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Prefrontal Cortex

Edited by Ana Starcevic and Branislav Filipovic

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and **Branislav Filipovic**

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Meet the editors

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Contents

Preface

The prefrontal cortex reaches its greatest development in the human brain, making up nearly one third of the neocortex. Due to its remarkable evolution, the prefrontal cortex plays an important role in higher integrative functions such as information processing, thinking, understanding, attention, behavior, motivation, emotions, working memory, and analysis. This book brings together theoretical and technical research advances on the prefrontal cortex, from the basic explanations of the neuronal architecture of the prefrontal cortex and its anatomy, presenting it as a morphological substrate for many psychological conditions, through normal and altered connectivity and its manifestation in different behavior and identification of organizational levels inside the prefrontal cortex through different neuroimaging methods. This book also provides an interdisciplinary view of the prefrontal cortex and its issues and discovers the main role of this part of brain in psychosocial, economic, and cultural adaptation.

In the first section of the book, *Neuroanatomical and Developmental Features of Prefrontal Cortex*, an overview of the developmental period of brain structure is presented with the most important moments that can contribute to possible clinical issues if damaged. Childhood presents the most vulnerable part of life and the developmental part of the brain structures that appear to be of major importance. Neuroanatomical and neurophysiological overview explains the connection and specific relationship between different brain structures, which are morphological substrates for integrated psychological function and consciousness.

In the *Clinical Presentation of Prefrontal Cortex*, an overview of hemoglobin-oxyhemoglobin variation in rehabilitation and consciousness and its issues in cerebro rehabilitation model is presented. The role of the prefrontal cortex in social interaction through language communication explains the importance of neurocognitive components and neuropragmatics. A new approach to understanding normal and abnormal relations between metacognition and mindreading discovers the main role of this part of the brain in psychosocial, economic, and cultural adaptation.

The prefrontal cortex is involved in managing complex processes like logic, problem solving, planning and memory, decision making, planning complex cognitive behavior, personality expression, and moderating social behavior. The higher cognitive *functions*, such as working memory, mental imagery, and willed action, are all intimately associated with consciousness. It is basic anatomical substrate or an integral link between individual life, its will to work and live, and healthy personality. This brain region has been implicated in many more undefined dynamic actions within the highest brain functions, and this area needs more investigation. Future perspectives include many interdisciplinary approaches and different methods as well as many organized research paradigms for the investigation of one of the most complex parts of the brain, the prefrontal cortex.

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Section 1

Neuroanatomical and Developmental Features of Prefrontal Cortex

Chapter 1

Development Period of Prefrontal Cortex

Merve Cikili Uytun

Additional information is available at the end of the chapter

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Abstract

This chapter outlines the issues associated with the development of prefrontal cortex in children and adolescents, and describes the developmental profile of executive processes across childhood. The prefrontal cortex plays an essential role in various cognitive functions and little is known about how such neural mechanisms develop during childhood yet. To better understand this issue, we focus the literature on the development of the prefrontal cortex during early childhood, the changes in structural architecture, neural activity, and cognitive abilities. The prefrontal cortex undergoes maturation during childhood with a reduction of synaptic and neuronal density, a growth of dendrites, and an increase in white matter volume. With these neuroanatomical changes, neural networks construct appropriate for complex cognitive processing. The organization of prefrontal cortical circuitry may have been critical to the occurrence of human-specific executive and social-emotional functions, and developmental pathology in these same systems underlies many psychiatric disorders; therefore, if we understand these developmental process well, we could better analyze the development of psychiatric disorders.

Keywords: development, prefrontal cortex, infancy, childhood

1. Introduction

In the past two decades, an increasing number of studies have examined the human frontal lobe and PFC utilizing a wide variety of methodologies including stereology, MRI, minicolumn analysis, and DTI [1]. A number of recent studies have examined the relative size of gray and white matter in the frontal lobe or PFC, while others have examined the volume, neuron density, and columnar organization of functional subregions within the PFC. The frontal lobe includes several anatomical components and different functional areas, and, so it is thought that as a discrete unit can only tell us so much [2].

PFC plays most important roles in executive functions, which includes the organization of several sensory inputs, the maintenance of attention, planning, reasoning, language comprehension, the working memory, and the coordination of goal-directed behaviors [3–6]. Therefore, the functions of PFC are certainly a crucial aspect of what we think of as "human" in cognition [7].

The development of the brain occurs through the interaction of several processes, some of these stages are completed before birth such as neurulation, cell proliferation, and migration, although others continue into adulthood [8]. It is showed that the PFC is one of the last regions of the brain to mature, based on most indicators of development [9], and that the neurons in these areas have more complex dendritic trees than primary somatosensory and primary motor cortex those that mature earlier [10, 11]. Brain development begins in utero in the third gestational week and continues into adolescence [12]. However, lateral regions of the PFC are the latest developing areas that involved in executive functions [9].

When discussing the role of the PFC, other brain regions with which it shares intensive interconnections, including the basal ganglia, thalamus, brainstem, hippocampus, amygdala, and other neocortical regions also play important role [13, 14]. Thus, its intrinsic connections with other areas provide access to emotional responses and other information [5]. The lateral PFC is implicated in language and executive functions, while the orbital and medial regions of the PFC are thought to be involved in the processing and in the regulation of emotional behavior [15]. The lateral orbital PFC, interconnected regions of the basal ganglia, and the supplementary motor area, these regions are called the frontostriatal system, and they work together with many of the cognitive capacities [16].

PFC includes the following Broadman Areas (BA): 8, 9, 10, 11, 12, 44, 45, 46, 47. "The dorsolateral frontal cortex (BA) 9/46 has been functioned in many cognitive process, including processing spatial information [17–19], monitoring and manipulation of working memory [20, 21], the implementation of strategies to facilitate memory [22], response selection [23], the organization of material before encoding [24], and the verification and evaluation of representations that have been retrieved from long-term memory [25, 26]. The mid-ventrolateral frontal cortex (BA 47) has implicated cognitive functions, including the selection, comparison, and judgment of stimuli held in short-term and long-term memory [21], processing nonspatial information [27], task switching [28], reversal learning [29], stimulus selection [30], the specification of retrieval cues [25], and the 'elaboration encoding' of information into episodic memory [31, 32]. BA 10, the most anterior aspect of the PFC, is a region of association cortex known to be involved in higher cognitive functions, such as planning future actions and decision-making [33]. BAs 44 and 45, include part of the inferior frontal and these regions' functions are language production, linguistic motor control, sequencing, planning, syntax, and phonological processing [34, 35].

Finally, the orbitofrontal cortex mostly (BA 47, 10, 11, 13) in the orbitofrontal cortex has been implicated in processes that involve the motivational or emotional value of incoming information, including the representation of primary (unlearned) reinforcers such as taste, smell, and touch [36, 37], the representation of learnt relationships between arbitrary neutral stimuli and rewards or punishments [38, 39], and the integration of this information to guide response selection, suppression, and decision making" [40, 41].

2. Structural development of the PFC

2.1. Development in gestational period

In the third week of gestation, the first brain structure to arise is the neural tube, which is formed from progenitor cells in the neural plate [42]. In the sixth week, neuron production begins. Between gestational weeks 13 and 20, neuronal count increases rapidly in the telencephalon [43], with $5.87 \cdot 10^9$ neurons at 20 weeks in the cortical plate and marginal zone [44]. Through some receptors and ligands, the nerve cells move from the source sites in the ventricular and subventricular regions to the main sites in the brain. Two basic types of cell migration, radial and tangential, have been described, and the most characteristic pattern is radial migration. The peak time period with these events is between 12 and 16 weeks of pregnancy [45, 46].

Cortical organizational events begin in 20 weeks of pregnancy and continues. The basic developmental pattern in the cortical organization includes: (1) neurogenesis and differentiation of neurons, (2) formation and organization of cortical neuron layers, (3) dendritic and axonal branching, (4) formation of synapses, (5) cell death and pruning of synapses, and (6) glial proliferation and differentiation [45].

Primary sulci (superior frontal, inferior frontal, and precentral) are the main regions of the PFC, and develop during gestational weeks 25–26 [42]. The dorsolateral and lateral PFC arise during gestational weeks 17–25 [47]. The dendrites in Layer III and V continue to mature, as spines develop, basal dendritic length increases, and interneurons differentiate in layer IV between 26 and 34 weeks [48].

Synaptogenesis begins around the 20th gestational week. The formation and organization of synapses in the PFC increases after birth, reaches a peak, and is followed by pruning and decline like other neurodevelopmental processes. Also, synaptogenesis occurs later in the PFC than it does in other areas.

After the other developmental stages, the latest developmental event is myelination [45]. Myelination begins in the 29th gestational week with the brain stem, and the development of white matter also follows a caudal to rostral progression like gray matter It continues until adulthood [49]. **Figure 1** shows the main developmental stages of brain intrauterine development.

2.2. Development in infancy

At birth, total brain weight is about 370 g [50]. In a meta-analysis, it is showed that in all PFC areas, neuronal number measurements increase at every age point postnatally (0–72 months). Assessing the cortex as a whole, neuronal number increases 60–70% between 24 and 72 months postnatally [51]. Neuron density is 55% higher in the frontal cortex of 2-year-olds than it is in adults [52].

Total gray matter volume is also greatest at the earlier stages of infancy. During infancy and childhood, gray matter volume in the frontal lobe is positively correlated with total brain

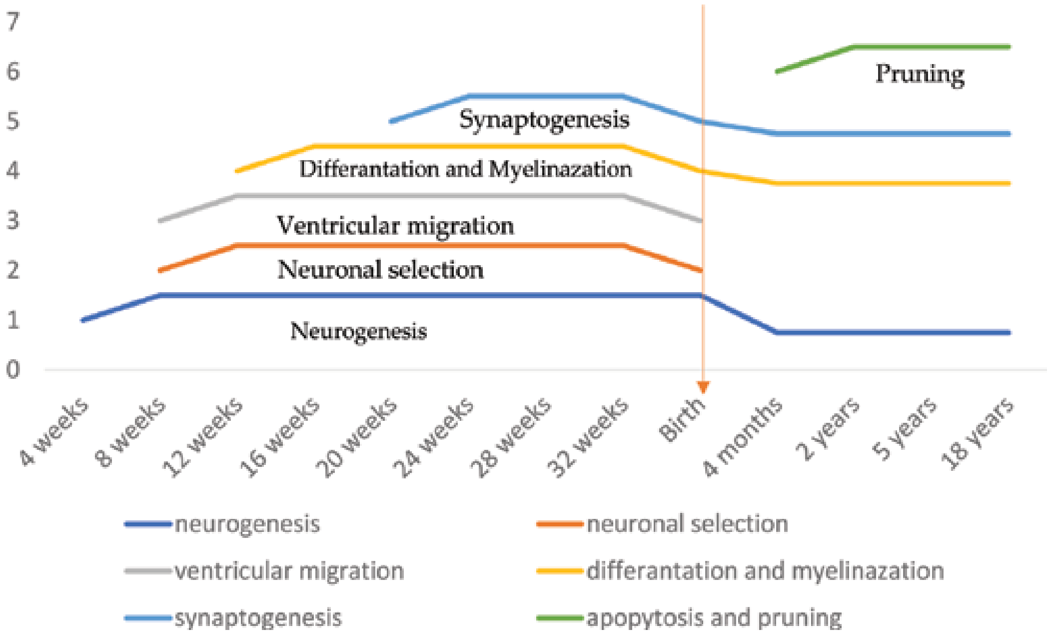

Figure 1. Timeline of brain development.

volume, and gray matter ratio with volume shows a decrease with age [53]. Around 6 months of age, dendritic length is 5–10 times greater than at birth and in the middle frontal gyrus, dendritic length is half of adult quantities at 2 years of age [54]. In infants, pyramidal neurons in frontal lobe that mature later, have less complex dendritic trees than regions that mature early, such as primary sensorimotor cortices [11].

At the age of 3 months, synaptic density in the PFC is less than half of what it will eventually reach, and synaptic density in the PFC reaches the net highest value at age 3.5 years, showing a level approximately 50% greater than that in adults [55]. White matter volume also increases from infancy and it is 74% higher in mid-adolescence than infancy [56].

2.3. Development in early childhood

The neuroanatomical structure of the PFC in humans undergoes maturation particularly during early childhood. During this period, the brain quadruples in size and grows to approximately 90% of the adult volume at age 6. The gray matter increases from early childhood until the age of 6–9 [56]. Neuronal density in layer III of the PFC decreases with age between 2 and 7 years, from 55% to about 10% higher in 7-year-olds than in adults [52].

Synaptic density in the PFC decreasing more and more through adolescence [55]. During early childhood, expansion of the dendritic trees of the pyramidal neurons has also been observed [57].

The results of fMRI studies in children suggested that the PFC of children aged 5 years, is also active during performance of the same task as that for the adults. The region and characteristics of the activity are similar in adults and children, but comprehensive comparison could not be done due to technical limitations [58].

2.4. Development in childhood and adolescence

During childhood and adolescence, both growth and then decline in gray matter volume, and increase in white matter volume are observed in brain development. In the longitudinal study of Giedd et al. across ages 4–22, showed that gray matter in the frontal lobe increases in volume during preadolescence including early childhood [59]. However, several studies have reported that during preadolescence, the increase in gray matter volume is observed especially in the PFC among other frontal lobe regions [60]. Inside of the frontal lobe, gray matter in the precentral gyrus develops the earliest, and the superior and inferior frontal gyri mature later. The ventromedial areas commonly reach maturity earlier than more lateral regions as well [9]. The rostral PFC develops more slowly than other regions, maturing into late adolescence and beyond [61]. Additionally, the development of the dendritic systems in rostral PFC matures later than in primary sensory and motor regions, and continue maturing until late adolescence [11]. Regions in the PFC that intercommunicate with Broca's area show an increase in gray matter thickness relative to other regions at between the ages of 5 and 11, it is thought to be associated with the maturation of linguistic capacity [62]. Gray matter volume reaches maximum volume in most of the frontal lobe between 11 and 12 ages [59]. The dorsolateral and medial PFC also expands nearly twice [63] and the dorsolateral PFC reaches adult grades of cortical thickness in early adolescence [8]. However, according to cerebral energy metabolism studies, lateral regions of the PFC and frontal pole mature earlier than the most anterior regions [64]. When the brain increases in size throughout childhood and adolescence, dendritic and axonal growth and synaptogenesis also occur such as many other microstructural changes [51]. Adult neuronal density in the frontal lobe is reached by 10 years of age [52]. Pyramidal neurons in frontal lobe that mature later and they have the most complex dendritic trees in adolescence and adulthood [10].

Moreover, reduction in gray matter volume and synapse elimination continues in the PFC until adolescence and early adulthood [65]. The gray matter density in rostral PFC observed a reduction in between adolescence (12–16 years) and adulthood (23–30 years) like as other prefrontal regions [65]. Although this decrease in gray matter volume in childhood is correlated with age, one study showed that gray matter decreasing in the frontal lobe is significantly and positively associated with verbal memory abilities, independent of the age of the child [53].

In addition, as gray matter volume declines during childhood and adolescence, cross-sectional and longitudinal studies have reported that white matter volume in the PFC increases significantly as fiber tracts grow and myelinate during childhood [49, 59]. From ages 7 to 16, the frontal lobe experiences an increase in white matter volume [53]. In the white matter, it was found that diffusion along fiber tracks was more and more anisotropic with age (range 6–19 years) in a number of prefrontal regions, including right lateral, and medial, rostral PFC [66]. White matter is primarily constituted of axons covered in myelin produced by oligodendrocytes, and myelination increases nerve transmission rapidity [67], thereby, reduces the effects of travel distance variability in networks and facilitating synchronous impulsion of neurons [68]. For this reason, increase in white matter volume in the PFC and distributed networks, may provide a structural basis for cognitive functions [69]. Additionally, macro and microstructural changes in gray and white matter both continue during developmental process, even after adolescence, and these structural changes are parallel to behavioral changes [70].

The myelination of the frontal lobe can continue into the 3rd decade of life [71]. The anteromedial aspect of the frontal lobe is one of the last regions, to myelinate postnatally [72].

When reviewed the fMRI studies, many of these studies have reported that the responsible regions in the PFC show age-related increases in activity through development in school-age children and adolescents [73–75]. In the Kwon et al. study, they observed an age-related linear increase in activity in the lateral PFC during the n-back working memory task from 7 to 22 years of age [73]. In contrast, in the brain regions less critical to the tasks tested has also been reported age-related decrease in neural activity [75]. These patterns of age-related activity changes are thought to indicate a developmental shift in functional neural organizations more focal, fine-tuned systems [76].

3. Cognitive development of PFC

PFC mediate several cognitive abilities and they develop fundamentally during early childhood in terms of age-related improvements, and functional neural systems for each function become more separable through development [58]. In this section, we reviewed cognitive abilities and their development which are mediated by the PFC.

3.1. Attentional development

The attention properties fall into five basic categories: alertness, set, spatial attention, sustained attention, and interference control [77].

Although by 3 years of age, children can make the occasional perseverative error; they inhibit instinctive behaviors well [78]. Improvements in speed and accuracy on impulse control tasks can be observed up to 6 years of age [78, 79]. However, an increase in impulsivity occurs for a short period around 11 years of age, children aged 9 years and older are able to monitor and regulate their actions well [80].

The components of attention seem to develop gradually toward full maturity at about 12 years, with maximum development between the ages of 6 and 9 [81, 82].

3.2. Memory

Neuropsychological and functional neuroimaging evidence implicated the importance of the PFC, supports particularly the development of episodic memory [83]. Functional neuroimaging studies consistently show increasing in PFC activation that supports the formation [84] and retrieval of episodic memories [85].

Although the frontal lobe damage usually does not cause loss of perceptual memory, it does in some cases especially if the lesion involves the left prefrontal cortex that causes the inability to encode and retrieve serial tasks [86], stories [87], and verbal material [88]. Particularly, if the lesion includes the orbitolimbic region, it can cause the presence of spontaneous confabulation and false recall or recognition [87].

In the recent study, the PFC contribution to subsequent memory (SM) in children, adolescents, and young adults was investigated. It is showed that regions in the lateral PFC showed positive SM effects, whereas regions in the superior and medial PFC showed negative SM effects. Both positive and negative SM effects increased with age. The magnitude of negative SM effects in the superior PFC partially mediated the age-related increase in memory. Functional connectivity between lateral PFC and regions in the medial temporal lobe (MTL) increased with age during successful memory formation [83]. In the study of Qin et al., they examined age-related changes in brain activity associated with memory-based arithmetic and found increased working of memory-based strategies for solving arithmetic problems across a period of 14 months in children ages 7–9. Paralleling these behavioral findings, increased functional connectivity between the lateral prefrontal cortex (IFG/MFG) and the hippocampus was observed [89].

3.3. Working memory

Working memory is the one of neural functions for temporary storage and manipulation of information [90]. It is necessary for other cognitive functions, such as language comprehension, reasoning, and learning [91]. Behavioral measures showed that working memory systems improve fundamentally during early childhood [92].

Kaldy and Sigala [93] observe that 9-month-old infants can integrate the visual features of an object with its location as part of the content of working memory. On the conclusion of findings, they speculate that the early development of the *what-where* integration in working memory [93].

Luciana and Nelson's study showed that in normal children, aged 4–8 years, the prefrontal working memory system emerges at around the age of 4 and improves between 5 and 7 years of age [94], and capacity of visual short-term memory increases also substantially between 5 and 11 years of age [95]. Additionally, age-related improvement of working memory for phonological information has also been observed during early childhood from 4 years of age [96]. Consistent with these findings, fMRI studies in children indicated that the lateral PFC functions in healthy children as young as 4 years, and the neural systems of this area responsible for working memory gradually mature at 4–7 years of age [97]. In conclusion all of them, the child reaches the mature level of performance by age 10–12 years [77].

In the development of working memory, not only PFC plays role, but also stronger fronto-parietal connectivity underlies the development of working memory. Edin et al. indicated that the weak connectivity among subregions of the PFC might also be important for the functional development of the PFC [98]. It can be summarized that functional maturation of the PFC is tightly linked to changes in several other brain regions [99].

3.4. Planning

The effective planning is crucial to self-organization and it involves setting a goal, formulating a checklist of tasks necessary to achieve it, and executing each one until the goal is achieved. Studies suggest that children and adolescents are identified as deficient in planning skills, which is not surprising given that executive functions improve especially through adolescence [100, 101]. The failure to formulate plans, especially new plans, is generally accepted as being a common feature of prefrontal syndromes. Especially, the symptom appears unique to dysfunction of the prefrontal cortex [77].

Simple planning skills are observed by 4-year-olds [102]. Similarly by 4 years of age children are skillful of create new concepts [103]. When the aims are made clear, at the age of 6 years children can make detailed plans [104]. Planning and organizational skills develop rapidly between 7 and 10 years of age [105] and gradually after into adolescence [102]. Young children use simple strategies, which are usually ineffective but between 7 and 11 years of age strategic behavior and reasoning abilities become more organized [106]. The planning seems to develop at about 12 years with the plateau and around 12–13 years of age, regression from conceptual strategies to piecemeal strategies may occur and it suggesting a developmental period in which cautious and conservative strategies are preferred. Improving of strategies and decision making continues during adolescence [107]. Studies have reported improved the planning skills into the 20s [108, 109]. In addition, the inter-correlations observed between planning skills and other neuropsychological tasks and IQ, during adolescent development of planning abilities [110].

3.5. Temporal integration

Temporal integration is the ability to organize temporally separate items of perception and action into goal-directed thinking, speech, or behavior. This ability derives from the joint and temporally extended operation of attention, memory and planning. In neural terms, it derives from the cooperation of the prefrontal cortex with other cortical and subcortical regions. In a study, age-dependent comparisons were made between 9–10- and 13–14-year-olds and these findings suggested that children used a similar strategy as adults and indicate a stabilizing and optimalizing process by the age of approximately 13–14 years with respect to subjective rhythmization [111].

In conclusion, the temporal integration seem to develop at about 12–13 years as same as development of working memory and planning [77].

3.6. Inhibitory control

Inhibitory controls the ability to suppress information and actions that are inappropriate situations and it is important for several cognitive abilities and adaptive behaviors [99]. The children aged 2.5 years were able to inhibit the prepotent tendency on the spatially incompatible trials and by 3 years, they were correct 90% of the time [112].

Several studies have demonstrated that performance on the cognitive tasks that requires inhibitory control, improves throughout childhood over the ages of 4 years [6, 99, 109].

The fMRI studies suggest a change in the recruitment of rostral PFC (BA10) in situations of response inhibition during late childhood and adolescence. An increase in BOLD signal in this region [113] initially and then a decrease in BOLD signal [114] seems consistent with the anatomical findings suggesting that gray matter volumes in the frontal cortex [59].

In summary, the ability inhibitory control develops both anatomically and functionally significantly during early childhood.

3.7. Language

The spoken language is based on the exercise of temporal integration and the cognitive functions. For this reason, language has been found to be adversely affected in a variety of ways by frontal damage [115].

In early childhood, increase in speed and verbal fluency of language is observed, particularly between 3 and 5 years of age [102, 116]. Processing speed and fluency continues to improve during middle childhood [80, 102] with significant gains in processing speed observed between 9–10 and 11–12 years [117]. Improvements in efficiency and fluency occur during adolescence [107, 117].

However, higher cognitive functions such as language and intelligence continue to develop into the 3rd decade of life, supported by the lateral prefrontal cortex, which does not seem to reach full maturity until that time [77].

3.8. Social behavior

Social cognition defines to identify and interpret social signals, and the use of those signals to guide the flexible performance of appropriate social behaviors given in changing situations [118]. The PFC is connected with several cortical and subcortical regions of the brain, including nucleus accumbens (NAc), amygdala, ventral tegmental area (VTA), hypothalamus, and regions of the cortex involved in processing sensory and motor inputs. PFC is also connected with which regions known as social brain, so PFC has been played rol in also social behavior [119, 120]. Many studies have demonstrated the importance of the vmPFC for social motivation and reward. The vmPFC is also engaged with social acceptance feelings and is activated learning with cues of related with social reward [121, 122]. The lateral PFC is also a part of a network that process in the social domain, such as imitation, abstract social reasoning, and resolving conflict in social cues [123].

The mPFC is responsive to social stimuli in developing infants [124]. In particular, the mPFC activates at the infant with viewing a mothers smile, or hearing infant directed speech [125]. Studies with children and adolescents focus on amygdala and findings of these studies showed an association between cerebral maturation and increased regulation of emotional behavior; the latter mediated by prefrontal systems [126, 127]. In another study, findings suggest that the adult brain better modulated OFC activity based on attention demands, while the adolescent brain better modulated activity based on the demands of emotion. So, if there were no attentional demands, emotional content of the stimuli-induced higher activity in ACC, OFC and amygdala in the adolescents compared with the adults [128]. These fMRI results show that both the brain's emotion processing systems develop during adolescence.

3.9. Theory of mind and mentalizing

Theory of mind (ToM) is the ability of an individual to mean the feelings, motives, opinions, and emotions of another on the basis of his or her expressions. It is a necessary ability for meaningful social interaction [77]. Some studies have investigated the development of mentalizing, which to have been associated with rostral PFC.

