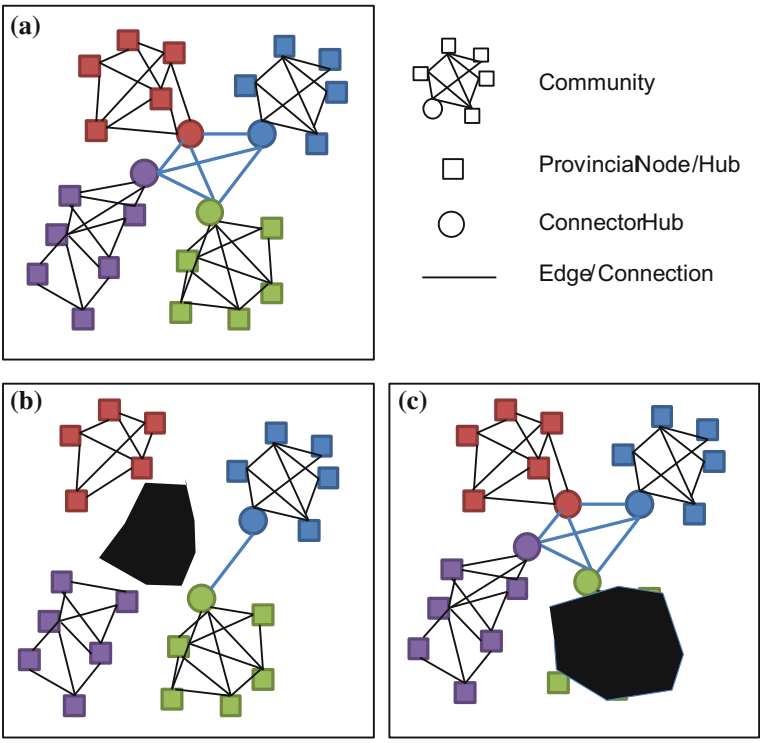

Fig. 10.2 Representation of the impact of the lesion on specialization and integration of the network. Adapted from Carrera and Tononi (2014). *Legend* Representation of a 'healthy' (**a**) and lesioned networks (**b** and **c**). **b** A lesion of connector hubs alters the functional integration of the different communities. Each disconnected community becomes more independent from the others. **c** Lesion of a community reduces the functional specializationof the network

small-world architecture after stroke, affecting either the specialization or the integration of this network, remains largely unknown (Fig. 10.2).

10.3 Anticipation

Is the brain really prepared to cope with a focal lesion? What is the evidence that brain can "anticipate" a focal lesion and limit its consequences? The study of brain architecture in healthy subjects provides several elements that strongly suggest that brain networks are organized in a way that make them less vulnerable to focal lesions.

Indeed, when studying the importance of the different nodes in the connectome, it appears that only few nodes have a large number of connections with the vast majority of nodes having far less connections (Hagmann et al. 2008). The

high-degree nodes, referred as hubs, are connected to other nodes of the network that are of lower degrees consistent with a "small-world" organization as previously described (see above). This distribution of node degree follows a power law and the architecture of the network is referred as a "scale-free" organization (Alstott et al. 2009). In other terms, the low-degree nodes belong to dense subgraphs that are connected to each other via high-degree nodes. By comparison, in random networks, the distribution of node degrees may follow a Gaussian distribution (Newman et al. 2001). In healthy subjects, a power-law distribution has been described in both the structural and functional connectome (Hagmann et al. 2008; Achard et al. 2006).

Does the scale-free distribution make brain networks more robust or vulnerable to focal lesions? Two major types of attacks against a network may be considered. A "random attack" affects randomly a hub of the network, whereas a "targeted attack" affects the high-degree nodes (Hagmann et al. 2008; Alstott et al. 2009). The robustness of scale-free networks to the different types of attacks is clearly different. Although scale-free networks are resilient to random failures because only few nodes are of high degree, and the chance to affect one of these is statistically low, these networks are highly vulnerable to targeted attack against high-degree nodes potentially causing, in the context of stroke, widespread changes in connectivity in the entire network.

In human brains, the location of high-degree nodes has been identified based on functional and structural connectivity data (Hagmann et al. 2008; Achard et al. 2006). These hubs are mainly localized along the midline within subregions of the medial frontal and parietal cortex, including the cuneus, precuneus, posterior and anterior cingulate cortices. Identification of these nodes is similar when using different parameters evaluating the importance of the nodes (degree, core, and centrality). Furthermore, the importance of these nodes is supported by the description of widespread alterations in brain networks when one of these hubs is "mathematically" removed by modeling (Alstott et al. 2009). In this study based on structural networks in healthy subjects, "virtual deletions" of high-degree nodes (the precuneus for instance), located at the medial part of the parietal lobe, seem to cause the most severe and diffuse alterations of the architecture of the whole network.

Why are lesion of critical hubs rarely observed in human and do not cause as much clinical deficits as data from healthy subjects would suggest? In fact, in human, isolated vascular lesions in the region of high-degree nodes are rare. For instance, although strokes involving the precuneus are independently predictive of unfavorable outcome (Yassi et al. 2015), isolated partial or complete lesions in this area are rarely described. Different hypotheses may explain this observation. The precuneus and other hubs along the midline may be particularly resistant to ischemia, because their blood supply originates from the three main intracerebral arteries (the anterior, middle, and posterior cerebral arteries) (Tatu et al. 1998). According to our hypothesis, even a complete occlusion of one of theses arteries, the anterior cerebral artery for instance, will not cause, in most cases, a reduction in perfusion severe enough to cause infarction in the region of interest. Another hypothesis may be the

existence of redundant functional networks, which prevent major clinical dysfunctions even when a high-degree node is affected.

We are also beginning to understand the environmental and genetic factors that are modulating the organization of the connectome and influence the robustness of the network. In healthy subjects, there is mounting evidence that these factors influence the architecture of the structural and functional networks. Based on structural imaging data from the U-TWIN cohort including 156 pairs of twins, two measures of network architecture (normalized clustering coefficient and normalized characteristic path length) were found to be substantially heritable (Bohlken et al. 2014). Based on another cohort of 200 twin subjects, resting-state functional networks and their internetwork coherences were found to be highly heritable, although both genetic and environmental factors seem to modulate network organization (Yang et al. 2016).

Finally, both structural and functional connectivity seem modulated by gene expression. In rodents, structural brain connections between 32 cortical and subcortical regions were correlated with gene expression in the respective regions (Richiardi et al. 2015). In human, a similar correspondence between resting-state activity and brain gene expression was recently reported (Richiardi et al. 2015; Wang et al. 2015).

In summary, if the connectivity profile may act as an individual "fingerprint" (Finn et al. 2015), we still have to determine whether a particular genetic profile or whether adaptation of the environmental conditions may improve the robustness of brain networks to focal lesions. Further studies are needed to determine whether modulation of brain architecture, for instance by training or noninvasive brain stimulation, may improve the robustness of networks to potential further brain lesions.

10.4 Diaschisis

When stroke occurs, widespread changes in brain network architecture are immediately observed. We recently proposed to describe this process as part of the concept of "diaschisis" defined generically as the "acute neurophysiological changes distant to the lesion" (Carrera and Tononi 2014). In the context of brain network after stroke, "connectional" diaschisis is employed to describe the changes in coupling between two nodes of a specific network distant to the lesion and "connectomal" diaschisis to depict the remote changes in the structural or functional connectome. As considered here, diaschisis is an exclusively passive process, which can be considered as an important and independent step in the process of resilience of brain networks, reflecting how they endure the impact of the lesion (Fig. 10.3).

Historically, the term "diaschisis" was introduced by von Monakow in 1914 to describe the dynamic neuronal excitatory changes observed remote to a brain lesion (von Monakow 1914). More specifically, diaschisis, as defined by von Monakow, referred to neuronal downregulation observed in areas distant but connected to the

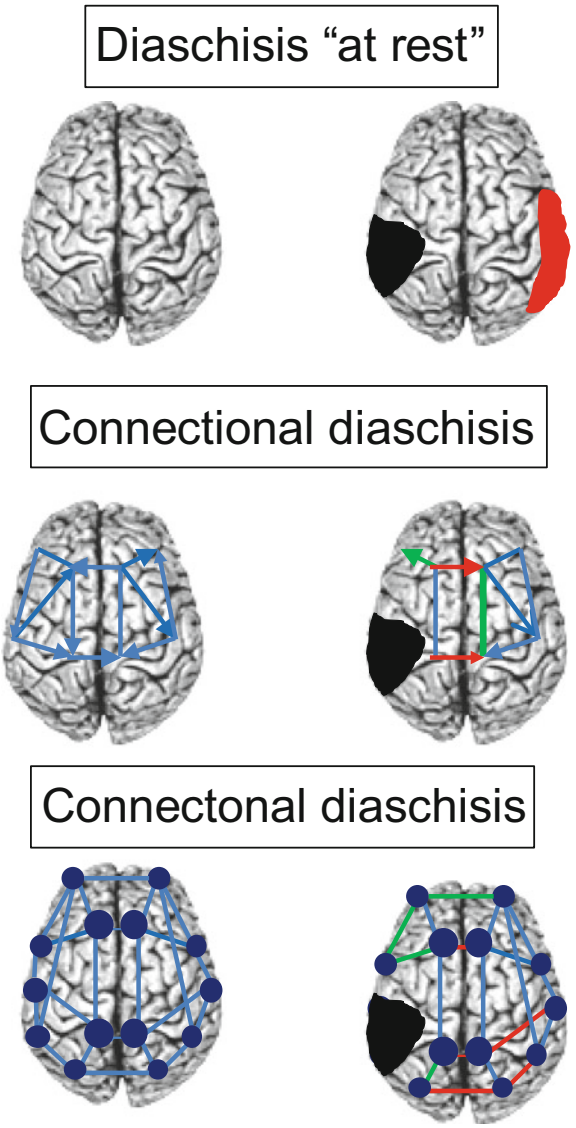

Fig. 10.3 Types of diaschisis. Adapted from Carrera and Tononi (2014). *Legend* Types of diaschisis before (*left*) and after (*right*) a focal brain lesion (*black*). Diaschisis at rest: a focal lesion induces a remote reduction of metabolism (*red*). Connectional diaschisis: distant strengths and directions of connections in a selected network may be increased (*green*) or decreased (*red*). Connectomal diaschisis: a lesion of the connectome induces widespread changes in brain network organization including decrease (*red*) or increase (*green*) in connectivity

lesion site (Finger et al. 2004). According to current concepts, diaschisis reflects, remotely, the consequences of neuronal dysfunction at the site of lesion, independently of mechanisms of adaptation such as plasticity or transneuronal degeneration, for instance (Feeney and Baron 1986; Fornito et al. 2015). It must be kept in mind that “diaschisis” may be difficult to distinguish from these other adaptive and maladaptive mechanisms, since they can occur simultaneously. Furthermore, the inevitable delay between the insult and experimental recordings in patients prevents, in most cases, the assessment of diaschisis within minutes after stroke.

With the development of electrophysiological (evoked potential, EEG) and imaging techniques [positron-emission tomography (PET)] in the late 1970 and early 1980, it has become possible to reliably assess focal changes in metabolism and neural activity remote to a lesion (i.e., "focal" diaschisis) (see Fenney and Baron for review) (Feeney and Baron 1986). Interestingly, the clinical relevance of focal diaschisis is notable after subcortical lesions. For instance, thalamic strokes frequently lead to focal area of cortical hypometabolism corresponding to the clinical symptoms (Carrera and Bogousslavsky 2006). The clinical impact of focal reductions in metabolism is far less relevant after cortical lesions (Andrews 1991). For instance, based on several imaging metabolic and perfusion imaging modalities, a decrease in metabolism in the contralateral cerebellar hemisphere is commonly observed after vascular and non-vascular hemispheric lesions (crossed cerebellar diaschisis) (Baron et al. 1981). Nevertheless, the relevance of these findings has never been clearly established. In addition, the interest of "focal" diaschisis is limited by the absence of evidence that therapeutic strategies aiming at restoring normal metabolism in remote areas of hypometabolism improve function.

The development of new methods to assess connectivity (see methodological section) has given a new impulse to the concept of diaschisis, which can be considered as an important step in the process of resilience. Based on these techniques, we can define "connectional" diaschisis as selective change in coupling between two nodes of a defined network (context-sensitive or not), involving areas distant from the lesion (Campo et al. 2012; Carrera and Tononi 2014). In human, the clinical relevance of this concept is most easily tested after ischemic strokes that represent the most relevant model of focal, acute lesions. For this reason, we will now focus on stroke to illustrate the concept of connectional diaschisis, which has mostly been described in the motor network. Several studies have shown an initial decrease in interhemispheric resting-state functional connectivity related to loss of motor function (Xu et al. 2014; Golestani et al. 2013; Carter et al. 2010; Grefkes and Fink 2014). Similarly, clinically relevant changes in effective interhemispheric connectivity in the motor network were reported after subcortical strokes (Jiang et al. 2013; Grefkes and Fink 2014). More specifically, an inhibitory influence from the contralesional primary motor cortex (M1) to the ipsilesional M1 was identified (Grefkes et al. 2008). In addition to interhemispheric changes, a significant decrease in the influence of the ipsilesional supplementary motor area (SMA) and premotor cortex to the ipsilesional M1 was found early after stroke (Rehme et al. 2011). The impact of stroke on functional networks was reported in other functional networks than the motor network. For instance, in the ventral and dorsal attentional networks, a decrease in interhemispheric functional coupling assessed with rs-fMRI was related to a loss of attention after right hemispheric strokes (Carter et al. 2010). A similar pattern was found in the language network after left hemispheric strokes (Bonilha et al. 2014). In the future, further studies will clarify the potential clinical relevance of changes in connectivity between each component of the different functional networks.

Based on the concepts derived from graph theory, we further defined "connectomal" diaschisis as the changes in the structural or functional connectome leading

to the reorganization of subgraphs (Carrera and Tononi 2014). In addition to improvements in methods to map brain connectivity, the application of graph theory to the analysis of brain networks gives a new framework for the interpretation of connectivity after stroke. In particular, the integrative properties of the brain can now be determined, which have led to redefining diaschisis as a measure of changes that affect the totality of whole network rather than a focal area or an isolated network (Carrera and Tononi 2014). Based on data from healthy subjects, it was revealed that the deletion of a high-degree node or hub that are located at the midline or at the temporo-parietal junction in the human brain leads to widespread changes in brain connections, affecting both the integration and specialization of the network (Alstott et al. 2009). Post-stroke changes in network configuration assessed by small-world indices have also been outlined based on functional connectivity (Wang et al. 2010; Cheng et al. 2012). Of note, a recent study failed to demonstrate significant changes in network efficiency as assessed by the small-world index in acute stroke patients (Zhu et al. 2016).

Clearly, we are only beginning to apply the concepts derived from network theory to patients. After stroke, the studies needed to test these concepts are nevertheless difficult to conduct. Indeed, the correlation between the impact of stroke on brain networks and the resulting loss of function is highly dependent on confounding factors such as patient characteristics, location, and size of lesions, for instance. Difference in methodologies to assess brain connectivity across studies may also be responsible for the challenge to reliably identify clinically relevant changes in connectivity after stroke.

10.5 Recovery

After the brain has endured the effect of stroke, mechanisms of plasticity and repair occur. During the days, weeks, and months after stroke onset, a profound reorganization of brain networks can be observed at the level of individual networks and in the connectome. As reported in the diaschisis section of this chapter, the motor network is the functional network that has most frequently been studied in relation to recovery. After a subcortical stroke, restoration of the reduced interhemispheric coupling, associated with a loss of function acutely (see above), appears to be essential for the recovery of function. Improvement of motor function was directly correlated with normalization of interhemispheric coupling between M1 areas. This has been demonstrated based on the measure of effective connectivity, with a normalization of the influence of the ipsilesional primary motor cortex (M1) on the contralesional M1 (Rehme et al. 2011; Grefkes et al. 2008), and on rs-fMRI with a restoration of interhemispheric coupling between M1 regions (Park et al. 2011; Wang et al. 2010; Zhang et al. 2016). Importantly, the changes in coupling between M1 regions are independent of M1 activations observed with fMRI during a motor task (Sharma et al. 2009; Campo et al. 2012). This underscores the importance of connectivity studies during brain recovery. When focusing on other connections in

the motor network, restoration of effective and functional coupling between the supplementary motor area and M1 (Grefkes et al. 2008, 2010; Wang et al. 2010; Rehme et al. 2011) may have its clinical importance. The interpretation of other changes in coupling in the motor network is more challenging, since they have not been consistently associated with recovery of function. For instance, in a study including 51 stroke patients with motor dysfunction, widespread changes in functional connectivity between ipsilesional M1 and other nodes of the network were observed. Initially, an increase in connectivity between ipsilesional M1 and ipsilesional frontal and parietal cortices, both thalamus and cerebellum, was observed. On the contrary, a decrease in functional connectivity was observed between the ipsilesional M1 and the contralesional M1 and the occipital cortex (Park et al. 2011). To improve our knowledge about the role of brain networks as predictor of outcome during recovery, new studies should be conducted including similar patients and using comparable methodological approaches and analysis (Fig. 10.4).

Based on brain graph analysis, the clinical relevance of changes in the architecture of brain organization over time has been investigated in animals and humans. The results of these studies showed conflicting results. In a rodent study, restoration of initial representation of the small-world organization was considered to indicate recovery of motor function (van Meer et al. 2012). More recently, a rs-fMRI studies in human suggested that attention deficit recovery is significantly correlated with a normalization of abnormal functional connectivity across networks (Ramsey et al. 2016). Discordant results were found in patients suffering

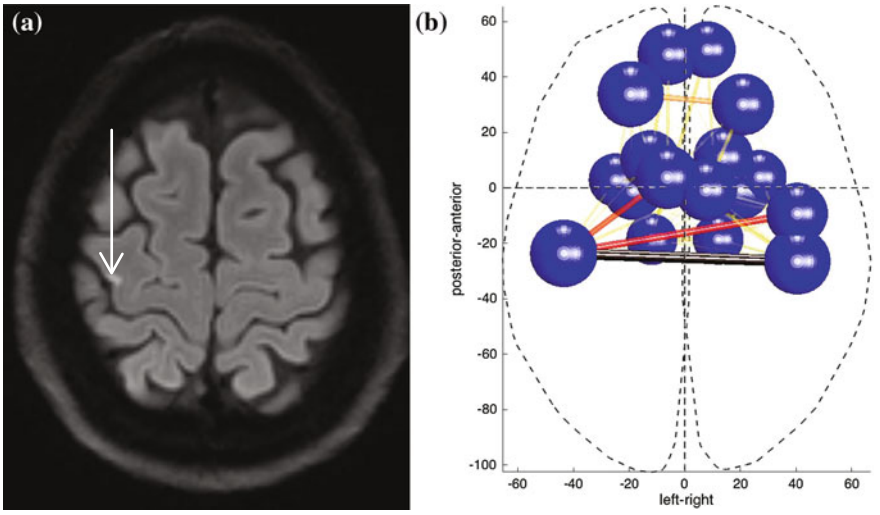

Fig. 10.4 Representation of node and connections strengths in the motor network after stroke. *Legend* **a** Isolated primary motor cortex (M1) stroke (DWI sequence) ; **b** The size and shade of connections reflects their weight. The size of each sphere is proportional to its regional weight (sum of the weights of all connections between this region and the rest of the network)

from subcortical strokes and hemiparesis (Wang et al. 2010). A shift toward a more random mode during the first months after stroke onset was related to motor recovery as assessed by different measures of motor function. As a consequence, it is not known whether restoration of small-world architecture determined by recovery of efficient integration between brain areas is an important step toward good clinical outcome. We can also hypothesize that a favorable functional recovery may be associated with different types of brain architectures depending on the function that has to be regained. For instance, restoration of an "over-specialized" architecture to improve a specific function (for instance, finger dexterity) may be detrimental to the global recovery of function (for instance, global arm function) and subsequent functional independence. It is important to mention here that, so far, most stroke studies in humans investigating brain networks have focused on small subcortical lesions. This approach is based on the assumption that the cortical areas are structurally unaffected by such lesions. However, because cortical atrophy may occur as a consequence of Wallerian degeneration, changes in ipsilateral cortical network function over time may reflect not only reorganization but also the consequences of atrophy (Fornito et al. 2015). This observation strengthens the need for longitudinal studies investigating also the impact of cortical stroke lesions on brain networks. Furthermore, and to clarify the role of network changes over time, it is crucial to compare the course of both structural and functional connectivity during recovery. In healthy subjects, structural connectivity seems to predict functional connectivity, when regions connected with direct structural pathways are investigated (Honey et al. 2009). The results may be different in stroke patients with damaged tracks. It is reasonable to hypothesize that reorganization of structural brain networks may precede functional brain networks and restoration of clinical function. The results of these investigations may be particularly important to predict functional outcome after stroke.

10.6 Therapy

We have now described how the study of brain networks can help understand how the brain anticipates, endures, responds, and adapts to focal aggressions. How can this knowledge, in light of the concept of resilience, change our current approach of stroke patients and instruct future therapy?

Before stroke, an objective would be to promote a configuration of brain networks that optimize function and improve the robustness to lesions. This goal could be achieved by specific training. As an example, recent studies have demonstrated that motor training impact on the configuration of the motor network can be determined using graph analysis (Sami and Miall 2013). Although studies in human would be difficult to conduct to test the hypothesis that a specific network configuration may improve the robustness to stroke, rodent studies may be more easily considered. In stroke patients, changes in the architecture of brain networks may impact rehabilitative therapy on an individual basis. In a recent study, chronic

stroke patients with hemiparesis benefit from an arm and hand rehabilitation intervention during 6 weeks. An increase in small worldness and a greater centrality were found at 6 weeks compared to baseline (Laney et al. 2015). Future studies have to determine whether changes in brain network in response to therapy may be used to refine the management of stroke patients at different time points during rehabilitation.