When investigating the development of ToM, children develop an understanding of desires, goals, and intentions at around 18 months firstly, and then the understanding of many mental states such as wanting, knowing, pretending, or believing is available in implicit form to 2-year-olds. Typical tests of mentalizing develop at about 4 years old in children [129]. At the age of 6 years, all typically developing children understand the tasks, involving more complex scenarios [130].

A functional MRI study investigated the development of mentalizing by the task and found that children (between 9 and 14 years old) engaged frontal regions includes medial PFC and left inferior frontal gyrus more than adults did in this task [131]. In another study, adolescent (12–18 years) and adults participants (22–37 years) were scanned with functional MRI and the results showed that adolescents activated part of the medial PFC more than adults did, and adults activated part of the right superior temporal sulcus more than adolescents did. These results suggest that the neural strategy for mentalizing changes between adolescence and adulthood. Although the same neural network is active, the relative roles of the different areas change, with activity moving from anterior (medial prefrontal) regions to posterior (temporal) regions with age [132].

4. Conclusion

In this chapter, we have attempted to link structural and functional findings of developmental studies to PFC. Our knowledge and understanding of the neural mechanisms, a growing body of evidence, point to the PFC as a central regulator. The review of the developmental literature indicates that, in the child, the cognitive and emotional functions of the prefrontal cortex develop in apparent synchrony with its structural maturation. The long-term development of executive functions is likely to be aligned with neurophysiological changes, particularly synaptogenesis and myelination in the prefrontal cortex.

All of cognitive functions seem to reach a relative plateau of maturity at about the age of 12 years. For example, development of attention reach maturity at about age 12, Working memory and planning seem to develop also at the same pace and toward the same plateau (about 12 years). Temporal integration development depends on both working memory and planning and it develops at the same time with the others. However, higher cognitive functions such as language and intelligence continue to develop into the third decade of life. In summary, these functions develop gradually, between 5 and 10 years of age, to reach completion at about age 12.

In the future, longitudinal studies will be required to verify our understanding of cognitive development. With the structural and functional neuroimaging studies, we are now in the position to concurrently track the development of neural systems and cognitive functioning, greatly enhancing our understanding of brain-behavior relationships.

It is known that abnormalities of PFC is associated with many of psychiatric disorders such as attention deficit and hyperactivity disorder, schizophrenia, obsessive compulsive disorder, depression, autism, etc. As we know more about the prefrontal cortex, we think that we could better understand these psychiatric disorders and could develop new treatment options.

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Chapter 2

The Dynamic Maturation Process of the Brain Structures, Visual System and Their Connections to the Structures of the Prefrontal Cortex during 4–6 Years of Age

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Additional information is available at the end of the chapter

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Abstract

The chapter summarizes an author's research in the field of child neuropsychology, devoted to the dynamics of non-verbal visual gnosis in 365 children aged 4–6 with typical development. Data from a study of perceptual operations in difficult conditions (a sample to identify incomplete images), the deficits in which they are considered as a predictor of dyslexia, are analyzed. Against the backdrop of a predominantly analytical (left brain) strategy in the processing of visual incentives, a progressive improvement in the holistic (right brain) strategy was also noted, especially in children aged 6. The positive dynamics of identifying visual stimuli in difficult conditions by integrating distinct signs in the 4–6-year period is explained both by the activation of the holistic processing strategy and by the increasing participation of the prefrontal cortex in the functioning of the complex forms of non-verbal visual gnosis.

Keywords: non-verbal visual gnosis, incomplete images, dorsal and ventral visual system, pre-school age, holistic visual information processing strategy, specific learning disability, prefrontal cortex

1. Introduction

In recent years, a new field of neuropsychology of individual differences has actively developed in child neuropsychology. Its aim is to record (register) the age norms of neuropsychic functioning, the sensational periods and the dynamics of the formation of the higher psychic functions within the broad framework of typical child development. The pre-school period is sensational to many of the higher psychic functions, which explains the author's interest in it. The rapid rates of genetically determined neurophysiological changes in children are the cause of the heterochronic nature of mental development and its individual variations. The main regularity of the period is the emergence of a wide range of new psychic qualities (intellectual, sensorimotor, linguistic and behavioral) resulting from the complex interaction of biological factors and the social requirements of the environment. Individual rates and partial deficits of neuropsychic development in childhood are one of the main goals of diagnostics as they form the group of children at academic risk.

Indications of delay in pre-literacy skills (both verbal and non-verbal) are predictors of the likely development of specific learning disabilities (specific dyslexia), one of the most prevalent school-age syndromes with increasing incidence rates. The question of his etiology and neuropsychological determinants is still open. The most common manifestations of dyslexia are associated with a disorder in phonological processes, as it is assumed that pre-school phonological skills predict future reading skills [1–3]. At the same time, a number of authors [4–11] maintain the thesis of the leading influence on the difficulties in reading the violations in visual processes (visual search and scanning tasks, selective visual attention, visuospatial attention and visual memory). There are also those who highlight the role of motor difficulties on the academic problems of children [12, 13]. Separate developments examine the symptoms of dyslexia as a result of complex sensorimotor disorders in combination with phonological deficits [14–16]. Data from longitudinal neurobiology studies of children with typical and atypical reading support the thesis of non-typical brain maturation, the features of which refer to the preliterate stage [17]. Some authors [18] pay special attention to persistent silent reading disabilities in primary school pupils, linking them to the complex influence of deficiencies in lexical-grammatical operations, difficulties in non-verbal visual perceptions and limited volume of iconic memory.

We maintain the view [19] that dyslexia is more accurately conceptualized as a complex interaction of different risk and protective factors, and each of these factors can vary across different individuals with dyslexia. It may be that inefficient auditory and phonological neural systems cause reading difficulties in one individual with dyslexia, but another individual may struggle as a result of predominant visual-orthographic integration problems. Literary analysis of the problem summarizes the following facts of the current research: the core neurobiological cause of dyslexia is still not fully understood; at-risk pre-readers display reliable left temporo-parietal and occipito-temporal differences and early connectivity problems fit with a multifactorial theory of dyslexia [20].

The prognostic value of neuropsychological diagnostics in childhood allows the early application of therapeutic strategies tailored to the nature and mechanisms of developmental deficits. Since non-verbal forms of visual gnosis have the earliest debut in childhood development, the dynamics of their formation can be seen as one of the neurophysiological prerequisites for school readiness. This is most relevant to the functioning of complex gnostic operations associated with the identification of visual stimuli in difficult conditions. Their ontogenetic aspects are poorly developed from a neuropsychological point of view, which explains the need for a careful analysis of their condition during the pre-school period.

2. Cortical organization of the processes of visual gnosis

Visual gnosis is a high mental function with very rapid development in early and pre-school age. It is one of the most sensitive indicators in the assessment of child development, and the deficits in its formation lead to specific problems in learning [21, 22]. The operation of visual gnosis has traditionally been associated with cortical associative posterior visual areas and in particular with the operation of both visual streams, vertical and dorsal. They start from the primary visual cortex (V1) and are a continuation of parvocellular (P-type cells) and magnocellular (M-type cells) pathways that bind ganglion cells of the retina with the striate cortex [23]. The ventral tract reaches the temporal-occipital zone, also called “What?” zone, and the dorsal is directed toward the parietal-temporal zone, labeled as “Where?” zone. The dorsal stream serves the analysis of visual motion and visual control of action. The ventral stream is involved in the perception of the visual world and the recognition of objects. In recent years, neuroimaging data identify the prefrontal cortex as a place to integrate visual information processed by the dorsal and ventral flow. This is supported by visual object recognition studies using degraded visual stimuli [24].

Neuropsychological studies traditionally suggest that visual object perception involves several processing stages. Most classical models distinguish between visual identification in the perception stage, which processes presented objects, and the memory stage, which verifies the resulting perceptual representations against representations stored in memory. The perception stage involves part-based analysis and analysis of global forms (feature extraction, segmentation and shape analysis). The memory stage perceptual information is matched to each form stored in memory, which includes memory about the form of an object, its semantic properties and its name [25]. The authors note that subtle perceptual deficits can produce naming problems, even when there is good access to associated semantic knowledge. Contemporary neuroimaging studies indicate that involvement of the right medial occipitotemporal region in the perceptual stage is consistent with the established role of this region in visual object recognition. On the other hand, the memory stage was characterized by the involvement of the posterior part of the rostral medial frontal cortex. It is assumed that this part of the frontal cortex is likely to be relevant in the monitoring process for the confirmation of recognition [24]. Depending on the nature of the stimuli and the cognitive tasks, visual recognition is performed with the participation of various types of memory related to the activity of various neural systems [26]. When recognizing known objects, the modality-specific cortex fields are mainly involved, whereas in difficult-to-recognize stimuli, processes rely on long-term memory information and are implemented with the participation of executive functions.

To explain deficiencies in dyslexia, Levashov [27] develops a model of visual perception. According to the model, with each eye fixation on a particular stimulus, the visual system decides three basic tasks sequentially: builds a map of areas of attention; analyzes familiar objects in them; visually decodes the visible scene; and makes spatial analysis of the objects. The right- and left-hemispheres process differently each input image by sharing results only when solving specific and complex tasks. Processes of attention during performance are related to the dorsal part of the parietal cortex, which suggests that it manages the parameter of so-called “caution.”

Visual analysis in difficult conditions (recognition of imposed shapes and incomplete images) is only possible in a time-shared hemisphere interaction from left to right, where the same object is analyzed first on the left and then on the right hemisphere. Levashov suggests the following possible scheme of this interaction in the resolution of visual tasks:

1. The visually received image is processed by the left-hemisphere mechanisms for schematic recognition (classification). In cases of insufficiently known objects, inter-hemispheric associative links and corresponding structures from the right hemisphere are activated. Engaging a certain area of memory naturally narrows the search area among the engrams in long-term viewing memory.
2. The view is moved so that the projection of the analyzed plot falls into the right hemisphere in which the visual working memory is concentrated and neural structures (engrams) of each object class are stored. The input image is matched with the activated animations and leads to the categorization of the object. In complex and weakly known objects, recognition is done by moving the view to other informative points from them.

Through studies with event-related potentials in identifying hierarchical visual stimuli [28], two types of recognition are distinguished—local and global. Local-level recognition is related to the activity of the inferior temporal and prefrontal cortex of the right hemisphere and leads to an assessment of the sensory qualities of the stimuli. At the global-level recognition, the activity of the parietal cortex of the right hemisphere is guided by the inclusion of mechanisms of early sensory selection. Global perception is supposed to be related to the operation of the dorsal visual system and the spatial analysis of the objects. In contrast, perception on a local level (ventral visual system) is directed to the analysis of the elements and properties of the objects. According to some authors [29] of the initial stages of visual perception, the processes are not sufficiently lateralized. They become such at the higher levels of visual analysis when stimulus processing acquires asymmetric organization.

In recent years, the role of feedback on the functioning of cognitive processes has been increasingly discussed. The data show feedback between secondary and primary vision fields and demonstrate the modulation action of the top-down mechanism [30, 31]. Reverse connections are assumed to stimulate the activity and spatio-temporal dynamics of large groups of neurons associated with the integration of visual information.

3. Particularities of non-verbal visual gnosis in the pre-school period

Ontogenetic research has made a major contribution to the study of visual perception. They define the stages of its formation, taking into account the mechanism of heterochronic maturation of brain structures. The data show that the transition from 5 to 6 to 7–8 years of age should be seen as a period of intense maturation of the fields related to visual information analysis. At the same time, complicated forms of visual gnosis (identifying images in difficult conditions) are not sufficiently developed due to the later inclusion of regulatory brain mechanisms.

Event-related potential studies of children with a typical development show significant differences in the system of perception of visual information before and after age 5 [32, 33]. It is found that at earlier stages the visual perception processes have diffuse characters, since similar reactive and configuration event-related potentials are recorded in all caudal regions. This explains the difficulties of the children in tasks to integrate signs and reproduce the overall images of objects [34]. After 5 years of age, a process of structuring and lateralization of visual perception processes begins. This is evidenced by differences in reactivity to individual components of event-related potentials in the projection and associative visual areas of the cortex. The data show an increasing specialization of post-center associative departments in the processing of complex visual stimuli, which improves analysis and discrimination of features when forms and building standards for complex images are compared.

In the period of 5–6 years, changes in the structural organization of neuronal ensembles in the caudal cerebral regions result in a qualitatively new functional organization of visual perception [35]. In children aged 6–7 years, in the realization of visual gnosis are included structures of the frontal partition, which is the beginning of its intellectualization. The identification of difficult-to-verbalize stimuli is associated with greater reactivity of structures from the temporal and occipital parts. When recognizing stimuli with a simple verbal formulation, the reactivity is shifted to the frontal lobe.

Dorsolateral prefrontal cortex is a high regulatory center and plays an important role in manipulating visual information. The insufficient maturity of the dorsolateral mechanisms during this period explains the weak reactivity of the negative wave, reflecting the cognitive component of visual recognition. The limited involvement of the prefrontal cortex in the analysis of incomplete images suggests a poor development of the regulatory component of perception during pre-school age. New research suggests that the complex of P200-N250 waves in the visual cortex, which is considered to be key in recognizing signs, shows a significant increase in the caudal and precentral cortical divisions after 7–8 years of age [36, 37]. In adults, it is most expressed in the post-temporal parts, which are part of the ventral visual system and play a major role in recognizing fragmented images.

Neurophysiological studies in complicated perceptual conditions of children show a leading activity of the occipital segments and a lack of significant increase in event-related potentials in the post-temporal regions [38, 39]. It is also stressed that at the age of 5–6 years, components of event-related potentials in the prefrontal cortex are not recorded. According to some authors [35], the low efficiency of fragmented image identification in this period is due to both the immaturity of the prefrontal cortex and the deficiencies in the functioning of the visual system. The low level of recognition under conditions of perceptual deficit is explained by the underdevelopment of regulatory mechanisms and insufficient involvement of the ventral visual system. In the period of 7–8 years, the role of the ventral visual system increases; this corresponds to the morphological data for significant transformations in the neuronal organization of the posterior temporal areas [39]. There is currently no unified opinion on the mechanisms of recognizing incomplete images in children. According to neurophysiological data in the period of pre-school and early school age in their brain organization there are both similarities and differences. Similarities refer to prefrontal cortex involvement in early stages of the analysis of complex visual stimuli.

The differences reflect the underdevelopment of the regulatory components of visual recognition in the pre-school period, shown by the large number of mistakes in children aged 5–6 [34].

Testing through event-related potentials for perceiving fragmented shapes in children aged 5–6 years separates two subgroups: A subgroup with a small number of errors and a B subgroup with a large number of errors [26]. In the second subgroup, a delayed development of two systems was recorded: the ventrolateral visual system and the dorsolateral prefrontal cortex responsible for regulatory functions and in particular for inhibitory control. Inhibitory control determines the successful recognition of the figures, whereas its absence explains the impulsive responses of children with low scores. The conclusion is that the morpho-functional maturity of the neuron systems processing sensory information and the state of regulatory functions determine children's individual abilities to visual recognition and their readiness for school education.

The image identification in conditions of sign shortness assesses the functioning of the right-hemisphere mechanisms and the implementation of a holistic perceptive strategy and is one of the most complex gnostic tasks. Difficulties in building hypotheses by children explain the cases of refusal to name individual figures and the presence of perseverations (use of a single word for different images).

The analysis of the existing data sets the period of 4–6 years as sensitive for the development of brain mechanisms for perceptive processing and for the formation of complex forms of visual gnosis. The specifics in the functioning of the gnostic operations in children with typical development in pre-school age have an important diagnostic and prognostic significance since the evocation of normative data allows for the separation of subgroups with different levels of perceptual functions and the differentiation of children at risk of learning difficulties. This is in line with the thesis [40] that any neuropsychological study in childhood pursues two purposes: the diagnosis of the condition of the function and the formulation of the treatment methods and approaches.

4. Description of the research

4.1. Aim

Assessment of the condition of complex forms of non-verbal visual gnosis in children with typical development at pre-school age and differentiation of subgroups with different levels of functioning of perceptive processes.

4.2. Method

For the study of visual gnosis under difficult conditions, the neuropsychological probe "Recognition of incomplete images" was used. The sample is based on the holistic principle of sensory integration and is widely used [26, 41]. In a manner of implementation, it is close to the image recognition test with a decreasing degree of fragmentation [42, 37].

As mentioned above, task execution activates the occipito-temporal part of the right hemisphere (ventral visual system) and prefrontal cortex. The results of recognizing objects in conditions of shortness of signs provide information on the state and dynamics of the functioning of these regions. Neural processes responsible for mental "filling--in" the missing information in visual incentives, some authors [37] mean by the term "perception of closing". The phenomenon is a combination of areas known as the lateral-occipital complex (LOC) that is linked to a wide network of dorsal and frontal regions. Studies with functional magnetic resonance imaging (fMRI) confirm the leading role of the lateral-occipital complex in detecting hidden objects [43].

The sample we use contains 12 black and white incomplete images of objects (lamp, sword, spoon, anchor, pliers, kettle, teapot, needle, key, guitar, scissors and ring). Some of them are presented below (**Figures 1–4**).

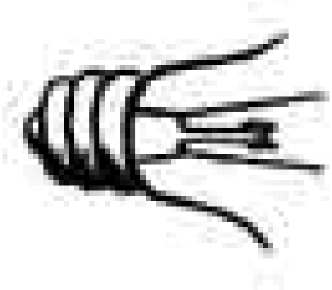

Figure 1. Lamp.

Figure 2. Anchor.

Figure 3. Teapot.

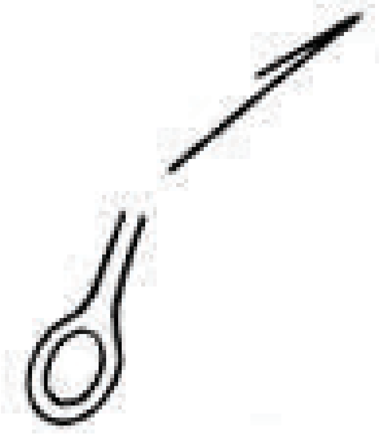

Figure 4. Scissors.

The investigation is individual and the answers are put in a separate protocol. Children look consistently at each of the stimuli and name it. All answers are noted regardless of their nature (correct or incorrect).

Assessment criteria:

- correct naming of an object—5 points,
- replacement of the name with a functional description of the object—4 points,
- wrong answers due to perceptual similarity—perceptively close (for instance instead of "pliers"—"scissors" and "spoon"—"shovel")—3 points,
- wrong answers due to association with one element of the image—fragmentary (for instance instead of "ring"—headphones"; "key"—"path")—2 points,
- wrong answers without perceptual similarity—perceptively distant ("kettle"—"chicken," "elephant"; "scissors"—"spoon")—1 point,
- without answer (does not name)—0 points.

The features of the functional system of visual perception are determined by indicators such as accuracy, completeness, volume and time for perception. In our case accuracy of perception is measured by using two parameters: number of correct answers and typology of the incorrect answers.

A total of 365 typically developing children without diagnosis of visual disorders took part in the research. All children attend state nursery schools and have Bulgarian as the mother tongue. They form three age groups: 4-year-olds (116 children); 5-year-olds (128 children); and 6-year-olds (121 children). Besides the age factor, the children were separated according to the size of settlement they live in (demographic criterion)—195 children from the capital, 90 living in a big city and 80—in a small town. The proportion according to gender is 173 males and 192 females.

The results are operated with a tri-factor dispersion analysis.

5. Results

The values of the F-criteria and the confidence probability (P) indicate that the two independent factors, age ($F = 15.75$; $p < 0.000$) and the location (settlement), ($F = 4.89$; $p < 0.008$) have a statistically significant impact on the dependent variable for recognizing incomplete images. There is also a significant impact of the paired interaction, Age*Settlement ($F = 3.93$; $p < 0.003$) and Age*Gender ($F = 3.7$; $p < 0.026$).

The profile of the age factor shows a graduate growth in the score for the test, most prominent for the 5-year-olds. The biggest differences are the average scores for children aged 4 and 5 (**Figure 5**), which emphasize the importance of the fifth year for the dynamics of the neuropsychic development.

Duncan's test establishes statistically significant differences between any two means (**Table 1**).

The influence and profile of the demographic factor on the development of the gnosis functions become obvious from the higher summarized score of the children from the big city (**Figure 6**). The average score of the children in the capital is lower, and the lowest is that of children from a small town. There is a statistical significant difference only between the average results of children from a large and a small town. The difference between the average points of children from a big city and capital is close to significance ($p = 0.055$), and among the children from a capital city and a small town the differences are not credible (**Table 2**).

Attention is paid to the interaction of age and gender factors. The data show identical average scores for girls and boys at 4 years of age, as well as similar ones for children at 5 years of age. Significant gender differences are only recorded in 6-year-olds. Duncan's test demonstrates the influence of both factors through specific differences between pairs of means (**Table 3**).

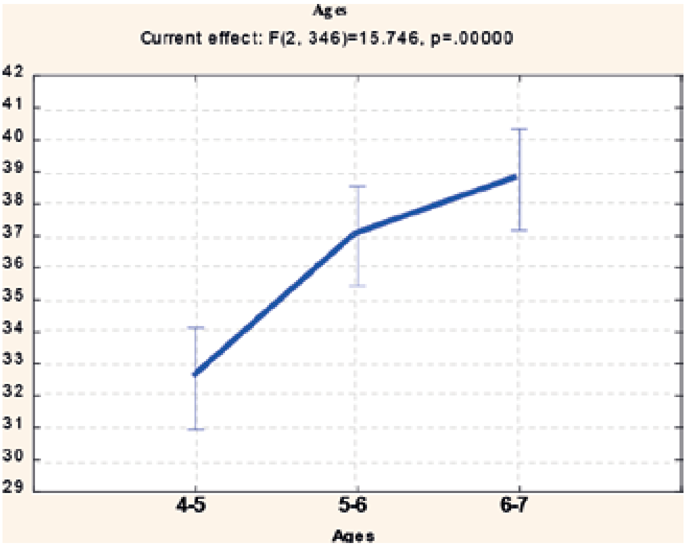

Figure 5. Effect of age factor on the results of recognizing incomplete images.

Ages	**{1}–32.313**	**{2}–36.890**	**{3}–39.467**
4 years		**0.000019**	**0.000011**
5 years	**0.000019**		**0.013385**
6 years	**0.000011**	**0.013385**	

Table 1. Significance of the average scores' differences of the children from each age group.

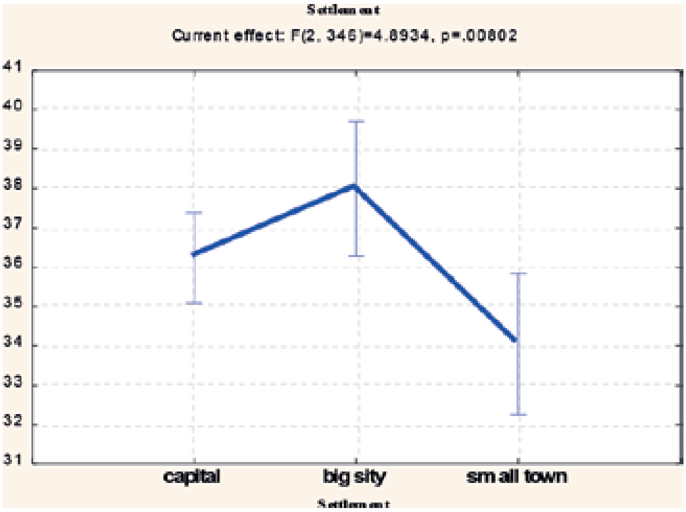

Figure 6. Effect of settlement factor on the results of recognizing incomplete images.

Settlement	**{1}–36.412**	**{2}–37.900**	**{3}–34.263**
Capital		0.185263	0.055564
Big city	0.185263		**0.001722**
Small town	0.055564	**0.001722**	

Table 2. Significance of the average scores' differences of the children from the three types of settlements.

Between groups of boys and girls at the age of 4 and 5, credible differences are not observed. The presence of credible differences between those aged 6 years ($p \leq 0.022$) is due to the higher mean values than girls.

Table 4 represents the percentage distribution of the correct answers and of the types of wrong answers (perceptively close, fragmented, perceptively distant and without answers) of the children from each age group. The data allow a more in-depth qualitative analysis of the condition and dynamics of complex forms of non-verbal visual gnosis in children with typical development from pre-school age.

Ages	Gender	{1}–32.621	{2}–32.000	{3}–36.649	{4}–37.086	{5}–41.129	{6}–37.750
4	Girls		0.674	0.006	0.004	0.000	0.001
4	Boys	0.674		0.002	0.001	0.000	0.000
5	Girls	**0.006**	**0.002**		0.767	0.004	0.486
5	Boys	**0.004**	**0.001**	0.767		0.009	0.653
6	Girls	**0.000**	**0.000**	**0.004**	**0.009**		0.022
6	Boys	**0.001**	**0.000**	0.486	0.653	**0.022**	

Table 3. Significance of the average scores' differences of the children of different gender and different ages.

Ages	True answers	Perceptively close	Fragmented	Perceptively distant	Without answers
4 years	28%	21%	10%	23%	18%
5 years	36%	21%	13%	17%	13%
6 years	46%	21%	9%	11%	13%

Table 4. Distribution of the type of answers for incomplete images for all age group children.