Neuromodulation techniques (transcranial magnetic stimulation (TMS) and direct transcranial direct current stimulation (tDCS) can be used to modulate long-range functional focusing either on the ipsi- or contralesional hemisphere (Auriat et al. 2015; Kang et al. 2016). For instance, in subcortical stroke patients with hemiparesis, repetitive transcranial magnetic stimulation (TMS) restored the inhibition of the contralesional M1 regions when applied to the contralesional M1 but also increased the effect of the ipsilesional SMA on ipsilesional M1 (Grefkes et al. 2010). Further studies are required to determine the optimal neuromodulatory regimen to improve function after stroke, based on the architecture of brain networks.

10.7 Conclusion

In this chapter, we discussed how the brain anticipates, endures, responds, and adapts to stroke in light of the concept of resilience. We are confident that, in the future and at each step of this process, a specific network-based approach may be considered to improve patient's functional outcome.

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Chapter 11
Functional Role of Physical Exercise and Omega-3 Fatty Acids on Depression and Mood Disorders

Stefano Farioli-Vecchioli and Debora Cutuli

Abstract In adulthood, depression is the most common psychiatric disorder and is projected to become the highest cause of disease burden by 2020. Major depression represents a debilitating condition that significantly impairs the function of the central nervous system and severely degrades the quality of life. Several hypotheses regarding the mechanisms that underlie the path physiology of major depression have been investigated. Indeed, major depression has a multifactorial etiology arising from environmental, psychological, genetic, and biological factors. Research over the past decades has clarified that depression is mainly associated with neurotransmitter and neurotrophic factor imbalances, HPA disturbances, deregulated inflammatory pathways, increased oxidative damage, neurogenesis dysfunction, and mitochondrial disturbances. In the recent years, the bulk of the research has concentrated on the study of the neurotransmitters, neurotrophins, neurogenesis, and neuroinflammation as the main factors involved in the pathogenesis of depression. Since recent evidence has suggested that sedentary life and poor diet contribute to the genesis and course of depression (Berk et al. 2013), in this chapter we have taken into account the effects of physical exercise and nutritional factors crucial for the central nervous system, such as omega-3 fatty acids, on depression and mood disorders.

Keywords Physical activity · Exercise · Diet · Omega-3 fatty acids · Depression

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11.1 Introduction: Depression and Mood Disorders

While the growth of the modern medicine has provided multiple technological and medical devices able to rise life expectancy, it has come at a high cost; in that range of lifestyle, issues are now negatively affecting our mental health (Hidaka 2012). In recent decades, the advent of computerization in synergy with the progressive urbanization of the world population has led to a very strong impact on levels of physical activity, and more than 30% of the world population is now considered as insufficiently physically active (Jacka et al. 2012). The sedentary lifestyle combined with other factors such as alterations of the sleep/wake cycle, abuse of psychotropic substances, and chronic stress might represent high risk factors for the onset of mood disorders, which many times can result in the pathogenesis of depressive syndromes.

In adulthood, depression represents the most common and serious psychiatric disorder, affecting more than 100 million adults worldwide and rating as the fourth leading cause of disease burden in 2000 (Moussavi et al. 2007). Major depression is a debilitating condition that significantly impairs the function of the central nervous system and severely degrades the quality of life (Saarni et al. 2007; Subramaniam et al. 2013). In humans, the depressed mood can disrupt fundamental activities, such as eating and sleeping; and the rate of suicidal behavior is significantly higher in depressed patients compared to the general population (Suominen et al. 2009; Beautrais et al. 1996). Several hypotheses concerning the mechanisms underlying the pathophysiology of major depression have been deeply investigated. Indeed, major depression has a multifactorial etiology arising from environmental, psychological, genetic, and biological factors. Research over the past decades has clarified that depression is mainly associated with neurotransmitter and neurotrophic factor imbalances, hypothalamic-pituitaryadrenal axis (HPA) disturbances, deregulated inflammatory pathways, increased oxidative damage, neurogenesis dysfunction, and mitochondrial disturbances (Lopresti et al. 2013; Leonard and Maes 2012; Raison and Miller 2011). In the recent years, the bulk of the research has concentrated on the study of the neurotransmitter/neurotrophin theory and neurogenesis and neuroinflammation hypothesis that consider the main factors involved in the pathogenesis of depression.

Since recent evidence has suggested that sedentary life and poor diet contribute to the genesis and course of depression (Berk and Jacka 2012), in this chapter we have taken into account the effects of physical exercise and omega-3 fatty acids on depression and mood disorders.

11.1.1 Neurotransmitter Theory

Imbalance in the endogenous production and transmission of mood-regulator neurotransmitters, such as serotonin, dopamine, and glutamate, are usually observed in the various regions of central nervous system (Maletic et al. 2007). In particular,

deficits in serotonin availability, the most studied neurotransmitter in depression, are sustained by recent data describing a significant decrease of serotonin receptors in depressed patients (Carr and Lucki et al. 2011). Moreover, depressive symptoms are strictly correlated with increased availability of monoamine oxidase, an enzyme that specifically metabolites serotonin and other monoamine in the brain (Meyer et al. 2006), and alterations in the production of the enzyme tryptophane hydroxylase, which plays an important role in the synthesis pathway of serotonin (Matthes et al. 2010). However, the strongest evidence of neurotransmitter disproportion in depression arises from widespread use and therapeutic efficacy of pharmaceutical antidepressant, such as selective serotonin reuptake inhibitors (SSRIs), which are thought to alleviate depression by increasing the availability of monoamines such as serotonin, noradrenaline and, possibly, dopamine (Connolly and Thase 2012).

11.1.2 Neurotrophins, Neurogenesis, and Neuroinflammation Hypothesis

Preclinical and clinical studies have suggested that chronic stress and depression induce a significant decrease in neurotrophin brain-derived neurotrophic factor (BDNF) levels. BDNF is the primary neurotrophin of the hippocampus and as a dimeric protein is involved in cell maintenance, plasticity, growth, and apoptotic cell death. BDNF is structurally related to nerve growth factor and is distributed widely throughout the brain. Major depressive disorders are strictly linked with a drop of hippocampal neurons (Steffens et al. 2000), indicating that smaller hippocampal volume might be considered an indicator of increased risk for mental health. There are several lines of evidence that associate BDNF to the hippocampal atrophy observed in depressed patients. Postmortem brain examinations of patients with depression have indicated significantly lower levels of BDNF in many regions including the hippocampus, while patients treated with antidepressant therapy do not show the equivalent reduction in BDNF protein levels (Duman and Monteggia 2006). Moreover, it has been demonstrated that antidepressant treatment is able to partially rescue the decreased serum levels of BDNF found in the depressed patients, indicating that antidepressant might modulate the hippocampal plasticity by means the mediating role of BDNF (Björkholm and Monteggia 2016). Other studies in animal models of depression have detected loss of serotonergic fibers and reduction of dendritic spine density. Moreover, it has been demonstrated that BDNF works through TrkB signaling cascade to enhance the growth and survival of serotonergic neurons (Mattson et al. 2004). In rodent experiments, acute and chronic immobilization stress induced a significant reduction of mRNA BDNF expression and analogous results were observed following administration of acute and chronic pain stimuli (Duric and McCarson 2005). In humans, patients treated with antidepressant therapy and healthy controls displayed a significant increase of serum BDNF levels in comparison with untreated patients suffered with major

depressive disease (Shimizu et al. 2003). Although, since the causal link between BDNF and depression is quite difficult to establish in human studies, it is not clear whether BDNF represents a contributing factor leading to depression or more simply a correlate of depression and hippocampal volume (Erickson et al. 2012). From the above observations, in the recent years the neurotrophic hypothesis has emerged as a major theory for explaining the pathogenesis of major depression. This model hypothesized that glucocorticoid levels are significantly elevated in response to stress and genetic vulnerability, inducing an alteration of cellular plasticity via the down regulation of growth factors and receptor sensitivity (Duman and Monteggia 2006). The decreased levels of growth factors, such as BDNF, influence negatively the structural and functional pathways within the limbic system, which include the hippocampus. For this hypothesis, recovery and remission of major depressive disorder would be dependent upon a reversal of these processes, such as an increase in BDNF levels.

Several studies indicated that in depression, both the decreased serum peak of growth hormone and the frequently increased serum glucocorticoid hormone may likely result in decreased insulin-like growth factor 1 (IGF-1) levels. Accordingly, the reduction of IGF-1 expression may be involved in the biochemical cascade alterations occurring in association with depression. This hypothesis is sustained by a study demonstrating that the intracerebroventricular administration of IGF-1 is able to mimic the behavioral response of SSRI agonists (Hoshaw et al. 2005). Furthermore, in vitro experiments have shown that serotonin activates IGF-1 (Lambert et al. 2001) as well as BDNF (Meller et al. 2002) synthesis. In recent years, it has been proposed that deficits in adult hippocampal neurogenesis may result in the etiopathology and progression of stress/depressive disorders (Malberg 2004). In the adult hippocampus, generation of new neurons continues throughout life, in a specific hippocampal subfield called dentate gyrus (DG), that recently has been found to mediate different aspects of learning and memory formation, and in particular, to contribute significantly to pattern separation, i.e., the ability to finely discriminate between two very similar objects or context (Clelland et al. 2009; Sahay et al. 2011; Tronel et al. 2012). The adult neurogenesis in the dentate gyrus is tightly regulated by multi-step mechanisms comprising the maintenance of stemness, recruitment from quiescence and division of neural stem cells, followed by the early differentiation and migration of intermediate neural progenitors, and finally the maturation and functional integration of newly generated neurons (Kempermann et al. 2004). As newborn cells undergo terminal differentiation, the dendritic arborization becomes progressively more complex and the neuritis extend deeper into the granule cell layers. These cells show similar electrophysiological responses to the surrounding older cells, and they receive synaptic inputs from GABAergic interneurons. Recent studies demonstrate that, similarly to differentiating neurons during brain development, newly generated granule cells display limited dendritic arborization and receive excitatory GABAergic synaptic inputs, because of their higher intracellular concentration of chloride ions. The early depolarization by GABA has been shown to facilitate the maturation of granule cells, as a significant decrease of neuronal maturation is strictly linked to the

absence of the chloride ion channel NKCC1 (Ge et al. 2006). About three weeks after birth, concomitantly with spine formation, the response of newborn neurons to GABA changes from depolarization to hyperpolarization, which coincides with the beginning of glutamatergic signaling. During this period, the developing progenitors are highly excitable with high membrane resistance and display a lower threshold for long-term potentiation (LTP), a putative model of learning and memory processes (Bliss and Collingridge 1993), in response to theta-burst stimulation (Ge et al. 2006; Schmidt-Hieber et al. 2004), with a concomitant enhanced synaptic plasticity. Fully matured newly generated neurons respond to glutamatergic and GABAergic inputs, similarly to the preexisting DG granule cells (Laplagne et al. 2006, 2007). Two independent studies have demonstrated that new hippocampal granule cells are recruited in learning and memory networks at a later stage of maturation (around 4–6 postnatal weeks; Kee et al. 2007; Farioli-Vecchioli et al. 2008). Before this time point, the differentiating granule cells, despite their lower threshold for LTP, do not express the activity-dependent immediate early genes (IEG). Intriguingly, however, the animal's experience in this time window can profoundly affect the expression of activity-dependent IEGs in newborn neurons at 6 weeks of age (Laplagne et al. 2006; Tashiro et al. 2007). Although convergent evidences support the hypothesis that adult DG newly generated neurons are specifically recruited in the preexisting memory network (Markakis and Gage 1999), the role of these cells in the context of hippocampal memory functions is still matter of discussion. Most of the relevant data on the role of the DG in learning and memory have been obtained by adopting strategies of ablation of adult neurogenesis with antimitotic drug administration (Shors et al. 2001), low-dose irradiation (Snyder et al. 2005), or genetic manipulation to eliminate proliferating neural progenitors. While both antiproliferative treatments and irradiation eradicate hippocampal cell proliferation non-specifically, causing detrimental effects on brain physiology and providing contradictory results, the use of more specific, noninvasive genetic approaches has provided clear proofs on the role of adult hippocampal neurogenesis in pattern separation (Aimone et al. 2011; Johnston et al. 2015). Indeed, it has been established that impaired neurogenesis abolishes the capacity of mice to finely discriminate similar stimuli delivered with little separation in space; on the contrary, when the same stimuli are presented separated in time or space, the defective neurogenesis does not exerted any detrimental effects in recognizing this events as different (Clelland et al. 2009). Moreover, it has been recently demonstrated that animals with defective adult neurogenesis are severely compromised in the discrimination of comparable contexts in a fear conditioning memory paradigm (Sahay et al. 2011; Tronel et al. 2012). Finally, computational models indicate that new hippocampal neurons would play an important role in avoiding interference between newly acquired and established memories (Aimone et al. 2009, 2010). It has well established that major depression seriously compromises hippocampal adult neurogenesis, neuronal plasticity, and the underlying neuronal network which in turn induces the subsequent onset of neurodegenerative symptoms (Lee and Kim 2010). These events result in stress-induced dysregulation of the signaling mechanisms regulating the number and morphology of neurons and

glia in brain regions of depressed patients (Duman 2009), decreased proliferation of neural stem cells and reduced survival of immature newborn neurons (Eyre and Baune 2012). Other studies have suggested that in major depression, the hippocampus-dependent neural system may be unable to promptly and adequately respond to stressful stimuli with adaptive plasticity and neurogenesis may represent one form of adaptive plasticity. The neurogenesis hypothesis of depression originated from several researches using animal stress models, revealing that stressful stimuli, such as long sleep deprivation with a subsequent increase of glucocorticoids (Mirescu et al. 2006), social status of subordination to a dominant animal (Kozorovitskiy and Gould 2004), absence of social interaction (Stranahan et al. 2006) and exposure to trimethylthiazoline, a component of predator (fox) feces (Tanapat et al. 2001), all reduce granule cells proliferation and differentiation, although not necessarily with comparable mechanisms (Duman 2004; Lucassen et al. 2010). Moreover, the adult neurogenesis hypothesis of depression has been repeatedly confirmed by several line of evidences (Ernst et al. 2006): (1) Situation of lasting stress inhibits adult hippocampal neurogenesis (in animals) and represents a serious risk factor for depression in predisposed individuals; (2) cognitive and intellectual impairment as well as volumetric decrease of the human hippocampus would represent the result of suppressed neurogenesis or altered cellular turnover in depression, also considering that neural degeneration does not occurred in depressed patients (Sheline et al. 1996; Mervaala et al. 2000); (3) antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), have been shown to increase the proliferation and the survival of hippocampal newly generated neurons in the adult mouse and a similar effect has also been detected after antidepressant shock electroconvulsive treatment (Brezun and Daszuta 2000; Malberg 2004); (4) latency of therapeutic effect of antidepressant treatment is similar to the time course required for differentiation and fully maturation of newly generated neurons (around 4–5 weeks); (5) ablation of hippocampal neurogenesis totally abolished the behavioral effect of antidepressant treatment. All these results strongly support the idea that the relief from depressive symptoms may be deeply correlated with the fully maturation of new dentate gyrus neurons and their functional recruitment into the preexisting hippocampal neural circuitry.

Finally, patients with chronic inflammation show often depression symptoms, while diagnosed depressed patients show increased levels of circulating cytokines (Dahl et al. 2014; Eyre and Baune 2012). Further studies revealed the activation of the brain immune cell microglia in depressed patients with a greater magnitude in individuals that committed suicide, indicating a crucial role for neuroinflammation in the brain pathogenesis of depression (Brites and Fernandes 2015; Yirmiya et al. 2015). It is still unclear whether a chronic inflammatory state may contribute to depression etiology or if inflammation occurs as a consequence of a depressive state. Many stimuli related to depression may trigger microglia activation, such as peripheral or central inflammatory challenges, or stress-related conditions derived from increase of glucocorticoids via HPA axis (i.e., changes in gut microbiota and psychological stress that promote microglial activation through the release of alarmins within the brain) (Erny et al. 2015; Maslanik et al. 2013; Sorrells and

Sapolsky 2007). This microglial activation may then promote the suppression of neurogenesis and neuroplasticity further enhancing the development of depression-like symptoms, suggesting that a prior inflammation may promote the emergence of depression. Furthermore, continuous activation of microglia may concur to microglia function decline which have more recently been observed in depressive patients (Hannestad et al. 2013) and reported in aging and several neurological conditions, such as Alzheimer's disease, which are associated with a higher prevalence of depressive disorders.

11.2 Effects of Exercise on Depression and Mood Disorders

Recent data provide clear evidence of a causal relationship between major depression and the subsequent development of a disability, and some diseases that have major depressive disorder as a comorbidity are associated with lack of physical exercise (Blay et al. 2007). Moreover, recently there has been an increasing interest in the role of alternative, non-pharmacological interventions to attenuate for depressive symptoms. Among these, physical exercise has been proposed as a complementary treatment which may support the improvement of antidepressant medication in patients with incomplete remission of depressive symptoms (Trivedi et al. 2006). From a strictly medical point of view, the physical activity has been defined as an activity that increases heart rate and energy costs starting from a basal level and, as above-mentioned, depression is usually associated with low levels of physical activity. While epidemiological and correctional studies do not necessarily corroborate a direct causation, the consistent relationship does exist across a number of populations. In adults, an active lifestyle was associated with reduced depressive symptoms independent of education and physical health status. Moreover, in a survey study in the population of USA and Canada, level of physical activity has been shown to be positively associated with lower levels of stress and depression, and with improved positive mood (Stephens 1988). Another epidemiological research that have evaluated over 4000 men and woman aged 20 years or more clearly established that depressive adults spent significantly less time both in light and moderate physical activity than non-depressed adults (Song et al. 2012). The possibility of developing depressive symptoms in adulthood may be best modified in early development; indeed, an epidemiological study reported that increased risk of pathogenesis of depressive symptoms in adulthood was consistently associated low physical activity during adolescence (Jacka et al. 2011a, b). A comparable protecting action of exercise on the risk to develop depressive and anxiety disorders was confirmed in the elderly people who accomplished a regular physical activity during adulthood (Pasco et al. 2011). Moreover, in a longitudinal study of over 9000 people, a lower likelihood of depressive symptoms onset at follow-up was correlated with a regular physical

exercise (Azevedo Da Silva et al. 2012). On the contrary, another analysis of action of exercise among homozygous twins established that an intensification of exercise did not necessarily forecast for fewer depressive symptoms (De Moor et al. 2008). A compelling body of evidences demonstrates that prolonged active lifestyle might represent a non-pharmacological therapeutic approach for relief from depression. Indeed, a recent study suggests that running might be categorized as first-line treatment for mild-to-moderate depression and might improve depressive symptoms when utilized in addition to antidepressant treatments (Carek et al. 2011). Another trial involving over 200 middle-aged and previously sedentary patients with major depression has compared three different therapeutic programs: a placebo pill with a supervised exercise program, a home-based exercise, and an antidepressant. Although each of the exercise interventions was comparable with pharmacotherapy, with all the treatments tended to be more favorable than placebo, the results at the end of the 4 months treatment period were uncertain, with no differences in outcomes between groups (Blumenthal et al. 2007). These results demonstrate that physical activity needs to be continued in the longer time for providing lasting beneficial effects on depressive symptoms (Mead et al. 2009). On the contrary, other researchers have failed to determine an antidepressant effect of exercise in patients with major depression while they have detected only a short term positive effect on physical outcomes, body composition, and memory (Krogh et al. 2012). Carter et al. have suggested that exercise delivery represents an important factor, with exercise of preferred (rather than prescribed) intensity shown to improve psychological, physiological, and social outcomes, and exercise participation rates in depressed individuals (Carter et al. 2012). From all these observations, it appears evident that the efficacy of voluntary exercise programs aimed to diminish the severity of depressive symptoms strictly depends on the level of adherence to an optimal exercise regimen; a combination of moderate-intensity aerobic training and high-intensity strength training may provide more positive benefits than other exercise programs (Lattari et al. 2014).

11.2.1 Effects of Exercise on Neurotransmitters

Our knowledge about the beneficial effect of physical activity on human brain is largely incomplete and the available evidences are predominantly obtained from animal studies (Deslandes et al. 2009; Dishman 2006). Studies in rodents have shown that physical exercise modulates the major central nervous system neurotransmitter that are correlated with an individual's state of alertness (norepinephrine), the pleasure and reward system (dopamine), and the level of anxiety (serotonin). Moreover, the antidepressant actions of physical activity may be dependent to its capacity to alter monoamine communication. In animal models, it has been shown that voluntary running strongly increases plasma level of free tryptophan, brain tryptophan, and levels of the serotonin metabolite, 5-hydroxy-indoleacetic acid (5-HIAA) (Bailey et al. 1993; Chaouloff et al. 1985), while human trials provide clear evidence of the

pro-serotoninergic action of exercise. Indeed, it has been observed that in 7-week exercise program, exercised group displayed lower levels of depression than the sedentary control group after the intervention. Moreover, the authors demonstrated that the exercise group showed a larger decrease in serotonin respect to the control group and that this reduction in blood serotonin after physical activity is quite similar to the effects of SSRIs (Wipfli et al. 2011). In another study, Melancon et al. evaluated the tryptophan (TRP) availability to the brain during prolonged exercise in older men and they found a significant elevation in TRP levels in the brain during sustained exercise, supporting the hypothesis that increase in serotonin synthesis due to activity might be responsible of the antidepressant action of exercise (Melancon et al. 2012). Three weeks of physical activity also enhanced serotonin receptors and serotonin transporter expression in sedentary males as evaluated by increased levels of 5-HT transporters (5-HTT) and 5-HT_{2A} receptors. On the contrary, four weeks of excessive training in well-trained athletes, are not able to improve the declined 5-HTT and 5-HT_{2A} receptor density. This data suggests that the role of physical activity on serotonin neurotransmission may be strictly correlated with the training state and the extent of exercise (Weicker and Strüder 2001).

Others line of evidences suggested that exercised animals may have an enhanced capability to increase dopamine synthesis as well as to reduce D2 autoreceptor-mediated inhibition of dopamine neurons when compared with sedentary animals. Furthermore, the habitually physically active animals might be better able to increase D2 receptor-mediated inhibition in indirect pathway of the basal ganglia (Foley and Fleshner 2008). Exercise has been shown to be able to modify noradrenergic transmission as demonstrated by exercise-dependent increase of tyrosine hydroxylase expression and increased noradrenaline levels in rodent model exposed to chronic exercise (Dishman 1997). However, acute physical activity comprising of 30 min of vigorous exercise in healthy adult volunteers did not change synaptic dopamine concentrations (Wang et al. 2000).

11.2.2 Effects of Exercise on Neurotrophins, Adult Neurogenesis, and Neuroinflammation

Aerobic exercise has been demonstrated to elevate BDNF mRNA levels in the hippocampus, particularly in neurons localized in the dentate gyrus, hilus, and CA3 region. The increment of BDNF expression appeared within days in male and female rats, was sustained even after several weeks of exercise, and was parallel by increased amount of BDNF protein (Neeper et al. 1996; Russo-Neustadt et al. 1999). In addition to hippocampus, exercise increased level of BDNF mRNA in the lumbar spinal cord (Gomez-Pinilla et al. 2001), cerebellum, and cerebellum (Neeper et al. 1996). Interestingly, the amount of voluntary running is positively correlated with the amount of BDNF detected in the hippocampus, suggesting a

dose-dependent effect of exercise on BDNF production. In human, the serum analysis in sedentary young man revealed an acute exercise-induced increase in BDNF concentration that had not quite returned to baseline at 30 min postexercise; however, it may presumed that the increase in serum BDNF is transient, according to most of the literature (Griffin et al. 2011). Several lines of evidence supported an interaction among BDNF-level hippocampal volume and physical activity in predicting risk for depression, while other researcher speculate that aerobic exercise could represent a treatment for depression by increasing BDNF and hippocampal volume. Consistent with this hypothesis, two studies found that exercise increased serum BDNF in elderly women with remitted major depression (Laske et al. 2010) and in patients with panic disorders (Ströhle et al. 2010).

The IGF-1 is another neurotrophic factor strictly correlated with exercise-dependent cognitive and mood improvement. Indeed, exercise increases IGF-1 levels in serum and brain, and it has been postulated that IGF-1 could mediate the proneurogenic action of physical activity (Aberg et al. 2006). Another factor that increases in the hippocampus after exercise is fibroblast growth factor-2 (FGF-2), which is a well-known mitogen on adult neural stem cells (Gomez-Pinilla et al. 1997). There are important interactions between IGF-1 and FGF-2, as FGF-2 has been shown to increase IGF-1 receptors and IGF-1 binding protein (Pons and Torres-Aleman 1992) and IGF in vitro has been shown to potentiate the effect of FGF-2 on progenitor proliferation (Aberg et al. 2003).

Previous studies have suggested the indispensable role of hippocampal neurogenesis in mediating antidepressive effects of physical exercise and antidepressants (Yau et al. 2011). As long-recognized remedy against depression, physical activity has been demonstrated to promote hippocampal plasticity from a variety of aspects, including neurogenesis, dendritic complexity, and synaptic plasticity (Eadie et al. 2005). The beneficial effects of exercise on depression-like behavior are linked to increased hippocampal neurogenesis in genetically depressed rats and depressed-animal models (Bjørnebekk et al. 2005; Trejo et al. 2008). Disrupting hippocampal neurogenesis with x-irradiation blocked the effect of antidepressive treatment on depressive-like phenotypes (Santarelli et al. 2003) and infusion of the antimitotic Ara-c for two week blocked not only proliferation but also ongoing neurogenesis. It is known that elevated corticosteroids (CORT) have profound effects on regulating the function and structure of the hippocampus; repeated CORT injection in rodents has been suggested to be a reliable animal model for studying the role of stress in depressive disorders (Zhao et al. 2008). A recent study has been demonstrated that, in a CORT-induced animal model of stress, exercise promoted hippocampal neurogenesis, BDNF levels, and triggered dendritic remodeling that were both critical for the beneficial effect of exercise on stress, suggesting a plasticity mechanism underlying the beneficial effect of exercise on stress which may involve restored hippocampal neurogenesis and dendritic remodeling (Yau et al. 2011).

Several lines of evidence have suggested the potential role of adiponectin, a protein hormone secreted by peripheral mature adipocytes, in mediating physical exercise-triggered enhancement of hippocampal neurogenesis and alleviation of depression. A recent study has clearly demonstrated that intracerebroventricular

over-expression of adiponectin replicated the beneficial effects of running, including the enhancement of hippocampal neurogenesis and the proportional reduction of depressive-like behavior, which supports the causal linking between these two parameters (Yau et al. 2014). Conversely, the adiponectin deficiency did not affect the basal level of neurogenesis but induced a remarkable attenuation of running-induced hippocampal neurogenesis in mice and strongly diminished the running-exerted antidepressant effects, suggesting that the antidepressant effects of physical exercise are mediated partly by inducing production of adiponectin, which in turn promotes hippocampal neurogenesis (Yau et al. 2014).

In human, only few data are available on the antidepressant action exerted by physical activity and mediated by adult neurogenesis. The only remark, albeit indirect, available in the scienitfic literature has reported that patients with long-standing depression have a tendency to have smaller hippocampus than healthy controls (Videbech and Ravnkilde 2004). Although not massive, this shrinkage is too large to be explained by a lacking contribution of new neurons to hippocampal volume alone.

In the recent years, physical activity has been also involved in the modulation of different aspects linked to neuroinflammation in pathogenesis or during aging. Following a pathogenic infection in the brain, the innate immune system provides a rapid and non-specific response, followed by a slow but specific response provided by the adaptive immune system, which is able to guarantee a long-term immunity and facilitate the neuroinflammatory recovery (Kohman and Rhodes 2013; Ryan and Nolan 2016). The main mediators of the innate response are represented by the microglial cells, which have the explicit role of surveying and maintaining the cell environment and more generally the brain homeostasis; to this aim, microglia cells (as referred as resting microglia) retain a typical quiescent morphology characterized by a small cell body and by multiple processes. In response to brain infection, microglia undergo to morphological and functional alterations characterized by amoeboid features (enlarged cell somas and retraction of the processes), phagocytic activity, increased proliferation rate, and release of a series of inflammatory mediators such as chemokines, cytokines, reactive oxygen species, and nitric oxide (Kettenmann et al. 2011). It has been previously reported that activated microglia is responsible of deleterious effects on neuronal activity even though more recent data have established that activated microglia might play an important role in neuroprotection and neural regeneration (Czeh et al. 2011). As a consequence of these conflicting results and of the opposing roles of microglia, it has been proposed that these cells might polarize into M1 microglia when express pro-inflammatory mediators, resulting in damage of neuronal structure and function or in M2 cells whether release anti-inflammatory molecules and neurotrophic/vascular factors that protect and repair inflamed brain (Orihuela et al. 2016).

During the last years, in vivo studies have shown a major role of resting microglia in providing trophic support and in removing apoptotic newly generated neurons during the first differentiation steps of hippocampal neurogenesis (Sierra et al. 2010, 2014), while in vitro assays have highlighted that resting microglia are able to mediate neuronal cell differentiation and increase neurogenic potential of the

cultured cells (Walton et al. 2006). However, the activation of polarized M1 microglia following exposure to infectious pathogens promotes the formation of a hostile microenvironment in the neurogenic niche which in turn results in the suppression of adult neurogenesis by reducing proliferation and survival of newborn neurons (Ekdahl et al. 2003; Belarbi et al. 2012; Fujioka and Akema 2010). It also has been shown that M2 microglia are able to stimulate adult neurogenesis through the release of anti-inflammatory mediators which in turn provide trophic support and govern synaptic integration of adult newly generated neurons (Sierra et al. 2014). To this regard, voluntary exercise has consistently been demonstrated to strongly provide some anti-inflammatory effects in brain and more specifically in adult neurogenesis. Indeed, exercise may influence anti-inflammatory response by promoting the alternative M2 microglia phenotype, as demonstrated by the augmented levels of anti-inflammatory chemokine CX3CL1 following wheel running or by the running-induced increase of neurotrophin BDNF released by microglia (Vukovic et al. 2012), which may create a favorable microenvironment supporting the production of new neurons in aged mice (Littlefield et al. 2015). Indeed, aging is characterized by increase rate of neuroinflammation, partly due the rise of activated microglia and the release of pro-inflammatory cytokines (Lynch et al. 2010), and this event has been suggested to contribute to the age-related drop of neurogenesis observed in the neurogenic niches (Gebara et al. 2013). To this regard, there is a clear consensus as to the role of physical exercise to counteract the age-dependent declined neurogenesis through a specific action on partially diminishing the neuroinflammatory events. It has been shown that physical exercise in 18-month-old mice is able to enhance the survival of hippocampal newly generated neurons, by reducing microglia proliferation and facilitating a shift toward the activated neuroprotective microglial phenotype (Kohman et al. 2012). Moreover, some other studies demonstrated that aged running rodents displayed decreased level of the pro-inflammatory interleukin IL-1b, with a concomitant increase in new born neurons, expression of BDNF and hippocampus-dependent learning and memory tasks (Speisman et al. 2013; Gibbons et al. 2014).

11.3 Effects of Omega-3 Fatty Acids on Depression and Mood Disorders

Although diet is one of the principal environmental factors impacting brain plasticity (Murphy et al. 2014), the notion that poor diet may be a risk factor for the onset of depression has only recently emerged (Berk and Jacka 2012). Specifically, in the past century there has been a shift in the common dietary style of Western societies to typically include high levels of energy, saturated fats, and refined sugar (Kant 2000). Cross-sectional data and prospective studies indicate that this dietary style is associated with depressed mood and anxiety (Aihara et al. 2011; Jacka et al. 2010a, b, 2011a, b; Mamplekou et al. 2010; Nanri et al. 2010; Oddy et al. 2009;

Overby and Hoigaard 2012; Samieri et al. 2008; Weng et al. 2012). On the contrary, the adherence to healthful ways of eating, such as Mediterranean dietary or feeding "whole food" versus "processed food" (Akbaraly et al. 2009; Chatzi et al. 2011; Kuczmarski et al. 2010; Park et al. 2010; Oddy et al. 2009; Sanchez-Villegas et al. 2009), has been associated with a reduced risk of depression and mental illness in several studies conducted around the world. While the mechanisms underpinning the association between diet and mental health are not fully understood, actions of various dietary factors on brain plasticity and mental health and disease have been scrutinized (Gomez-Pinilla and Gomez 2011). Recent studies show that select dietary factors have mechanisms similar to those of exercise affecting molecular events related to the synaptic plasticity (Gomez-Pinilla and Gomez 2011). In particular, although far from conclusive, growing evidence suggests a role for omega-3 fatty acids in major depressive disorder (Appleton et al. 2015). Omega-3 fatty acids are a family of polyunsaturated fatty acids, named as such because of the positioning of the first double carbon bond on the third atom from the methyl end of the acyl chain (Haag 2003; Ruxton et al. 2005). All members of the family are derived from parent fatty acid 18:3n-3 (α-linolenic acid, ALA), via de-saturation and elongation. ALA, however, cannot be synthesized by humans and thus must be obtained from the diet (Haag 2003; Ruxton et al. 2005). Dietary sources of ALA include certain nuts and seeds, such as walnuts, flaxseed, and rapeseed oil. Dietary sources of the longer omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoicacid (DHA) include fatty fish, shellfish, seafood, seaweed, and certain animal products dependent on diet (James et al. 2000; Luchtman and Song 2013; Ruxton et al. 2005).

Omega-3 fatty acids have provided some of the strongest evidence for the profound effects that dietary factors can have on the brain (Gomez-Pinilla and Gomez 2011). In fact, as neuronal membrane major components, omega-3 fatty acids exhibit a wide range of regulatory functions (Luchtman and Song 2013) contributing to synaptic membrane fluidity and regulation of cell signaling (Luchtman and Song 2013; Salem et al. 2001). Animal studies have consistently shown the prophylactic and therapeutic use of omega-3 fatty acids in concussive or traumatic brain injuries linked to the promotion of energy homeostasis, the decrease in axonal and neuronal damage, inflammation, oxidative stress and apoptosis, and the normalization of BDNF and neurotransmitter levels (Huang et al. 2007; Mills et al. 2011; Wu et al. 2004, 2007, 2011, 2013, 2014). Because of the human body's inefficiency in producing the omega-3 fatty acids, dietary supplementation of these essential fatty acids can be extremely important for the success of rehabilitative strategies after central nervous system injury (Gomez-Pinilla and Gomez 2011).

Similarly, the identification of modifiable environmental factors that could prevent and alleviated depression and mood disorders, such as nutritional factors, is a research priority (Gomez-Pinilla 2008; Sinn et al. 2010). In particular, nutritional research indicates that Western diets do not provide the brain with an optimal supply of omega-3 fatty acids (Woo 2011). Up-to-dately, a growing number of animal and human studies has indicated that reductions in omega-3 fatty acids are implicated in depression and mood disorders, while omega-3 fatty acids

supplementation may have beneficial effects on depressive symptomatology (Appleton et al. 2015; Jacka and Berk 2013; Levant 2013; Mischoulon 2011; Sublette et al. 2011). These findings point to many mechanisms by which omega-3 fatty acids affect neurobiological substrates of depression including regulation of neurotransmitters, neurotrophins, adult neurogenesis, and neuroinflammation.

11.3.1 Effects of Omega-3 Fatty Acids on Neurotransmitters

In animal studies, low-dietary omega-3 fatty acids levels result in a number of alterations in the serotoninergic system that are similar to the neurobiological alterations reported in depression. Decreased concentrations of serotonin in the frontal cortex and lower expression of the serotonin synthesizing enzyme tryptophan hydroxylase in the midbrain were detected in rats fed diets deficient in omega-3 fatty acids (Levant et al. 2008; McNamara et al. 2007, 2009, 2010). Moreover, feeding a diet containing α-linoleic acid reversed the effect on serotonin turnover (McNamara et al. 2010). Similarly, decrease in brain serotonin levels induced by unpredictable chronic mild stress, a rodent model of depression, was reversed by feeding a diet supplemented with omega-3 fatty acids in mice (Vancassel et al. 2008). Many studies reported associations among serotonin decrease, omega-3 fatty acids reduction, and depressive symptoms also in humans (Su 2009). Recently interactions between 5-HTT genotype and omega-3 fatty acids intake as risk factors for postpartum depression have been reported in women (Shapiro et al. 2012).

Omega-3 fatty acids intake result in ameliorated serotoninergic neurotransmission. In fact, adult rats supplemented with DHA and EPA for 90 days exhibited increased concentrations of serotonin in the frontal cortex and hippocampus (Vines et al. 2011). Biochemical studies have also shown that omega-3 fatty acids increased cerebrospinal fluid 5-HIAA concentration and somatotrophin release (Nizzo et al. 1978), which are commonly associated with the improvement of depressive symptoms. Administration of EPA and DHA for 12 weeks induced antidepressant-like effects in rats associated with increased plasma serotonin concentration, over-expression of hippocampus c-AMP-response element binding protein (CREB) expression, and decreased interleukin-6 expression (Park et al. 2012).

Also the central nervous system dopaminergic systems are affected by variation in dietary omega-3 fatty acids content. Rats feeding a diet deficient in omega-3 fatty acids showed a DHA-level brain reduction and a decrease in the number of D2 dopamine receptors in the ventral striatum (Davis et al. 2010). This decrease in expression of ventral striatal D2 receptors is in line with the hypoactivity of the mesolimbic dopamine system that is hypothesized to occur in depression and is also consistent with the decreases in the density of the D2 receptors observed in rat models of depression, such as learned helplessness, chronic mild stress-induced anhedonia, and the socially isolated Flinders Sensitive Line rat (Bjornebekk et al.

2007; Kram et al. 2002; Papp et al. 1994). There is a robust negative relationship of omega-3 fatty acids with dopaminergic plasma indices suggesting that omega-6: omega-3 fatty acids balance may impact depression pathophysiology through effects on the dopaminergic system (Sublette et al. 2014). Interestingly, high cerebrospinal fluid concentration of dopamine and serotonin metabolites has been shown to be associated with high plasma concentration of omega-3 fatty acids among healthy subjects (Hibbeln et al. 1998). Furthermore, Chalon (2006) reported that dietary fish oil increases serotonin and dopamine concentrations in the frontal cortex of rats.

Finally, alterations in the noradrenergic system, such as increased density of β-adrenergic receptors in the frontal cortex and alterations in α1and α2 receptors, have also observed in postmortem brains of suicide completers (Arango et al. 1990; Biegon and Israeli, 1988; Rivero et al. 2014). Similar to serotonin receptors, cortical β-receptors downregulate in depressed patients after treatment with tricyclic antidepressants (Charney et al. 1986; Vetulani and Sulser 1975). Furthermore, β3-adrenergic receptor agonists have been demonstrated to exert antidepressant effects comparable to fluoxetine or imipramine for the treatment of anxiety and depressive disorders (Stemmelin et al. 2008). The role of omega-3 fatty acids in modulation of noradrenergic neurotransmission has received relatively little attention, so data on this issue are still controversial. In animal studies, decreased cortical, hippocampal, and striatal norepinephrine levels associated with behavioral disturbances were observed in rats fed a diet deficient in omega-3 fatty acids from birth (Takeuchi et al. 2002). As for human studies, in healthy young adults EPA and DHA supplementation for 2 months lowered plasma norepinephrine concentrations (Hamazaki et al. 2005). This depression of sympathetic tone could be one of the basic mechanisms of anti-arrhythmic and antihypertensive action of omega-3 fatty acids.

11.3.2 Effects of Omega-3 Fatty Acids on Neurotrophins, Adult Neurogenesis, and Neuroinflammation

Low-dietary omega-3 fatty acids levels lead to decreased expression of BDNF. In fact, rats fed a diet deficient in omega-3 fatty acids exhibited decreased cortical and hippocampal BDNF levels, and TrkB and CREB signaling that were accompanied by increased anxiety and depressive behaviors, reduction in the anxiolytic-related neuropeptide Y-1 receptors, and an increase in the anxiogenic-related glucocorticoid receptors in the cognitive-related frontal cortex, hypothalamus, and hippocampus (Bhatia et al. 2011; DeMar et al. 2006; Levant et al. 2008; Rao et al. 2007).

Conversely, higher-dietary omega-3 fatty acids levels result in increased expression of hippocampal BDNF. Several studies indicate that rodents supplemented with omega-3 fatty acids, or injected with ALA, had higher BDNF

expression, especially in the hippocampus (Adachi et al. 2007; Blondeau et al. 2009; Cysneiros et al. 2010; Venna et al. 2009; Vines et al. 2011; Wu et al. 2004). Moreover, a DHA-enriched diet resulted in higher levels of calmodulin kinase II and activated Akt, which are involved in BDNF signaling (Wu et al. 2007). Higher levels of mediators involved antidepressant-induced increases in BDNF, such as c-AMP-response element binding protein (CREB), are also reported after omega-3 fatty acids dietary supplementation (Park et al. 2012).

Accumulating translational evidence suggests that omega-3 fatty acids, in particular DHA, play a role in the maturation and stability of cortical circuits that are impaired in mood disorders. Specifically, rodent and cell culture studies find that DHA preferentially accumulates in synaptic and growth cone membranes and promotes neurite outgrowth, dendritic spine stability, synaptogenesis, and microglia-mediated synaptic pruning (McNamara et al. 2015). Importantly, DHA deficits during perinatal development are associated with impaired LTP and a significant reduction in glutamate synapses in the rat hippocampus leading to impaired learning functions (Cao et al. 2009; Fedorova et al. 2009; Greiner et al. 2001; Hichami et al. 2007; Moriguchi et al. 2000). In non-human primates, omega-3 fatty acids deficiency during perinatal development leads to widespread reduced functional connectivity in adult frontal cortical networks compared to primates raised on fish oil fortified diet (Grayson et al. 2014). Additional evidence from clinical imaging studies suggest that low DHA levels during perinatal development may lead to long-standing impairments in functional connectivity in cortical networks as well as the emergence of cognitive impairment and emotional symptoms in children (McNamara et al. 2015). In rodents, omega-3 fatty acids deficiency have been associated with hippocampal plasticity reduction, while omega-3 fatty acids supplementation may improve neurogenic and synaptogenic functions (Denis et al. 2013; Fedorova and Salem 2006; Hooijmans et al. 2012; Luchtman and Song 2013; Maruszak et al. 2014). Namely, increased hippocampal neurogenesis has been observed in mice and in rats fed diets supplemented with DHA and EPA, as well as in mutant mice expressing fat-1 that are able to metabolize omega-6 fatty acids into omega-3 fatty acids, and thus not requiring omega-3 fatty acids in the diet (Dyall et al. 2010; He et al. 2009). Recently, beneficial effects of omega-3 fatty acids on adult neurogenesis have been reported to be mediated by interactions with the endocannabinoid system, as EPA-induced increase in neural stem cells proliferation was associated with enhanced levels of the endocannabinoid 2-arachidonylglycerol (2-AG), thus highlighting the therapeutic potential of their interplay in brain repair (Dyall et al. 2016). Furthermore, omega-3 fatty acids neurogenic effects are also evident at old age when hippocampal neurogenesis results accompanied by increased neuronal density, neurite outgrowth and microglial cell number, and decreased neurodegeneration signs (i.e., lipofuscin, caspase-3, astrogliosis levels), better cognitive functions and more active coping skills (Cutuli et al. 2014, 2016). Omega-3 fatty acids have demonstrated a marked neurite-promoting potential also in the sensory neurones of the dorsal root ganglia from aged rats (Robson et al. 2010).