6. Discussion

The statistical analysis shows a leading influence on the development of complex forms of non-verbal visual gnosis of age and settlement (demographic) factors. The state of perceptive skills under difficult conditions is characterized by a positive age dynamics and a progressive increase in properly recognized figures. This is confirmed by the results of Duncan's test (**Table 1**) for the presence of meaningful differences between two age groups of children: 4- and 5-year-olds ($p \le 0.000019$), 4- and 6-year-olds ($p \le 0, 000011$) and 5- and 6-year-olds ($p \le 0.013385$). The data support the thesis of improving the right-brain holistic strategy of stimulus processing and the increasing involvement of prefrontal cortex in the processes of visual perception.

The significant increase in correct responses in children at 5 years shows the particular place of this period in the general neuropsychic development. In terms of visual gnosis, the period is characterized by increasing specialization of the post-central associative regions, improving the performance of the ventral visual system in conditions of deficiency of signs [34, 35] and gradual inclusion of the regulatory mechanisms of the prefrontal cortex. We assume that the age range of 4–6 years can be considered as sensitive for the development of complex perceptive functions and the cases of delay in their formation as prognostic markers for future learning difficulties.

The proven influence of the demographic background on the development of non-verbal visual gnosis confirms the thesis of the specific interaction of biological and social factors within the framework of the neuropsychic functioning. Data show the highest average results for children from a big city, followed by a capital and a small town. According to statistical analysis (**Table 2**), there are significant differences only between the results of children from a big city and a small town ($p < 0.001722$).

The interactions of the biological factors, age and gender, have a particular place in the development of complex forms of visual gnosis (**Table 3**). The statistical analysis does not show significant differences in recognizing incomplete images between girls and boys at the age of 4 and 5 years. These are only evident in children at 6 years of age. The observed differences are explained by the higher mean values of the girls—a fact that is indicative of gender influence on the neuropsychic development of these children. It can be assumed that in girls the ventral visual system and the neural complexes of the prefrontal cortex develop faster, the signs of which become obvious at the end of the pre-school period and explain the better functioning of perceptual and controlling functions.

The qualitative analysis of the results is based on the responses of the children differentiated in several types: correct answers, wrong answers based on perceptive similarities (perceptually close), wrong answers due to one element recognition (fragmentary), wrong answers without perceptive similarities (perceptively distant) or no answers. It is assumed [41] that when recognizing unfinished images, the child must remember the elements and connect them to those memory engrams that contain similar signs. In cases of the complete match between them, the object is recognized correctly. In the case of partial correspondence errors are observed on the basis of close or distant similarity. When the child does not count all, but only the individual signs of the image, the errors are of a fragmentary type. If there is no answer, the reasons are two: missing engrams in memory or an inability to generate an adequate perceptive hypothesis. Errors of perceptual similarity are defined as lighter and fragmented and perceptually distant as heavier.

After a study of a large child population, Ahutina and Pylaeva [41] conclude that perceptually close errors have left-brain mechanisms and are due to weaknesses in the analytical processing of visual information. Fragmented types of wrong answers are explained by right-brain deficits of holistic processing, because on one or two fragments the child draws the conclusion of the whole image. Perceptively distant wrong answers are associated with right-brain or bilateral weakness.

Here are examples illustrating the different types of wrong answers in our survey.

Wrong answers based on perceptual similarity: saber—“knife”; spoon— “shovel,” “broom”; water can—“shower”; pliers—“scissors.”

Wrong fragmentary-type responses: anchor—“arrow,” “hanger”; kettle—“bird,” “pig”; needle—“hand,” “figure,” “pinch.”

Perceptively distant wrong answers: sword—“octopus,” “spoon,” “trunk”; spoon—“man,” “rod,” “umbrella”; scissors—“magnifying glass,” “needle”; ring—“headphones,” “banana,” “heart,” “river.”

The quantitative distribution of all responses in the 4–6 years of age period provides valuable information on the ontogenesis of cortical mechanisms in perceptual processing under difficult conditions (**Table 4**). Data show that children at 4 years only recognize truly 28% of the images, with similar results of perceptively close (21%) and perceptively distant (23%) responses. In 18% of cases, there was a lack of response. The results support the thesis of incomplete functioning of the ventral visual system, hampering the holistic processing of stimuli and underdevelopment of prefrontal areas, resulting in a large number of impulsive responses.

Significantly higher results in children at 5 years confirm the presence of evident age dynamics in the development of gnosis functions. Against the backdrop of an increased proportion of correct recognized figures (36%), the proportion of perceptually distant answers (17%) and lack of response (13%) decreased. Perceptually close responses remain the same (21%). A significant improvement in perceptual abilities is the reason why the fifth year is considered critical for neuropsychic development.

Similarly to the 5-year-olds, the distribution of the types of responses remains in children at 6 years: the number of faithfully recognized figures (46%) increased and perceptibly reduced distant answers (11%). The ratio of perceptually close errors remains unchanged (21%). The data support the thesis [38] that the transition from 5 to 6 to 6–7 years is a time of intensive maturation of the systems, providing visual information analysis and significant changes in the organization of the neural ensembles in the caudal cortex. Despite the positive changes, the number of faithfully recognized figures in children at 6 years does not exceed half of all answers—a fact that is supported by data [35] of insufficient maturity of the prefrontal cortex and the cortical sections of the visual system (in particular the ventral visual system) during 4–6 years.

The summarized results clearly outline the age dynamics of visual perceptions under difficult conditions. If the number of faithful and perceptively distant answers prevails in children at 4 years of age, the number of correct and perceptively close answers prevails over the age of 5 and 6 years. The ratio of responses to perceptual closeness does not change over the three age sub-periods, while perceptibly distant reductions are significantly reduced from 4 to 6 years of age. The results could also be explained by the abovementioned data on the diffused nature of visual perceptual processes before the age of 5.

The impact of the demographic factor on the distribution of responses is as follows: in the capital, perceptually distant answers and cases of lack of response are leading; in the big city the perceived errors and lack of responsiveness predominate; in the small town the leading place occupies the replaced by a perceptively close and perceptively distant similarity. Existing analyzes [41] give reason to assume that the mistakes in the capital are mainly due to right-brain difficulties, in the big city, it is the left-brain difficulties, and in the small town, the mistakes are related to both types of difficulties. This is supported by the better functioning of holistic right-hemispheric mechanisms and higher outcomes of children from a big city.

The additionally outlined age norms for the accomplishment of the sample to recognize unfinished images show interesting tendencies of prognostic nature. They are determined by the children's individual results and lead to the separation of three subgroups: leading group, medium group and behind group. Their distribution in the direction of 4- to 5- and 6-year-old children is as follows: leading group: 30–28–27%; medium group: 45–46–47%; and behind group: 25–26–26%. It is noteworthy that the state of subgroups during the various stages of pre-school age is practically unchanged. We believe that this fact has important prognostic significance and allows an early diagnosis of deficits in complex forms of visual gnosis.

Particular attention is paid to the results of the 6-year-old children who are about to go to school. Exported data show that one-fourth of them fall behind a group characterized by the incomplete processing of the right-brain ventral visual system and insufficient involvement of control functions of the prefrontal regions. The engrames of objects in long-term memory are not sufficiently built up, making it difficult to form proper perceptive hypotheses. We assume that children in this group will face obvious difficulties in recognizing and differentiating graphical characters (alphanumeric, numeric and geometric), allowing them to be identified as a risk group for specific learning disorders (dyslexia).

The unsatisfactory development of the complex forms of visual perception could be viewed as a predictor for future reading difficulties and proves the diagnostic and prognostic validity of the sample to recognize incomplete images for the pre-school age period.

7. Conclusion

The analysis of the represented data shows that for the age period 4–6 there is a process of dynamic maturation of the right-brain structures of the ventral visual system and their connections to the structures of the prefrontal cortex, leading to gradual improvement of the children's abilities for visual discrimination of objects in difficult circumstances (incomplete images). Impact on the development of complex forms of non-verbal visual gnosis has the combination of age, demographic and gender factors, among which a special place is the age of 5 years. The positive dynamics of the mechanisms of holistic processing of complex non-verbal stimuli started in the pre-school period, but their formation continued in the next stages. Particular attention is paid to the fact that over the 6-year period most of the children with typical development continue to show great difficulty in recognizing incomplete images. They enroll at school with underdeveloped perceptual and control functions, which is why the group should be considered as risky for the development of dyslexic symptoms.

The neuropsychological probe "Recognition of incomplete images" is a sensitized option for the diagnosis of non-verbal visual gnosis in childhood. It has a high prognostic value and allows an early detection of cases of delayed development within the broad childhood norm. The application of the task (in isolation or in combination with others) supplemented by a competent quantitative and qualitative analysis responds to the leading tendencies in modern child neuropsychology and allows the timely identification of children at risk of learning difficulties.

Conflict of interest

Author declares no conflict of interests.

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Chapter 3

Frontal Lobe: Functional Neuroanatomy of Its Circuitry and Related Disconnection Syndromes

Rafael Batista João and Raquel Mattos Filgueiras

Additional information is available at the end of the chapter

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Abstract

Disconnection syndromes are classified as higher function deficits that result from lesions to white matter or association cortices, the latter acting as relay stations between primary motor, sensory, and limbic areas. In 1965, Norman Geschwind brought disconnection to the fore after publishing a paper entitled "Disconnexion syndromes in animals and man." In the last decades, a large number of studies concerning this topic have been published in order to elucidate new perspectives of localizationist view of brain functioning. In view of those considerations, it is noteworthy to mention that the understanding of connection pathways involving frontal lobe is one of the most challenging fields of research in neuroscience. The better comprehension of those concepts is an important mark for the multidisciplinarity of neurology, neurosurgery, and psychiatry. The purpose of this chapter is to expose relevant data of recent literature embracing the association between disconnection syndromes and frontal lobe dysfunction.

Keywords: disconnection syndromes, frontal lobe, cortex, connection pathways, brain functioning

1. Introduction

Disconnection syndromes are classified as higher brain function deficits that result from lesions to white matter or association cortices, where the latter act as relay stations between primary motor, sensory, and limbic areas [1].

Regarding the historical aspects of these clinical entities, there are case studies in the literature on neural disconnection mechanisms dating back to the nineteenth century which, at the time, illustrated the importance of the functional subdivisions of the classic topographic divisions of the brain [2]. In 1965, Norman Geschwind brought discussions on disconnectivity to the fore after publishing a paper entitled "Disconnexion syndromes in animals and man." The article is considered seminal in cognitive neurology given its contents which served as a basis for furthering understanding on brain function in recent decades. In the publication, Geschwind emphasized the role of white matter tracts and their projections between different cortical and subcortical regions in generating specific behaviors, descriptions which broadened understanding of this topic beyond the strictly localizationist theories which had hitherto prevailed [3].

An introductory passage of Geschwind's paper reads as follows:

> *In the pages which follow I hope to give an account of the implications of thinking in terms of disconnexions for both clinical practice and research. The synthesis presented here was developed piecemeal out of study of the literature and clinical observation. I will not, however, present it in the order of its development but rather will try to organize the facts and theories along simple anatomical lines. There is, I believe, a unity in the theory which justifies this approach, and I hope that it will significantly contribute to clarification of the presentation. There are many facts recorded in the following pages; there is also much speculation which is, however, nearly all subject to the checks of future experiment and clinical observation.* [4, 5]

Although written over 50 years ago, the article hailed the development of a branch of neuroscience of increasing importance today, which seeks to improve understanding on brain connectivity pathways using neuroimaging techniques, such as diffusion weighted magnetic resonance imaging (DWI), diffusion tension magnetic resonance imaging (DTI), and functional magnetic resonance imaging (fMRI). Thus, these techniques have helped improve studies on disconnective syndromes and their various different presentations [3].

In this context, the importance of the frontal lobe, more specifically the prefrontal cortex and its complex circuitry, should be highlighted, given its status as the most developed brain segment in the integration of the cortical and subcortical functions [6]. The relationship between the need for knowledge on the mechanisms involving disconnectivity and this lobe is so marked in the history of cognitive neurology that three cases considered classic and seminal on this matter have suggested the possible existence of disruption of the associative pathways in frontal white matter as the underlying physiopathogenic basis of the clinical conditions observed. These reports shall be outlined in more detail later in this chapter [2].

In summary, in order to gain an understanding of how cognitive functions are produced, it is important to recognize that there are various neural networks interlinking different brain areas which maintain their organization and functioning. Classic knowledge holds that certain isolated areas have defined functions; however, it is now known that the dynamic interactions between areas, acting as connective networks, underpin the complexity of systems which govern the higher cortical functions, such as cognition, language, and memory [7].

The aim of this chapter is to present data available in the literature on the association between disconnection syndromes and frontal lobe dysfunction. To this end, a brief review of the basic functional neuroanatomy of the frontal lobe, its circuitry, and associated clinical manifestations is given, together with a description of the main fasciculi forming the connections of the frontal structures and of these with other regions of the brain. In addition, for reasons of didactics and practical applicability, illustrative cases recently reported in medical journals indexed on major databases will be presented.

1.1. Basic functional neuroanatomy of the frontal lobe, its neuronal circuitry, and associated clinical manifestations

With regard to the lobes comprising the brain segments, the frontal lobe is considered the largest. Macroscopically, the cortical layer of the lobe accounts for approximately 37–39% of the cerebral cortex [6], where part of this structure is composed of the prefrontal cortex (PFC) [8]. This cortical region forms part of an extensive connective network involved in socioemotional abilities and in the executive function of humans and other primates. Comparative studies suggest that the characteristic differentiation of the prefrontal lobe of humans compared to that of other primates lies more in circuit organization than mere size of the structure [9]. From a phylogenetic perspective, it is believed that the relatively recent reorganization of the frontal cortical circuitry has been pivotal to the emergence of the specific cognitive functions of the frontal lobe in humans [10].

Classically, the PFC is held to encompass several specific Brodmann areas, situated anteriorly to the primary motor cortex and premotor cortex. The higher cognitive functions related to the functioning of the PFC can be subdivided into executive function, where this is more specifically linked to the dorsolateral portions of the frontal lobe (Brodmann areas 9, 10, and 46); language (Brodmann areas 44 and 45); and emotional processing and sociability, related to the orbitofrontal cortex (Brodmann areas 10, 11, 13, and 47) [10].

Three different circuits originating from the anterior frontal gray matter are considered of major importance for the functioning of the PFC, namely the dorsolateral circuit, orbitofrontal circuit, and the circuit involving the anterior cingulate portions of the frontal lobe. These connective pathways start and terminate in the PFC, while their trajectory can project them to specific structures, such as the caudate nucleus, globus pallidus, thalamus, and other neocortical regions [10].

More specifically on the functions of each circuit cited, the dorsolateral circuit (DLC) basically promotes organization ability, planning, and attention. From a clinical point of view, damage to these pathways can cause perseveration, reduced ability for abstraction, organization and planning, loss of decorum, impaired verbal fluency, poor performance on complex figure copying, and difficulty in sequencing motor acts [9].

According to Burruss et al., Brodmann areas 9 and 10 (dorsolateral) contain neuron cellular bodies that correspond to the start and end of the DLC. The neurons of this region project to the dorsolateral portion of the caudate nucleus, from which juncture they develop direct and indirect pathways which appear to have a reciprocal modulation mechanism via excitatory and inhibitory stimuli. The direct pathway enters the dorsolateral region of the external and internal globus pallidi and the rostrolateral portion of the pars reticulata of the substantia nigra. The indirect pathway connects to the dorsal portion of the external globus pallidus, adjacent to the lateral subthalamic nucleus. In the anterior ventral and dorsomedial thalamic portion, there is an input of fibers from the internal globus pallidus and pars reticulata of substantia nigra, structures where the direct and indirect pathways join. From the thalamus, the circuit returns to the lateral portion of the anterior frontal lobe (place of origin of the cited connections) [9].

In addition, it is important to note that these pathways have additional interaction with other areas, including the parietal, temporal, and occipital association cortices, as well as the limbic system [9]. In a reciprocal fashion, the superior and inferior longitudinal and frontal occipital fasciculi convey information from the relatively distant cortical regions connected to this complex cortical-subcortical association [6]. A simplified schematic diagram showing the direct pathway of the dorsolateral circuitry is depicted in **Figure 1**.

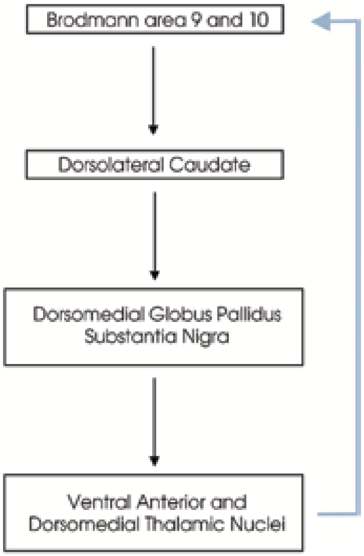

Figure 1. Basic schematic diagram of the direct pathway of the dorsolateral frontal circuitry (adapted from [9]).

When considering the orbitofrontal circuit (OFC), this performs the function of modulating adequate social behavior and is fundamental for maintaining empathy. Disruptions in the pathways of this system lead to certain neuropsychiatric manifestations such as impulsivity, emotional lability, personality changes, explosive behavior, and lack of interpersonal sensitivity. Akin to the dorsolateral circuit, which contains neuronal cell bodies situated in Brodmann areas 9 and 10 (dorsolateral portion), the orbitofrontal circuit starts and ends in Brodmann areas 10 (inferomedial portion) and 11. The axonal projections from these areas run to the ventromedial portion of the caudate nucleus, where they diverge into the direct and indirect pathways. The direct pathway enters the medial portion of the dorsomedial external and internal globus pallidi and the medial rostral region of the pars reticulata of the substantia nigra, where they continue to the anteroventral and dorsomedial portion of the thalamus, subsequently returning to the PFC (**Figure 2**). The indirect pathway of the orbitofrontal circuit performs a modulatory function through its connection to the dorsal region of the external globus pallidus and to the lateral subthalamic nucleus, prior to projection to the loops of the direct pathway via internal globus pallidus and substantia nigra. The indirect pathway of the OFC modulates the direct pathway through the connection to the dorsal region of the external globus pallidus and the lateral subthalamic nucleus. The indirect pathway of the orbitofrontal circuit is believed to run parallel to the indirect pathway of the dorsolateral circuit [9, 11].

Externally to this circuitry, the lateral portion of the OFC receives afferences mainly from the temporal pole, cerebral amygdala, and ventral tegmental area. In this case, the connections to the distal collateral areas are also reciprocal, as occurs with similar integrative pathways in the dorsolateral circuitry [9, 12].

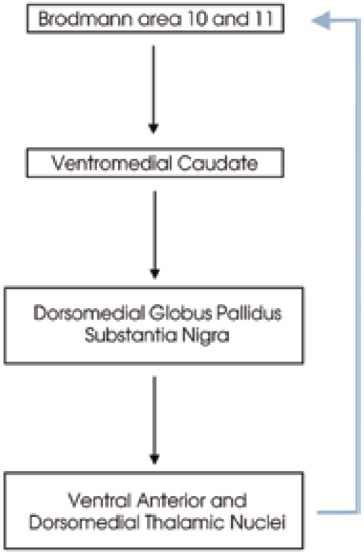

Figure 2. Basic schematic diagram of the direct pathway of the orbitofrontal circuitry (adapted from [9]).

The circuitry involving the anterior cingulate regulates motivation by modulating inhibitory input in the supplemental motor area, through its own stimuli which maintain wakefulness and alertness states. The most evident deficits of interruptions of any of the circuits situated in the prefrontal cortex are related with bilateral lesions of the anterior cingulate. Under these conditions, the principal clinical manifestations described are akinetic mutism, apathy, abulia, urinary incontinence, and lack of expressiveness to sensory stimuli. As occurs with Brodmann areas 9/10 (dorsolateral) and 10 (inferior-medial)/11 in the case of the DLC and of the OFC, respectively, Brodmann area 24 is the site where the anterior cingulate circuit starts and ends [9].

The subcortical connections of the anterior cingulate circuit are constituted by fibers that connect to the ventral striatum (more specifically the ventromedial portions of the caudate nucleus and ventral portion of the putamen), the nucleus accumbens, and to the olfactory tubercle. From these structures, the circuit projects to the ventral and rostromedial globus pallidus and to the dorsomedial thalamic nucleus, subsequently returning to the anterior cingulate cortex. The indirect pathway of the anterior cingulate circuit is thought to connect to the external globus pallidus and to the medial subthalamic nucleus before reentering the circuit of the direct pathway (**Figure 3**) via the internal globus pallidus. The reciprocal integration of the pathways with the structures situated externally to the circuit occurs through connections of the ventral striatum with the hippocampus, amygdala, and the entorhinal and perirhinal cortices [10].

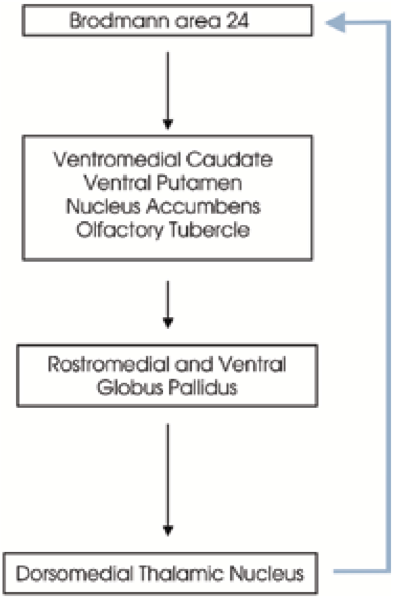

Figure 3. Basic schematic diagram of the direct pathway of the anterior cingulate circuitry (adapted from [9]).

Finally, it is noteworthy that besides the three main circuits of the frontal subcortical neuronal network, some authors have cited further two circuits, namely the inferior temporal cortical circuit (ITCC) and a circuit situated between the posterior parietal region (Brodmann area 7) and the prefrontal region (Brodmann area 46). Reports associate lesions involving the ITCC with psychosis, deficits in visual discrimination, and visual hallucinations and cite that damage to the circuit between Brodmann areas 7 and 46 is associated with impaired interpretation of visuospatial stimuli [6].

Given that neuropsychiatric manifestations secondary to disruption of the frontal circuitry have been cited in this section, it follows that other semiological changes that can feature in the clinical picture of "frontal syndromes" should also be mentioned. Some of these changes include grouping, grasping, perseveration, snouting, imitation and utilization behavior, palmomental reflex, and persistent glabellar tap reflex [13, 14].

1.2. Brain's major fasciculi and frontal lobe tracts

The previous section of this chapter outlined the classic knowledge on the functional neuroanatomy of the neuronal circuits of the frontal lobe, along with the main neurological and psychiatric manifestations resulting from interruption in functioning of these specific pathways. The aim of this section is to delve deeper into the connectionist theory of brain function, which is key to understanding the physiopathogeny of disconnection syndromes. This requires outlining the main pathways involved in the connection of structures encompassing the frontal lobe and beyond.

As described earlier, disconnection syndrome is defined as the group of clinical manifestations secondary to lesions to white matter or to the association cortices, where the latter acts as a relay station between the primary motor cortex, sensory areas, and limbic system [1].

In recent years, publications have reported clinical cases with neuropsychiatric manifestations hitherto attributed to certain lesions to specific cortical topographies. However, complementary investigation using neuroimaging has disclosed changes in other brain sites [15, 16]. A number of authors have stated that this phenomenon can be explained by disruption of the subcortical associative pathways involved in the neuronal network integrating the higher cortical functions [1]. In this context, it is important to cite major fasciculi (MF), which help maintain the complex brain circuitry, whose main common function is refinement of processing of information necessary for the adaptation made by the frontal lobe to environmental changes, which occur, essentially, through interaction between pyramidal functions and cognitive/emotional processes [6]. Some of these fasciculi are described in more detail below (**Figure 4**).

Brain's Major Fasciculi

- U fibers
- Occipito-frontal fasciculus
- Superior longitudinal fasciculus
- Inferior longitudinal fasciculus
- Perpendicular fasciculus
- Uncinate fasciculus
- Arcuate fasciculus
- Corpus callosum
- Cingulum
- Fornix

Figure 4. Brain's major fasciculi [6].

Among the MF, the corpus callosum is important for its interhemispheric connective function, particularly via the fibers of the anterior commissure [17]. More specifically, it is also important to mention in detail the pathways involved in the intra and extralobar frontal integration, such as the fronto-orbitopolar tract, frontal aslant tract, and frontal superior and inferior longitudinal fasciculi [18].

The fronto-orbitopolar tract connects the posterior orbital gyrus to the anterior orbital gyrus and to the medial-ventral region of the frontal pole and has the function of associating the storage of memory with the senses, such as taste, smell, sight, and hearing. The frontal aslant tract connects Broca's area with the region of the anterior cingulate and the supplementary motor area. Damage to this tract can lead to impaired inhibitory response and speech initiation difficulties [18]. In 2013, Catani et al. confirmed the evidence of involvement of this tract in a clinical condition called agrammatic progressive primary aphasia (PPA) after publishing a study comparing controls and patients with other PPA variants [19].