Mood disorders are often associated with age-related atrophy in the hippocampus and prefrontal cortex (Erickson et al. 2012; McNamara 2010; Vu and Aizenstein 2013). Interestingly, in mice administration of omega-3 fatty acids increases hippocampal volume, effect accompanied by increased syntaxin 3 and synaptophysin expression, and in line with the actions of antidepressants (He et al. 2009; Venna et al. 2009). Omega-3 fatty acids-induced brain volume modifications have been reported also during aging, as demonstrated by hippocampal, retrosplenial, and prefrontal volumetric increases shown by aged mice supplemented for 8 weeks with omega-3 fatty acids (Cutuli et al. 2014, 2016). As for human studies, several studies have suggested the potential preventive role of omega-3 fatty acids against age-related cognitive decline and brain atrophy (Bowman et al. 2012, 2013; Pottala et al. 2014; Raji et al. 2014; Samieri et al. 2012; Tan et al. 2012; Titova et al. 2013; Virtanen et al. 2013; Witte et al. 2014). Recently in human studies using morphological MRI-based techniques, a putative neuroprotective effect of omega-3 fatty acids also in depression and mood disorders is emerging, with positive associations between peripheral omega-3 fatty acids levels and more favorable gray and white matter volumetric measures (Bowman et al. 2012; Cockayne et al. 2015; Marriott et al. 2016; Puri et al. 2001; Samieri et al. 2012). However, despite the strength of the observational data, the limitation of the existing interventional studies (Appleton et al. 2015, 2016) makes further randomized controlled trials crucial to demonstrate the therapeutic impact of omega-3 fatty acids supplementation in depressed adults.

Another potential mechanism of omega-3 fatty acids antidepressant action is via regulation of neuroinflammation, a further mediator in the underlying pathology of depressive illness (Ganança et al. 2016; Miller et al. 2009; Rosenblat and McIntyre 2016; Song et al. 2016; Swardfager et al. 2016).

Omega-3 fatty acids may mitigate inflammation through multiple ways. For example, beyond alteration in serotoninergic transmission, rats that consumed -deficient diets from birth showed also higher plasma levels of interleukin-6, C-reactive protein, and tumor necrosis factor-α, which were reversed by subsequently feeding an α-linoleic acid-containing diet (McNamara et al. 2010). Similarly, omega-3 fatty acids reduce serum interleukin-6 and tumor necrosis factor-α levels in overweight, sedentary middle-aged and older adults, a population at high risk for depression (Kiecolt-Glaser et al. 2012). Omega-3 fatty acids are also inversely associated with depressive symptoms among individuals with elevated oxidative stress biomarkers (Bigornia et al. 2016).

Moreover, a number of studies indicate that omega-3 fatty acids may be effective antidepressants in the context of depression associated with inflammation (McNamara 2015; Kiecolt-Glaser et al. 2015). As for humans, a 2-week double-blind randomized clinical trial found lower rates of interferon-α–induced depression in EPA-treated patients (Su et al. 2014). Omega-3 fatty acids have been shown to attenuate both endotoxin-induced inflammation and sickness behavior in rodents and humans (Carlezon et al. 2005; Song et al. 2003; Pittet et al. 2010; Pluess et al. 2007; Su et al. 2010). Further, in rats omega-3 fatty acids supplementation mitigated the behavioral changes induced by doxorubicin, a chemotherapeutic agent

widely used in human malignancies whose long-term use can cause depression (Wu et al. 2016). This antidepressant effect was mediated by reduction of neuronal apoptosis, pro-inflammatory cytokines, and oxidative stress in the prefrontal cortex and hippocampus.

In addition, omega-3 fatty acids are a source of docosanoids such as resolvins and protectins that are produced mainly from controlled oxidative breakdown of DHA within the membrane and have anti-inflammatory properties (Farooqui et al. 2007; Serhan 2005). In particular, DHA and EPA are precursors of the D- and E-series resolvins, respectively, which modulate the level and length of the inflammatory response (Bannenberg 2009). Another DHA metabolite, neuroprotectin D1, protects neurons from the cytotoxic action of various noxious stimuli, such as the production of tumor necrosis factor-α and interferon-γ by activated T cells (Ariel et al. 2005; Bazan 2005). A recent preclinical study demonstrates that resolvin D1 decreases postmyocardial infarct depressive symptoms (Gilbert et al. 2014). Since this research line seems very promising, future researches on the antidepressant effects of omega-3 fatty acids via docosanoids are advocated.

11.4 Additional Effects of Exercise and Omega 3 Fatty Acids

Recent studies have shown that dietary factors can complement the action of exercise, thus suggesting the combined approach as a noninvasive and effective strategy to help promoting mental health and counteracting neurological disorders (Gomez-Pinilla 2011). For example, using an instrumental learning paradigm to assess spinal learning, Joseph et al. (2012) observed that mice fed a diet containing DHA and curry spice curcumin performed better in a spinal learning paradigm than mice fed a diet deficient in DHA and curcumin. The enhanced performance was accompanied by increases in BDNF, CREB, CaMKII, and syntaxin 3mRNA levels. The concurrent exposure to exercise increased the dietary treatment effects on the spinal learning and on most of the molecular markers.

The combination of diet and exercise has also the added potential to facilitate functional recovery following traumatic brain injury. In rats receiving mild fluid percussion injury and then maintained on a diet high in DHA with or without voluntary exercise for 12 days, Wu et al. (2013) found that the effects of traumatic brain injury on lipid peroxidation, syntaxin 3 and BDNF were optimally counteracted by the combination of DHA and exercise. Furthermore, in rats supplementation with DHA associated with voluntary exercise for 12 days boosted the beneficial effects of the dietary supplementation alone by additionally increasing spatial learning abilities as well as hippocampal BDNF, CREB, synapsin I, Akt, and CaMKII levels, and by reducing hippocampal oxidative stress (Wu et al. 2008).

In another study in rats, voluntary exercise potentiated the effects of a 12-day DHA dietary supplementation regimen on increasing hippocampal levels of specific

elements of the synaptic membrane, such as syntaxin 3 and GAP-43 (Chytrova et al. 2010). The DHA diet and exercise also enhanced spatial learning performances and elevated levels of the NMDA receptor subunit NR2B, which is important for synaptic function underlying learning and memory.

In a recent study by Hutton et al. (2015), mice exposed to a 4-week unpredictable stress protocol were given a complex dietary supplement containing omega-3 fatty acids, a running wheel that permitted them to exercise, or both the dietary supplement and the running wheel for exercise. Interestingly, the combination of dietary supplementation and exercise increased hippocampal neurogenesis, BDNF mRNA, and serum vascular endothelial growth factor levels. In contrast, these benefits were not observed in chronically stressed animals exposed to either dietary supplementation or exercise alone.

The overall findings emphasize the capacity of select dietary factors and exercise to elevate the capacity of the adult brain for axonal growth, BDNF-related synaptic plasticity, neurogenesis, and cognitive functions either under normal and challenging conditions. Given the noninvasiveness and safety of the modulation of diet and exercise, these interventions should be considered in light of their potential to enhance cognition, mood, and brain plasticity with important clinical implications for those suffering from chronic stress-related disorders, such as major depression. Indications about the combined effects of exercise and omega 3 fatty acids as preventive interventions for depression and mood disorders have been proposed in the "Antidepressant-Lifestyle-Psychological-Social (ALPS) depression treatment model" that integrates non-pharmacological interventions (such as complementary medicines, lifestyle advice, and psychosocial techniques) for use by clinicians (Sarris 2011).

11.5 Conclusions

Exercise and diet are two principal environmental factors impacting brain plasticity (Gomez-Pinilla 2011). Although there is much to be clarified about the specific molecular mechanisms through which exercise and dietary components, such as omega-3 fatty acids, influence brain plasticity, the growing literature here summarized supports the idea that both these factors can modulate brain structure and function, exerting their influence throughout the entire life span.

Moreover, the benefits provided from exercise also have a strong evolutionary connotation as the feeling of euphoria and well-being during and soon after running has represented in the course of time the evolutionary drive that made human efficient hunters, by increasing their ability to focus and awareness strictly dependent from physical activity. In fact it has been suggested that the primitive humans tried a feeling of mental well-being that over time would constitute a kind of neurological positive feedback that would lead them to repeat that behavior (Raichlen et al. 2012). However, the real evolutionary advantage would be represented by the better chance to survive and reproduce linked to regular physical

activity. The radical change in lifestyle over the past centuries has produced a growing scarcity of the need to run to survive with following deleterious consequences on human health and social costs. From here emerges the awareness that an active lifestyle and a balanced diet can represent the major low-cost prevention policies to reduce the dramatic increase of cardiovascular diseases, diabetes, obesity, and mental diseases related to stress.

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Chapter 12
Estrogen Neuroprotective Activity After Stroke and Spinal Cord Injury

Adriana Maggi

Abstract Morphological studies have revealed that in mammals the brain is a sexually dimorphic organ and estrogen are responsible for brain masculinization which occur perinatally. These morphological differences underline significant functional divergences that are not all directly associated with the control of reproductive functions and are very relevant to the control of cognitive functions as well in the response to physiopathological insults. An appreciation of the sexually dimorphic functions of the brain will facilitate the development of more efficacious therapies for sex-prevalent disorders; in addition, the understanding of the molecular pathways lessening the incidence of neurological or neuropsychiatric diseases in a given sex will shed novel light on their etiology and provide new avenues for a therapeutic intervention.

Keywords Brains sexual differentiation · Estrogen · Neurosteroids · Estrogen receptor · Brain ischemia · Spinal cord injury

12.1 Introduction

During evolution, a positive selection was exerted on the organisms that were better fit for their ecological niche and this likely led to generations of males and females characterized by a very similar physiology. With placentation, however, females ceased to reproduce via eggs where the embryo development occurred outside the maternal body and female mammals adopted a reproductive mechanism safer for the progeny by harboring the embryo in the maternal womb and taking care of the newborn with lactation. The payload for this change in the reproductive strategy must have been dramatic as female metabolism had to adapt to tremendous

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variability of energy requests of the various reproductive stages. Thus, in mammals, female and male physiology must have substantially diverged. This phenomenon has been largely undervalued in the biomedical field, and in the past years, most experimental and clinical observations have been carried out without taking the genetic sex into a specific consideration. More recently, mainly under a sociological pressure, researchers have been forced to compare the two sexes in their physiopathological studies: This new wave of investigations revealed an unexpected array of sex-related dimorphisms that, for the first time, highlighted the widespread influence of the reproductive capacity on the entire female physiology. At present time, we are still listing sexual dimorphic functions, with little understanding of their underlaying mechanisms. We understood that in the adult organisms, sex steroids (estrogens, androgens, and progestins) play a major role; however, molecules other than those strictly involved with reproduction may be triggered or act in a sex-specific manner during the ontogenesis: The identification of these molecules and the biochemical pathways involved is very relevant from the medical point of view because it will lead to a significant sexual differentiation in the diagnosis and therapy of a large number of pathologies. In addition, the understanding of the sex prevalence of a series of diseases will provide unique insights for their etiology.

The fact that the brain is sexually differentiated has been known for decades and we learned that such a difference is not associated with societal, cultural influence, namely to the gender impact, but has strong genetic influences and thus is relative to the individual sex. We therefore started to investigate and understand the mechanisms underlaying a number of neurological and neuropsychiatric disorders in which the sex determines a differential incidence. The aim of this chapter is to review current knowledge on the mechanistic determinants of the brain sexual dimorphism and on the role of sex hormones in the modulation of brain recovery after stroke and injury which have significant differences in the two sexes.

12.2 The Brain is a Sexually Dimorphic Organ

It has been long known that in mammals, several morphological features characterize the brain as female or male: The total brain volume, normalized for the body size, is significantly larger in males and the female brain has a larger proportion of gray matter. Anatomical investigation demonstrated that sex-dependent differences are also present at neuronal organizational level by identifying a sexual dimorphism in selected brain regions such as the bed nucleus of the stria terminalis, the sexually dimorphic nucleus of the preoptic area, subregions of the hypothalamic chiasmatic nucleus where neurite length and branching of specific neuronal populations are significantly different in the two sexes (Arnold and Breedlove 1985; Gorski 1985; Bao and Swaab 2011). More recently, the existence of sexual dimorphisms in the brain morphology was confirmed with imaging technologies (fMRI, functional magnetic resonance imaging or PET, positron-emission tomography) (as reviewed by Sacher et al. 2013). These methodologies led to a better definition of the

dimorphic regions, but also indicated the presence of a differential functional activity. For instance demonstrated that, dopaminergic, serotonergic, and gamma-aminobutyric acid (GABA)ergic neurons have differential functions in the two sexes (Cosgrove et al. 2007; Sacher et al. 2013). These observations provided a first explanation for the known sex-different mental processes (such as the mechanism of reward and possibly drug abuse) and pathologies with a sex prevalence (Diekhof et al. 2012); the higher activity of dopaminergic neurons in women was proposed as an explanation for the lower prevalence of Parkinson's disease in females or the sex differences in the onset and progression of schizophrenia (Gillies et al. 2014; Di Forti et al. 2007). Thanks to these studies, the existence of a sex-dependent dimorphism in brain morphology and function is now well accepted by the scientific community; however, we are far from understanding the full extent of such a diversity and the mechanisms involved in each sex-prevalent physiopathologic manifestation. Even the exact contribution of neural cells other than neurons (astroglia and microglia) or the global cerebral blood flow (more elevated in females than in males) (Gur and Gur 1990) remains to be investigated and understood.

12.2.1 Mechanism proposed for Brain Sexual Differentiation

Thus, the question to be asked is what is the determinant of brain sexual differentiation and when, during development, this occurs.

Studies carried out more than thirty years ago by the group of Gorsky (Gorski et al. 1978), and then confirmed by several other laboratories, have shown that sex steroids are essential for brain sexual differentiation (Maggi and Zucchi 1987; Garcia-Segura et al. 1988; Arnold 2009). Indeed, during embryogenesis and in early postnatal life, male gonads are activated to synthesize testosterone, in the brain this hormone is converted to 17β-estradiol by the enzyme aromatase (CYP19). Estradiol, possibly leading to the creation of specific neuronal networks and to the elimination of unnecessary neurons, determines a male-specific "organization" of the nervous centers for the control of gender identity (Hutchison 1997; Bodo et al. 2006), behavior, and several other, sex-related, endocrine functions (Fuente-Martin et al. 2013; Della Torre et al. 2014). We now know that the major sex-related differences induced by sex steroids take place in specific hypothalamic nuclei, which directly regulate sex functions. Other brain areas showing sexual dimorphisms are the medial portion of the amygdala, the angular gyrus, the bed nucleus of the *stria terminalis*, and selected areas in the fronto-medial cortex (Mann et al. 2011; Allen and Gorski 1990) also involved in the regulation of the endocrine system, but also in behavior and, possibly, selected cognitive capacities.

In conclusion, perinatally estradiol primes irreversible lifelong lasting changes, referred as "brain masculinization" of selected brain structures; in the course of life,

however, it is believed that changes in circulating or locally produced sex steroids may connote largely reversible neurophysiological functions contributing to the manifestation of sex differences in behavior, endocrine functions, and response to pathological events with reversible effects.

12.2.2 Sex Hormone Receptors Distribution in the Brain

The effects of sex steroids are mediated by the activation of their cognate receptors that are hormone-regulated transcription factors (Dahlman-Wright et al. 2006). Thus, the brain localization of their receptors provides an insight on the potential for activity of sex hormones in the various brain regions (Maggi et al. 2004). The receptors for all sex steroid receptors (estrogens, androgens, and progestins) are present in the central nervous system; in addition to that, most of the steroidogenic enzymes are expressed in the central nervous system; thus, still matter of intense study is the exact contribution of this enzymatic apparatus to the local de novo synthesis of steroids and to the metabolism of these circulating hormones.

12.2.3 Estrogen receptors (ER)

Estrogen receptors (ER) are the most widely expressed of all sex steroid receptors in the mammalian brain, and their distribution is quite reproducible throughout species (Ishunina et al. 2000). The widespread distribution of the two ER isoforms (ERα and ERβ) (Heldring et al. 2007) explains why estrogens modulate a variety of neural functions ranging from mood, anxiety, fear, and cognitive functions including learning and memory (Jacome et al. 2010). ERs protein distribution in neural cells differs in the two sexes; in rodents, females have a higher concentration of both ERα and ERβ in the hippocampus, and ERα is more expressed in the hypothalamic ventromedial nucleus, the periventricular and medial preoptic area, the periaqueductal gray neurons, and the bed nucleus of the *stria terminalis* (Romeo et al. 2005; Kruijver and Swaab 2002; Loyd and Murphy 2008). In women, the major difference with men is in the diagonal band of Broca and in the medial mammillary nucleus where very high nuclear ERα-immunoreactivity (ERα-ir) is detectable and less pronounced sex differences are present in other brain areas: Women have more nuclear ERα-ir in the suprachiasmatic nucleus and ventromedial nucleus, and in men, a more intense nuclear ERα-ir is present in the sexually dimorphic nucleus of the medial preoptic area, paraventricular nucleus, and lateral hypothalamic area. With regard to the cellular distribution, all neuronal cells are able to express ERs; indeed, ERα-ir is present in the cytoplasm of neurons, astrocytes, microglia, and oligodendrocytes (Santagati et al. 1994; Vegeto et al. 2001).

Using the ERE-Luc reporter mouse model, (Ciana et al. 2003) Ciana and coll were able to study the activity of ER in the brain of adult female and male mice. In females, circulating hormones actively induces ER-mediated transcription in the *substantia nigra*, thalamus, and arcuate, where ER activity at proestrus is significantly higher than at diestrus. In male, the activity of ER is quite uniform among the different brain regions and slightly lower than in females; in the piriform cortex, *substantia nigra*, thalamus, and arcuate, however, male ER activity is significantly lower than in females at proestrus (Stell et al. 2008). Therefore, in addition to the differential expression, also ER activation by ligands may considerably differ between sexes. This is conceivable as brain ER activation is mainly associated with the circulating levels of sex steroids; thus, in males, the activation depends on the expression of aromatase and of 5α-reductases/3β-HSDs enzymes converting circulating testosterone to estrogens with different ER binding characteristics (17β-estradiol (E_2 and 3β-diol, a selective ER β ligand) (Marron et al. 2005). The differential localization and activity of the ERs explain several of the sex-dimorphic brain functions mentioned above, including the luteinizing hormone pattern of release by hypothalamus (Petersen et al. 2012), hippocampal synaptic plasticity (Fester et al. 2012), neuroprotective response to neurotoxic insults (Al Sweidi et al. 2012), control of energy metabolism, and sensitivity to oxidative stress (Murray et al. 2003).

Estrogens may control brain functions also utilizing a membrane receptor: A recently identified G-protein-coupled receptor, GPR30, is able to bind 17β-estradiol with high affinity (in the nanomolar range) and its activation by the ligand may explain estrogen rapid effects of Ca^{++} mobilization (Revankar et al. 2005; Levin 2005).

12.2.4 Progesterone Receptor

The two forms of PR, a full-length (PR-B, 110 kDa) and the *N*-terminally truncated form (PR-A, 86 kDa), are present in the brain but their distribution is much more restricted than the ERs; in addition, IHC studies did not reveal any sexual dimorphism, at least in rodent brain; a comprehensive study in humans is still lacking. As in peripheral organs, 17β-estradiol may induce PR-A mRNA accumulation: Apparently, this is not the same in the two sexes, for instance, in males, 17β-estradiol induction of PR-A mRNA appeared to be restricted to the cerebellum (Guerra-Araiza et al. 2002, 2003). PR mRNA is present in neurons (Romano et al. 1989), in newborn rat primary cultures of CNS-derived oligodendrocytes and astrocytes (Jung-Testas and Baulieu 1998), and in PNS derived in Schwann cells, but not in microglia (Sierra et al. 2008). Little is known on the relevance of PR activity in the brain functions. PR is known to control the reproductive behavior (Kow et al. 2007; Pollio et al. 1993), and a few studies have suggested a role for this

hormone in the control of anxiety processes (Silva et al. 2016); several studies recently showed that in females, progesterone may have a significant role in the regulation of the myelination process, particularly after traumatic injury, neurogenesis and regeneration, inflammation (Brinton et al. 2008; Giatti et al. 2015). The physiological functions of progesterone in males remain largely unexplored.

12.2.5 The Brain Androgen Receptor (AR)

The AR gene is located on the X chromosome, and a single allele is expressed in males and females because of the X chromosome inactivation. The AR is transcriptionally activated by the two endogenous ligands: testosterone (T) and dihydrotestosterone (DHT) (Jenster et al. 1993; Tyagi et al. 2000).

In humans, AR is mainly localized in selected hypothalamic nuclei, in the horizontal diagonal band of Broca, in neurons of the mammillary nuclei, in the preoptic area (SDN-POA), and in the infundibular nucleus AR; AR is also highly expressed in the hippocampus and temporal cortex. Generally, AR is expressed at higher levels in the male brain (both in humans and rodent), with the exception of hippocampus and cortex where its content appears to be similar in the two sexes (Beyenburg et al. 2000).

A peculiarity of this receptor is its high expression in the spinal cord (somatic motoneurons located in the anterior horn and in the bulbar regions for the control striatal skeletal muscles functions and sensory neurons located in the dorsal root ganglia (DRG), which project their axons both to peripheral sensitive areas and to posterior regions of spinal cord). The androgenic activation of AR may play a role in the maturation of motor functions in males. Indeed, AR activation enhances the formation of neuromuscular junctions and induces the growth (and the regeneration after resection) of adult dendrites and axons, thus modulating their plasticity in males (Fargo et al. 2008). Still unclear is the extent to which sex is playing a role in the development of male and female motoneurons, and to what extent these differences reflect motor coordination in striatal muscles of the skeletal apparatus, which are also direct target of AR in male.

12.2.6 Activity of Brain Sex Steroid via Non-genomic Action

In addition to the classic, receptor-mediated interaction, gonadal hormones may directly and indirectly regulate neural functions via rapid, non-genomic actions. In this, the local production of steroids, named neurosteroids, may play a major role. Neurosteroids (derived from progesterone and deoxy corticosterone such as allopregnanolone and allotetrahydrodeoxycorticosterone(THDOC), or from testosterone like androstanediol) and their sulfated derivatives (pregnanolone sulfate and dehydroxyepiandrosterone sulfate) are able to modulate neuronal firing by

modulating the activity of receptors for neurotransmitters. For instance, THDOC and androstenediol may act on GABAergic neurotransmission regulating neuron excitability thus inducing sedative-hypnotic anticonvulsant and anxiolytic effects.

12.3 Estrogens and Brain Recovery

Receptor localization and de novo synthesis of neurosteroids in the brain indicate that the activity of sex steroids in the brain may not be limited to the strict regulation of reproductive functions, but involves a larger variety of functions. To date, however, we know very little about the non-reproductive activities of progesterone and androgens as the focus of studies has been mainly on estrogens. Contributing to this lack of studies is the fact that PRs are less widespread than ERs in neural cells and the relatively non-fluctuating profile of androgen secretion in men impaired investigations on the impact of testicular hormones on AR action. The discovery of the broad spectrum of brain activities exerted by estrogens, on the other hand, was facilitated by the fact that the manifestation of several neurological disorders correlates with specific changes of the peripheral synthesis of estrogens due to puberty, reproductive cycle, pregnancy, lactation, menopause, or exposure to environmental estrogens. These changes were found to impact the release and metabolism of neurotransmitters and neuromodulators in neurons, regulate the activity of glial cells (oligodendrocytes and astrocytes), and modulate microglia immune functions, all these giving rise to a host of neuropsychiatric conditions including the following: vascular, metabolic, inflammatory, and degenerative disorders. Germane to the central theme of this review are the involvement of this sex steroid and its receptors in the ability of the brain to recover after immune insults or stroke causing neuronal death.

12.3.1 Neuroprotective Effects of Estrogens After Cerebral Ischemia and Stroke

Experimental models such as blockage of the middle cerebral artery, that causes neuronal death within hours, enabled to get a specific insight on the temporal events occurring after an ischemic insult. The early stages of the post-insult are characterized by excitotoxicity and peri-infarct depolarization, and at later stages, inflammation and apoptosis play a more relevant role. The largely protective effects of pharmacological and physiological levels of estrogens were clearly demonstrated by several laboratories adopting this stroke experimental model (Simpkins et al. 1997; Brown et al. 2009; Cai et al. 2014). These studies highlighted the complex

array of cellular and molecular mechanisms by which estrogen intervenes after the insult. In the neurons exposed to ischemia, the ability of estrogen to regulate the activity of glutamatergic and GABAergic transmission plays a role downmodulating the extent of depolarization limiting the damage due to excitotoxicity; on the other hand, through an ERα-mediated action, estrogen may regulate the synthesis of anti-apoptotic proteins such as Nip-2 or Bcl-2 and minimize the activation of the caspases initiating the apoptotic response (Meda et al. 2000; Corvino et al. 2015; Guo et al. 2016). At the same time, estrogens may modulate the activity of microglia attracted to the insult site by accelerating microglia progression from the highly inflammatory to the anti-inflammatory and neuroprotective polarization stage (Villa et al. 2015; Cordeau et al. 2016), whereby these cells act in concert with astrocytes (also prompted by estrogens to synthesize growth factors) (Sohrabji 2015) to produce the healing molecules necessary to repair the damaged site and provide neurons with all factors indispensable to re-establish a metabolism actively promoting the survival and possibly neuritogenesis and regeneration of synaptic connections at the dendritic spines (Villa et al. 2016). The protective mechanism exerted by estrogens in the ischemia model appears to be reproduced in estrogen-dependent structural recovery occurring after diabetogenic diabetes (Zhang et al. 2004), immunotoxic lesions (Martinez and de Lacalle 2007), or infection (Bertrand et al. 2014).

A few authors also suggested a further neuroprotective effect of estrogens as these hormones may induce proliferation of the neural stem cells located in the subventricular zone and cause their differentiation and migration to the insult site (Zhang et al. 2011). Differently from what observed with estrogens, the concentration of circulating progesterone prior or after the ischemic insult is not beneficial (Gibson and Bath 2016; Coomber and Gibson 2010) while the effect of estrogens per se (and not aromatized to estrogens) has not been sufficiently investigated (Gibson and Attwood 2015).

In line with these observations, the biological sex appears to be an important factor predicting the vulnerability of the brain to an ischemic insult, with the males being at higher risk than females of the same age to ischemic insults. However, this difference normalizes with age and the women protection against such insults disappears after menopause when the levels of circulating estrogens decline significantly (Anderson et al. 1991; Gibson and Attwood 2015). More controversial is the issue of estrogen therapy to prevent ischemic insults after the menopause. In fact, in spite of the numerous observational and retrospective studies demonstrating that estrogen therapy provided benefits for cardio- and cerebro-vascular diseases after the menopause, the WHI clinical trial failed to show and beneficial effect of the replacement therapy. Current view is that E2 fails to provide neuroprotection when the hormonal therapy is started at longtime after the cessation of ovarian functions (or ovariectomy) possibly due to a down-regulation of the estrogen receptors in the different target cells and to the neuroinflammatory processes ensuing the cessation of estrogen production by the ovaries that determine a hyperreactivity of the system to ischemic insults which cannot be overcome by estrogen administration.

12.3.2 Recovery After Spinal Cord/Brain Acute Injury

The protective effects of estrogens are exerted also in the peripheral nervous system. Studies in rats indicate that the administration of estrogens after traumatic spinal cord injury correlates with an improved neurological outcome (Zlotnik et al. 2012) such as increased locomotor functions at relatively short time after injury. The mechanisms underlining such an event are ERα-dependent and several author proposed that in this case the main target for estrogen action would be the oligodendrocytes, where the activated estrogen receptor would trigger an antioxidant response limiting the apoptosis of these cells thus improving the functional recovery (Lee et al. 2012). On the other hand, in a model of spinal cord compression where a strong inflammatory response is induced, the beneficial effects of estrogens injected immediately after the insult appeared to be associated with the ability of the hormone to accelerate le immune response increasing significantly the concentration of IL1a, IL1b, and IL-6 at short time after the insult to then facilitate the recovery from the inflammatory phase thus limiting the expansion of the damaged area to the surrounding region by limiting in time the attraction of CD68 cells. The effect of the hormone was transient, but sufficient to speed up the recovery of locomotor functions (Ritz and Hausmann 2008). Interestingly, the administration of dihydrotestosterone, that cannot be converted into estradiol, worsened the outcome of spinal cord injury possibly because of the inhibitory activity of androgens on cell-mediated immunity (Hauben et al. 2002). A large study carried out by Sipski on about 14,000 subjects with a variety of spinal cord injuries supported the experimental evidence with the observation that women have more neurological recovery than the male counterpart even if male do better than women at the time of discharge: This might be due more to a gender than a sex effect due to the higher familiarity of men with muscular activities (Sipski et al. 2004).

12.4 Conclusions

Gonadal hormones exert potent organizational and activational effects within the mammalian neuraxis and influence a large number of neurological functions. We here provided a limited view on some of the beneficial functions that estrogens have in the case of stroke and injury. However, the relationship between endogenous and exogenous sex hormones and many neurological disorders such as epilepsy, chorea, and neurodegeneration are well established. A better understanding of the mechanisms involved in female resistance to injury could lead to targeted therapies.

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Chapter 13
Appraisals of and Coping with Acquired Brain Injury: Resources for Functional Recovery

Crystal L. Park

Abstract This chapter presents a model of meaning and coping that highlights the centrality of meaning appraisal and coping in adjusting to adverse events. This model is then applied to adaptation to acquired brain injury (ABI) by drawing on relevant theories and empirical findings. The important roles of appraised meanings, violations, coping, and meanings made in promoting functional recovery are detailed. This chapter concludes with ideas drawn from this model to promote innovative treatment strategies for brain injury recovery.

Keywords Acquired brain injury · Meaning-making · Meaning · Coping · Appraisals · Post-traumatic growth

Injuries to the brain are a major cause of disability worldwide. Acquired brain injury (ABI) refers to any non-progressive injury to the brain after birth and results primarily from strokes and traumatic brain injuries (TBIs). ABIS also result from tumors, encephalitis, and hydrocephalus. Following ABIs, people often suffer from long-lasting cognitive, behavioral, and emotional deficits that can interfere with many aspects of their daily life and psychosocial functioning. Post-ABI, most people experience diminished functioning, such as difficulties with social or community integration, cognitive deficits, and symptoms of psychological distress. ABI is associated with lifelong functional challenges, including physical, cognitive, emotional, and behavioral changes. Many people who have acquired a brain injury experience both personal and social difficulties (Wilson 2008). Given the long-term consequences of brain injury, survivors often face a dramatically altered life. Although ABI is highly prevalent, the problems experienced by those affected, such as impairments in cognition and perception, are often not visible. Hence, brain injury has been referred to as a "silent epidemic" (Goldstein 1990).

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Given the high prevalence of ABIs and the extensive disability typically left in their wake, promoting functional recovery is critical. Although most research on functional recovery from ABIs focuses on biomedical factors, more recent research has begun to examine psychosocial influences and processes as well. Among the most important psychosocial aspects of functional recovery from brain injury are the meanings that people with brain injuries assign to their situation (e.g., the injury, what recovery requires, what they are capable of) and the coping strategies they use in their efforts to achieve functional recovery. This chapter presents a model of meaning appraisal and coping with brain injury, drawing on relevant theories and empirical findings and concludes with ideas drawn from this model to promote innovative treatment strategies for brain injury recovery.

13.1 Conceptual Model of Meaning and Coping

The model elaborated in this chapter, shown in Fig. 13.1, is based on notions of meaning, including global meaning systems, which consist of people's fundamental beliefs—about themselves, the world, their place in the world, and their sense of meaning and purpose—as well as their unique hierarchies of goals and values. Global meaning systems inform people's understanding of themselves and their lives and direct their personal aims and projects (Park 2010).

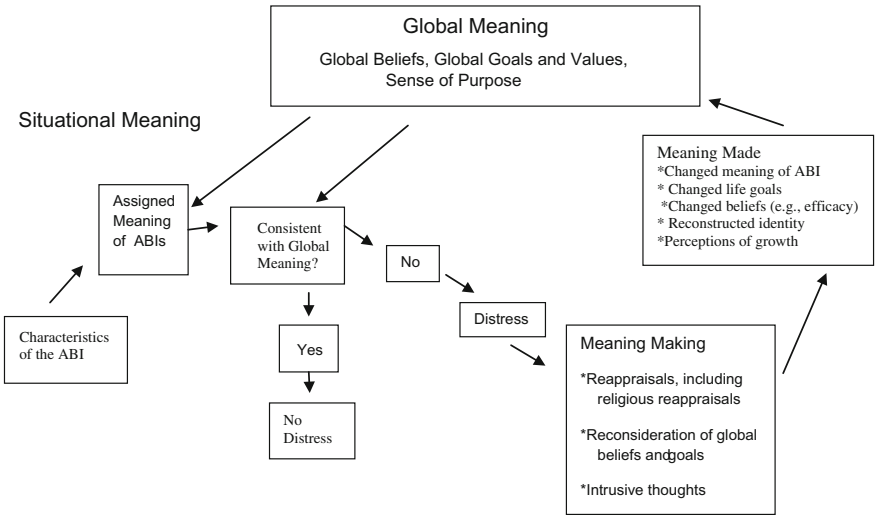

Fig. 13.1 Conceptual model of meaning and coping

Through their global meaning systems, people interpret and label the situations that they encounter (i.e., appraisals of events' meanings). In the case of ABIs, these appraised meanings may include the relevance, cause, controllability, implications, and degree of threat, harm, and loss that the ABI represents. These appraisals of meanings then shape the emotional and behavioral consequences of these events (Lazarus and Folkman 1984; Park 2010). Situational meaning encompasses not only the meanings individuals assign to their experiences, but also the potential discrepancies between their global and appraised meaning, the processes involved in reconciling those discrepancies (termed "meaning-making"), and the changes resulting from these reconciliation processes (termed "meaning made").

13.1.1 Global Meaning

The essential elements of global meaning are overarching beliefs, goals, and sense of meaning and purpose that together provide the frameworks through which individuals interpret, evaluate, and respond to their experiences (Park and Folkman 1997). Global beliefs are widely encompassing assumptions about the self, others, and world, such as beliefs regarding the benevolence and fairness of the world, personal control, luck, randomness, human nature, and how and why events occur (Koltko-Rivera 2004). Global beliefs also include peoples' beliefs about themselves that form their sense of personal identity (Leary and Tangney 2003). Global goals constitute individuals' highest motivation for living; and these goals are the high-level ideals, states, or objects toward which people work to attain or maintain (Karoly 1999; Klinger 2012). Commonly reported global goals include relationships, work, health, wealth, knowledge, and achievement (Emmons 2003).

13.1.2 Situational Meaning

Situational meaning refers to how global meaning, within the context of a particular situation, influences one's responses to that situation. Specifically, situational meaning includes the appraised meaning of the situation, detection of similarities and violations between that appraised meaning and global meaning, meaning making processes, and meaning made from the situation. In the case of an ABI, situational meaning refers to how an individual understands, copes with, and makes sense of his or her injury and all of its sequelae.

13.1.3 Appraised Meaning and Violations

People appraise or assign meanings to situations that they encounter to understand their value and significance (Lazarus and Folkman 1984). After appraising the initial meaning of an event, individuals must determine the extent to which that meaning is congruent with their global views of the world and themselves and their desires and goals. The degree to which global meaning has been violated corresponds to the extent to of the resultant distress (Janoff-Bulman 1992; Steger et al. 2015). As is detailed below, ABIs strongly violate individuals' global meaning.

Violations or discrepancies provide the impetus for initiating cognitive and emotional processing—"meaning-making" efforts—to rebuild meaning systems in a manner that in some way accounts for the reality of the trauma. Meaning-making involves efforts to understand and conceptualize stressors in ways that are more consistent with their global meaning and to incorporate that understanding into their larger system of global meaning through processes of assimilation and accommodation (Park and Folkman 1997).

13.1.4 Coping and Meaning-Making

Mismatches between global and appraised meaning are distressing, and people are often highly motivated to alleviate this distress (Park 2010). When experiencing situations discrepant with their global meaning, people may attempt to alleviate this distress in many different ways; these attempts are called coping efforts. Coping is typically defined as "the person's cognitive and behavioral efforts to manage (reduce, minimize, master, or tolerate) the internal and external demands of the person-environment transaction that is appraised as taxing or exceeding the person's resources" (Lazarus and Folkman 1984, p. 141). Coping can focus on emotions, such as seeking social support, expressing the emotions, distracting oneself, or even avoiding reminders and trying not to think about a problem. Coping may also attempt to directly solve or change the situation, often referred to as problem-focused coping (Aldwin 2007). In addition to these types of coping focusing on emotions or problem-solving, stressful situations such as ABIs create discrepancies between global and situational meaning that cannot be directly solved and thus require meaning-making and coping to reduce the discrepancies.

Meaning-making refers to attempts to resolve violations of global meaning by reaching a more acceptable appraisal of a distressing event to better incorporate it into one's existing global meaning system or changing one's global meaning to accommodate it (Park 2010; Park and Folkman 1997). Meaning-making processes can include both automatic processes (such as intrusive thoughts and dreams) and more deliberate efforts (Park 2010). The process of making meaning can be

difficult, but people typically experience better adjustment to stressful events when they engage in them (Park 2010).

13.1.5 Meanings Made

Meanings made refer to outcomes of these meaning-making processes, including changes in appraisals of a stressful event (e.g., coming to see it as less damaging or perhaps even fortuitous), changes in global meaning (e.g., changing one's identity to embrace the experience), and post-traumatic growth (e.g., experiencing increased appreciation for life, stronger connections with family and friends, or greater awareness of one's strengths; Park 2010).

13.2 The Model of Meaning and Coping in the Context of Acquired Brain Injuries

13.2.1 ABIs and Their Consequences as Stressors

ABIs represent highly stressful experiences yet each ABI is unique, meaning that every individual with ABI faces a unique constellation of problems and challenges. The consequences of ABI are often debilitating, with long-term adverse impact on occupational activities, interpersonal relationships, and living situations. The prevalence of psychiatric disorders is also high. Survivors of ABI face myriad difficulties, including motor, sensory, cognitive, behavioral, social, and physical problems (Wilson 2008).

13.2.2 Appraised Meaning

Given the extensive range of difficulties individuals with ABI may experience, it is critical to know how they appraise their ABI. Specifically, how do survivors understand why the injury happened, how extensive the damage is, how much functional recovery is possible, what they need to do to achieve recovery, and whether they possess the needed resources to recover.

Much of this research has focused on how people understand why they experienced an injury. In a study of people who had experienced a stroke, most reported having searched for a cause (Thompson et al. 1990). Further, those who were able to identify any cause were better off than were those who could not come up with an attribution (Thompson 1991). However, some studies have found that the specific causes that ABI survivors identified make a difference in terms of their distress.

A study of people with severe TBI found that attributing the cause of the injury to others was associated with more severe PTSD symptoms (Williams et al. 2002). One study examined attributions of blame to self and to others by both intentional (violence-related) and unintentional (accidental) TBI patients in rehabilitation and followed up with them one year later. At both time points, participants with intentional TBI blamed others more, while those with unintentional TBI blamed themselves more, but for both groups, other-blame at 1 year predicted depression but self-blame did not (Hart et al. 2007).

Other appraisals of ABI have also been associated with recovery. One study of people within three months following a mild TBI found that making appraisals that the injury was part of their identity and holding expectations of lasting severe consequences at baseline predicted poorer adjustment and greater distress six months later (Snell et al. 2013). In a study of people with fairly long-term ABIs (mean time since injury of six years), seeing the injury as part of their identity was associated with distress, but perceiving that they could control the sequelae of the ABI was associated with the use of more adaptive coping and less distress (Rogan et al. 2013). These studies suggest that the ways that individuals understand their ABI may have long-term implications for their recovery.

13.2.3 Violations

The meaning-making model of recovery focuses on violations or discrepancies as the core of distress and disability and views the resolution of discrepancies as the primary task of rehabilitation. This model has been elaborated in the context of ABI by Gracey et al. (2009). They proposed a Y-shaped Model of rehabilitation in which the process of adaptation and reintegration into society following brain injury initially involves becoming aware of, understanding, and adaptively resolving social and psychological violations. The key types of violations identified in the Y-shaped Model were social (e.g., fear of stigma resulting in withdrawal from social groups and loss of relationships), interpersonal (e.g., client and relative holding different views about the nature of difficulties or needs), and personal (e.g., between pre-injury and current self or current and hoped-for self).

Clearly, ABIs will violate many beliefs about one's self and the world and are almost by definition highly discrepant with individuals' goals. Perhaps most profoundly affected among beliefs is one's sense of identity (Cantor et al. 2005; Gracey et al. 2008). ABIs typically produce violations between one's sense of self post-injury and the pre-injury or aspired self (Gracey et al. 2009). One study of longer-term survivors of TBI who had experienced a TBI on average over 11 years prior found that survivors generally viewed their current self as negative in comparison with their pre-injury self. Perceived identity change due to the ABI was positively associated with depression and grief and negatively associated with self-esteem (Carroll and Coetzer 2011). Further, ABIs may disrupt individuals' global beliefs about the larger world. For example, McGrath (2011) described how

ABI raises fundamental existential questions, such as "Is the world meaningful?"; "Is the world controllable by me?"; "Am I worthy of approval?"; "How should I live my life aright?" (p. 86).

In addition to violations of beliefs, many important goals are rendered less attainable or even impossible by the sudden and possibly permanent functional impairments presented by ABI (Kuenemund et al. 2013). For example, in the above-mentioned Y-shaped Model (Gracey et al. 2009), difficulties in maintaining social relationships following ABI were considered a central problem. In a study of ABI patients assessed during acute rehabilitation and at 19 months following discharge, participants reported significant decreases over time in the general attainability of their life goals and of their present success in achieving their life goals (Kuenemund et al. 2013). Another study assessed goals in people with recent ABIs and found declines in attainability of goals over the subsequent year; further, only 13% of participants' initial life goals had been achieved one year later (Brands et al. 2015). Goals may be rendered less attainable for many reasons, including disruptions in processes of goal pursuit, including executive function and self-regulation (Brands et al. 2015).

13.2.4 Coping

Increasingly, evidence demonstrates that functional recovery following ABI is influenced by the way survivors cope with the injury and its myriad sequelae as well as other stressful situations (Gregório et al. 2014b). How individuals manage ABI and its sequelae determines in large part the effects of the injury on productivity, social activity, emotional stability, and quality of life (Gregório et al. 2014a). Coping is driven by efforts to alleviate distress that is produced by violations between survivors' global meaning and their appraisal of the ABI and its implications.