The superior and inferior longitudinal tracts have the function of integrating, at different levels, the frontal regions involved in decision-making, i.e., to connect the inferior level processing in the posterior frontal regions to superior level processing in more anterior regions needed for complex cognitive control. In addition, the superior longitudinal tract (SLT) also integrates the neuronal network which extends beyond the frontal lobe, having, for example, involvement in the selection of sensory stimuly related to processing of attention, which occurs through the functioning of the frontoparietal circuitry. In this context, the authors suggest the subdivision of the SLT into three segments, namely the SLT I, SLT II, and SLT III, which connect, respectively, the superior parietal region to the dorsal prefrontal and dorsal premotor cortex; the inferior parietal region to the dorsolateral prefrontal and medial premotor cortex; and the supramarginal gyrus to the premotor ventral cortex [20].

Other examples connecting the frontal lobe to different cortical regions include the superior fronto-occipital fasciculus (SFOF), which corresponds to the long association system of the dorsal visual pathways and appears to have a role in the interaction of the visuospatial function with superior integrative functions. This tract has a hemispheric trajectory located medially, with projections located on the superior edge of the anterior branch of the internal capsule and along the length of the lateral portion of the caudate nucleus, laterally to the posteroinferior elongation of the lateral ventricle horn. Thus, the SFOF connects the mediodorsal parts of the occipital lobe, angulate gyrus (located in the inferior parietal lobe), Brodmann area 19, and the precuneus (Brodmann area 7) to the dorsal and medial portions of the premotor and prefrontal region (Brodmann areas 6 and 8). The inferior fronto-occipital fasciculus (IFOF) has the primary function of connecting the inferolateral and dorsolateral frontal cortices with the posterior temporal and ventral occipital cortices, via a lateral hemispheric route, along the lateral portion of the lentiform nuclei, claustrum, and the external and extreme capsules. Studies show that this fasciculus connects the visual (Brodmann areas 20 and 21) and auditory (Brodmann area 22) associative areas, situated in the temporal lobe, with the prefrontal cortex, playing a role, together with other tracts, in complex visual integration and language and memory processing [17].

Other important structures include the external capsule and the extreme capsule. The external capsule is situated between the putamen and the claustrum and has associative pathways coursing through it connecting the ventral and medial prefrontal cortices, ventral premotor cortex, precentral gyrus, rostral superior temporal, inferior temporal, and preoccipital regions. These pathways are made up of fibers of the SFOF and IFOF, uncinate fasciculus (part of the limbic system), and fibers of the anterior commissure. The extreme capsule is situated between the claustrum and caudal insular cortex and between the claustrum and orbitofrontal cortex in its rostral portion, representing the principle connective pathway between the ventrolateral prefrontal cortex and the caudal fronto-orbital cortex with the superior temporal region [17].

Some of the connecting pathways cited in this subsection are exposed in **Figures 5–10**.

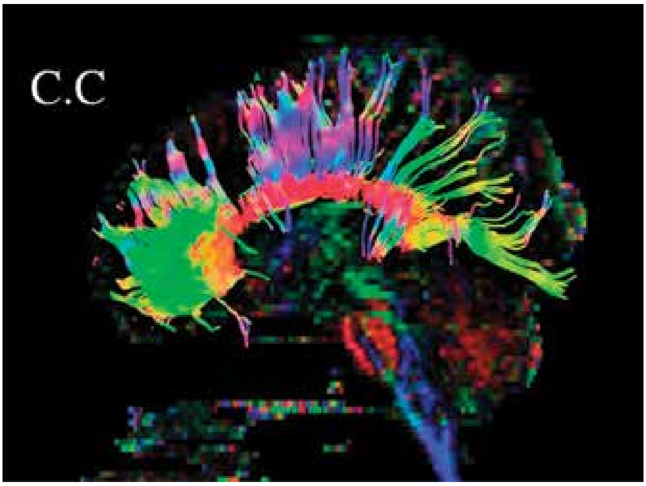

Figure 5. MRI tractography in sagittal view showing corpus callosum (C.C) fibers.

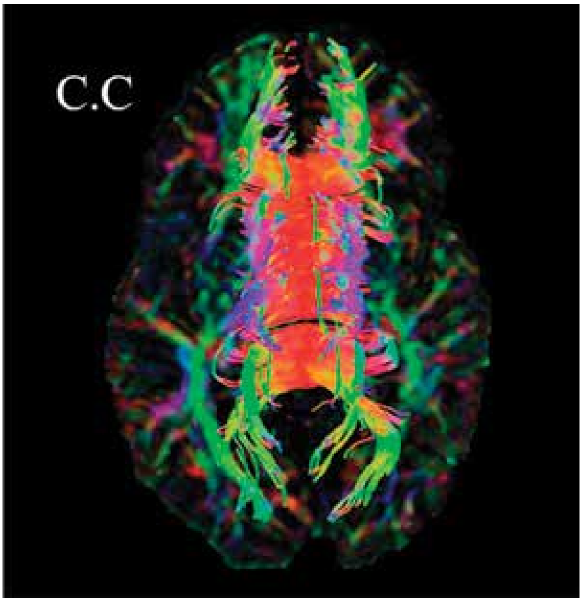

Figure 6. MRI tractography in axial view showing corpus callosum (C.C) fibers.

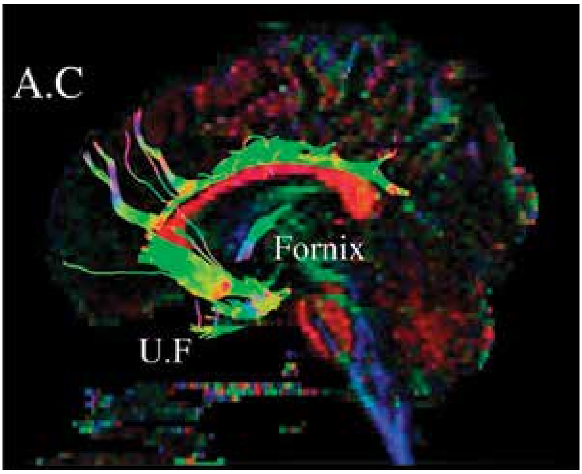

Figure 7. MRI tractography in sagittal view showing anterior cingulate (A.C) fibers, fornix and uncinate fasciculus (U.F) fibers.

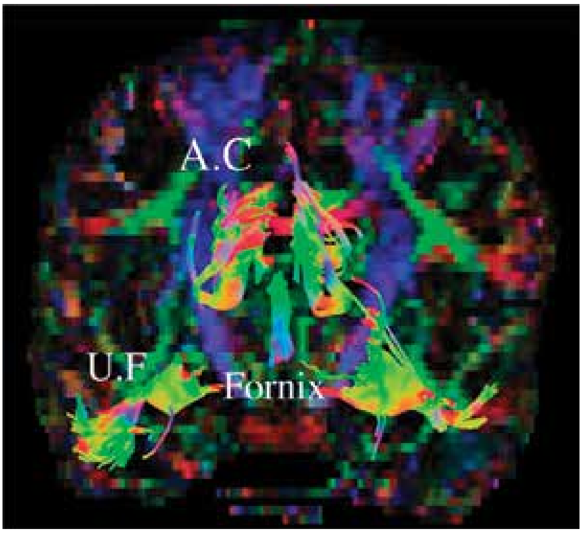

Figure 8. MRI tractography in coronal view showing anterior cingulate (A.C) fibers, fornix and uncinate fasciculus (U.F) fibers.

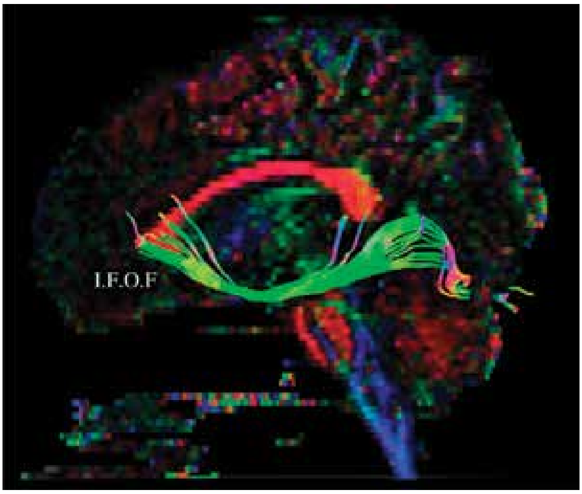

Figure 9. MRI tractography in sagittal view showing inferior fronto-occipital fasciculus (I.F.O.F) fibers.

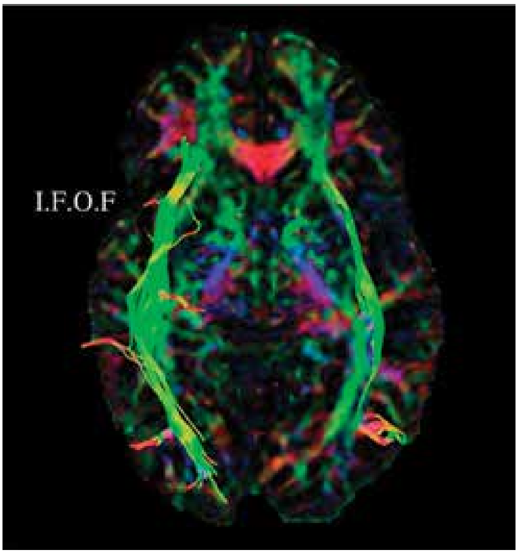

Figure 10. MRI tractography in axial view showing inferior fronto-occipital fasciculus (I.F.O.F) fibers.

In addition, with the advancement of knowledge on cognitive science made possible by technology, important examples of network models showing the broad cerebral neuronal connections have been demonstrated recently. These networks are denoted as default mode network (DMN) [21] and salience network (SN) [22].

The DMN is basically a network associated with passive task conditions and with self-referring mental activity, whose main structures are the posterior cingulate and adjacent precuneus cortex, medial prefrontal cortex, and inferior parietal lobe [21]. The SN is related to functions such as self-awareness, communication and social behavior, constituting a large-scale network anchored at the anterior insula and dorsal anterior cingulate cortex, also including the amygdala, ventral striatum, and substantia nigra/ventral tegmental area [22].

Thus, it is important to recognize the concept that lesions external to the frontal lobe can lead to the typical manifestations of "frontal syndromes," and also to understand that damage to the frontal lobe or in its vicinity can cause abnormalities classically described as being secondary to more posterior brain lesions, a mechanism involved in the physiopathogeny of the disconnection syndromes [16]. For didactic purposes and practical applicability, several cases illustrating these clinical situations will be reported in the ensuing subsection.

1.3. Disconnection syndromes: clinical description and history of classic cases from the literature

In 2015, following the publication of an original article entitled "From Phineas Gage and Monsieur Leborgne to H.M.: Revisiting Disconnection Syndromes," Schotten et al. reported the results of a study in which neuroimaging methods were used to provide a clearer understanding of the probable disconnection associated with damage to white matter in the abovementioned cases. To this end, the authors described the lesion of Phineas Gage (Illustrative case 1) by performing computed tomography of his skull and documented the magnetic resonance images of Louie Leborgne's brain (postmortem) (Illustrative case 2) and Henry Molaison (*in vivo*) (Illustrative case 3). Subsequently, the lesions were reconstructed using tractography based on the atlas of white matter obtained from the diffusion tension imagings (DTIs) of 129 healthy adults [2].

1.3.1. Illustrative case 1

In 1868, Harlow described the case of Phineas Gage, a 25-year-old man who sustained perforation of the left frontal part of his skull by an iron bar after an accident in the workplace. According to the descriptions, after the event, Gage became unrecognizable to his friends; he became more flippant, used foul language, was more impatient when disagreed with, failed to display empathy and, although no neuropsychological description was made at the time, the clinical manifestations were believed to be linked to deficits in decision-making and emotion processing after sustaining the lesions to the frontal lobe.

In Gage's case, the analyses derived from neuroradiological reconstruction revealed disconnection secondary to lesions in the orbitofrontal cortex, dorsolateral frontal cortex, and temporopolar cortex. In addition, there was partial disconnection of the frontal lobe in relation to the amygdala, thalamus, and striatum. With regard to the fasciculi, the authors cited damage of the inferior longitudinal, superior frontal, and uncinate fasciculi. There were also lesions occurring in the orbitopolar and frontal aslant tracts. Other partially affected connective pathways were the frontostriatal, frontopontine and anterior thalamic projections [2].

1.3.2. Illustrative case 2

In 1839, Louie Leborgne, a 30-year-old man, was admitted to a French psychiatric hospital (Bicêtre Hospital) after having presented sudden loss of speech. At the time of hospitalization, Leborgne was divorced and had recently lost his father, which may have explained his long stay at this clinic. He remained a patient at this hospital for the next 21 years until, when changing sector, he was assessed by Leborgne, a physician who had begun studying aphasia at that age. On the postmortem analysis of Leborgne, Broca identified damage to the posterior third of the left inferior frontal lobe.

The analysis of Leborgne's case concluded that besides Broca's area, there was damage to other distant areas in the frontal, parietal, and temporal regions. The following connective pathways were affected: arcuate fasciculus, the first third of the superior longitudinal fasciculus, the frontal inferior longitudinal, frontal orbital polar, and the frontal aslant tracts. There was also partial involvement of the frontopontine, frontostriatal, and corticospinal tracts, the second third of the superior longitudinal fasciculus and anterior thalamic radiations [2].

1.3.3. Illustrative case 3

Henry Molaison (H.M) was described as a patient who had a history of epilepsy since childhood (absence seizures which began at 10 years of age) and at age 15 years had a pattern of convulsive seizures which became refractory to drug therapy. In 1953, his case was assessed by William Scoville, a neurologist who was studying the effects of temporal lobectomy in reducing the frequency of epileptic seizures. That same year, H.M. underwent bilateral medial temporal lobectomy. After surgery, there was an improvement in the frequency of the epileptic seizures but, unexpectedly, the presence of severe anterograde amnesia was evident, along with apparent problems remembering new facts and events as a result of the predominant impairment in recall memory.

The results of the analysis showed that besides the medial temporal lobe, there were changes in the orbitofrontal cortex, retrosplenial cortex, and gyrus rectus. In relation to the connective pathways, the main observation was damage to the right uncinate fasciculus, while other tracts were partially affected, such as the anterior commissure, fornix, and left and right ventral cingulate.

In the three cases, analysis using functional MRI showed that the abnormalities were compatible with the damage to most of the fasciculi involved in the computed structural reconstruction [2].

1.4. Disconnection syndromes: posterior brain lesions leading to "frontal symptoms"

In 2011, Krause et al. published in the scientific journal Cortex a study in which 2982 subjects were assessed from a database of the Westmead Hospital between 1983 and 2009. In that sample, there were 15 patients with severe executive dysfunction associated with brain lesions outside the frontal lobe. Some examples taken from this study will be cited below [15].

1.4.1. Illustrative case 4

A 38-year-old male patient presented, around 2 weeks after a heart by-pass, onset of progressive behavioral changes. During follow-up, approximately 5 months later, the neurological exam, besides pyramidal and extrapyramidal manifestations, revealed the following findings: presence of palmomental reflex, snouting, grasping and grouping, abulia, utilization behavior, imitation behavior, impulsiveness, clonic perseveration, and memory decline. The brain magnetic resonance imaging (MRI) scan performed 6 months after the procedure revealed hyperintensity (T2-weighted sequence) in globus pallidus bilaterally with no changes in the frontal lobe. This fact suggested a possible disruption of the circuitry involving modulation of the frontal cortical functioning, even without cortical or subcortical white matter lesions [15].

1.4.2. Illustrative case 5

A 15-year-old female patient, one week after an infection of the upper airways, presented an acute clinical picture characterized by neuropsychiatric manifestations followed by awareness impairment. Among the initial complementary exams, the brain MRI (FLAIR-weighted sequence) disclosed bilateral hyperintense lesions in the posterior parietal regions, posterior thalamic, hippocampus, internal globus pallidus, caudate nuclei, and occipital optic tract. After improvement using pulsotherapy, the radiologic abnormalities were later considered components of the diagnosis of acute disseminated encephalomyelitis (ADEM), since there were no conclusive results on other exams (cerebrospinal fluid, Anti Nuclear Factor, serology, brain biopsy). The reassessment at around 6 months after onset of clinical symptoms revealed sequela changes compatible with severe abulia, apathy, severe grasping and grouping, visual grasping, and utilization behavior. Another follow-up brain MRI performed around 8 years later showed marked cerebellar and occipital atrophy in association with hypersignal in globus pallidus bilaterally with sparing of the frontal lobe [15].

1.4.3. Illustrative case 6

A 58-year-old male patient was admitted after onset of sudden dysarthria, left hemiparesis, ataxia, and fluctuation in level of consciousness. Brain MRI disclosed bilateral cerebellar and thalamic infarcts affecting the dorsomedial and centromedian nuclei and parts of the right pulvinar, without evidence of damage to the frontal lobes. After around 2 weeks of steady improvement of the initial symptoms, neuropsychiatric abnormalities became evident (abulia, apathy, tonic preservation, daytime sleepiness, and severe grasping and grouping). These symptoms partially improved during the course of the next year, but the patient remained dependent for care and memory deficits persisted [15].

1.4.4. Illustrative case 7

A 71-year-old female patient presented rapidly progressive disorientation, gait and balance difficulties, dysarthria, and transient hemiparesis to the right side. Previously, an active individual engaged in social activities, since the stroke she displayed abulia, grasping and grouping, visual grasping, imitation behavior, clonic perseveration, utilization behavior, ideomotor apraxia, and parkinsonism. Brain MRI (T2-weighted sequence) revealed hypersignal in the anterior two-thirds of the putamen, besides lesions to the anterior portions of the lateral ventricles. The clinical and radiological pattern suggested involvement of the occipitofrontal fasciculus [15].

1.5. Appendix: cerebellar cognitive-affective syndrome

1.5.1. Illustrative case 8

In 2013, Starowicz-Filip published a case of a 43-year-old male patient who presented, besides ataxic manifestations, typical symptoms of frontal lobe damage (euphoric mood, inappropriate social behavior, loss of decorum, tendency to encroach on personal space) secondary to a stroke affecting the right cerebellar hemisphere (confirmed by computerized cranial tomography and brain MRI) [23]. In the discussion of this case report, the authors cited the original paper of Schmahmann and Sherman (1997), reporting a case series of 20 patients with cognitive-behavioral symptoms, as well as motor abnormalities due to cerebellar damage (vascular, infectious, and autoimmune nosology). At the time, this clinical entity was coined cerebellar cognitive-affective syndrome, a term used to this day [24].

Since 1970, major advances have been made to elucidate the different connections of the cerebellum with supratentorial cortical structures, which are related to nonmotor language, cognition, and emotions. Apraxia of speech, for example, caused by deficits in motor planning of speech and in coordination, occurs as a result of injury, typically, to the region of the motor area of language in the dominant hemisphere. Characterized by impaired speech articulation, which can also be inconsistent, marked by hesitancy, with phonetic changes in vowel and consonants, dysdiadochocinesia, abnormality in prosody and slow articulation [25], apraxia of speech is an entity which shares many semiological features with ataxic dysarthria (result of lesion in the right superior vermis region and paravermis regions, characterized by slow, monotone, slurred speech which tends to be explosive and with phonation—all classes of consonants—affected more than articulation) [26, 27]; therefore, these similarities suggest that both conditions occur as a result of disconnection between the anterior motor region of planning of speech and coordination, which suggests a functional interaction between the anterior motor speech area (in the dominant hemisphere of language) and the contralateral cerebellar hemisphere [25].

Neuropsychological studies have also shown that patients with cerebellar abnormalities have less capacity for word retrieval (phonologic fluency) and for producing words according to a semantic rule (semantic fluency). Therefore, the cerebellum may be responsible for changes in the dynamic of language, resulting in transcortical aphasia behavior and even mutism due to inhibition of speech and of language production involving circuits connecting with frontal regions. Those findings warrant further elucidation [24, 28, 29].

Many other changes, in terms of cerebellum involvement and cognitive domain of language, can be found in patients with cerebellar lesions besides those cited above.

Thus, the role of the cerebellum regarding another cognitive function should be noted: that of working memory. Cerebellum damage is believed to cause deficits in attention related to working memory and in executive functions, where functional studies including the use of methylphenidate, a dopamine receptor inhibitor, have shown activation of the left side of the cerebellum with subsequent improvement in working memory performance [30, 31].

It is believed that symptoms of cerebellar cognitive-affective syndrome occur due to extensive disconnection of neuronal circuits involving the cerebellum and prefrontal, superior temporal, posterior parietal, and limbic cortices [32]. This also explains the visuospatial change found in patients with vermis lesions [33].

There is also a relationship of the cerebellum with many pathologies that are highly characterized by behavioral changes, such as autism, schizophrenia, and attention deficit hyperactivity disorder (ADHD). There is a clear similarity between the autism spectrum syndromes and the behavioral syndrome exhibited by children surgically treated for posterior fossa tumors. These behaviors include intolerance to proximity of others, absence of physical and eye contact, rhythmic repetitive movements, language limited to some stereotyped expressions and absence of empathy, attributable to damage to the cerebellar connections with supratentorial cortical areas [34, 35].

The association of ADHD with structural or functional changes in the cerebellum has not been widely investigated. Some imaging studies have consistently shown lower volume cerebellum in patients diagnosed with this clinical condition compared to healthy individuals, particularly for inferior-posterior segments of the cerebellar hemisphere and of the vermis [34–36]. The behavioral changes, besides the well-recognized cognitive deficits (difficulties in attentional control—divided and sustained attention—difficulty of abstraction, comprehension, and reproduction of content involving ideas, especially written texts, problems with working memory, difficulty in inhibition tests, and time management), include impulsiveness and mood swings [24].

Some functional studies using different cognitive paradigms have shown frontal-cerebellar-thalamus hyperactivity in patients with schizophrenia [37]. In addition, discrete neurological signs often present in these patients—slight ataxia of gait, difficulties for fine coordination of limbs, dysdiadochokinesia, mild intentional tremor, dysmetria of saccade eye movements—are also highly suggestive of cerebellar pathology or dysfunction. Lastly, not only is there frequent emergence of psychotic symptoms in individuals with median cerebellar lesions but also a greater resemblance between many cognitive-behavioral changes of patients with cerebellar deficits and the negative symptomatology of schizophrenia, such as emotional blunting, concrete thinking, poor discourse and fluency, passivity, avolition and isolation, difficulty in summarizing and logical sequencing of information and visuospatial difficulties [38, 39].

1.6. Disconnection syndromes: frontal lobe lesions leading to typical "nonfrontal" manifestations

As outlined earlier in the chapter, in the same way that more posterior lesions can lead to symptoms classically described as due to frontal lobe lesions, it is known that the inverse also occurs, i.e., damage to frontal lobes can also lead to impairment in functions classically described as associated with the functioning of more posterior brain regions. Some examples are provided in the text that follows.

1.6.1. Illustrative case 9: Gerstmann syndrome secondary to fronto-insular damage

Gerstmann syndrome (GS) is a neurological condition characterized by a group of cognitive alterations making up the tetrad of acalculia, agraphia, right-left disorientation, and finger agnosia. Classically, this syndrome was attributed to lesions involving the angular and supramarginal gyri of the dominant hemisphere; however, its localization value has been questioned in the decades following the first publication [16]. Recently, a number of cases have been reported suggesting that disconnectivity may be the physiopathogenic basis of GS. Some of these cases were secondary to lesions involving the frontal lobe and its association pathways [16, 40–42].

In 2017, João and Filgueiras et al. described the case of a 46-year-old male right-handed patient, an engineer student with past medical history of atrial fibrillation who presented a sudden language deficit associated with right hemiparesis. At hospital admission, around 6 hours post-ictus, the neuropsychological exam revealed that besides changes compatible with expression aphasia, the patient presented with acalculia, agraphia, right-left disorientation, and finger agnosia, findings compatible with the tetrad of Gerstmann syndrome. On the second day of the hospital stay, mild expression difficulty and mild right hemiparesis persisted, although the patient no longer displayed the cognitive findings seen on admission. Follow-up computerized cranial tomography performed 72 hours after the onset of clinical symptoms disclosed a hypodense area in the left inferior frontal gyrus (**Figure 11**). Brain MRI (FLAIR-weighted) and diffusion magnetic resonance imaging (DWI) performed during out-patient follow-up revealed, respectively, hypersignal in the anterior and posterior insular cortex to the left side and diffusion restriction in the left insular region with preservation of the angular and supra marginal gyri.

The authors considered that the diagnosis of the case in question was compatible with transient Gerstmann syndrome secondary to stroke, likely resulting from disconnection between frontal and left parietal lobes. This hypothesis was based on the knowledge that lesions situated deep in the insular cortex, more specifically in the extreme capsule, can promote loss of connectivity of the short association fibers between the frontal and parietal opercula, leading to disruption of the frontoparietal circuitry, which is integrated via the arcuate and superior longitudinal fasciculi [16].