The transactional stress and coping model of Lazarus and Folkman (1984) has been usefully applied to the recovery processes of people with ABI. For example, both the stress–appraisal–coping model (SAC; Godfrey et al. 1996) and the theoretical framework of Moore and Stambrook (1995) described the importance of cognitive appraisals and specific coping efforts in the rehabilitation process. Moore and Stambrook usefully noted how cognitive beliefs (e.g., beliefs in low personal control over contingencies) and unsuccessful interactions with the environment could produce a negative cycle of frustration, distress, and perceived helplessness. However, studies of coping based on these general coping models have produced disappointing results. Their findings generally mirror those from the broader coping literature: A few specific types of coping, such as wishful thinking, avoidance, worry, self-blame, and using drugs and alcohol, are fairly consistently associated with poor adjustment. However, identifying coping strategies that are adaptive is far

more elusive, with results often inconsistent and inconclusive (see Brands et al. 2012 and Gregório et al. 2014a, for reviews).

Building on these models, Brands and her colleagues posited that the lack of consistent findings regarding coping may be at least partly due to the fact that ABI requires adaptation to different types of stressors, some of which require striving toward maximal restoration of functioning, while others require adaptation to the changes and losses that have occurred in the survivors' physical and psychosocial functioning. Thus, long-term well-being following ABI may require a "mix of restoration-oriented coping and loss-oriented coping" (Brands et al. 2012, p. 841). Thus, both emotion-focused and problem-focused coping may be needed simultaneously, but to deal with different aspects of recovery. Because most studies of coping with ABI have simply asked about coping with the ABI in general rather than with regard to specific aspects of the injury, interpretation of this literature is particularly difficult. Further, as mentioned above, a third type of coping, meaning-focused, has generally received little research attention even though it is highly useful in dealing with major life stressors that are not amenable to being solved but instead require major shifts of meaning to resolve (Park 2010). Successful meaning-focused coping can help to reduce violations between ABI survivors' global meaning and their appraised meaning of the ABI.

Indeed, research has shown the importance of meaning-focused coping with ABIs. For example, in the above-mentioned study of stroke patients, searching for meaning was driven by greater distress, but those who reported finding meaning through their search had better long-term adjustment (Thompson et al. 1990). Meaning-making can take the form of finding ways to understand the ABI and its implications for one's life in more benign ways, typically through reappraisal processes. For example, a study of stroke survivors found that reappraising the stroke in more positive ways and comparing their own recovery favorably relative to others (downward comparison) were related to lower levels of depression and anxiety (Gangstad et al. 2009). In a qualitative study of TBI, several participants appraised their injury as a catalyst to improve their unhealthy lifestyles and give up alcohol and drug use (Nochi 2000).

Given the profound and permanent nature of many ABIs, however, at least some remodeling of global meaning is likely to be required; such remodeling is in fact often quite extensive. The remaking of one's identity in light of the ABI is a major task of meaning-making. A number of qualitative studies have described the restorying that individuals undergo following ABI as they reform their identities. For example, Nochi (2000) highlighted narrative themes on which study participants drew in constructing adaptive stories about themselves post-TBI. Some of the participants constructed themselves in narratives of being okay or worthwhile "despite" the injury by describing being better off than others with disabilities (i.e., making downward comparisons), by focusing on the "here and now" rather than the past or future, and by maintaining hopes for recovery to a state closer to the pre-injury self.

Reduction in violations between one's life goals and one's actual performance is also central to functional recovery following ABI (Brands et al. 2012). Through their successes and failures in managing their day-to-day ABI-related problems, patients learn about the attainability of their long-term higher-order global goals. A continuous process of evaluation takes place in which the gap between goals and achievement informs the need to revise or persist in one's global goals. This reduction in violations will largely be accomplished by letting go of goals that are no longer tenable and developing new, more realistic goals in light of the ABI. One study of patients shortly after an ABI found that those who attained their important life goals one year later had higher quality of life and lower distress. Individuals differed in their continued goal pursuit: Those who persisted had higher levels of goal tenacity, but did not differ in level of self-efficacy compared with patients who disengaged (Brands et al. 2015). In the above-mentioned longitudinal study of ABI and subjective well-being, pursuing life goals one considers attainable was related to increases over 19 months following discharge (Kuenemund et al. 2013).

Those who are unable to make meaning may experience continued or increased distress. In the above-mentioned study of recently acquired intentional or accidental brain injuries, increasing concern over cause/blame for injury from acute rehabilitation to follow-up was associated with high levels of emotional distress (Hart et al. 2007).

13.2.5 Meanings Made

Meaning-making coping, and other meaning-making processes (e.g., rumination) can result in new appraised meanings of the injury, altered global beliefs and goals, or both. The creation of a new identity and the development of new perspective about life and expectations about the future are the key aspects of adaptation. These positive changes are the basis of long-term adjustment following ABI. Positive changes in self-concept are central to well-being (Doering et al. 2011). Among the most important self-beliefs is a strong sense of self-efficacy. In a study of patients with recent ABI, higher baseline self-efficacy and increases in self-efficacy over the subsequent year predicted better quality of life and social participation one year later (Brands et al. 2014). In addition, the restoration of life goals that are comprehensive, meaningful, and perceived as attainable is a critical outcome of the meaning-making process. Following ABI, having a set of life goals perceived as attainable has been associated with higher well-being and lower distress (Brands et al. 2015).

One other common outcome of meaning-making following ABI that is receiving increasing research attention is the phenomenon of *post-traumatic growth* (PTG) (Gangstad et al. 2009; see Grace et al. 2015, for a review). PTG refers to perceptions of positive changes in one's self brought about by a trauma (in this

case, by an ABI) (Park 2009). The meaning of these perceptions remains uncertain —they are not closely tied to actual or observable changes (Frazier et al. 2009) and are often but not always related to higher levels of distress (Park 2009). Thus, these perceptions of positive changes appear to often function as reappraisal coping efforts, attempts to see the event as having some redeeming features. Yet perceptions of positive changes may have some adaptive value, especially in situations where a return to one's previous status is impossible, and positive relations between PTG and distress seem to diminish over time, suggesting that these perceptions may have adaptive value long-term (Grace et al. 2015). In one study of people post-ABI, an enhanced appreciation for life was the most commonly endorsed aspect of PTG, followed by improved relating to others (Collicutt McGrath and Linley 2006). Thus, PTG may reflect the possibility that individuals can identify or create positive meanings of their ABI that facilitate their adjustment and improve the quality of their lives.

13.3 Clinical Implications of a Meaning Model of ABIs

The research on meaning and coping with ABI has been primarily based on observational studies rather than on interventions. However, given the pervasive roles played by meaning-making throughout the recovery process, increased efforts should be made to incorporate this perspective into existing rehabilitation programs. Much of this integration can be accomplished simply by making more explicit how meaning is involved in recovery. For example, current models of rehabilitation following ABI focus intensively on goal setting (Wilson 2008). Studies that have demonstrated long-term deterioration of life goal attainability highlight that increased emphasis should be given to realistic appraisals of goal attainability during rehabilitation processes. Further, these results highlight the need for outpatient treatment to promote disengagement from unobtainable life goals and to offer ways for ABI survivors to engage in alternative life goals in order to promote their functional recovery (Kuenemund et al. 2013).

Similarly, many interventions already focus on helping survivors rebuild a functional belief system; such interventions could be improved by a more specific focus on the attributions and other beliefs that individuals with ABI make about their injury and about their sense of control and self-efficacy (Brands et al. 2014, 2015; Snell et al. 2013). In addition to emphasizing the roles of meaning-relevant concepts in current approaches, some interventions with a basis in positive psychology have been applied to ABI which highlight meaning and promote adaptive ways of thinking about one's life through techniques specifically focused on positive meaning and growth (see Evans 2011). Together, the increased attention to meaning throughout the processes of recovery may promote a more holistic functional recovery that strives to not only reduce deficits but also incorporate positive functioning and growth.

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Chapter 14
Premorbid Personality Traits and Brain Recovery: Another Aspect of Resilience

Daniela Laricchiuta, Sebastian Markett, Martin Reuter and Christian Montag

Abstract The concept of "reserve" is defined as the resources being available to deal with adverse environmental influences on the human brain, and it has been proposed to account for the mismatch between brain pathology and clinical expression. New multidimensional approaches take into account the complexity and dynamic relation between the construct of reserve and post-damage neurobehavioral changes associated with negative consequences of neurological damage on functional outcomes, caregiver distress, and social reintegration following the traumatic event. In this framework, environmental factors, emotional aspects, and premorbid personality traits have increasingly been considered as potential moderators of traumatic brain damage. The present work constitutes a preliminary attempt to define and characterize the role of premorbid personality within the context of resilience against the detrimental effects of traumatic brain damage on adaptive functioning. Premorbid personality features appear to be a relevant factor of resilience that predicts brain recovery efficiency.

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14.1 Introduction

Traumatic brain injury (TBI) and stroke have been reported as the most common causes of brain damage (Langlois et al. 2006) and death related to brain damage (Faul et al. 2010). Different individuals, however, may be affected differently by an event that looks similar at first glance. A brain insult of a certain magnitude may result in severe cognitive impairment in one person while having little effects on another one. To explain the mismatch between brain damage and its clinical expression, it has been proposed to consider the concept of "reserve" as potential buffer between brain pathology and symptoms (Stern 2002, 2006). Reserve could be defined as resources being available to deal with adverse environmental influences on the human brain. A distinction is typically made between *brain reserve* and *cognitive reserve*.[1] The brain reserve is typically indexed by total brain volume, intracranial volume, ventricle-to-brain ratio, neuronal density, and synaptic connectivity, whereas the cognitive reserve is commonly measured by indices of premorbid educational level, occupational attainment, general cognitive ability/intelligence (IQ), as well as measures of specific cognitive functions (Bigler 2007; Levi et al. 2013; Rassovsky et al. 2006a, 2006b; Satz et al. 2011). Moreover, Stern (2002) characterized models of brain reserve as *passive* models (i.e., the amount of damage that can be sustained before reaching a threshold for clinical expression) and models of cognitive reserve as *active* models.

Despite the conceptual utility and broad application of these constructs, brain and cognitive reserves do not account for the entire variability in TBI or stroke outcomes. Regardless of the TBI or strokes' severity, changes in behavioral and emotional attitudes are symptoms commonly reported. These manifestations can be quite diverse including changes toward irritability, apathy, impulsivity or intolerance/disagreeableness. They often represent the biggest barrier to rehabilitation in the acute phase of the treatment of the brain lesions as well as to social, professional, and familial reintegration on the long term (Kreutzer et al. 1994a, b). In fact, the mentioned emotional and behavioral changes have been related to negative consequences on the Quality of Life (QoL) of patients but also of their family, friends, and caregivers (Ciurli et al. 2011).

In the clinical practice, it is assumed that the behavioral changes after traumatic events are most often related to cognitive function impairments due to brain

[1]The distinction between "brain" and "cognition" is merely descriptive and refers to the methodological approach used (tools from neurobiology *vs.* tools from psychological science). The distinction does not neglect reciprocal relationship between the two perspectives.

damage, but increasingly data report that these manifestations are underpinned by a variety of mechanisms partially related to personality traits and environmental context of the patient.

As *personality* represents the special focus of this review chapter, we shortly want to introduce the concept. Although many definitions exist, the common denominator can be found in the *trait concept*. A trait (in contrast to a state[2]) refers to time stable characteristics of a person. In the context of personality, a trait manifests itself in individual differences in emotional reactions to a large number of different situations, cognitive thinking patterns and actual behavior (Montag et al. 2012, 2013a, b). It has been outlined that individual differences in emotional tendencies might reflect the phylogenetically oldest part of personality (Davis and Panksepp 2011; Montag 2014; Montag and Reuter 2014), and personality traits are likely mediated by cortical and subcortical brain networks (DeYoung et al. 2010; Kaasinen et al. 2005; Laricchiuta et al. 2014a, b, 2015; Petrosini et al. 2015, 2016; Picerni et al. 2013; Sollberger et al. 2009).

In addition, personality has been proven to be rather stable across life (McCrae et al. 2000; Soldz and Vaillant 1999; Whittle et al. 2006; see some exceptions to this rule put forward by Ardelt 2000). In contrast, the concept of cross-situational stability has very often been challenged and somewhat resolved by so-called *if-then functions* proposed by Mischel and Shoda (1995). In short, both authors argue to search for stability of personality depending on distinct environmental variables. Therefore, stability of personality is observable, but only when considering the kind of a situation a person is facing. Of note, in this short section, we refer to (time and situational) stability of healthy persons, neglecting somewhat personality changes due to brain injuries. Precise identification and consideration of the multiple mechanisms—including personality variables but also the inclusion of distinct environmental variables—are needed to promote adapted and effective care management for brain-damaged patients.

14.2 The Relationship Between Post-Brain Damage Depression and Premorbid Personality

Depression and depressive symptoms are often reported after TBI or other types of brain damage. Even though depressive symptoms may reflect a reaction to impairment and handicap in the context of an adjustment disorder, it has become clear that depressive symptoms can also be a direct consequence from the injury itself (Rickards 2006). Depression following brain damage has been positively associated with emotional and cognitive disabilities, reduction of QoL, time of hospitalization, non-adherence to treatment schedules, repeated use of community

[2]A state could be assessed by an item of a questionnaire asking how a person feels right now *versus* in general. The latter would more grasp the trait concept.

health services, and increase in mortality (Jia et al. 2006; Poynter et al. 2009). Many attempts have been made to identify the predictors and early signs of depression symptoms after brain damage. The main predictors of depressive symptoms after injury or stroke include physical disability, damage severity, and cognitive decline (Ayerbe et al. 2011; Hackett et al. 2005). The few studies focusing on psychological aspects as predictors of depressive symptoms have indicated that premorbid personality dimensions may be associated with the development of post-damage depression (Aben et al. 2002; Hwang et al. 2011; Storor and Byrne 2006).

According to Prigatano (1992, 1999), emotional and motivational factors, which largely reflect premorbid personality features, play an integral role in patients' recovery process following Brain damage. Along these lines, McCauley et al. (2013) found that measures of psychological resilience and mood predicted severity of anxiety and post-concussive symptoms following mild brain insult.

Despite their potential predictive utility, there is still a substantial gap in knowledge regarding the influence of psychological factors on depression outcome, a gap mostly due to challenges in measuring premorbid variables (Nelson et al. 1998; Prigatano 1999).

14.3 Personality Traits and Attachment Style as Risk or Resilience Factors

In the hypothesis that various aspects of personality confer risk and resilience for important health outcomes, two major factors of personality received notable attention: personality traits and attachment style.

14.3.1 Personality Traits

Personality traits exert significant influence on adaptive behavior, predicting behavioral responses, and influencing the development of social skills (Mathiesen and Prior 2006; Mathiesen and Sanson 2000). Personality traits have been typically studied within the context of resilience and coping with stressful events (Friborg et al. 2005). One of the most important concepts in personality psychology represents the Five Factor Model of personality, which has been put forward among others by Fiske (1949) and was refined substantially later on (McCrae and John 1992). The Five Factor Model of personality has been derived from a lexical approach. This approach operates under the assumption that meaningful individual differences in personality should be reflected in natural language and can therefore be extracted from linguistic co-occurrence and similarity data. Independent from the cultural background and the particular language of the populations under investigations, this study led to define five personality dimensions that can be easily being

memorized by the acronym OCEAN: Openness to Experience, Conscientiousness, Extraversion, Agreeableness, and Neuroticism. These factors have been the focus of numerous studies ranging from topics of health behavior to longevity. In the following, we would like to very shortly summarize some of this research to provide some more insights into these personality dimensions.

Each big five personality trait is conceptualized as unidimensional, bipolar construct. This means that a given individual can be characterized by her or his individual position along a continuum whose extreme ends describe ideal manifestations of the trait. Traits cannot be directly observed but inferred from behavioral observations or from self-descriptions on standardized questionnaires. The traits are thought to be independent from each other, and the essence of an individual's personality is thought to be captured in the combination of his or her scores along all five dimensions. High Openness to Experience reflects a developed emotional life, sensitivity to art, imagination, intellectual curiosity, and behavioral flexibility; high Conscientiousness describes morality, organization, and diligence; high Extraversion refers to the tendency to experience positive emotions, sociability, talkativeness, and energy; high Agreeableness reflects the ability to trust, feel sympathy toward and cooperate with others; high Neuroticism refers to the individual's tendency to experience psychological distress, including aspects of depression and anxiety. High levels of Extraversion, Openness to Experience, and Conscientiousness as well as Agreeableness (Davey et al. 2003) are positively associated with mental resilience, whereas high Neuroticism traits are found to have the opposite effect (Campbell-Sills et al. 2006; see also a review by Lahey 2009).

Besides the Five Factor Model of personality, a more biologically grounded personality has been put forward by Cloninger (1986, 1988). While the Five Factor Model has been carved out from a lexical approach, the biopsychosocial personality model of Cloninger tremendously relies on different data sources including human biology. In his theory, the personality dimensions Harm Avoidance, Novelty Seeking, Reward Dependence, and Persistence are called temperaments and manifest in unique emotional/behavioral patterns expressed in response to environmental stimuli. Harm Avoidance is characterized by the tendency to respond intensely to aversive stimuli and avoid punishment. High Harm Avoidance scores stand for high tendency to pessimistic worry in anticipation of problems, fear of uncertainty, shyness with strangers, rapid fatigability.

Novelty Seeking is described as the tendency to respond with strong excitement to novel stimuli, leading to the pursuit of reward. High Novelty Seeking scores stand for high tendency to exploratory activity in response to novelty, impulsive decision-making, extravagant approach to reward cues, and quick loss of temper.

Reward Dependence is defined as the tendency to respond intensely to reward signals and to maintain behaviors previously related to reward or relief from punishment. High Reward Dependence scores stand for being tender-hearted, sensitive, dedicated, dependent, and sociable.

Persistence refers to a tendency to the maintenance of behavior despite frustration, fatigue, and intermittent reinforcement. High Persistence scores stand for

hard working, perseveration, ambitiousness, and perception of frustration as a personal challenge.

Many studies have found that the Harm Avoidance is a sensitive predictive marker of the incidence and severity of depression as well as other mood disorders (Cloninger et al. 1998, 2006; Gil and Caspi 2006). As presented in Montag et al. (2012) Harm Avoidance shows substantial overlap with Neuroticism, as well as Novelty Seeking with Extraversion.

14.3.2 Attachment Style

Attachment style is another factor of personality that predicts future adjustment to challenge (Svanberg 1998). According to attachment theory (Bowlby 1969), the nature and quality of attachment to the primary caregiver in early childhood provide the basis for the subsequent development of interpersonal behavior. Bowlby (1973) maintains that the nature of this early attachment explains individual differences in ability to cope with stressful situations. In this view, individuals who have experienced the attachment figure as available and supportive will believe in their own ability to bear distress, whereas those who have experienced the attachment figure as distant and non-supportive will grow with doubts regarding their own coping ability. Based on this theory, Ainsworth et al. (1978) defined three major attachment styles: secure attachment, avoidant attachment, and anxious/ambivalent attachment. Using this classification scheme, numerous investigators predicted successful or maladaptive emotional coping responses in a variety of contexts (Mikulincer 1998; Mikulincer et al. 2009; Solomon et al. 2008; Svanberg 1998).

14.4 Personality Factors in the Context of Reserves

Premorbid personality components may provide a buffer against the detrimental effects of brain damage on adaptive functioning. Prigatano (1987, 1999) proposed a three-level connection between personality and TBI: (a) neuropsychological disorders, represented by cognitive, emotional, and motivational responses arising from neuropathology; (b) responsive disorders that reflect a failure to cope with environmental demands; and (c) premorbid personality that reflects previous emotional and motivational responses.

How does the premorbid personality contribute to the clinical picture following brain damage? Specifically, does premorbid personality predict social, occupational, and psychological functioning impaired in TBI or stroke patients?

Such an issue has been only recently addressed. For example, it has been advanced that Harm Avoidance may be an innovative independent predictor for depression and QoL after brain damage. Namely, patients with high Harm Avoidance scores have twice a risk for experiencing behavioral and psychological

troubles compared to participants with low Harm Avoidance scores (Afanasiev et al. 2013). Since individual differences in personality may be linked to variability in brain structure and function (Laricchiuta et al. 2014a, b, 2015; Montag et al. 2013a, b; Petrosini et al. 2015, 2016; Picerni et al. 2013; Yamasue et al. 2008), Biological mechanisms are possible explanations for the role of Harm Avoidance or Neuroticism in depression and QoL following brain damage. The Harm Avoidance temperament dimension has been positively linked to activity of the serotonergic system (Cloninger et al. 1993) and may therefore play a role in depression and psychiatric disorders (Quilty et al. 2010). The monoaminergic hypothesis assumes that depression features are mirrored by deficits or changes in serotoninergic neurotransmission.[3] These might include low brain cell production of serotonin, a reduction of serotonin receptors, the inability of serotonin to reach the receptor sites, or a shortage in the serotonin precursor (Cowen 2008). In accordance with the serotonin-Harm Avoidance link, Ramasubbu et al. (2006) demonstrated that a short variation of serotonin transporter-linked promoter region (5-HTTLPR) functional polymorphism might be a potential candidate variation to be studied in the context of susceptibility to post-stroke depression. Moreover, it has been reported that a biogenic amine insufficiency including a lack of the indolamine serotonin in the frontal and temporal lobes, as well as in the basal ganglia, or the failure to upregulate serotonin receptors may trigger depression symptoms after brain damage (Santos et al. 2009). The low cerebrospinal concentrations of the serotonin metabolite 5-hydroxy-indoleacetic acid in brain-damaged patients with depression support this proposal (Bryer et al. 1992). Furthermore, a positive association between the serotoninergic system and QoL has been also demonstrated in non-depressed subjects (Tsai et al. 2003). Furthermore, the worsening in QoL of these patients was associated with lower dopamine concentrations and higher noradrenaline concentrations in the plasma, indicating that other neurotransmitter systems contribute to the picture as well.