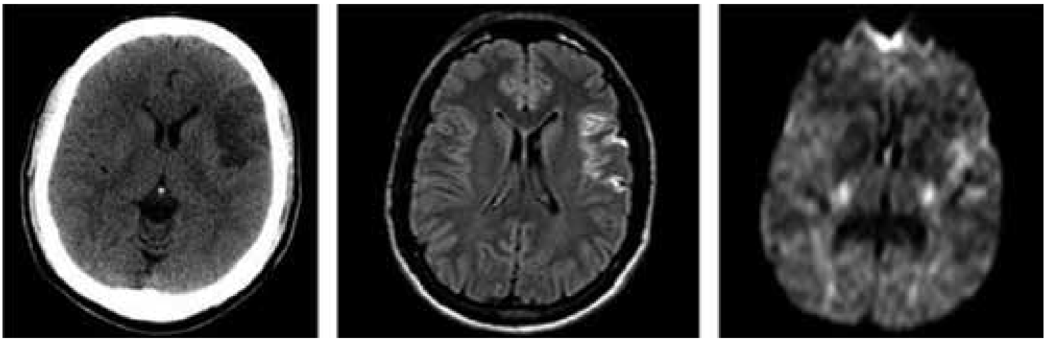

Figure 11. Cranial computed tomography, brain MRI (FLAIR-weighted), and brain diffusion MRi (DWI) showing, respectively, hypodense area in the left inferior frontal gyrus, hypersignal in the left anterior and posterior insular cortex, and restricted diffusion in the cortical region of the left insular topography, with sparing of the left angular and supramarginal gyri in a patient with transient Gerstmann syndrome [16].

In the past 5 years, other authors have reported in the literature GS cases where lesions were detected in areas such as the medial frontal lobe, posterior insula of the dominant hemisphere, inferior frontal gyrus, pars opercularis, pars triangularis, and basal ganglia, all showing preservation of the angular, supramarginal gyri, and adjacent regions [40–42].

2. Conclusion

After highs and lows in scientific output on brain connectivity in recent years, the technological advances in neuroimaging have revolutionized the knowledge on mechanisms of neural networks, and this fact represents a major milestone for the multidisciplinarity of neuroscience.

From a clinical standpoint, the illustrative cases reporting syndromes of disconnection to the frontal lobe cited in this chapter exemplify the pressing need for future studies to elucidate the physiopathogenic process of different classic neuropsychiatric syndromes. These studies may gradually oppose the localizationist view of brain functioning. Based on the data available in the literature, this knowledge will likely have growing impact in the academic setting and become increasingly important in the interface among different areas such as neurology, neurosurgery, and psychiatry.

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Conflicts of interest

The authors declare no conflicts of interest.

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Section 2

Clinical Presentation of Prefrontal Cortex

Chapter 4

Prefrontal Cortex: Role in Language Communication during Social Interaction

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Additional information is available at the end of the chapter

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Abstract

One important question that remains open for the relationship between the brain and social behavior is whether and how prefrontal mechanisms responsible for social cognitive processes take place in language communication. Conventional studies have highlighted the role of inferior frontal gyrus (IFG) in processing context-independent linguistic information in speech and discourse. However, it is unclear how the medial prefrontal cortex (mPFC), the lateral prefrontal cortex (lPFC), and other structures (such as medial superior frontal gyrus, premotor cortex, anterior cingulate cortex, etc.) are involved when socially relevant language is encountered in real-life scenarios. Emerging neuroimaging and patient studies have suggested the association of prefrontal regions with individual differences and impairments in the comprehension of speech act, nonliteral language, or construction-based pragmatic information. By summarizing and synthesizing the most recent functional magnetic resonance imaging (fMRI) studies, this chapter aims to show how neurocognitive components underlying the social function of prefrontal cortex support pragmatic language processing, such as weighing relevant social signals, resolving ambiguities, and identifying hidden speaker meanings. The conclusion lends impact on an emerging interest in ***neuropragmatics*** and points out a promising line of research to address the mediating role of prefrontal cortex in the relation of language and social cognition.

Keywords: neuroimaging, speech act, nonliteral meaning, pragmatics, social interaction

1. Introduction: indirect language and social inferential networks

Language is uniquely human in that the communication via language is inherently social [1]. Unlike other cognitive systems such as visual perception which does not necessarily involve the input from social interaction, the human acquisition of language-processing abilities heavily rely on the social input. One of the main functions of language is to establish, maintain, and modify social relations. The meanings that are conveyed by language are situated in social settings and are hence highly negotiable. Newly emergent research in cognitive neuroscience of language argues that the meaning at different linguistic levels depends on social interactions and ongoing representation of body actions [2]. This chapter therefore elucidates the neural representations underlying social language processing, summarizing the representative studies that showed the involvement of prefrontal regions during processing language that conveys social information or supported by social interaction. We highlight that multiple neurocognitive components underlying social functions in the prefrontal cortex have successfully guided humans to understand language in social contexts. We will extend our perspectives into (1) indirect language and social inferential networks, (2) recognizing speech/communicative acts and action-related networks, the relation between prefrontal deficits, pragmatic impairments, and the role of theory of mind (ToM) and executive functions; (3) neural correlates of reading emotion-laden literary; (4) transmission and learning of language in social contexts; and (5) cognitive empathy and pragmatic language processing.

To detect that a conversational turn is intended to be ironic or sincere, the listener must go beyond the literal meaning. The medial prefrontal cortex (mPFC), together with the precuneus and bilateral temporal parietal junction (TPJ), forms the neuronal network for mentalizing that is correlated with the speaker meaning on the overhearers (e.g., [3–5]). These regions were more active when listeners heard the ironic utterances (*Tonight we gave a superb performance* said by an opera singer after a disastrous performance; [6]), and sentences with ambiguous references (*When Beyonce met Madonna she had just had a little accident at the hairdressers*) as compared with the literal or unambiguous control sentences. Some irony comprehension tasks also found the medial prefrontal cortex (mPFC) and middle temporal gyrus (MTG)/superior temporal sulcus (STS) [7]. The irony comprehension also involved areas related with the high executive demands and integrative processes, including the inferior frontal gyrus (IFG), MTG, and dorsolateral prefrontal cortex. Recognition of communication intention during language comprehension, in particular, the comprehension of a speech act, recruits extended neural networks. Uchiyama and colleagues found prominent activation in the IFG, MTG, and mPFC during recognizing ironic meaning [8]. The authors interpreted activation in the mPFC as being related with mentalizing activity, and activation in the IFG and MTG being related with activity in the semantic-executive system engaged in the semantic retrieval, selection, and evaluation during sentence comprehension. Harada et al. examined the neural correlates using the task where the participants judged whether the protagonist in a story uttered a speech act with the intention to deceive, or whether their behavior was morally acceptable [9]. The deceit recognition task activated the bilateral TPJ, inferior parietal lobule (IPL), the right MTG and dorsal lateral PFC (dlPFC), with the dlPFC activation related with the executive demands set by the task. Both tasks activated the IFG and the right mPFC, suggesting the mPFC may more universally function as a social inference region.

While the irony is used as a prosocial communicative tool that mitigates the face-threatening of the speaker, the deceit violates the social norm that requires the speaker to make a truthful statement. However, the understanding of both speech acts involves a contrast between what a speaker affirms and his private knowledge and requires the derivation of the shared knowledge between the speaker and the listener [10]. When the speaker produces the irony, they expect the listener to detect whereas the speaker does not expect the listener to recognize the deceit. One study explored the neural activations underlying the irony and deceitful statements [11]. Healthy individuals read statements used in sincere, deceitful, and ironic way (e.g., It's a beautiful day.). In both deceitful and ironic statements, the speaker implies the opposite of what he says [12, 13]. Compared with the since voice, both deceitful and ironic voices increased activations in the left fronto-temporal network, including the left IFG, dlPFC, and middle frontal gyrus (MFG). The IFG suggests that a demanded inferential process of the correct intended meaning from the (wrong) literal meaning of the utterance. The dlPFC suggests the involvement of executive functions to combine the inferences necessary to understand the speaker's intention to deceive with the comprehension that social norms are violated. The ironic statements uniquely activated the left MFG as compared with the deceitful statements. These findings highlight the role of prefrontal areas underlying both executive functions and social inference processes in the interpretation of pragmatic meanings from the statement.

The ability to detect the literal meaning maybe disrupted in schizophrenia patients who showed difficulties in successfully decoding meaning of ironic conversational turns [14] and in perspective taking and second-order theory of mind processes that the irony comprehension heavily relies on [14, 15]. Lesion and functional magnetic resonance imaging (fMRI) evidence has found the involvement of medial prefrontal cortex in theory of mind processing [16], and the involvement of right lateral temporal lobe [17] or the left MTG/superior temporal gyrus (STG) or the left lateral prefrontal cortex (lPFC) [18] in detecting nonliteral meanings. One study demonstrated that, as compared with literal statements, reading ironic statements ending the text vignettes activated a bilateral network including the left medial prefrontal and left inferior parietal gyri [18]. The increased activation in the mPFC suggests the involvement of second-order "theory of mind" processing in the ironic and sarcastic stimuli. The increased activation in the bilateral middle temporal gyrus in reading ironic statements were negatively associated with the reader's schizophrenic trait score (measured by schizotypal personality questionnaire, SPQ), suggesting that the more activated the bilateral MTG, the lower SPQ score when the participant read the ironic statement. These findings suggest that individuals with schizotypical personality traits are associated with a dysfunctional lateral temporal language rather than a prefrontal theory of mind network; moreover, the processing of ironic language maybe interrupted by neural mechanisms underlying the functional impairment of schizotypical personality [19]. A positive correlation was found between the activation in the left IFG when participants read irony and the SPQ possibly suggesting an involvement of additional semantic integration processes when the nonliteral sentence was encountered.

Indirect response is a "face-saving" strategy and serves as a tool for manipulating the addressee by a socially navigating individual. One study scanned the participants' brain when they listened to a reply from a job candidate that was either addressed to them (when they imagined themselves as the addressee) or to the interviewer in a job interview setting (when they overheard the conversations from the candidate and the interviewer [20]). They observed that the indirect reply, which functioned as a politeness strategy to mitigate the potential verbal threatening on the speaker's face (e.g., *I am planning to take a language course this summer.*

as indirect response to: *Are you fluent in any foreign languages*? vs. direct response to *What are your plans after graduation*?), activated mPFC, bilateral IFG, bilateral TPJ, and bilateral MTG in both conversation settings. The ventral salience network (dorsal portion of insula and anterior cingulate cortex (ACC)) was additionally involved in certain social scenarios when the participant was addressed directly. These findings suggest that the face-saving indirect languages engage perspective-taking and discourse mechanisms associated with the increased inferential complexity which may be irrelevant to whether the speaker was the first person or third person involved in the comprehension. Moreover, affective processing mechanism which determines whether the participant is the direct recipient of the address, with the regions encoding emotional salience involved when the listener's evaluative process is stronger as the direct addressee toward the indirect reply. These findings suggest that the social inference and selection of the appropriate meaning may serve as crucial mechanisms that draw upon medial prefrontal cortex to resolve any types of unspecified or implicit meanings which are contextualized, including the derivation of the pragmatic implicatures in nonliteral statements.

2. Recognizing speech acts and action-related networks

Language is a powerful tool to communicate the speaker's intended action. The neural correlates of speech were examined in a study in which the participants were presented with videos with the same critical utterances [21] embedded in different communicative scenarios (to name or to request the possession of the objects from the conversational partners). Speech (or communicative) acts are various in terms of one's possession of action-related and socio-interactive knowledge, which are considered to be linked with the action perception and prediction in the fronto-central sensorimotor cortex [22], the human homolog of the mirroring system across premotor inferior frontal and anterior inferior parietal cortex [23], and the mentalizing networks [24] over mPFC, ACC, and TPJ. The speech act of naming or requesting something does not differ according to the linguistic utterance used to perform the action or the physical setting during the communicative event (e.g., object and the communicative partners), but in the expectation of the action sequences in which the speech act is embedded (e.g., to point to the target to be named or to fetch the object to fulfill the request) and the intentions and assumptions of communicating partners (e.g., the speaker's desire to obtain the object during request). The request activated the bilateral premotor, the left IFG, and temporo-parietal areas that support the prediction of the subsequent actions following speech and representation of social interactive knowledge. However, the naming activated the left angular gyrus that establishes the referential relationship between a lexical item and the referred targets. A similar study focusing on the indirect request, such as *it is cold in here* used to request to close the window, as compared with the same expression for informing others of the temperature. The visual context that accompanied the utterances differed between the informing (images of a desert landscape) and the requesting (images of a window). Stronger activation in the indirect requests was observed in the fronto-central action system as well as the parietal areas related with the mirror neuron intention understanding; and in the mPFC, TPJ for theory of mind (ToM) processing [24].

Another fMRI study focused on the role of modality-preferential sensorimotor areas in processing meaning of abstract emotion words, such as "love," and mental words, such as "thought" [25]. While the prefrontal cortex (e.g., the dorsal lateral and prefrontal areas) served to activate the multimodal meanings regardless of word types, the sensorimotor regions (e.g., premotor areas, [26]; left posterior IFG and MFG, [27]; rostral part of ACC, [28]) were selectively engaged more in the abstract words. Participants read silently abstract emotional and mental nouns along with concrete action-related words. The regional-of-interest analysis showed that the face motor areas in the left precentral somatotopy was involved when the mental nouns and the face-related action words were encountered, while both the precentral hand and face motor areas were recruited when participants read abstract emotion words [29]. The sensorimotor systems in semantic processing are not restricted to the concrete action words but should be extended to some mental concepts. The causal role of prefrontal regions in the abstract emotion and interpersonal mental words were also demonstrated. For example, patients with a focal lesion of the left supplementary motor area (SMA) showed selective deficit in processing abstract emotional nouns. The interpersonal words (such as "convince," [30]) were found to activate the medial prefrontal, post-cingulate cortex (PCC), and orbitofrontal cortex, areas identified to be involved in mentalizing and social cognition processes. The prefrontal region, especially those which are necessary for integration of social knowledge and one's action, participated in the understanding of communicative (speech) acts.

3. Prefrontal deficit, impairment in pragmatic ability, theory of mind, and executive function

Injuries in the prefrontal and other regions are shown to causally involve in the impaired communicative-pragmatic ability. Traumatic brain injuries are typically characterized by the damage to the frontal lobes, resulting in deficits in executive functions, and the ability to manage goal-directed behavior. ToM difficulties were able to predict poor performance in speech production task. Moreover, the impact of ToM on one's communicative performance was more pronounced when the task involved stronger inhibition, for example, when participants were asked to initially think about a specific event from their own perspective, inhibit that perspective and switch to someone else's perspective. Individuals with the traumatic brain injury (TBI) suffer from a general difficulty in managing social communication in everyday life, for example, they display poor ability to negotiate efficient request [31] or at giving right amount of information to the interlocutor [32], conversational problems including turn taking [33], and narrative disorders [34]. In a study on the communicative ability in TBI individuals [35], 30 patients with traumatic brain injury and 30 healthy individuals were tested on executive function, theory of mind, and communicative-pragmatic functions using the Assessment Battery of Communication (ABaCo). Among all TBI patients, 25 suffered from focal damage in the frontal regions (among whom 15 were lesioned in the right frontal, 6 in the left frontal, and 6 in bilateral frontal or frontal-diffuse areas). The TBP participants were poor in the comprehension and production tasks in the ABaCo, on both linguistic and extralinguistic measures, as well as in the EF (higher-level executive control tasks including the working memory, planning, and cognitive flexibility) and ToM tasks (including the first- and second-order theory of mind, or mentalizing the other person's mind or the another's knowledge toward others), the latter of which predict individual's performance in the communicative-pragmatic tasks.

4. Neural correlates of reading emotion-laden literary

Reading literaries (such as poems and novels) bring various affective feelings, such as sadness, feelings of suspense, and beauty. The literary reading is a constructive process, linking to perspective taking and relational inferences associated with the extended language network [36], the ToM network [37], and regions associated with the mood empathy [38] and esthetic positive feelings [39]. The emotional connotation of single words recruits attention and can induce engagement for readers of texts and seems to be the supported by the activities of prefrontal affective networks. Ferstl et al. [40] revealed the auditory presentation of the emotion-laden text passages activated ventral mPFC (vmPFC), the left amygdale, and the pons. Wallentin et al. further showed the neural correlates of intensity ratings of each line of the text in the bilateral temporal, IFG, and premotor regions, and the right amygdala [41]. An fMRI study by [42] presented 120 short passages from the Harry Potter book series. Three levels of emotional ratings were used as the regressor for the parametric analysis: the rating of single words, the rating of the relation between words (e.g., the contrast in the emotional valence between words), and the rating of a whole passage. The contrast between the literary reading and fixation engendered activations in the dorsal lateral PFC, TPJ, anterior temporal lobe (aTL), precuneus, and amygdala which are associated with the ToM or affective empathy processing [43] and aTL and vmPFC associated with the multimodal integration and emotional conceptualization [44]. They also demonstrated that the arousal ratings on the lexical items and inter-lexical items were correlated with the activity in areas associated with emotional salience, emotional conceptualization, situation model building, multimodal semantic integration and theory of mind. For example, the more positive valence was found in the left dlPFC, left premotor, bilateral aTL, left TPJ, left PCC, precuneus. Lexical valance span varied in the left amygdala which was demonstrated to involve salience detection and the effects of arousal span were significant in the anterior insula, extended from IFG, which was demonstrated as integration of autonomic processes with emotional and motivational functions. However, no effects of ratings on passages were demonstrated in emotion-associated regions, but in ToM or affective empathy processing and multimodal semantic integration (IFG, dlPFC, aTL, TPJ, precuneus, dorsal ACC, vmPFC). This finding was different from the observation in Altmann et al. [45]. Stories with negative valence were found to activate stronger connectivity between the mPFC and left amygdala and bilateral insula, regions involving affective empathy and ToM processing. Moreover, the mPFC was more activated when the reader showed more positive judgments toward the negative stories. Whether the emotion potential of short texts can be uniquely predicted by lexical and inter-lexical affective variables or also by passage-wise rating is worth further investigation.

A related question is how one's language experience (e.g., familiarity, age of acquiring the language) affects the brain responses (especially the prefrontal involvement) underlying the reading of emotion-laden literature. Reading fictions involves language-related processes including constructive content imagination and simulation [46], perspective taking and relational inferences [47]. These processes were represented by the extended language network associated with discourse comprehension, the neural mechanisms underlying high-level/multimodal semantic integration [44, 48], and theory of mind network, generally including vmPFC, dmPFC, IFG, aTL, TPJ, PCC, precuneus, and left amygdala. The effects of emotionality were demonstrated to predict the left amygdala, vmPFC, and the pons when listening to emotion-laden text passages [40]. Ref. [49] showed that the happy passage activated left precentral gyrus (the head/face area on the somatotopy) and bilateral amygdala when the literature was presented in reader's first language (L1 reading, German) only; while regardless of the language status, the emotion-laden literature activated emotion-related amygdala and lateral prefrontal, anterior temporal, and temporo-parietal regions associated with the discourse comprehension, high-level semantic integration, and ToM processing. Moreover, the multivariate pattern analysis approach revealed better accuracy of differential patterns of brain activity in predicting different emotional contents in L1 than second language (L2), with the sensitivity attenuated in the L2 relative to the L1. These patterns showed the neural activations that support provide stronger and more differentiated emotional experience in reading our native than the second language texts.

5. Transmitting and learning language in social contexts

How are messages propagated? What are the underlying neural mechanisms? One key aspect regarding how our language is grounded into the social interaction is the synchronized linguistic behavior between communicative partners. The tendency to become more similar in the use of nonverbal cues (e.g., [50]), linguistic structures (e.g., [51]), and neural activity associated with producing and decoding narratives (e.g., [52, 53]). Are the mechanisms of verbal synchrony or linguistic style matching between communicators applied to the relationship between the use of social language by one communicator and that by the listener who subsequently retransmit the message? One fMRI study addressed the neural mechanisms underlying the processing and retransmission of social language in the context of word-of-mouth sharing [54]. The brain systems that are engaged in considering the mental states of others are particularly engaged by social features of language (e.g., words associated with social interaction, which referred to individuals who maybe participate in a social interaction, such as "friend", or those used to describe these interactive processes, such as "exchange"), and the activity within the brain's mentalizing system during exposure to ideas predicts the subsequent extent to which social language is employed in describing the ideas to others. In particular, the brain mentalizing system included the bilateral TPJ, dorsomedial prefrontal cortex (dmPFC) as well as the precuneus and PCC [55]. Previous literature has examined the mechanisms of successful communication in pairs [52, 53] and how simulation of other's mental states can facilitate effective idea retransmission [56, 57]. They showed that the use of more social words to introduce ideas was associated with increased neural activation in the dmPFC, bilateral TPJ, and temporal pole in the participants, the networks that were typically responsible for mentalizing. Moreover, the higher levels of activity in left TPJ and dmPFC during idea exposure were positively associated with greater usage of words from social categories after the experiment. Here, the dmPFC is considered as functions associated with considering other's attributes and motivations [58, 59], and reflected the pursuance of specific motivational goal for the speaker (e.g., to look good by communicating good ideas in a compelling way to others). These findings consolidated the idea that the social cues in language (here the lexical item related with social interaction) can activate the medial prefrontal and other systems implicated in understanding the mental states of others (who introduced the ideas toward a new object) and successfully retransmission of ideas.

Social communication is fundamental to human daily activity [60–62] and is contributed considerably by nonlinguistic social cues [63]. A growing number of literatures have suggested that the social inference networks, including understanding other's mental states and monitor other's feelings, maybe implicated during communicative tasks. One may recognize other's intention by two ways. One may recruit the motor simulation process which involves the premotor cortex (PMC) and the anterior intraparietal sulcus (aIPS), especially in tasks which require the understanding of the intention conveyed by body motion [64]. The other is related with inferential processes based on "theory of mind" [65] or mentalizing, which has been typically represented by regions non-overlapping with the motor system, including the mPFC, the TPJ as well as the posterior superior temporal sulcus (pSTS) [66]. These regions are mainly involved when intentions were embedded in stories or cartoons in which the goals or beliefs of the characters are not explicitly encoded by communicative cues [67], or when individuals were instructed to identify the intentions of actors they observe [68].

Nonverbal communicative cues (e.g., gaze, voice) are essential social signals in language communication. To understand how the mentalizing and mirroring system contribute to the recognition of intention via nonverbal communicative cues, an fMRI study focused on communicative (e.g., looking at a person) and private intentions (e.g., looking at an object) as well as other-directed and self-directed intentions (whether facing the camera and therefore the participants [69]). Previous studies on cartoons have demonstrated that mentalizing areas was involved when cartoons contained more social interactions, the characters showed less private intentions and more social prospective intentions (e.g., preparing future social interactions, which is considered as more "communicative intentions") [67, 69]. The right TPJ was activated regardless of the intention type, the mPFC was selectively activated in the social prospective and communicative intentions. The dmPFC was considered uniquely involved in the decoding of intention during movement observation. The dmPFC has been associated with the social gaze shift, with increased activity when participant's gaze shift is directed at another person [70] or when they follow the gaze of another person to engage in joint attention [71], suggesting a role of medial prefrontal cortex in the engagement of social communication in a second-person perspective. The participants watched videos in which the actor either faced and looked toward the camera, faced toward but looked away from the camera (at an object at his/her hand), or faced 30° away from the camera and looked toward another person outside of the camera, faced away and looked away from the camera. Observing actions performed with a communicative intent (looking toward the person) versus private intent (looking away from the camera) activated in mPFC, bilateral pSTS, and left TPJ for the mentalizing network and bilateral PMC, bilateral aIPS fo the mirroring system. The mPFC activity increased as the increasing of the individual's trait empathy. Self-directed (0° away from the camera) versus other-directed orientation (30° away from the camera) activated the visual cortex, and the enhanced activation was found in mPFC for the self-directed orientation in the communicative as compared with the private intention. Moreover, the communicative intent further strengthened the connectivity between the mPFC and the bilateral pSTS for the mentalizing system and the left PMC and bilateral aIPS for the mirroring system. These findings suggest a collaboration between the medial prefrontal cortex and other social inference networks during intention recognition in nonverbal communication.

Studies also demonstrated that the prefrontal cortex is more involved during language acquisition that occurs in a social interaction scenario. Infants must be immersed in a language in a socially interactive situation to develop speech perception [72]. Similar to the spoken language, the sign language provides rich grammatical rules and both activate the left IFG during syntactic comprehension [73]. The live communication, as compared with the pre-recorded videos, is more rewarding, more arousal, provides richer sources of information (such as responsive eye gaze), and more attention-grabbing (e.g., [72]). In a study on the neural correlates of language acquisition [74], naïve Japanese participants learned Japanese sign language through an interaction with a deaf signer or via watching videos for a comparable amount of time. The group who received a live exposure showed the modulation of BOLD signals in the left IFG between two sessions of the testing when making grammatical judgments toward a sequence of signs which was absent in the group received the video exposure. The left IFG was considered as crucial for processing syntactic and other linguistic rules in the native adult which demonstrated a clear role of exposure toward the communicative environment on acquiring new linguistic knowledge (e.g., foreign language). The group receiving DVD exposure revealed the activation in the right IFG and right supramarginal gyrus, suggesting that they developed the knowledge of sign language through incorporating multimodal information from different senses and from imitation learning [75].