Alternatively, apart from the importance of the summarized neurobiological substrates, the coping style of a person in response to a stroke or brain injury may increase the likelihood of depression (Ayerbe et al. 2011). The nature of the association between disease and depression after brain damage is multifaceted. It can be speculated that people scoring high on measures of Harm Avoidance or Neuroticism, whose behavior is characterized by frequent worrying about future outcomes, fear of the unknown, as well as shyness and fatigability, would show a pronounced emotional reaction toward interferences in their routine caused by insults on the brain including stroke or injury. Such an extreme reaction to the new threatening medical situation likely results in a QoL decline. In this framework and consistent with previous findings (Dikmen et al. 1995; Macmillan et al. 2002; Rassovsky et al. 2006a, 2006b; Ropacki and Elias 2003; Tate and Broe 1999), Sela-Kaufman et al. (2013) found that TBI severity predicts lower

[3]This also explains why a majority of depressed patients is treated with selective serotonin reuptake inhibitors these days, upregulating serotonin levels by blocking the serotonin transporter in the presynapse.

social and occupational functioning and higher psychopathological symptoms in the recovery stages. More importantly, premorbid personality traits predicted social and occupational functioning as well as attachment style predicted occupational and psychological functioning after stroke/brain injury. In detail, Neuroticism, Extraversion, Conscientiousness, and an Avoidant Attachment Style influenced the impact of injury severity on post-TBI occupational functioning. It is of note that the same variables were previously reported to predict adaptive behavior following TBI and other neurological diseases (Magai et al. 1997; Malec et al. 2004; Rush et al. 2006; Schretlen et al. 2000). Some further information on methodological implications need to be mentioned: in the study by Sela-Kaufman et al. (2013), the assessments regarding patients' premorbid personality and attachment style was collected by using questionnaires completed by family members, who were asked to assess the relevance of the statements regarding the patient prior to the brain damage. However, the use of family members to provide data on premorbid personality is not free from complications, given that any retrospective assessment may introduce faulty memories of what a person was like previously (Chatterjee et al. 1992).

Thus, the above reported analyses support the hypothesis that personality changes are not solely the consequence of biochemical changes occurring in the presence of brain damage, but rather they are related to premorbid personality traits predisposing to specific coping styles and to patterns of interpersonal relationships. In fact, personality disposes toward the quality and quantity of significant relationships with others, a sense of confidence and organization, and coping capabilities, factors representing protective buffers against the detrimental effects of brain damage.

Conversely, in the scarcity of reports on the influence of premorbid personality on resilience capacities to trauma, it is noteworthy that no relation between premorbid and post-morbid personality was found in people affected by TBI (Tate 2003).

14.5 Premorbid Personality and Neurodegenerative Conditions

A substantial body of literature sustains that dementia gives rise to behavioral and psychiatric syndromes characterized by personality changes (von Gunten et al. 2009). Clinical experience suggests that personality characteristics may have a coping effect on symptoms of psychiatric syndromes and cognitive decline (Lykou et al. 2013). Thus, the conceptual links between dementia and premorbid personality appear to be manifold. Initially, it was proposed that the emerging changes of personality as dementia progresses reflect an aggravation of premorbid personality traits (Welleford et al. 1995). Furthermore, some personality traits are linked to health behaviors known to be associated with increased dementia risk. For example, low Conscientiousness and Agreeableness and high Neuroticism and Extraversion scores are associated with greater likelihood of smoking, drinking alcohol, being under- or over-weight, factors that in turn increase the dementia risk (Bogg and

Roberts 2004; Kendler et al. 1999). Personality may also impact on dementia risk by influencing the number and quality of social relationships, cognitive activity, and reactions to stress over the lifespan (Friedman 2000).

It has been reported that premorbid Neuroticism is linked to premorbid anxiety levels and continues to be associated with anxiety levels even as dementia progresses (Strauss et al. 1997). Correlation between high premorbid Neuroticism levels and depression in dementia has been reported (Chatterjee et al. 1992). These data are corroborated by the observation that Neuroticism often co-occurs with depression or predicts depression also in non-demented subjects (Jang et al. 1996; Kendler et al. 2004). A longitudinal study demonstrated that depressive symptoms were predominant in demented subjects who showed premorbid levels low of Openness to Experience and high of Agreeableness, possibly experiencing more distress when confronted to increasing dependence in the presence of the neurodegenerative disease, given that these subjects cannot explore the world anymore as they could (Wilson et al. 2008). The high rates of negative affect and the low rates of positive affect described in the presence of dementia have been associated with premorbid hostility (Magai et al. 1997). Severe affective disturbance was found in demented subjects with high premorbid Agreeableness levels (Low et al. 2002). Case control and prospective findings on the influence of personality on risk of dementia and mild cognitive impairment evidenced that high Neuroticism levels are associated with increased risk of dementia and that high Conscientiousness levels are protective against dementia incidence (Low et al. 2013). Dependent and inhibited personality styles were associated with great levels of withdrawal and irritability in dementia (Gould and Hyer 2004). Furthermore, vocally disruptive behavior of demented patients has been linked to premorbid levels of Introversion, psychic rigidity, and emotional control (Holst et al. 1997).

Patients affected by Alzheimer's disease (AD) are generally characterized by a neurotic premorbid personality and, thus, by an emotionally labile and tense temperament when demented in comparison to patients affected by Parkinson's disease (PD) (Meins and Dammast 2000). In AD patients, low premorbid Agreeableness levels are associated with agitation and irritability (Archer et al. 2007), while high premorbid Neuroticism levels are associated with troublesome behavior (Meins et al. 1998). Premorbid experience of psychological distress has been related to impaired episodic memory in AD patients (Wilson et al. 2004).

Interestingly, in PD a rigid and introverted personality, traits have been suggested as possibly associated with risk of disease (Hubble et al. 1993; Glosser et al. 1995; Ishihara and Brayne 2006; Menza et al. 1990; Poewe et al. 1990). PD patients were often introverted, nervous, cautious, socially alert, conventional, and tense before disease onset. Furthermore, several studies have reported a reduced propensity to smoking, alcohol consumption, and caffeine intake in the presence of PD, probably related to the restrained and rigid Parkinsonian personality characteristics (Benedetti et al. 2000; Hernàn et al. 2002; Ragonese et al. 2003).

Finally, high levels of post-traumatic stress disorder found in patients with spinal cord injury were associated with negative cognitions of self, anxiety-related personality traits, and difficulty in identifying feelings (Hatcher et al. 2009).

14.6 Conclusion

Premorbid personality traits are significant predictors of post-damage resilient behaviors and represent moderator factors between the brain damage severity and interpersonal relationships (Sela-Kaufman et al. 2013). In this sense, the biopsychosocial approaches should be encouraged in the management of neurobehavioral difficulties, since these approaches apprehend behavioral changes as a result of complex and dynamic interactions among neurobiological (type and severity of injury, time post-injury), social (psychosocial history, family context), personal (medical history, personality traits, pre- and post-morbid coping strategies), and environmental factors (problematic and anxiogenic situations related to brain injury) (Arnould et al. 2015; Jumisko et al. 2007; Zasler et al. 2013).

Future longitudinal studies would be optimally suited to provide a more objective assessment of the impact of premorbid personality features on long-term adaptive functioning in brain-damaged patients. In parallel, it is essential to validate additional measures in order to index the diverse personality constructs as potential proxies of brain and cognitive reserves. One prominent biological oriented personality approach to be included would be the theory on primary emotional systems putatively representing the biological basis of the Five Factor Model of personality (Davis and Panksepp 2011). Therefore, it will be informative to evaluate the shared variance among personality constructs and reserves (Montag et al. 2012), as well as the combined and specific moderating effects of each factor on behavioral outcome in healthy and pathological conditions.

Further, given that lesions in different brain regions influence functional outcomes in different ways, it will be informative to examine if premorbid personality plays a differential role on behavioral pattern according to the kind of injury. Future researches will be able to improve our understanding of this important, albeit complex, new role of personality as factor of resilience.

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Chapter 15
Psychodynamic Factors of Recovery After Brain Injury: A Role for Defence Mechanisms?

Alberto Costa, Salvatore Gullo and Carlo Caltagirone

Abstract Brain injury may cause serious motor, cognitive, and affective *sequelae* that significantly affect individual's functioning, interfering with his/her autonomous living. Psychopathology and maladaptive coping styles are frequently observed in these patients and are associated with poorer physical, occupational, and social outcomes. Psychological reactive mechanisms and premorbid cognitive–affective coping style are reported to play a significant role in the patient's recovery processes. Among these, mechanisms of psychological defence such as repression/denial may be active in patients that, after brain injury, show emotion/affective dysregulation and tend to use less efficient coping strategies. Moreover, repression/denial could influence the patient's ability to correctly acknowledge the illness and its consequences, in so way hampering his/her productive participation to the rehabilitative programme and social reintegration. In this paper, we discuss the possible role of psychodynamic mechanisms in the recovery after brain injury, with the aim to provide some clues for the purpose of the clinical intervention.

Keywords Brain injury · Recovery · Coping abilities · Defence mechanisms · Repression

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15.1 Introduction

Neurorehabilitation after brain injury is a current challenge for neurology. Motor, cognitive, and affective symptoms are often copresent dramatically affecting patient's functioning and, thus, their quality of life. Indeed, job, social life, and, more in general, project for self-realization may be significantly impaired by the illness. These changes often require a reorganization of the *modus vivendi* that involves not only the patient himself but also their family. In this regard, it was reported that caregiver may experience an overburden, leading to dysfunctional reactions. In particular, Rueckriegel et al. (2015) showed that more than 50% of close relatives of patients with traumatic brain injury and subarachnoid haemorrhage reported symptoms referring to the post-traumatic stress disorder (PTSD). A lower but significant proportion of the patients' relatives reported selective anxiety and depression symptoms (Rueckriegel et al. 2015). This aspect represents an important issue to take into account. Accordingly, research in rehabilitation is crucial to find models of intervention that are able to respond to the patient's (and their social network) needs, i.e. to efficiently treat symptoms and to reduce the impact of injury consequences.

Due to complexity of brain injury *sequelae*, it is widely accepted that the therapeutic approach should include different health workers that form a multidisciplinary equip. Neurologists, physiatrists, psychologists, neuropsychologists, psychotherapists, other rehabilitation technicians, and nurses are generally involved in the different phases of a rehabilitative protocol. In fact, within a multifactorial model, several dimensions should be considered that could influence the therapeutic process. Size of brain lesion and severity of motor/behavioural impairment are undoubtedly two major factors. Psychosocial and psychological aspects may also significantly modulate the effects of the rehabilitative intervention. In particular, psychopathological symptoms may represent a highly relevant factor. Post-stroke depression was reported to occur in more than the 30% of the population and to negatively affect the therapeutic outcome (Shi et al. 2015). Post-traumatic stress disorder (PTSD) is also frequently diagnosed in patients with acquired brain injury significantly affecting quality of life (Gill et al. 2015). Premorbid personality and cognitive functioning may also play a relevant role especially on the way the patient will cope with the disease-related changes. Above observations apply not only to the consequences of brain pathology but, globally, to the effect of severe organic diseases and to related interventions.

Among the various factors potentially modulating the effects of a therapeutic intervention with the brain-injured patient, poor interest has been devoted to the study of the possible role of psychic defence mechanisms. Within the traditional psychoanalytic framework, these mechanisms are described as psychic operations the individual adopts to keep far from consciousness aspects of his/her emotional experience that may cause severe anxiety and mental sufferance. After brain injury, patients may present a stable response conditioned by the adoption of a particular defence mechanism, such as regression to maladaptive behavioural schema or

repression of emotions that can significantly affect compliance with treatment and reduce his ability to use rehabilitative devises and opportunities. In pure psychological terms, the tendency to use a particular defence mechanism may rely upon the premorbid cognitive/affective style of functioning of an individual that should be correctly recognized. This represents an apparent problem, as premorbid examination of the patient is often possible only by interviewing their family components.

This chapter will discuss the psychological mechanisms involved in the behavioural response to brain damage that may potentially affect recovery. A particular focus will be placed on the potential role of defence mechanisms with the aim to give some clues to consider these elements in the therapeutic approach with brain-injured individuals.

15.2 Psychological Factors Involved in the Adaptation to Organic Disease

Severe organic disease, such as those related to vascular, neoplastic, metabolic, or traumatic aetiopathogenesis, represents a highly stressful condition for the affected individual and his/her caregivers. Lifestyle often undergoes to significant modifications that may hamper the achievement of job-related objective and may impair social and affective relationship. Indeed, as emphasized by Paykel et al. (1971), severe illness is reported by individuals as one of the most stressful conditions and requires the adoption of coping abilities to sustain functional adjustment.

Engel (1977) proposed a multifactorial model, namely a bio-psychosocial model, to understand and treat the behavioural responses to organic disease. According to this model, they should be considered the (i) biological factors represented by the specific substrates and phenomenology of the illness, (ii) psychological factors that refer to the personality characteristics and the internal psychodynamic mechanisms of the individual, and (iii) social factors represented by the cultural matrix in which the individual lives and is grown up that can influence attribution of meaning to the condition. From a psychodynamic perspective, the two latter points appear to be very important as they underline a specific issue: the adjustment in response to the disease condition is strongly dependent by the way the individual perceives the condition itself and his/her role in facing consequences. The concept of "sense of coherence" specifically evidences this aspect. It refers to a global orientation of the individual that makes him to interpret internal and external events as manageable, understandable, and foreseeable (Antonovsky 1993). In particular, according to Antonovsky (1993), it would include three main aspects: the feeling that the events are predictable, that the individual has resources enough to cope with life problems, and that it is useful to sustain efforts to face with potential negative situations. In fact, the sense of coherence was consistently found to be associated with psychological well-being and to reduced risk to develop disease (Ristkari et al. 2006;

Surtees et al. 2003) and to stress-related symptoms after stroke (Nilsson et al. 2001). Within this frame, Leventhal (Hagger and Orbell 2003; Levenhal et al. 1998) proposed the so-called commonsense model that is a self-regulatory model according to which the adaptation process to organic illness would follow a cognitive evaluation of the condition by which the individuals try to build a mental representation of the illness. This meaning, together with stable personality features, would contribute to modulate cognitive/behavioural coping strategies (Peter et al. 2014).

Therefore, premorbid psychological factors and cognitive styles may play a role in the ability to manage stress related to organic disease. In line with this observation, some latent dimensions of psychological functioning were found to be associated with lower capacity of the person to implement successful coping strategies. Among these, high anxiety levels for being injured by health diseases, a body-centred perspective, pessimism, denial of illness, and emotion inhibition appear to be the most relevant (Hagger and Orbell 2003; Pilowsky 1997). In this regard, alexithymia, that is the difficulty to identify and describe own feelings and a more general reduced aptitude to deal with emotions (Taylor et al. 1997), is reported to be related to a maladaptive response to illness and to an higher risk to develop psychopathology (Lumley et al. 2007). These findings emphasize the importance of the individual's style of emotion regulation in the adjustment processes to severe health problems.

15.3 Psychological Factors Implied in the Adjustment Response After Acquired Brain Damage

Vascular and traumatic brain injuries cause serious consequences in the affected individual who often experiences significant cognitive and physical impairments that are associated with functional disability. Several psychological modifications are involved in stroke adjustment (Mukherjee et al. 2006). Significant changes in mood, in personality functioning, in identity, in self-image, and in social participation with the risk of isolation are relevant psychological aspects frequently involved and can influence the potential effect of the therapeutic intervention.

Depression is a particularly common report in these patients. In a recent review paper, Kouwenhoven et al. (2011) underlined that at a 2-year follow-up major depression may affect the 20% of stroke patients. In the immediate post-acute phase, however, significant depressive symptoms were found to involve up to 50% of patients. Moreover, Visser et al. (2015) found that within one year after ischaemic stroke, about 39% of patients showed high depression rates. In a recent study, Dou et al. (2015) investigated suicidal ideation in a group of 281 consecutive patients with ischaemic stroke admitted to a neurological department. The authors found a prevalence rate of suicidal ideation higher than 10%. Moreover, by means of the application of a linear regression model, they also documented that

post-stroke and prestroke depression as well as confidence in the treatment were significant explicative factors of suicidal thinking (Dou et al. 2015). Depression strongly affects the recovery process, and suicidal ideation is rick factor for life itself. Apathy is also frequently observed after stroke, associated with depression or as an independent dimension. In an interesting recent investigation with 117 stroke patients, Matsuzaki et al. (2015) documented that apathy was significantly associated with physical recovery.

Current views see depression after stroke as a multidimensional syndrome in which psychological mechanisms are etiologically implied. To sustain the role of psychological factors in post-stroke depression is some evidence of a relative low predictive power of the brain localization of damage on depressive symptoms (Singh et al. 2000), and results showing no significant difference on depressive symptoms between stroke and orthopaedic patients (Fang and Cheng 2009). In this regard, Lieberman et al. (1999) compared depression symptoms between 221 stroke patients and 295 persons suffering from hip fracture. Authors found similar rates of depression in the two groups. Other studies showing that post-stroke depression was associated with stroke severity, functional recovery, and cognitive status strengthen the hypothesis on the role of reactive psychological mechanisms (Fang and Cheng 2009).

In line with above observations, a study by van Mierlo et al. (2015) documented that stable personality traits and state-dependent psychic dimensions were associated with post-stroke depression, whereas stroke-related factors (e.g. stroke severity) did not. More specifically, in 344 stroke patients, by applying a multivariate hierarchical logistic regression model, the authors showed that passive coping, more helplessness, less acceptance, and perceived benefits significantly predicted the occurrence of post-stroke depression (van Mierlo et al. 2015). This is one of the few studies investigating above relationship and findings need to be replicated in other stroke populations. However, it underlines the important issue of the influence on the adjustment after brain injury of premorbid cognitive–affective style of the subject and of the self-perception of the current situation.

Snell et al. (2013) directly investigated the relationship between illness beliefs and representations on functional outcome in 147 patients who suffered mild traumatic brain injury. Patients were assessed at three and at nine months after injury had occurred. Results showed a significant association between the expectations of relevant long-lasting difficulties and high damage identity belief with poorer outcome (Snell et al. 2013). In a further examination of their data, Snell et al. (2015) showed that patients could be early classified as low, medium, and high adapters according to their beliefs, expectations, and representation of injury, in particular, low adapters where those patients who structured beliefs and expectations about the consequences of the injury that were more negative in respect to the other two groups and also experienced meaninglessness of their condition. At the six-month follow-up, low adapters showed worse recovery for various cognitive, emotional, and somatic symptoms compared to both high and medium adapter individuals (Snell et al. 2015). Moreover, individual belonging to these latter two groups reported participating in the treatment at a greater extent. These findings are

very important wherein they suggest that the characteristics of self-elaboration processes and emotion regulation may significantly affect the trajectory of the recovery after brain injury.

15.3.1 Coping Strategies After Brain Injury

Emotion regulation and coping strategies are strongly related. Briefly, according to Lazarus and Folkman (1984), coping abilities are represented by non-routine capacities used to functionally respond to changed internal or external demands that are perceived as exceeding usual resources of an individual. Therefore, coping abilities are strongly applied in stressful conditions and require changing of usual functioning. Different coping styles such as problem- or emotion-focused were distinguished: the former referring to the aptitude to actively modifying the stressful condition, the latter referring to the tendency to modulate emotions by reappraising the situation, or by keeping far from awareness the stressful conditions. The usefulness of adopting one or the other coping style may depend on various factors such as, for instance, the time since from the injury (Hepp et al. 2005).

Wolters Gregório et al. (2015) assessed individuals with acquired brain injury in the post-acute phase and three months after the injury had occurred. They found that passive coping style was associated both with perceived reduced executive efficiency and with lower quality of life rates (HRQoL). Moreover, Visser et al. (2015) investigated the relationship between coping style, depression, and health-related quality of life in 166 stroke individuals receiving outpatient rehabilitation. Results documented that the adoption of an emotion-oriented and avoidance style was associated with high depression that, in turn, was associated with poorer HRQoL (Visser et al. 2015). Very interestingly, Wood and Doughty (2013) documented a significant association between alexithymia and avoidance coping style in individuals who suffered from traumatic brain injury. In particular, the authors found that patients with alexithymia had higher avoidance and psychological distress rates than individuals without alexithymia. As mentioned above, alexithymia refers to a condition mainly characterized by a difficulty to identify, describe, and by a general difficulty to deal with emotions. Therefore, results from this study evidence that difficulty in emotion elaboration may be associated with coping strategies that are less problem-oriented. As a matter of fact, impaired ability to regulate emotion was also reported to significantly predict functional outcomes in 75 stroke patients such as social participation and quality of life (Cooper et al. 2015).

The adoption of problem-focused coping style, thus, seems to enhance the adaptation process to the consequences of illness in the chronic post-injury phase, whereas using emotion-focused or avoidant strategies is associated with poorer outcome (Hepp et al. 2005; Ponsford 2013). However, patients with brain disease frequently tend to use maladaptive coping style. Wolters et al. (2010) clarified this point in a longitudinal research focused on the effect of neurorehabilitation in a

group of 110 brain-injured individuals. They showed that coping style changes over time, passing from an active problem-oriented to a passive emotion-focused style, and confirmed the relationship between the use of active strategies and better perception of quality of life (Wolters et al. 2010).