Many forms of social interaction are not carrying explicit mentalizing demands. These implicit mentalizing processes include tracking mental state content [76, 77] and monitoring other's communicative intent [70] which are more engaged when processing communicative cues from a real-time social partner than those from a pre-recorded video. A similar experiment invited the participants to listen to short vignettes and were persuaded to believe half to be pre-recorded and the other half to be presented over a real-time audio-feed by a live social partner [78]. Mentalizing regions (which were defined from an independent localizer paradigm with a typical false belief task, in particular dorsal/middle/ventral mPFC and bilateral TPJ [79]) and activations associated with social engagement [66] were observed when participants believed that the speech was live than they listened to recorded matched human speech. The right dmPFC was further correlated with the subjective rating of the liveness for the live speech versus the matched speech and with the individual's autistic traits (measured by autistic quotient [80]). The increased activity in the dmPFC was, the higher rating of liveness for the live speech versus the matched speech, and the lower score in the autistic-like traits. As the mentalizing regions were observed in fMRI studies of speech comprehension [43, 81, 82], the increased activity in the prefrontal mentalizing networks maybe attributed to the increased belief state reasoning during live interaction, or due to an ongoing representation of a social partner that underlies phenomena such as a social resonance, synchrony, and coordination. These findings suggest that the medial prefrontal cortex as a key region to indicate the ongoing mentalizing about social partners, were shaped by social context, and may be crucial for understanding the implication of social context for typical and atypical social processing, especially for neurodevelopmental disorders like autism who suffer more from social difficulties in live interaction.

The studies on language communication should be better fit into the large picture of the emergent contributions to the social brain, especially in the study of brain-to-brain coupling for learning, (re)constructing and using language through multi-participant experiments [2]. An fMRI study scanned the speaker's brain when they produced a 15-min-long real-life narrative and the listener's brain when they listened to the same narrative [83]. The brain regions specific to production and comprehension, and those that are overlapped between the two processes were examined. The left hemisphere and the bilateral temporal networks under the production of the narrative were shared with those under the comprehension system. Moreover, areas in which the neural activity was coupled between the speaker's and the listener's brains in both linguistic and extralinguistic areas during production and comprehension of the same narrative were shown. The narrative production engendered activations in social aspects of the story processing (e.g., mPFC, precuneus, dlPFC, PCC), as well as in motor speech areas (e.g., bilateral premotor cortex, bilateral insula, and basal ganglia), in the bilateral IFG associated with the construction of grammatical structures, and in bilateral STG/MTG previously linked to speech comprehension. The coupling between the speaker's and the listener's brain responses was found in precuneus and mPFC, bilateral temporal–parietal areas associated with the comprehension, and left IFG, bilateral insula, left premotor cortex associated with the production. The involvement of the medial prefrontal cortex and precuneus in a range of social functions suggests that the ability of a listener to relate to a speaker and to understand the content of a real-world narrative seems to rely on the higher-level social processing, including the reward-based learning and memory, empathy, and ToM (for mPFC), and first-person perspective taking and experience of agency (for precuneus). In particular, the inference of another's intention through verbal cues plays an essential role during exchange of information between the speaker and the listener and is integral to the success of real-world communication [84].

6. Cognitive empathy and pragmatic language processing

The last but not the least, one important goal of neurocognitive study of language processing is to reveal how the brain operates to make pragmatic inference, that is, to derive the broader meaning of a sentence according to world knowledge, discourse, and social context, and to resolve pragmatic incongruence or failure which arises from the conflict between linguistic input and the information derived from pragmatic inference and world knowledge. Studies on nonliteral language processing has revealed that the increased inferential process associated with the derivation of the nonliteral meaning from statements such as ironic remark or indirect requests may activate the regions associated with cognitive empathy (the ability to simulate others in a fictional or real world interactive setting [24, 85, 86]), in particular, in the mPFC and TPJ. Moreover, sentences with meanings incongruent with one's real-world knowledge or other types of contextual information (such as speaker identity, counterfactual context, etc.) activated the left IFG [87–91], and some general executive control networks including right IFG, IPL, medial superior frontal gyrus (mSFG) when pragmatic incongruence between linguistic representations or meanings has to be resolved (e.g., [6, 92]). Among the prefrontal executive control networks that are involved in resolving the pragmatic incongruence, the right IFG may subserve a process that inhibits the irrelevant information to ensure a representation that is congruent with the contextual information whereas the mSFG is more generally involved regardless of contextual type. For example, Nieuwland [91] reported the right IFG only responsible for the world knowledge violation in the counterfactual context (e.g., *If NASA had not developed its Apollo Project, the first country to land on moon would be *America*) but the mSFG in both counterfactual and real-world context (e.g., *Because NASA developed its Apollo Project, the first country to land on moon has been *Russia*).

In an fMRI study, Li et al. [4] demonstrated that the cognitive empathy of readers (as measured by the interpersonal reactivity index, IRI [93]) predict the neural activations when they read sentences in which the language use failed the pragmatic constraint. In a sentence with "even" which constrained an event of low expectedness, the neutral or highly likely events were embedded, creating the underspecified (e.g., *Even such a sound can be heard by Zhang, he has a sharp hearing*) and incongruent sentences (e.g., *Even such a *loud sound can be heard by Zhang, he has a sharp hearing*). They demonstrated that when the underspecified sentences were read, the activity in the ventral mPFC was associated with the reader's fantasizing ability (an individual's trait to transpose him or herself to the character of a fictional situations, e.g., novel). The observation of mPFC and its individual differences may indicate that participants may engage an action-related fantasizing or imaging process when making inferences for the underspecified scalar implicature. When the incongruent sentences were encountered, the mSFG extending to ACC was activated and bilateral IFG was correlated with their perspective taking ability (an individual's tendency to adopt the perspectives of others and see things from their point of view). The bilateral IFG was further connected with a number of prefrontal regions such as bilateral mSFG, SMA and ACC (for the left IFG) and right dlPFC and left IPL (for the right IFG) during the processing of incongruent versus congruent sentences. These conflict control networks were involved to unify information from different sources and select the appropriate representation (inhibit the inappropriate representation) for the incongruent sentences. Most importantly, these findings suggest that the cognitive empathy (including those that involve the shift of one's perspective to the fictional character and to another's perspective) supports the neurocognitive mechanisms in making pragmatic inference and in resolving pragmatic failure.

The involvement of prefrontal cortex in pragmatic processing is also supported by evidence in individual differences in autistic-like traits during language comprehension. Individuals with autism spectrum disorders demonstrated reduced neural activities in the mPFC when they inferred pragmatic meanings from metaphors or ironic remarks [94]. Using structural neuroimaging, Banissy et al. [95] demonstrated that an individual cognitive empathy was related with the gray matter volume of the prefrontal cortex. In particular, the volume of the dlPFC was positively correlated with one's fantasy scores and the volume of ACC was positively associated with one's perspective taking scores. The functional neuroimaging further demonstrated that the activation in mPFC for fiction reading relative to nonfiction reading, positively correlated with reader's fantasizing scores [96]. Neurophysiological studies (such as electroencephalograms (EEG)/event-related potentials (ERPs)) showed that the words embedded in sentences with under-informative use of scalar quantifiers (e.g., *some people have neck*s) elicited an increased N400 [97], an ERP effect which are considered to be the product of the underlying sources in inferior frontal cortex, than the words informative use of some [87]. This N400 enhancement was only observed in those showing higher pragmatic abilities (measured by Autism-Spectrum Quotient Questionnaire) but not in those with lower abilities [97]. Other studies also observed that those with higher empathic ability demonstrated larger N400 response in spoken sentences which contained words mismatching the speaker identity (e.g., *I want a teddy bear* in a man's voice) or larger late positivity effect in sentences that required the resolution of ambiguous referential representations based on a social context (e.g., a respectful second-person pronoun that is used in a directly quoted utterance that was addressed by a lower-status speaker to two potential addressees one of whom was of higher status [98, 99]). These neural mechanisms associated with pragmatic processing were either absent or altered in those with lower empathic ability.

7. Conclusion

To summarize, latest emergent literatures suggests a promising trend that researchers in language cognitive neuroscience are growingly attracted to address topic relevant to the neural correlates underlying social language processing. Despite the exciting new contributions in the relationship between neural networks underlying mentalizing/ToM, social inference, executive function, action, cognitive empathy and the understanding of different forms of nonliteral language, speech act, affection-charged literary, and pragmatic forms, it is still at the very beginning to characterize the precise role of prefrontal cortex in language communication in social contexts. More works taking advantage of the latest advancements in neuroimaging, neuropsychological testing, and even neurostimulation (transcranial magnetic/direct-current stimulation) should be facilitated to enlighten this new line of research in the broad context of neuropragmatics and cognitive neuroscience of human communication.

One future perspective is to examine the functional coupling between prefrontal regions and other parts of the brain that support the social inference via linguistic cues (e.g., vocal cues [100]) and the individual differences that modulate the strength of the functional coupling. Despite growing recent evidence with behavioral measures showing that language communication is deeply grounded in sociocultural conventions [84], few neuroimaging studies have dedicated to how culturally related linguistic and speech cues (e.g., linguistic accent) can contribute to the understanding of the role of the medial prefrontal cortex in perceiving sociocultural groups [100]. Another related question is how the knowledge regarding prefrontal cortex can illuminate the neural underpinnings of the socio-communicative deficits in special populations such as autism and schizophrenia, with a particular interest in the various types of pragmatic and social language processing as the medium for indexing their social interactive ability. These new proposals (with some of them being currently undertaken) will undoubtedly instigate more new endeavors to address the mediating role of prefrontal cortex in the relationship between language and social cognition.

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Conflict of interest

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Chapter 5

Hemoglobin (Hb) - Oxyhemoglobin (HbO) Variation in Rehabilitation Processes Involving Prefrontal Cortex

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Additional information is available at the end of the chapter

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Abstract

The prefrontal cortex is the anterior part of the frontal lobe, situated before the primary motor cortex and the premotor cortex and plays a role in the regulation of complex cognitive, emotional and behavioral functioning. It includes various Brodmann areas, such as 9, 10, 11, 12, 46, 47. The basic function of this region is guiding thoughts and actions toward one's goals. The goal of the study is using functional near-infrared spectroscopy (fNIRS) to identify the most suitable rehabilitation model in subacute post-ischemic pathologies and impairments involving directly or indirectly the prefrontal cortex. The aim is to measure threshold parameters for neural fatigue through Hb-HbO2 variation. The overall purpose is the ongoing evaluation of Hb-HbO2 variation throughout the entire tailored rehabilitation program with the observation of patient's clinical changes, which represents the heart of the Cerebro rehabilitation model.

Keywords: rehabilitation, PFC damage, fNIRS, Hb-HbO2 variation, cerebro rehabilitation model

1. Introduction

Although not yet widely used, probably because of lacking clinical education, near-infrared spectroscopy (NIRS) shows several methodological advantages if compared with other non-invasive measurements of neural activation.

NIRS specific and unique features make it a prospective tool for studying stimulus-based responses to emotion processing in the prefrontal cortex (PFC). However, there are obstacles for the implementation of NIRS on emotional research that must be considered.

This study focuses on NIRS ability to express suitable measures for the most adequate rehabilitation process with results that permit to evaluate the effects of PFC activation over emotions. Specifically, the neural mechanism underlying these processes is based on a bidirectional interaction between emotion and action, excellent to be measured using NIRS technique.

The Cerebro procedure aims at setting the fundamentals for NIRS application in those fields whose aim is to evaluate suitable rehabilitation models in prefrontal cortex related disorders by analyzing task-related stimuli that are mediated by pathways involving sensory processing, memory and emotion. To do so, NIRS parameters during recording will be considered along with the NIRS level of criticality in order to determine the good practice for functional processing of the required result.

When talking about prefrontal cortex (PFC), we need to remember that the associative cortex in the frontal lobe has a lagging development in the neocortical regions. PFC is one of the cortical regions which undergoes a major expansion during personal maturation and evolution. In human adults, PFC represents approximately one-third of the whole neocortex. The PFC ongoing and wide development is demonstrated by its impeccable structure.

In developing brains, like infants', PFC's delayed maturation is marked by a late myelination of axonal connections.

Prefrontal cortex in primates is necessary not only for keeping relevant information in mind to complete a task but also for the active suppression of the irrelevant stimuli. Patients with ictus or pathological aging, affecting the lateral portion of the PFC, can discriminate between auditory tasks but fail when irrelevant auditory stimuli are included [1].

This information is important in order to define the NIRS-fNIRS ratio (fNIRS: functional near-infrared spectroscopy since this is used when a stimulus is given, and the outcome is a measurement of how the stimulus affects brain activity; if not it is a resting state registration that we call NIRS) where inhibitory responses or noise can influence the assessment of the result. Noise is the key point for the identification of an optimal functional assessment; therefore, in the following paragraph, we focus on specific measurements, precautions to be taken and the right procedure to follow, step by step, in the preliminary phase of testing.

2. NIRS and fundamentals of measurements

For the evaluation of rehabilitative activity that involve prefrontal cortex (PFC), we used the NIRS functional detector systems: near-infrared spectroscopy uses low-intensity optical radiations to measure changes in light absorption by the cortical vascular tissues in order to detect changes in local concentration of oxy- and deoxyhemoglobin as a correlate of functional brain activity.

Each measurement channel is formed by an optic emitter (source) and a receiver (detector) placed on the subject's head. Due to the scattering (light diffusion) properties of the tissue, a portion of the received light will deeply pierce in the tissue structure, where it interacts with chromophores like hemoglobin. The degree of penetration and the shape of the probing volume are determined by the source-detector distance and by the optical properties of local tissues. Cortical NIRS signals are estimated to originate from an area that is placed between source and detector and from a tissue depth that is no more than the half of the source-detector distance (see **Figure 1**). Optical signals are weakened by biological tissues; intensity will decrease in terms of centimeters, therefore the optimal distance between source and detector is a compromise that must be verified in order to reach the maximum depth while maintaining a sufficient signal quality (signal-to-noise ratio). The optimal distance used in this study is the verified one of 30 mm and the cortical detection depth is around 25 mm.

To achieve spatial imaging of the PFC, we used the NIRX imaging equipment that employs matrixes of paired source-detectors arranged on the area of interest, where each source channel forms a measurement channel with each detector channel. Therefore, a setup with X sources (S) and Y detectors (D) will produce an X*Y measurement channel. This is true despite the position and the source-detector distance although only those channels whose distance is within a certain limit will produce signals with usable amplitudes and noise levels. Due to this model, there are no restrictions on how to set up sources and detectors, thus allowing us the maximum flexibility and freedom in realizing this functional study. At the same time, we focused on the experimental design ensuring signal quality during the set up and consequent optimal signal values data analysis. Meanwhile, we aimed at a perfect positioning which could guarantee signal quality and consequently adequate data analysis.

In order to achieve the abovementioned goals, calibration procedures were made for each functional assessment in which each source-detector combination was optimized. According to the quantity of light emitted by the source and received by the detector, the system predicts the optimal amplification signal, that is, the best signal quality that can be achieved. This process is automatically run by the control system during the calibration phase.

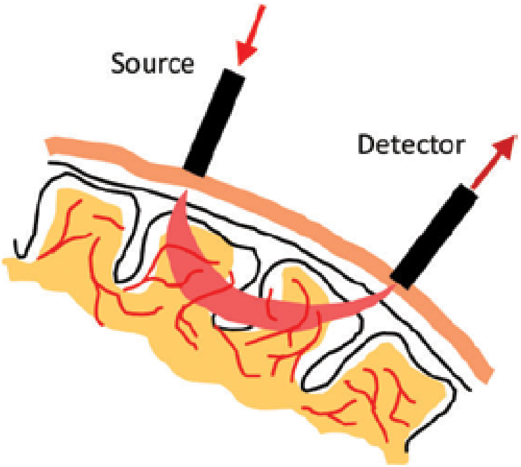


Figure 1. (Courtesy of NIRx Medical Technologies) Each measurement channel is formed by an optic emitter (source) and a receiver (detector) placed on the tissue surface. Cortical NIRS signals are estimated to originate from an area that is placed between source and detector and from a tissue depth that is no more than half of the source-detector distance.

One-year effort was needed in order to gain familiarity and competence with this system, and this amount of time is largely recommended in order to avoid hardware failure resulting in variations of the identified values.

The NIRS model used in this study is named NIRSport (**Figure 2**, 8 × 8 imaging system (8 × 8 mean 8 sources and 8 detectors). This NIRS hardware is attached to a pre-configured tablet or PC throughout a USB 2.0 cable. Every NIRS montage cap, on which sources and detectors are attached, follows the 128 standard EEG positions (known as the 10/20 international system).

2.1. Optimal system check

Before running the system, sources and detectors must be placed on subject's head. The montage, in this case the Prefrontal Cortex (PFC) one, was chosen among a wide selection of different montages provided by NIRX. By starting the program, a system data sheet is displayed with a typical configuration setup for data acquisition.

Signal quality is the pre-requisite for a good functional recording; thus, before starting to record, it is necessary to run a source-detector calibration to verify it.

NIRS provides quality signal for each channel, classified by color (**Table 1**):

- Excellent (green): this quality level allows a clear view of heart fluctuation in the HBO signal and is appropriate for highest demands such as single-trial/single-subject evaluation. Cardiac signal may not be discernible on the display due to physiological reasons, but the output allows to detect the current noise and pull out neural activity with a suitable statistical analysis (filtering, SPM event-related mean, group mean).

If signal quality is low (red or white), neural activation may not be visible and blocked by noise signal. The most probable reason is the optical quality of the tissue itself. Losing the signal and consequently losing a channel information data are mostly due to the erroneous location of sources and detectors.

Figure 2. (Courtesy of NIRx Medical Technologies) NIRSport 8 × 8 imaging system; detectors and sources must be placed in the corresponding slot, equally for triggers sent to the software through a specific equipment (if necessary), the connection USB cable and, on the other side, the power supply connector.

Table 1 shows signals criterion that are considered from right to left; algorithm quality scale checks if optimal level is reached for each channel, then evaluates signal strengths for each wavelength (760–850 nm) and estimates the detected noise level. The final signal quality classification for a given channel depends on the worst marker obtained.

Figure 3 shows a signal quality map where every channel has been judged to be "excellent" (in green) or "acceptable" (in yellow); this means that each channel achieved amplification gain intervals from 1 to 6. Levels ranged from 0.09 to 1.40 and the corresponding noise level is <2.5%. These values are shown in an appropriate software window.

The button "Refresh" allows us to update quality assessment without running a new calibration. It is important to keep in mind that a quick and well-done montage setup will shorten this calibration phase in order not to stress out the subject emotionally. The topographic layout helps to locate each channel and to act on a specific channel to set optimal signal quality.

Signal Quality	NScout Gain [10^x]	NSport Gain [10^x]	Level [V]	Noise [%]
Excellent	1 - 6	0 - 2	0.09 - 1.40	< 2.5
Acceptable	7	3	0.03 - 0.09 1.40 - 2.50	2.5 - 7.5
Critical	0 8		0.01 - 0.03 > 2.50	> 7.5
Lost	-	-	< 0.01	-

Table 1. (Courtesy of NIRx Medical Technologies) shows signals criterion that are considered from right to left; the final signal quality classification for a given channel depends on the worst marker obtained.

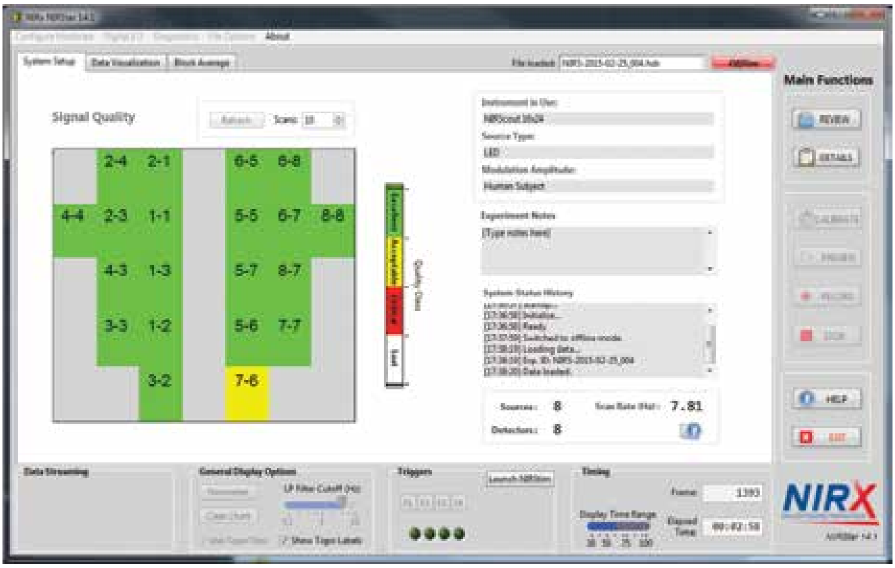


Figure 3. (Courtesy of NIRx Medical Technologies) shows a topographic layout in which excellent signal quality are displayed for each channel except for one that is acceptable.

By clicking on the "Details" button, a detailed calibration window will open with individual maps of gain, level and noise. Gain map: an inverse relationship exists between gain and intensity of the received light, intensity of light must be more amplified if the light signal is weak. If the outdistance between sources and detectors is between 2.5 and 3.0 cm, we expect a gain of 4, if lower than 4 there is a low level of light attenuation. If channels do not reach a maximum gain level of 7, the signal levels will be marked red and a new calibration phase needs to be run after having improved the contact between optodes and skin. Important is that the displayed layout is qualitatively reproducible across different subjects attending the experiment.

Signal level: Signal levels and noise ratios can be examined for each wavelength differently to the gain levels. Signal levels are mapped according to a logarithmic scale and expressed in voltage units.

Noise: In order to quantify the noise level, the system uses coefficient of variation (CV = standard deviation/mean × 100) of those recorded data used to assess signal levels.

Dark noise: high levels of dark noise may be due to environmental light disturbance or if the NIRS system is connected to power.

As default, the color combination is set according with the traffic light colors (excellent, acceptable, critical and lost). If "Quality Scale" button is deactivated, the older color scheme is displayed as shown in **Figure 4**.

2.2. Data visualization and recording

If the configuration phases and the calibration have been followed correctly, real-time data are displayed in a preview or can be directly recorded. Side-by-side there is a trace display and a topographic map for Hb and HbO concentration (**Figure 5**). Data presented in the topographic map represent estimated changes of oxy and deoxyhemoglobin concentration. The recorded data are raw signals of individual wavelengths.

The estimated data of oxy and deoxyhemoglobin concentration vary for each channel and are shown on the left side of the data visualization panel. In order to set an appropriate rehabilitation approach this allows us to visually inspect the ongoing fluctuations and verify them according to a given stimulus. For a clinical assessment, being able to analyze temporal sequences of each channel by selecting them individually is important. Amplifying the signal level (**Figure 6**) allows us to enlarge the fluctuations in order to better inspect the recording data. If no scale factor is applied, the unit of Hb state is mmol/L but may be scaled up to a factor of 2000 mmol/L.

Before starting the recording, in the preview data visualization, it is important to apply the low-pass frequency filter to remove high-frequency noise or the heartbeat component (**Figure 7**).

Despite the trace display, the Hb-HbO concentration is shown as a 2D map where channels are depicted (**Figure 8**).

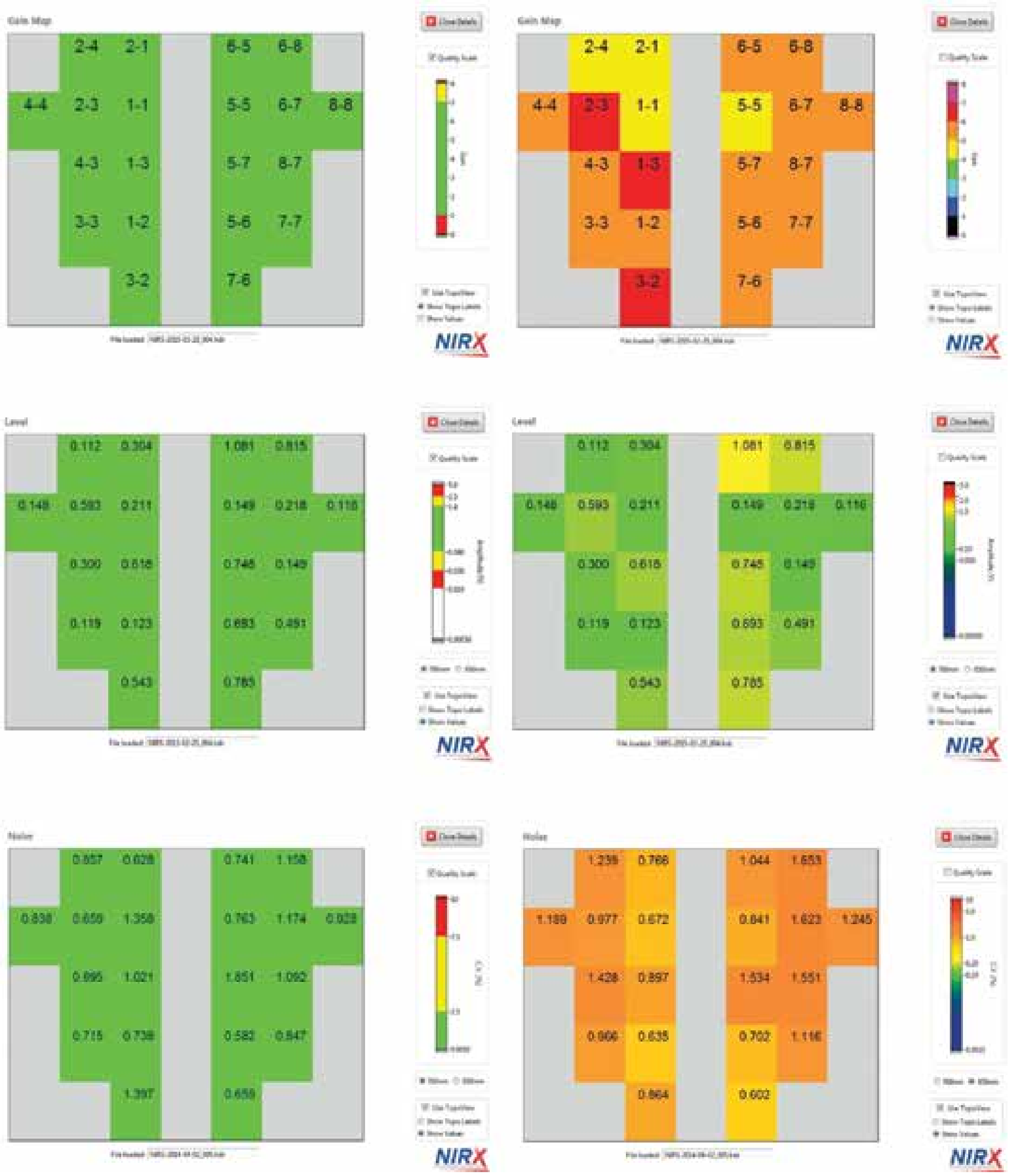
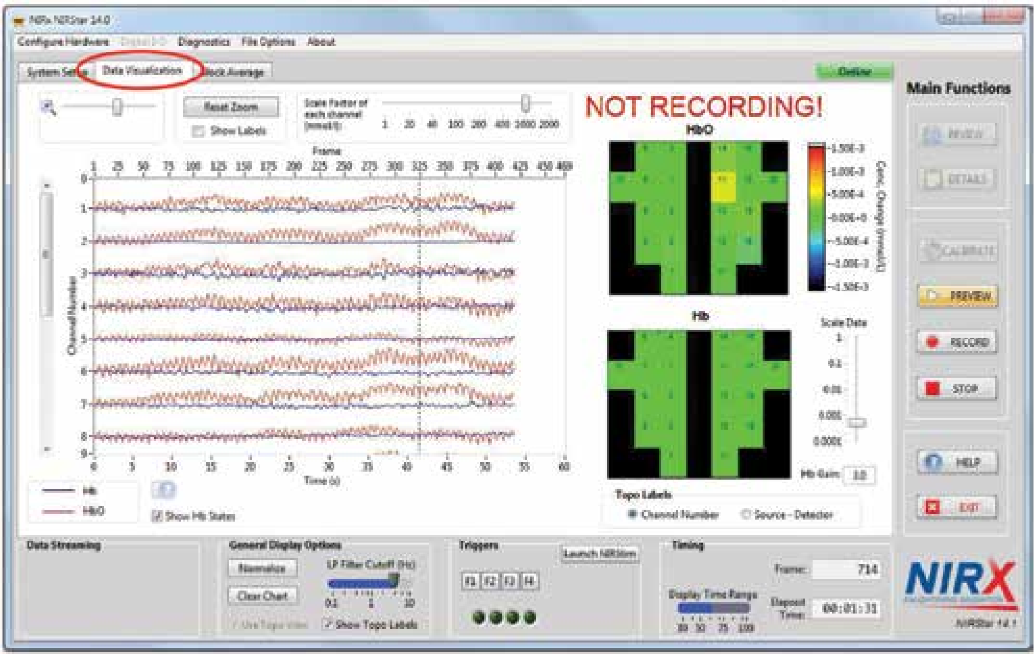


Figure 4. (Courtesy of NIRx Medical Technologies) shows gain map, signal level and noise in a topographic layout for each channel. In the left column, the option "quality scale" is activated; in the right column, the option "quality scale" is deactivated, where the only thing changing is the color scheme.

In order to enhance Hb dynamics on the display, the Hb gain can be scaled up for better clinical observations purposes. The trace display in **Figure 8** has been filtered to remove high frequency and 1 Hz heartbeat frequency.



Frame: 714

Elapsed Time: 00:01:31

Hb Gain: 3.0

Figure 5. (Courtesy of NIRx Medical Technologies) Data visualization with a trace display on the left side of the screen, topographic layout on the right side of the screen expressing changes in Hb-HbO concentration. Remember that the recorded data are raw data, based on individual wavelengths.

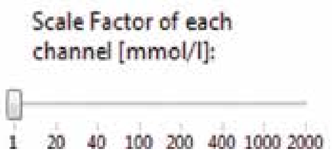


Figure 6. (Courtesy of NIRx Medical Technologies) This scale factor allows signal levels to be increased from 1 to 2000 mmol/L.

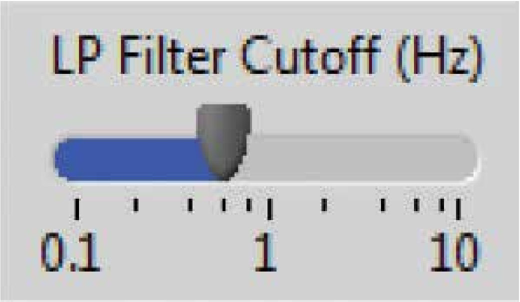


Figure 7. (Courtesy of NIRx Medical Technologies) shows the low-pass filter; in this case, the 1 Hz heartbeat frequency is filtered out.

In clinical assessment, responses to psycho-physiological stimuli (audio, visual, tactile, etc.) are interesting to examine; therefore, NIRS signal must be correlated to event-related stimuli. Markers are necessary to set the beginning and the end of a task or subjects response. NIRS can be provided with internal or external trigger signals (**Figure 9**) coming from other equipment that allows stimulus presentations.

The software allows to set markers manually during the experiment in case of unexpected experimental event such as motion artifacts or subject distraction.

A block average feature allows to visualize real-time topographic areas in multiple conditions (**Figure 10**).

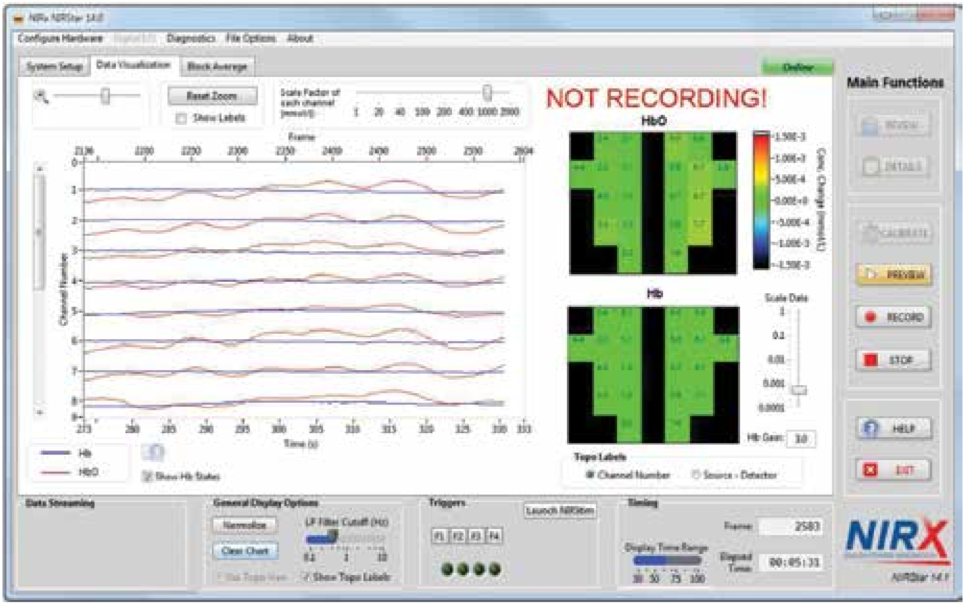


Figure 8. (Courtesy of NIRx Medical Technologies) shows the data visualization panel. On the right side of the screen, Hb and HbO concentration are represented for each channel, and on the topographic map, there are channel numbers or source-detector labels.

Figure 9. (Courtesy of NIRx Medical Technologies) shows different trigger signals that can be used to set the end and the begging of psycho-physiological stimuli; the marker is set by clicking on the respective button (e.g., F1) or by pushing F1 key on the computer keyboard.

2.3. Topographic display

By using a NIRS technique, a rendering function is useful since it provides a hemoglobin topographic data into realistic 2D-3D coordinates. This function is given by another software that is in any case necessary in order to visualize hemoglobin fluctuations following psycho-physiological stimuli (**Figure 11**).

2.4. How to set and prepare the NIRS system properly: a recap

The NIRS hardware is attached to a pre-configured tablet or PC throughout a USB 2.0 cable. Every NIRS montage cap, on which sources and detectors are attached, follows the 128 standard EEG positions (known as the 10/20 international system).

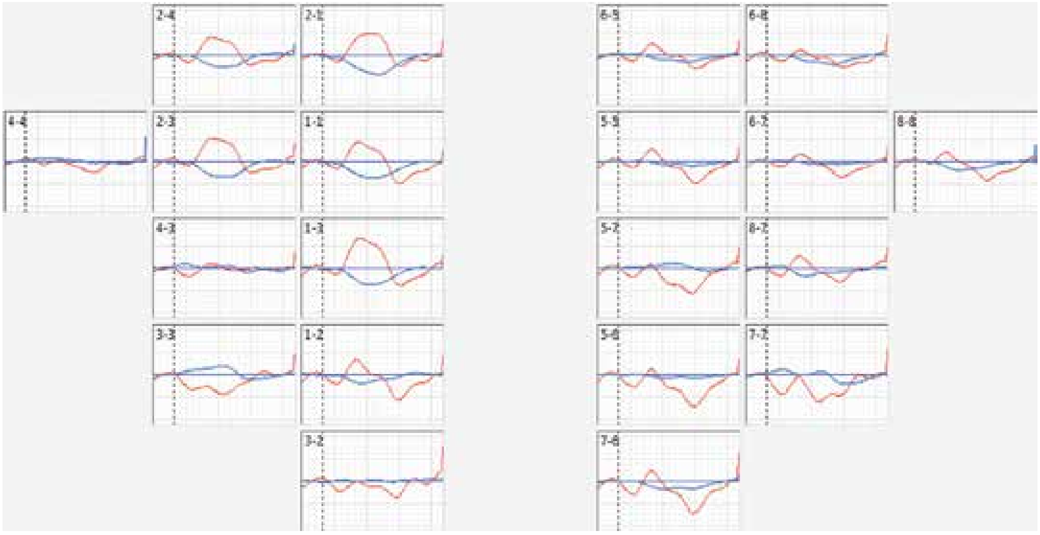


Figure 10. (Courtesy of NIRx Medical Technologies) shows an example of block averaging display that has to be set before starting the recording session. Number of conditions need to be arranged in order to identify them graphically. The oxy (red) and deoxyhemoglobin (blue) traces displayed are a mean of the fluctuation during a fixed stimulus duration (3–10 s). Stimulus duration and number of conditions are required to be set before the recording session.

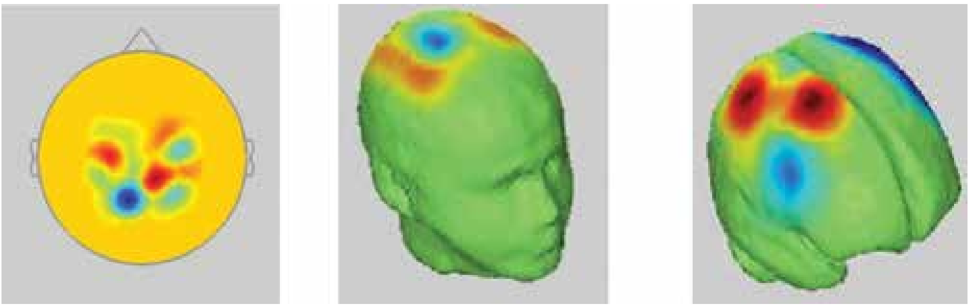


Figure 11. An example of the possible topographic view, in 2D or 3D mapping. (Courtesy of NIRx Medical Technologies).

Once the software is configured, the cap can be placed on the subject's head according to the pre-selected montage, in this case the prefrontal cortex montage.

Before starting to record, a calibration phase is necessary. The system will automatically determine the quality of emitted (sources) and detected (detectors) light signals by assigning a quality indicator for each defined channel. If optodes are placed correctly, signal quality is good or acceptable (see **Figure 3**) and the subject is in resting state, the calibration session can start.

Signal quality derives from multiple factors such as photodetectors' amplification level, estimated noise level (carefully inspect environmental light interferences), optode and skin contact, optimal distance between sources and detectors (30 mm). At the end of calibration, the channel quality signal allows to identify if the following steps have been considered:

1. Optode to skin optical contact.
2. Check sources and detectors position according to the defined montage.
3. Optimal distance between sources and detectors: 30 mm.
4. In case of complete loss of all channels, check the cable connection.
5. Avoid spreading of environmental light into the cap; do not place the subject under a bright light or put on the cap an additional black cap that avoids light to pass through.
6. Optode perpendicularity (both sources and detectors must stay in vertical position attached to the subject's skin).
7. Skin color, hair color or hair products such as hair gel can influence light reflection and absorption.

The criterion is to adjust signal quality each time in order to achieve a channel quality that is colored in green or yellow, not red or white that describes a critical loss of signal and a consequent exclusion of that channel during the subsequent data analysis.

If everything is fine, each channel is in its optimal condition and the recording phase can take place.

3. fNIRS: Beware of methodology!

The main challenge for researchers is to apply NIRS technology to emotional research as standardized NIRS and fNIRS methods are not yet available.

The first problem is represented by noise, caused by heart-rate variation and Peripheral responses following emotional stimulation. Physical changes often go along with induced state of arousal such as facial muscle contraction or, as said before, increase in heartbeat. The NIRS technique can mitigate this problem by downranging the heartbeat frequency rate (see Section 2.2) although, if not properly set, this can bring to error of data assessment.

Aerobic process and energy consumption associated to muscular contraction may induce significant changes in oxyhemoglobin. However, Schecklmann et al. [2] found no relationship between electromyographic signals and oxyhemoglobin variation during a fluency task. Nevertheless, the influence of peripheric responses was analyzed including limited condition.

Further signal falsification is given by neural activation to emotional stimulation since variation in Hb-HbO concentration in this case may be due to vasoconstriction. A solution to this is to elicit two different emotional responses and statistically analyze the differences in Hb-HbO concentration between the two responses.

Another problem appears to be the time range (TR) selection that is the time needed for cortical activation to be visually inspected; many studies suggest that oxyhemoglobin drop values indicate cortical activation [3]. Suh et al. [4] claim that cortical direct stimulation induces a rapid increase in deoxyhemoglobin (1–2 s after stimulation) while the total hemoglobin value remains constant. This problem is avoidable by using high temporal resolution in order to evaluate statistically significant changes in Hb-HbO concentration variation.

3.1. Potential fNIRS application

Theories on PFC's role in emotion processing [5–7] agree on PFC being the key area in which emotional reactions, motivation, attentional processes and behaviors take place.

As PFC is important in emotional processing, the evaluation of emotional intensity with NIRS becomes crucial.

Studies suggest that individual sensitivity to reward and stress may promote depression disorders [8, 9]; these results induce a deeper analysis of eventual biological predisposition that may lead to specific PFC responses to stimuli-induced emotions. Individual differences in terms of emotional responses can help in identifying eventual risk factors.

Using NIRS to analyze PFC activity when stimulated during rehabilitation and the evaluation of the rehabilitation program intensity, considering the abovementioned biological factors, may help to select the optimal rehabilitation method for each patient.

Primary function of emotion is to guide adaptive motor behavior [10]. Few studies focused on this important statement. It is well known that motor activity directly interacts with emotions and mood [11], and it has been shown that there is a bidirectional relationship that has been established between motor function and individual emotional experience [12].

4. From fNIRS to the definition of a rehabilitation model

The ability of the brain to reorganize itself and change its activity associated to a given function in order to achieve a neurological control is well supported by studies in neural activation. This is a goal to be kept in mind while using a verified and controlled neuronavigation technique such as fNIRS. Nowadays, everyone is trying to find the best standardized rehabilitation process while the entire scientific community agrees on the brain specific individuality that cannot be encoded. We can claim to know each functional brain area, but the information encoded inside is individual and only in a small part conventional. This is the main starting point in order to set individualized rehabilitation models through the use of neuronavigation techniques such as fNIRS.

In order to allow a cortical reorganization process, there is the need of a specific environmental stimulation, aimed at compensating the impairments. Regardless of which brain area is involved, the aim is to set up a model that can be verified each time with optical imaging techniques. According to this kind of rehabilitation model, the environmental stimulation needs to be grounded on the person's real life experiences so that the choice between different rehabilitation programs is based on the brain activity of a specific area involved during stimulation and verified thanks to NIRS. This choice has to be based not only on customary, logistic and organizational needs but also on cognitive, emotional and motivational patient's needs according to a functional brain activation point of view.

The main goal of the Cerebro rehabilitation model is to improve the functional outcome by supervising rehabilitation choices from time to time and to evaluate the emotional outcome by analyzing Hb-HbO variation in PFC since it is an area involved in emotional control [13].

4.1. Cerebro model's application fields

This neurofunctional rehabilitation model is applied to patients with behavioral cognitive impairment due to brain injury after a complete neuropsychological assessment.

Neurofunctional impairments are:

- Cognitive: like neglect, visuospatial disabilities, aphasia, agnosia, apraxia, amnesia, dyscalculia and attention deficit.
- Emotional-motivational: like apathy, emotional lability, irritability, depression and anxiety.
- Executive (behavioral): like disinhibition, control reduction, discriminatory ability, thought disorder, disorganization, reduced problem solving and lack in self-awareness.

Each of these impairments involves directly or indirectly the prefrontal cortex since it is charged with emotional control.

Others that can benefit from this rehabilitation processes are post-stroke patients, cerebrovascular diseases, traumatic brain injuries, multiple sclerosis, encephalitis and post-surgical cancer patients.

Neurodegenerative diseases are excluded from this rehabilitation procedure, apart from multiple sclerosis due to its remittent nature, since there is no evidence yet on how to treat them and due to lack of compliance. However, in case of a motor impairment together with cognitive impairment, that are usually not rehabilitated, our neurofunctional rehabilitation method may be applied in order to monitor brain areas and determine more appropriate choices that would not be taken because of lack of compliance. The most important achievement in order to obtain autonomy in everyday life is being able to perform an adequate motor act and this can be done even if cognitively impaired.

4.1.1. Definition and evaluation of neurofunctional impairments

First, neuropsychological assessment needs to be integrated with neurofunctional measurement of the area involved using neuronavigation techniques such as NIRS and to be combined with the patient life experience and peculiarities such as everyday life, work, family, house, hobbies and emotions experienced.

Next step is to evaluate neuropsychological impairments from a behavioral and cognitive point of view.

- For cognitive impairments, preserved and altered networks reflecting impaired cognitive functions are evaluated with psychometric and standardized tests.
- For executive impairments and motivational disorders, direct evaluation of motivational levels is observed by analyzing patient's willingness and effort in taking part in the rehabilitation program together with suitability of social behavior, ability to control and inhibit thoughts and behaviors, static/fluid thinking and problem solving. These observations are measured with NIRS technique in order to set a starting value of Hb and HbO variation that will be taken as a baseline during each rehabilitation session in order to control metabolic brain fatigue.

Many questionnaires can be handed out and functionally measured with NIRS such as: Quick Exposure Check (QEC) [14], Cognitive Failures Questionnaire (CFQ) [15] and so on.

- Emotional functioning can also be observed with neuronavigation techniques; presence and entity of emotional disorders, such as emotional lability, irritability, depression and anxiety, changes in personality and caregiver relationship quality.

As before, analyzing brain activity while administering standardized questionnaires is very important in order to exclude misunderstanding of items and have a responsive measurement of brain activity while reading the questions. Standardized tests that can be administered are Neuropsychiatric Inventory Questionnaire (NPI-Q) [16], Beck Depression Inventory (BDI) [17], Geriatric Depression Scale (GDS) [18], Minnesota Multiphasic Personality Inventory (MMPI) [19], European Brain Injury Questionnaire (EBIQ) [20] and Big-Five Questionnaire (BFQ) [21].

- Emotional engagement and self-awareness deficits must be assessed through clinical observation and neurofunctional investigation with NIRS. Patient's compliance sometimes does not reflect the undergoing neurofunctional responses; patient may act as collaborative as usual despite his true engagement.

Collected data taken from the neuropsychological assessment allow a faster and more precise identification of neurofunctional impairments.

4.2. Rehabilitation goals

Defining the optimal rehabilitation program is the fundamental basis of the Cerebro model. Prefrontal cortex (PFC) activity is indeed one of the most significant areas involved in executive functions, therefore it is extremely interesting.

The main goal is achieved through a variety of subgoals directed to arouse natural daily-life responses.

Goals are structured according to three different rehabilitation phases:

- First phase must provide deficit awareness through rehabilitation processes based on life experience stimuli. Keep in mind that mirror neurons are everywhere not only in the motor cortex.
- Second phase must provide practical skills in order to compensate cognitive, emotional and behavioral impairments.
- Third phase is the conclusive one. It consists in strengthening acquired rehabilitation skills in order to match patient's life necessities.

4.2.1. Methods

Experiential living is what makes individuals unique; that is why the Cerebro rehabilitation program takes it into account.

The methodology used is based on cognitive and behavioral studies that can be outlined as follows:

- Specific stimulation of a cognitive impaired process. Check of excessive stimulation in the impaired area. The stimulation can facilitate information access that is relatively intact but no more accessible due to the impairments.
- Stimulation and functional reorganization of preserved cognitive processes.

Irrespective of the selected technique, cognitive and behavioral deficits must be assessed by Hb-HbO concentration analysis provided by neuronavigation (fNIRS).

Choosing strategies and rehabilitation goal depends on different factors:

- Deficit assessment of cognitive and behavioral impairment and related impact on everyday life.
- Proficiency level in coping strategies.
- Cognitive function analysis for goal-oriented activities.
- Individual features assessment like socio-cultural and educational context as well as experiential living.

- Etiology and localization of brain lesions.
- Emotional response following brain lesion.
- Motivation and compliance to treatment.
- Changing in personality.
- Disability and psycho-social consequences.
- Deficit awareness.
- Presence or absence of a good family support.

Time of monitoring with fNIRS is influenced by patient's hospitalization period. If the prefixed goal has not been achieved or if there are still dysfunctional areas that could be usefully considered for an optimal rehabilitation program, then a day-hospital formula is needed.

Changing in patient's behavior can be monitored throughout the rehabilitation period because the neuronavigation systems like fNIRS allow to change and adjust the rehabilitation program according to the patient's needs.

At the end of the rehabilitation program, a neuropsychological assessment is necessary to evaluate the improvement or stationarity of the early impairments via neuropsychologic standardized tests, questionnaires and so on. The results obtained are analyzed and serve to establish a long-term rehabilitation program applicable in everyday life.

Neurofunctional rehabilitation is planned by the psychologist in charge with the neuropsychologist experience in test administration according to the reported cognitive impairments. A speech therapist is needed to evaluate speech disorder in case of aphasia.

In addition, other health professionals are needed such as occupational therapists and physiotherapists for motor function disorders in order to improve everyday life autonomy in activities of daily living (ADL) or to discourage maladaptive behaviors.

Finally, care givers are important in order to set proper individual life-based stimuli, which is essential to this kind of rehabilitation model.

5. Conclusions

Near-infrared spectroscopy (NIRS) uses low-intensity optical radiations to measure changes in light absorption by the cortical vascular tissues in order to detect changes in local concentration of oxy- and deoxyhemoglobin as a correlate of functional brain activity. Several precautions are needed to obtain a clear and optimal signal that reflects the patient's brain activity. Due to its features, NIRS is the best and most practical way to depict emotional responses in prefrontal cortex (PFC).

Despite technical limitations, NIRS is a reliable method to quantify a stimulus reaction especially in PFC functioning in emotion processing. It allows to establish the optimal rehabilitation program according to a visual inspection of Hb-HbO concentration variation and by checking the functional area involved.

By measuring individual experience-based emotions encoded by PFC, it is possible to choose between different rehabilitation programs according to life experience but also to individual Hb-HbO variations.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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Chapter 6

Consciousness and Social Cognition from an Interactionist Perspective: A New Approach on Understanding Normal and Abnormal Relations between Metacognition and Mindreading

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Tomasz Cyrkot and Remigiusz Szczepanowski

Additional information is available at the end of the chapter

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Abstract

Contemporary discussions on relations between metacognition and mindreading result in several theoretical accounts allowing various combinations of both mechanisms in the process of formation of beliefs, intentions, and decisions with respect to oneself or others. In fact, various prefrontal areas of the brain are activated when individuals mentalize about themselves and about other people. Interestingly, the latest accounts of the relationship between mindreading and metacognition clearly favor arguments for interactionism between functionally different mechanisms in the formation of our social knowledge. In particular, a two-level architecture enables a mutual interaction within a complex metacognitive system that is evolutionarily structured into higher and lower level metacognition with different functions and tasks. In our opinion, cognitive architecture of such systems needs to include conscious mechanisms that incorporate information accessibility as activation through the interaction. Here, we will argue that the combination of the two-level account on mindreading and metacognition along with a global broadcasting architecture embedded in the human brain is a good starting point that explains formation of accurate social knowledge and access to such knowledge. In our opinion, it becomes clear that consciousness via the interaction activates many unconscious brain regions, including interpreter systems such as metacognition and mindreading.