Coping strategies may be affected by several factors (e.g. severity of brain damage and psychosocial supports) among which the premorbid personality and preinjury coping style are reported to play a significant role. In this regard, Sela-Kaufman et al. (2013) recently demonstrated that personality traits of neuroticism and extraversion moderated the impact of brain injury on some outcomes such as occupational and social functioning of 61 patients sustaining moderate to severe traumatic brain injury. Moreover, Gregório et al. (2014) studied a group of 147 individuals with traumatic brain injury with the aim to investigate the relationship between premorbid and post-injury psychological functioning. Their results document (i) that coping style used by the patient before the brain insult did not significantly change thereafter and (ii) that adoption of non-productive strategies devoted to regulated emotional response to the stressful condition (e.g. self-blame and avoidance) predicted poorer outcome at 1 year after brain damage.

To synthesize above discussion, available data document that psychological and psychodynamic mechanisms involved in the reaction to the stressful consequences of brain injury significantly affect rehabilitation outcomes. Premorbid functioning of the individual is also an important factor accounting for psychological reactions and for functional adjustment, improving or interfering with his/her recovery. In this perspective, particularly important appears to be the ability to regulate emotional components of the complex condition the individual experiences. This ability strictly depends from the cognitive/affective aptitude of the individual in dealing with negative emotions.

15.3.2 Self-awareness and Psychological Defensive Mechanisms After Brain Injury

We above discussed that repression-related coping strategies, such as avoidance and denial, represent maladaptive reactions to the illness. The activity of repression and denial mechanisms could also affect patient's ability to be fully aware of the disease and of its consequences on cognitive, motor, and behavioural functioning. Self-awareness decrease is frequently observed after traumatic brain injury, stroke, and in neurodegenerative diseases. As discussed by Prigatano and Schacter (1991, p. 13), self-awareness may be defined as the "ability to perceive the self in relatively object ways while maintaining a sense of subjectivity". It involves the objective knowledge of the existence of deficits, as well as the understanding of the subjective significance of those deficits. From a clinical perspective, the issue of self-awareness after brain injury is quite relevant. Reduced self-awareness significantly interferes with the recovery process and hampers the possibility for the

patient to accede to the rehabilitative programmes itself. Indeed, self-awareness is often impaired after brain damage at different levels. Crosson et al. (1989) proposed a hierarchic model of awareness named the pyramidal model of awareness in which he distinguished three levels of awareness: cognitive–intellectual levels that represent the fundaments for the developing of the levels of emergent and anticipatory awareness. Accordingly, patients may present with difficulty to perceive changes in their functioning after the insult and may fully ignore and disclaim the illness. In other words, they may show *anosognosia*. For instance, in these cases, patients with hemiplegia may state that their arms and legs are normally functioning, as well as patients with memory deficits may state that their mind does work as usual. Otherwise, patients may also exhibit *anosodiaphoria*, that is reduced emotional reactivity (blunted affect) to the consequences of the disease that, in this case, are cognitively acknowledged by the individual. In other cases, the disorder of awareness may by more nuances. In these cases, the individual can acknowledge the illness, but he/she undervalues the related consequences, in so way forming the idea that he may early achieve preinjury level of functioning (Prigatano 2014, for a discussion of a clinical model of self-awareness disorders).

Since the initial description of anosognosic patients by Babinski (1914) and subsequent observation by Gerstmann (1942), several clinical data have been reported that, however, do not fully clarify its nature. As discussed by Vuilleumier (2004) in a review published about 10 years ago, anosognosia remains a complex phenomenon that could be understood solely by adopting a multifactorial approach. In this vein, the current view sees anosognosia or unawareness for the brain damage and its consequences as due to neurological, cognitive, and emotional/motivation mechanisms that can both be involved by the brain lesion and pre-exist to the lesion itself (Prigatano 2014; Turnbull et al. 2014; Vuilleumier 2004).

Indeed, it is consistently reported that self-awareness is more frequently impaired after damage involving frontal lobes and the right hemisphere (Marcel et al. 2004; Prigatano 2014; Vallar and Ronchi 2006), and in patients with more severe cognitive impairment (Levine 1990; Levine et al. 1991). Nevertheless, these factors cannot account for all features associated with reduced awareness. In this regard, Marcel et al. (2004) reported various observations sustaining the possible involvement of a motivated defence reaction, aimed at keeping out of consciousness the effects of damage that would dramatically hurt self-esteem and identity. Recently, Turnbull et al. (2014) suggested arguments that support the idea that anosognosia could involve a process of psychological defence. In particular, the authors suggested that defensive denial could shed light on some emotional reactions shown by patients during the awareness process of their deficits.

From a psychodynamic point of view, the defensive mechanisms of denial are a process that protects individual against anxiety. In others words, it is an unconscious reaction that represses, unpleasant stimuli despite individual being somehow aware of them (McGlynn and Schacter 1989). It may represent a stable mode of functioning that characterizes the way a person usually reacts to conditions that exceed routine resources constituting a kind of coping style applied to manage life

events. Denial and repression are often used as synonyms even if they refer two different objects, external stimuli the former and internal drives the latter.

Moreover, although denial and repression were the most commonly recognized defence mechanisms in patients with brain injury or stroke, others defensive behaviours have been observed after injury. For example, it was noted (Rosenthal 1983) that patients rarely deny the injury itself or the physical defects resulting from the injury. Rather, they tend to use *minimization* as prominent way to cope with cognitive deficits. Alternatively, a patient may be engaging in *rationalization* by attributing a deficit to some unrelated but reasonably plausible cause (e.g. "I have always had a bad memory"). Similarly, in *projection,* the deficit is attributed to others attenuating in this mode anxiety (e.g. a patient may thought that everybody would be slow at doing a particular task if they had never done it before). Other possible forms of defence include *displacement*, *disavowal,* and *avoidance*.

Summarizing, the terms prevalently reported in the literature as "denial" and "repression" collect a broad spectrum of defensive mechanisms that can be clustered into two levels (DSM-IV, American Psychiatric Association 1994): *disavowal* defences characterized by keeping unpleasant or unacceptable external or internal stressors or responsibility out of awareness with or without a misattribution of these to external causes, and *inhibitions* defences that keeps potentially threatening ideas, feelings, memories, wishes, or fears out of awareness.

15.3.2.1 Specific Characteristics of Defensive Denial and Clinical Implications

As it was extensively reported in the literature, unawareness of deficits in head-injured patients for rehabilitation can cause various clinical consequences. Reduced self-awareness significantly interferes with the recovery process and hampers the possibility for the patient to accede to the rehabilitative programmes itself. Unaware patients may lack motivation for treatment, fail to implement compensating strategies, show uncooperative attitude in therapy, set unrealistic goals for rehabilitation, and fail to benefit from therapy. In these cases, rehabilitation can be a frustrating exercise for both the patient and rehabilitation team as a result. Vice versa, individuals with higher levels of self-awareness are more likely to actively participate in rehabilitation, experience stronger therapeutic alliances, and achieve better rehabilitation outcomes in terms of level of community integration.

In this regard, it is necessary to investigate the degree to which patients with awareness deficits related to neuropsychological factors are responsive to rehabilitation compared to patients with awareness deficits related to psychological factors. Preliminary results (Ownsworth 2005) showed different efficacy of interventions for clients with defensive and non-defensive coping styles. According to Prigatano (1999), it seems that individuals who adopt non-defensive coping strategies respond better to neuropsychological rehabilitation programmes, while those with defensive coping benefit from psychotherapy approaches at a greater extent.

The influence of psychological defensive mechanisms on rehabilitation outcome has not been exhaustively studied yet. Interestingly, it has been observed that defensive denial may have opposite effect on rehabilitation. Evidence shows that patients frequently cooperate with rehabilitation efforts to remediate mental deficits even though they persistently deny the problems. Vice versa, several authors report that the use of defensive denial make patients to refuse rehabilitation programme or to react with hostility. These patients can also actively undermine rehabilitation programme, for example, by avoiding task that challenges their skill. In this regard, Katz et al. (2002) reported clinical vignettes in which patients avoided the occupational therapy tasks by cancelling scheduled appointments, or by recalibrating his home computer before therapist arrived at his home for the computer-drawing activity.

Marcel et al. (2004) described patients that showed an overestimation of their functioning more frequently when the question was presented in 1st compared to 3rd person, suggesting that, although showing anosognosia, these patients may exhibit implicit knowledge about the impairment. This observation is in line with other reports published by Bisiach and Geminiani (1991) and by Bisiach and Berti (1995), who outlined that anosognosic patients, although exhibiting, for instance, severe unawareness for functional impairments, seem to acknowledge the impairments themselves wherein they accept to "stay in a bed of an hospital". Indeed, various findings show the existence of a kind of implicit awareness of the deficit in patients with anosognosia (Turnbull et al. 2014).

In this regard, very interesting are findings reported by Ramachandran (1994) and discussed by Kaplan-Solms and Solms (2000, pp. 157–160) within the framework of neuropsychoanalysis. This author examined a patient who suffered from a brain lesion involving perisylvian region of the right hemisphere. At the clinical examination, the patient showed neglect and anosognosia for hemiplegia of the left arm. Neglect is a condition in which the patient mainly shows impaired ability to orient their attention to stimuli belonging to the contralesional side of space that includes parts of their own body, although presenting with spared sensory and motor functions. Neglect may occur with different levels of severity, and it is particularly apparent in the acute and immediate post-acute phase. Following previous results by Bisiach and Geminiani (1991), Ramachandran (1994), after clinical examination was performed, administered 10 ml of ice-cold water to the left ear of the patient. As shown by Bisiach and Geminiani (1991), this operation may reduce neglect manifestations. Thereafter, Ramachandran (1994) re-examined the patient's anosognosia for hemiplegia. In fact, the reduction of the neglect signs was associated with a different level of elaboration of own deficits. In this case, patient exhibited a good level of awareness for them. More interesting for the present discussion, patient also acknowledged that their deficit was present since several days, thus including the moment in which he/she had denied it (Ramachandran 1994). In other words, he/she showed implicit/unconscious perceptual information about the impairments. In a subsequent phase of the experiment, when the effect of the caloric stimulation finished, anosognosia was assessed again. The author found that unawareness for physical impairment re-emerged, although the patient

remembered to have acknowledged the deficit itself during the previous phase of the experiment (Ramachandran 1994). Kaplan-Solms and Solms (2000) interpreted these findings as a possible evidence of the fact that the individuals actively avoid their unconscious knowledge about a condition that, by reaching the consciousness, could cause mental sufferance to the individual himself.

To summarize, we can conclude that when patients do not progress unexpectedly, are uncooperative, and/or have strange or inconsistent emotional reactions, it could be the case a psychological defensive component is in place. When defence mechanism "actively works", the individual does not let any emotional tension to come out. However, individuals frequently experience uncertainty, feeling that something is "wrong", although they are not able to state "what is actually wrong". With such, individuals attempt to cope with their situation as best they can, and thus, they can actively use premorbid defensive style (or coping strategies). In this regard, denial after brain injury has been considered as "positive" symptom. From a psychological perspective, it is very important to outline that denial is not merely an obstacle to be overcome. Rather, it could be an adaptive strategy aimed at protecting the individual from the overwhelming reality. In this vein, denial could be considered as the attempt to cope and make "sense" of the world according to past experiences (Prigatano and Klonoff 1998), a strategy to integrate impairment in the individual's social setting avoiding catastrophic feelings, in order to spare their self-image and manage one's emotional reactions (Gainotti 1993). Therefore, a better comprehension of these qualities of defensive reactions could help to develop ad hoc interventions to improve both efficacy and effectiveness of treatments.

However, although the tendency to underestimate or deny post-injury deficits may initially protect individuals from emotional distress, persisting denial may also cause negative emotions or aversive reactions. Indeed, when patients acknowledge that previous methods are ineffective, they can become angry or resistant towards rehabilitative programmes. Clinical observations show that patients with defensive coping styles may show resistance to therapy and accuse therapists of obstructing them from achieving their goals (Fleming and Ownsworth 2006). It is important to notice that this could have implications on the quality of the relationship between patient and clinician, potentially producing, in the latter, negative reactions (countertransference). Useful indications involve understanding and mastering the distinction between feelings and actions, and sparing patients from two actions: assault or abandonment. Suggestions for management include better knowledge of basic psychodynamics; working towards continuous self-awareness; special group meetings; and selective use of educationally oriented psychiatric consultations.

The approach to the patient suffering from brain injury should adequately recognize psychological and psychodynamic processes potentially implied in the adjustment response. Understanding the clinical relevance of above dimensions is a challenging task. Nevertheless, this could improve therapeutic approach in the context of a trusting and safe interpersonal relationship. According to Katz et al. (2002, p. 289), the degree of challenge and confrontation used by the clinician must be carefully calibrated "on the extent to which factors of unawareness and denial are interacting in any one individual. The danger is that attempting to break

down protective mechanisms of denial may expose the client to undue emotional distress, possibly resulting in a catastrophic reaction. For clients who present with high levels of denial, mainly of psychological aetiology, ongoing support and monitoring may be a preferred strategy".

In brief, improving self-awareness and self-insight is prerequisites for a patient's active personal investment, progress, and recovery after brain injury. Absence of introspection, disturbances in self-continuity, self-monitoring, and self-regulation are crucial psychological aspects of the patient's current degree of awareness. Through the evaluation of the degree of this deficit, clinicians can better predict the patient's predisposition for awareness training (Kneebone and Lincoln 2012). The patient's defensive strategy should also be assessed via structured interviews, questionnaires, and/or clinical observations. The degree of adjustment of awareness training interventions to patients' level of defensive functioning is a key point in the establishment of a good alliance and patient adherence to treatment (Klonoff 2010).

In this regard, the individuation of defensive denial or other defence mechanisms, such as minimization or rationalization, that patient uses can help clinicians to adopt adequate therapeutic approaches. For instance, therapist can gently present data on the expected and the current performance of tasks. This helps educating the patient about his/her strengths and difficulties and, in turn, allows the prevention of negative reactions that have considerable impact on the quality of the doctor–patient relationship. In these cases, psychotherapeutic interventions are recommended as they may enhance intrapsychic competence by rendering the individual less anxious and more confident about the therapeutic processes.

15.3.2.2 Assessing Deficit of Awareness: Neurological and Psychological Factors

Various terms are used to describe disorders of self-awareness including lack of insight, unawareness, denial, neglect, anosognosia, anosodiaphoria, indifference, or unconcern. However, these different terms have been used in unclear ways, producing confusion (Nurmi Laihosalo and Jehkonen 2014). Indeed, from a clinical point of view, it is important to be able to make appropriate inferences regarding the nature of unawareness following brain damage. It is crucial, for instance, to disentangle the contribution of the defensive denial from the neurogenic component to anosognosia and, accordingly, to identify tools and procedures clinicians can use to determine the nature of awareness impairments. Current methods to diagnose these problems are heterogeneous (Fleming et al. 1998). In fact, no reliable and shared criteria to differentiate neurogenic and psychodynamic components have been developed yet. One difficulty in finding reliable tools is likely due to the fact that psychological and neurological mechanisms present some degree of phenomenological overlapping (Prigatano 2014). In this regard, Prigatano and Klonoff (1998) reported that individuals with primary impaired self-awareness and with primary denial of disability show common behaviours. In their perspective, defensive denial of disability and impaired self-awareness could be considered as continuous

phenomena which may interact in an individual, with the degree of interaction changing over time. For instance, an individual with brain damage may initially show a significant lack of awareness of his/her deficits because of brain dysfunction (i.e. a direct symptom). As he/she begins to recover and attain partial knowledge of his/her deficits, he/she may be prone to use the mechanism of denial to support him/her in sustaining the adjustment process (an indirect symptom).

Although the presence of a partial phenomenological overlapping between psychodynamic defensive mechanisms and neurogenic processes, some researchers acknowledged that, compared to patients with impaired self-awareness with a prominent neuroanatomic components, patients with denial of disability show a set of quite different characteristics. Indeed, the latter group seems to show different emotional reactions regarding feedback concerning their functional states and aversive attitude towards rehabilitation (2005). Some findings suggest that patients presenting with impaired self-awareness with specific neurologic aetiopathogenesis show blunted emotional reactions in response to feedback about deficits and may be surprised or even perplexed in response to failure experiences (Giacino and Cicerone 1998). Vice versa, when patients with predominantly psychologically based denial are confronted with their difficulties, they exhibit more frequently resistance or angry response or try to rationalize their behaviour. In particular, they may show active struggle to accept and use new information about themselves and aversive reactions (such as resistance or angry) regarding functional limitations and/or rehabilitative activities. Clinical observations report denial essence in these terms: "… there is a real obstinacy to not admit it, a resistance to the recognition that is truly striking and a little disconcerting when it is found in a subject whose intellectual faculties are otherwise well preserved" (McGlynn and Schacter 1989, p. 147, line 11).

However, at the best of our knowledge, few empirical measures are currently available to assess impaired self-awareness and denial of disability. In particular, Prigatano and Klonoff (1998) developed the *Impaired Self-Awareness and Denial of Disability Scale*, a measure that consists of two 10-item subscales "Impaired Self-Awareness" and "Denial of Disability" and is rated by a clinician who is familiar with the client's behaviour. Initial validation of the measure showed good inter-rater reliability($r = 0.77$) and provided a starting point to understand behavioural indices therapists can use to determine whether lack of awareness is directly related to neuroanatomic or psychological dysfunctions (Prigatano 2014). Defence mechanisms of brain-injured patients were also assessed by specific standardized interview (Ghika-Schmid et al. 1999) and by unspecific measures, such as the *Marlowe-Crowne Social Desirability Scale* (M-CSDS; Crowne and Marlowe 1960). The latter scale specifically measures tendency of the individuals to deny problems due to their desire to present themselves in a favourable light (Ownsworth et al. 2002).

Since no further specific measures have been developed to assess lack of awareness or defence mechanisms in patients with brain injury, some tools currently used in counselling research could be suggested. The Toronto Alexithymia Scale (TAS; Bagby et al. 1994) that assesses alexithymia, a difficulty identifying and describing emotions associated with a minimization of emotional experience, or

the Defence Mechanism Inventory (DMI; Gleser and Ihilevich 1969), a paper-and-pencil forced-choice test that assesses the relative strength of five defensive clusters, is an interesting example. In particular, the latter test consists of 10 brief stories designed to reproduce conflicts in several areas. Each vignette is followed by four questions concerning the respondent's overt behavioural reaction, fantasy or impulsive response, thoughts, and feelings (e.g. "How would you feel and why?"). The DMI assesses defence included in "principalization" cluster, which deals with conflicts through the split of thought content from affect which is repressed, and the "reversal" cluster, which includes defences that aim at minimizing the severity of perceived threats by responding neutrally or positively towards a frustrating object. Another interesting scale is represented by the Defence Mechanism Rating Scale (DMRS, Perry 1990), a quantitative, observer-rated method that is similar to the qualitative Provisional Defence Axis in Appendix B of the DSM-IV (American Psychiatric Association 1994). Recently, a Q-sort system (Di Giuseppe et al. 2014) based on the DMRS was construed to quicker assess mental states, relational dynamics, verbal and non-verbal expressions, behaviours and coping skills, and distorted perceptions that arise when subject experiences internal or external distress.

Based on the above discussion, it is apparent that in order to achieve valid and reliable assessment tools to be used in the evaluation of psychodynamic defence mechanisms involved in brain injury adjustment, further investigation is needed. Since above-mentioned tools have been extensively used to assess the change of patient's defensive style in psychotherapy, their validity and reliability could be worth of investigation in individuals with brain damage.

15.4 Conclusions

This chapter proposes a brief discussion on the psychological and psychodynamic aspects potentially involved in the recovery after brain injury, with the aim to give some clues for better taking them into consideration for the purpose of the clinical management.

Brain injury may cause serious motor, cognitive, and affective *sequelae* that significantly affect individual's professional and social functioning, interfering with his/her autonomous management of daily living. Changes may occur suddenly, such as after stroke or traumatic brain injury, representing a highly stressful condition for the affected individuals and their family. Indeed, brain trauma may provoke a kind of discontinuity in the feeling of self and requires cognitive reintegration to regain a unitary image of body and of the self.

The first months after injury appear to be crucial for the recovery processes that can be maximized through the adoption of functional strategies by the individual. However, maladaptive coping styles are frequently observed in these patients in both post-acute and chronic phases. The adoption of these cognitive/behavioural styles is consistently reported to be associated with poorer physical, occupational,

and social outcomes. It is also recognized that neurological, cognitive, and emotional factors modulate the patient's ability to cope with the trauma. Size of brain lesions and severity of subsequent deficits are main factors. However, a growing body of evidence suggests that psychological reactive mechanisms and premorbid cognitive–affective coping style may also play a significant role. Among these, the ability that individual usually adopts to elaborate and deal with negative emotions that are associated with life events appears to be particularly important. Mechanisms of psychological defence such as repression/denial may be active in patients that, after brain injury, show emotion/affective dysregulation and tend to use less efficient coping strategies. Moreover, repression could also influence the patient's ability to correctly acknowledge the illness and its consequences, in so way hampering his/her productive participation to the rehabilitative programme and social reintegration.

We conclude that, as also suggested by Turnbull et al. (2014), in order to improve the clinical approach to the patient suffering from brain injury, psychological and psychodynamic processes potentially implied in the adjustment response should be correctly recognized and adequately treated. In this regard, an important issue is represented by the paucity of valid and reliable tools to assess above mechanisms in individuals suffering from brain injury. Further research is apparently needed.

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