Keywords: consciousness, metacognition, mindreading, global workspace theory, borderline personality disorder, schizophrenia

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1. Introduction

The questions about the nature of how we know other people's minds (mindreading, "theory of mind" [1]) and how we know our own mind (metacognition [2, 3]) are intensely debated in a variety of research fields such as cognitive sciences, psychology, or psychiatry [4, 5]. The term "metacognition" describes cognitive processes that are involved in "thinking about own thinking" by which people can reflect upon (monitor) their own internal mental states and use their knowledge to evaluate and regulate (control) their own mental states [6, 7]. On the other hand, the notion of mindreading is related to our own cognitive processes that can be applied to other people ("thinking about the thinking of others") in terms of recognizing others' intentions, mental states, emotions, as well as predicting possible behavior of other people [1, 4, 8]. In fact, Bateman and Fonagy [9] point out that both mental capacities (metacognition and mindreading) can be a form of mentalization engaging cognitive processes that are aimed at implicit and explicit interpretation of our own actions and actions of other people as meaningful. In fact, both components influence one another and involve complex and critical operations in human social life [8].

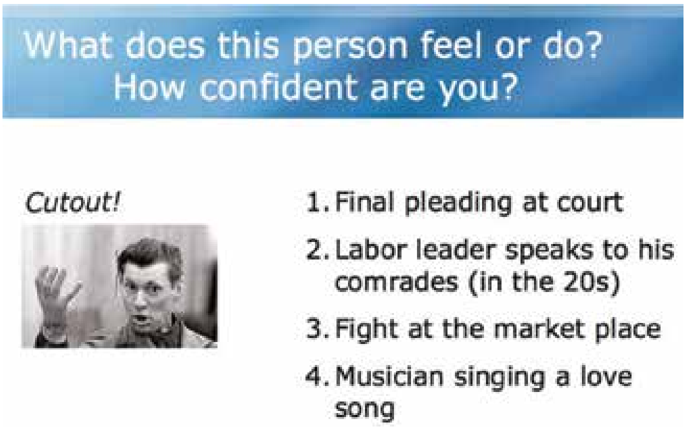
Crucially, clinical research interest focuses also on attempts to explain various mental disorders in relation to deficits in mindreading [10], dysfunctional metacognition, [11] as well as an abnormal relationship between both cognitive facilities [11]. Typically, clinical researchers define mindreading deficits as limitations or complete loss of capacity to recognize and attribute mental states in order to understand other people, including their intentions, beliefs, emotions, and possible behaviors [4, 11]. For instance, such persistent mindreading deficits are commonly observed in a group of patients with schizophrenia [11]. In turn, impairments in metacognition are thought to be involved in formation of abnormal recognition and understanding one's own mental states and deficits in proper control and monitoring of one's own internal states [12]. Apparently, deficits in metacognition are demonstrable in a variety of mental disorders. Some clinical studies demonstrate influence of dysfunctional metacognitive beliefs on the development of and formation of psychotic symptoms, including hallucinations and symptoms of anxiety accompanying mental disorders [13]. For instance, a core positive symptom of schizophrenia, which is a lack of insight, clearly represents a failure of metacognition. Over the last decade, the empirical research emphasizes the role of dysfunctional metacognitive beliefs (declarative knowledge) or metacognitive thought control strategies (procedural knowledge) as predictive to development of psychosis in normal and clinical populations [14–16] and maintenance of neurotic symptoms [17]. A vast body of research gives also indication that patients with psychosis have also dysfunctional meta-beliefs. For instance, in a nonclinical sample, García-Montes and colleagues [18] based on Metacognitions Questionnaire construct (MCQ construct; [19]) in their correlation study showed that both metacognitive factors such as thought control strategies about worry as well as loss of confidence were indicative to hallucination proneness when trait anxiety was controlled.

Nonetheless, the present article considers a more complex cognitive architecture of social cognition that may possibly underline the dysfunctional interaction between mindreading and metacognitive capacities. For example, recent clinical studies on various causes of mental disorders identify abnormal patterns of recognition and attribution of mental states either to themselves or others in patients suffering from schizophrenia [20, 21], social phobia [10], as well as patients diagnosed with borderline personality disorders (BDP) [22, 23]. It is important to emphasize that new approaches to conceptualization of the interaction between metacognition and mindreading become important not only for understanding abnormal social cognition but also for finding effective treatments of mental disorders and offering appropriate psychological care to patients. Our paper aims to demonstrate that combination of an interactionist approach on metacognition and mindreading [6] with a theory of consciousness mechanisms [24, 25] is a convenient cognitive perspective that takes into consideration the interaction between both mental capacities and conscious access to information in ensuring effective social behavior.

2. Metacognitive therapy and role of consciousness

Before going ahead with our theoretical discussion, it is first instructive to start with discussing a case from clinical intervention that shows cognitive complexity and real challenges behind the relation between social cognition and consciousness. Recently, there has been a substantial progress in the field of cognitive-behavioral interventions for treatment of psychiatric disorders (for instance, see [26]). Empirical studies on new therapeutic approaches based on metacognitive training provide solid evidence that corrective experiences are efficient in handling cognitive biases in psychiatric populations [27]. Positive clinical results are achieved through a variety of metacognitive technique exercises including the "theory of mind" skills (https://clinical-neuropsychology.de/metacognitive_training/). Research studies clearly show that psychiatric patients who underwent intervention of metacognitive training for psychosis can substantially reduce their cognitive biases [26]. For instance, patients undergoing a therapeutic intervention based on the "theory of mind" module for psychosis by engaging conscious evaluation may diminish overconfidence in errors, frequency of jumping to conclusions, etc.

Let us imagine an omnipotent patient that attempts to identify the actor as a leader who speaks to the crowd and may be overconfident in his/her wrong response. The example shown in **Figure 1** can help us to capture the phenomenology of social cognition and conscious evaluation. It is most likely that abnormal information processing in this patient would lead to biased responses (distortion in social cognition) and overconfidence (abnormal metacognition) in his/her attempts to recognize social information. We can see that in these circumstances the patient can fail to construct accurate knowledge. Although after therapeutic intervention and engaging mechanisms of conscious access to his/her interpretation, it comes to a symptom's reduction, and the patient gains accurate knowledge about their surrounding others. This particular situation illustrates how faulty interpretation can be potentially corrected by conscious evaluation. How then the patient eventually gains accurate knowledge and forms the proper interpretation? Here, we will attempt to answer these research questions from a cognitive perspective by demonstrating that conscious access is an important mechanism for correcting our theories and judgments intended to interpret and predict behavior of other people.



What does this person feel or do?
How confident are you?

Cutout!

1. Final pleading at court
2. Labor leader speaks to his comrades (in the 20s)
3. Fight at the market place
4. Musician singing a love song

Figure 1. An example of cognitive intervention from the metacognitive training course aimed at cognitive enhancement of social cognition (https://clinical-neuropsychology.de/metacognitive_training/). The exercise activates formation of social understanding by asking a client to infer emotional states of the actor on the picture. During this exercise a patient attempts to recognize an emotional state of the actor presented on the picture by choosing one of four options and then expresses confidence in his/her responses. The therapist analyzes the client's answers and helps the client to reach a correct answer (option no. 4).

3. Cognitive models of mindreading-metacognition relation

Contemporary scientific discussions on the relation between metacognition and mindreading result in several theoretical accounts allowing various combinations and configurations of both mechanisms in the formation processes of beliefs, intentions, and decisions with respect to oneself or others [4]. Cognitive architecture that considers possible configurations of these sets of mechanisms must embrace different functions, knowledge structures, as well as mechanisms that provide access to the information [6]. Yet, it seems that the discussion on the adequacy of each theoretical account is still open, and there is no unambiguous evidence pointing out clear superiority of the specific theoretical account on the relation between metacognition and social knowledge.

For example, Nichols and Stich [28] in their theoretical description of how we access and utilize self-knowledge and other-knowledge propose a hybrid architecture composed of metacognition and mindreading as distinct and innate mechanisms. According to this view, the basis of self-knowledge is formed by two metacognitive mechanisms of self-monitoring nature: one responsible for recognizing and providing knowledge about internal states (our own propositional attitudes) and one for recognizing and providing information on our experiential states [4]. Whereas the mindreading faculty constitutes independent mechanism that deals with the attribution of mental states to understand other people. Since metacognitive and mindreading systems are modular, there is a superior coordinating mechanism that manages the interaction between components [28].

In other theoretical proposals, cognitive architecture on social cognition takes on a more radical form, as the cognitive system is greatly simplified to only one capacity, which is, namely, mindreading or metacognition. For example, Carruthers [4] in his theoretical approach denies that there is an introspective access to propositional attitudes and postulates the existence of only one mindreading mechanism that underlie our social cognition. This view claims that metacognition is only grounded on mindreading and therefore attribution processes of mental states to oneself and other people are results of prior unconscious interpretation. Adoption of such a one-system architecture indicates that knowledge about our own state results only from mindreading mechanisms that accesses a variety of information sources (percepts): incoming perceptual states or quasi-perceptual states [4]. This account clearly implicates that introspection of propositional states is replaced by interpretation without conscious access [4].

Indeed, the idea of one-system architecture ignores conscious access to the information that is, in fact, in contradiction with commonsense observations of the role of consciousness in regulating our behavior. In fact, although our cognitive system in various situations is dominated by unconscious events and shows some limitations, we can consciously correct our theories and judgments to interpret and effectively predict behavior of other people (see, for instance, [29]). In fact, it is important to emphasize that the one-system architecture by Carruthers [4] excludes clear activation of conscious access through the interaction between modules, because the architecture implicates a homogeneous mechanism that processes the content of various kinds from different functionally levels and the inputs. The same conclusions may come also from consideration of another architecture which postulates that mindreading and metacognition are parts of the one metacognitive mechanism [30–32]. In this account, it is believed that the attribution of mental states to other people depends on our direct access to these mental states (introspection) via subsequent processes of simulation and inference. Thus, human capacity for mindreading is based on the introspective data, which are initially accessed to imagine other's state, and then is used to make the attribution of this state to interpret or rationalize other's behavior (simulation).

4. Interactionist approach in social cognition

Interestingly, the latest accounts of the relationship between mindreading and metacognition clearly favor arguments for interactionism in the formation of social knowledge. In particular, Arango-Muñoz [6] presents a two-level architecture (two different levels of complexity) enabling a mutual interaction within a complex metacognitive system that is evolutionary structured into higher- and lower-level metacognition with different functions and tasks. Both metacognitive systems "start to interact and influence each other" by forming a complex social cognition [6]. In particular, mindreading is the higher level structure that engages rational knowledge, which is a psychological concept or naive psychological theory, to interpret and rationalize others' behavior. The main function of this level is therefore to interpret others' behavior, although self-interpretation from this level is possible but is not a priority. Within lower level structures operate unconscious processes of control and evaluation that serve to adjust epistemic states (e.g., subject's feelings) to the individual's current behavior. The dual-process account makes predictions of cognitive regulation based on the bidirectional interactions: (i) a "from-low-to-high-level" direction that predicts possible evaluation and monitoring and then the attribution of a psychological content and (ii) a reverse interaction in a "from-high-to-low-level" direction that activates rational knowledge and control processes to regulate current social responses to others people.

To sum up, the higher-order structures deal with our rationality which is linked with attribution of available psychological concepts and folk theories to interpret oneself and others' behavior, while lower-level functions of control and monitoring attempt to adjust one's cognitive activity in automatic and unreflective manners [6, 20]. Since the dual-process theory implicates different levels of metacognition, the role of interaction itself is to link such different levels of complexity in a single unit of metacognition [20]. This, in turn, indicates that both levels of metacognition influence one another via such interaction [20], which is critical in dynamic formulating and executing complex cognitive operations in our social responses. Therefore, one can expect that selective impairments in the high-level structures can give rise to impairments in the low-level metacognition and vice versa. For instance, impairments in mindreading processes that develop from childhood onward may cause specific abnormalities in metacognition among individuals later in their adulthood diagnosed with schizophrenia [56].

5. Consciousness as a vehicle of interaction

Nonetheless, in case of formation of social knowledge predicted by the two-process theory [6], it is important to identify possible mechanisms of accessing the content within such complex capacity. The two-level account proposed by Arango-Muñoz [6] implies that activation of the current content occurs via the interaction which depends on a specific level of processing and a specific psychological context (either related to oneself or other people). This model indicates that higher-order inferential mechanisms should interact with the low-level control and monitoring mechanisms activated in the automatic and unconscious way. Thus, this interactionist account suggests that at the lower level there is no conscious control or monitoring of others' behavior as well as no conscious attribution when handling a specific psychological context of individual either related to the self or others. Clearly, this conclusion is contradicted with common sense that people are often aware of their attributions and can finally formulate accurate and realistic interpretations about others even though they initially produced false attributions.

How conscious control or evaluation of social cognition is then possible? It should be emphasized that interactionists (see [6]) claim no explicit architecture of consciousness mechanisms that are responsible for managing the information content within the system. In our opinion, cognitive architecture of such system needs to include a conscious access mechanism that ensures accessibility of information understood as activation through the interaction. Here, we will argue that a combination of the two-level structures of mindreading and metacognition [6] along with a global broadcasting architecture of consciousness [25, 33, 34] is a reasonable theoretical proposal that explains how conscious access contributes in formation of accurate social knowledge.

6. Global workspace, social cognition, and their neural substrates in the brain

For over two decades now, we have been observing the rapid development of research on consciousness [35–37]. This research by addressing questions about subjective nature of experience has resulted in well-empirically established theories that describe formation of conscious knowledge as well as determine directions of contemporary empirical studies on the brain [35, 36]. One of the most well-known accounts on consciousness is a global workspace theory (GWT) postulated by Bernard Baars [33, 38]. The GWT theory has originated in several empirical studies implicating a notion of a neuronal global workspace that has contributed to numerous findings and concepts on possible neural architecture of access consciousness in the brain [39]. The GWT theory has been also found useful in several computational applications, including the field of artificial intelligence or neural network modeling [40].

The central claim of GWT is that consciousness has an integrative function that organizes and provides access to a distributed set of knowledge sources that otherwise work as independent structures [25, 34]. According to the conscious access hypothesis, consciousness is considered as an agent that makes the content globally available to unconscious systems [34]. In other words, consciousness enables exchange, coordination, and control of broadcasting the information content among a set of unconscious, specialized, and separate processors [25]. GWT also assumes that the unconscious contents of the mind compete or cooperate with each other in order to gain access to the global workspace. In other words, when the specific information content wins the competition for access over other information, it gets into the neural global workspace that allows its broadcasting to other regions of the brain (specializes processors) in which other processes and resources are activated. In this way, conscious events are results of the interaction between unconscious processors that attempt to spread the information content via the global workspace for other specialized areas of the brain [25, 34, 38].

In the area of brain research, significant progress has been made in understanding the cognitive and neuronal basis of consciousness [41]. Given the cognitive division into conscious and unconscious processing, brain research shows that architecture of consciousness in the brain may be reflected by functionally separate brain regions that are associated with conscious representation and other brain regions responsible for the unconscious processing of lower-order information to which conscious re-representations are referred [37]. According to the cognitive architecture based on GWT, it is assumed that neural underpinnings of conscious access occur in the prefrontal region (hub) of widely distributed reentrant circuity [41]. Other consciousness studies based on metacognitive approach provide evidence that higher-order representations of consciousness are associated with the activity of prefrontal and parietal cortical structures [42] with a high degree of interconnectivity [43]. It is likely that mechanisms of conscious access localized in the prefrontal and parietal regions receive different kinds of inputs that are required to formulate accurate social interpretation. Following the GWT assumption, unconscious, special-purpose brain processes linked with metacognition and mindreading attempt to get access to a neural global workspace which enables reversible broadcasting to the whole system [44, 45]. Therefore, since mindreading and metacognition constitute unconscious domain-specific processes ("modules"), their neural architecture should be also distinct from conscious structures. For instance, Dimaggio and colleagues [8] show that people who mentalize about themselves (metacognition) and about others (mindreading) activate regions associated with medial prefrontal cortex (mPFC). Interestingly, several regions of the mPFC specialized in social cognition are dissociable when individuals think of others who are perceived as similar or who are dissimilar to the self [8]. Some researchers also suggest that other brain areas such as a bilateral temporal parietal junction (TPJ) may be involved in social cognition as it may be a solid candidate for representing mindreading module [46]. Interestingly, functional neuroimaging studies of clinical population have demonstrated that mindreading deficits are associated with decreasing activation within the medial prefrontal cortex [47]. Some other fMRI study on mindreading deficits in patients with schizophrenia also shows abnormal activation within the left medial prefrontal cortex [48]. Obviously, the actual organization of brain circuity resulting from the proposed framework of linking the dual-process social cognition and the global workspace is considerably more complicated. However, such simplified cognitive architecture of conscious social cognition can allow us to understand how normal and abnormal behavioral and neuronal patterns that accompany conscious processes in social cognition can be developed.

7. Clinical implications of dual-process framework of social cognition and consciousness

Given the proposed framework of dual-process social cognition [6] and access in the global workspace [33, 34, 38], we attempt to explain abnormal social cognition in clinical disorders. We demonstrate how our framework can bring new light into understanding selected examples of clinical disorders in which there are deficits in mindreading and metacognition. Here, we show examples of clinical disorders such as borderline personality and schizophrenia.

A vivid of example showing abnormality in conscious access may be presented by patients with borderline personality disorder. Individuals diagnosed with BDP characterize instability of emotional and behavioral reactions as well as unstable relationships with others [49]. It has been argued that BDP symptoms arise from deficits in perceiving and interpreting social signals [50–52]. Several researchers believe that patients with BPD have difficulties in their ability to correctly ascribing mental states to oneself and recognizing others' mental states; therefore, BPD is considered to be a metarepresentation disorder [53]. It is believed that a lack of long-term bonds with others may be due to the difficulty in maintaining a stable representation of others' mind and one's own mind [54]. Moreover, Semerari and colleagues [53] point out that impairments in BPD in reflecting one's own thoughts and emotions are of selective nature, since they are mainly associated with integrating representations of self and others in consciousness. In particular, these researchers have video-taped four patients suffering from BDP and then evaluated clinical outcomes of therapeutic intervention over the first year of their therapy with the Metacognition Assessment Scale [55]. The MAS focuses on measuring basic metacognitive functions such as monitoring, integration, and differentiation [55]. Here, we focus on monitoring dimension associated with the ability to identify one's inner states, and other functions of metacognition linked with integration defined as the "ability reflect in different mental states and or contents giving them an order and hierarchical relevance" [55]. The study clearly has demonstrated that four patients had the ability to identify their own internal states, although their integration functions aimed at organizing metacognitive representations of self and others were impaired. Following our theoretical framework of dual-process cognition and consciousness, this abnormal pattern of the metarepresentative functions in patients with BPD may indicate that the low-level structures of control and evaluation are preserved; however, there may be difficulties in consciously accessing higher-level structures containing available psychological knowledge. Since conscious access should endorse integrating nature of the metacognition-mindreading relation, its disturbances can lead to abnormal information flow between both subsystems [3]. Here, one can interpret this situation as results of abnormal regulation in accessing the information content that goes in the "from-low-to-high-level" direction. Therefore, low-level processes of evaluation and monitoring work properly, but the further attribution of psychological contents fails. Thus, our theoretical proposal is that patients with BPD may have disturbances in conscious access that affects activation of interpretative data from metacognition and mindreading to establish proper social behavior.

Now, turning to the domain of schizophrenia, we attempt to present how development of clinical symptoms in schizophrenic patients suffering from persecutory delusions can be understood within our proposed framework. With reference to delusional beliefs in schizophrenia, cognitive theories suggest that persecutory delusions often emerge as misinterpretation of social interactions [56]. Therefore, individuals with persecutory delusions are preoccupied with intensions to others [57]. Thus, psychotic patients fail to make accurate judgments in relation to their experiences attributed to others. It has been also suggested that delusional impairments in inferences on the social data may arise from the mindreading deficits. Apparently, deficits in mindreading are demonstrable in schizophrenia as indicated by the meta-analysis by Sprong et al. [21]. Frith [58] hypothesizes that mindreading skills in people with persecutory delusions develop normally; however, those theories of mind capacities are "lost" during psychotic episodes. There is also substantial evidence for mentalizing deficits in patients with first-order episode schizophrenia in the early course of schizophrenia [59]. In fact, mentalizing skills have been shown empirically to be impaired in psychotic patients with persecutory delusions. Patients that follow a paranoid subtype of schizophrenia perform poorly on a wide range of the "theory of mind" tasks including those exercising the attribution of intentions [60]. Moore et al. [61] have explored cognitive etiology of persecutory delusions in patients with late onset of schizophrenia and found that patients performed poorly in a deception task by making more mentalizing errors as compared to healthy participants.

Interestingly, theoretical developments in the conceptualization of relation between metacognition and mindreading skills underlie an interesting casual formation of persecutory delusions. As we mentioned above, the Carruthers' account [4] views metacognition as beliefs of our own attitudes that arise from turning mindreading capacities on ourselves. This implicates that mindreading deficits are prior leading in consequences to dysfunctional metacognition capacities. On the other hand, another explanation is possible as at least deficits in both capacities are paired and may be explained by the interactionist view on social cognition [6]. Indeed, an empirical study by Köther and collaborators [62] on schizophrenic patients could support such interactionist view on persecutory delusions as results of mindreading deficits accompanied with relevant dysfunctional metacognition capacity. In particular, the researchers by employing Reading the Mind in the Eyes test (Eyes Test; [63]) with an additional confidence measure showed in schizophrenic patients not only impaired social cognition in terms of perceiving emotional and social cues but had also commitments to make more high-confidence errors and at the same time made fewer high-confidence correct responses. Obviously, this raises questions about specificity of delusions that may be due to the failures of mentalizing skills and subsequently failures in lower-level metacognition that mirrors mindreading deficits in delusional-prone individuals. Following our framework on social cognition and consciousness, it is likely that unconscious interpretative contents from the higher-level structures are not properly broadcasted to other systems via global workspace in order to get proper monitoring and evaluations from the low-level structures. Moreover, because the information contents remain unconscious, correction of faulty beliefs and interpretations is not possible.

Interestingly, disturbances in conscious access presented in schizophrenia seem to be confirmed by studies on metacognitive and mindreading malfunctioning by Lysaker and colleagues [64]. Researchers have investigated the impairments within self-generated personal narratives in terms of perceiving one's own state and mental states of others in adults with schizophrenia spectrum disorders. The researchers by using the MAS measure (MAS measure; [55]) have identified three groups of patients: the first one with impaired metacognition ("minimal reflectivity") and poor mindreading, the second group with intact basic self-reflectivity and poor mindreading, and the third group characterized with intact self-reflection and mindreading ability in terms of attributing thoughts and emotions to other people. It turned out that individuals with impaired metacognition and mindreading facilities performed worst in recognizing negative affective cues in others' faces and voices in the video-typed material. According to Dimaggio and colleagues [8], these findings could fit into the concept of the simulation theory (see above) proposed by Gallese and Goldman [65]. Thus, these findings can support the idea of priority of having direct access to one's own internal states to further involve simulation and inferences to interpret and understand others' mental states. Since the study by Lysaker and colleagues [64] was of the correlation nature, alternative interpretations cannot be ruled out. In particular, the study showed that performance results in emotion recognition task were positively correlated with general metacognitive functions ($r = 0.44$) assessed with the "Understanding one's own mind" subscale and to some extent with mindreading capacity ($r = 0.26$) as indicated by scores on the "Decentration" dimension (the ability to perceive others as having their own emotions, thoughts, and perspectives) [64]. These results may have also implication to the idea of dual-process model of social cognition and global workspace. Clearly, better performance in recognizing affective cues in other's faces and voices was linked with activation of both higher- and lower-level structures. Subsequently, the MAS measure "Understanding one's own mind" subscale including also metacognitive function of integration could indicate that low-level metacognitive functions in emotion recognition were supported by conscious access to some extent.

8. Conclusions

In our opinion, it becomes clear that efficient interactions between metacognition and mindreading capacities should be supported by access consciousness. The GWT framework by Baars [33, 38] indicates that consciousness can mediate the interaction between metacognition and mindreading subsystems by managing the access to interpretative contents from both mental faculties. Since the GWT assumes the interaction of unconscious and conscious processes, it becomes crucial how and under what conditions interpretative data of a mentalizing and propositional nature are broadcasted globally within a cognitive system. According to Baars' theory [33, 38], we predict that consciousness mobilizes two levels of processing in "from-low-to-high" or "from-high-to-low" directions depending on a psychological contexts (related to self or other people) and integrates metacognitive and mindreading functions in such a way that interpretative contents are globally available for other specialized areas of the brain. Thus, the combined framework of dual-process social cognition and global workspace explains the basic processes that may potentially underlie normal and abnormal regulation of social behavior. This account suggests that global broadcasting enables corrective interpretation in case of detecting erroneous information about themselves and false assessments of others' behaviors, intentions, etc. We believe that this framework offers a useful cognitive perspective for better understanding of clinical disorders characterized by abnormal relations between mindreading and metacognition and elaborating their therapeutic interventions.

In fact, psychological and psychiatric research clearly shows (see [12]) that people in terms of social interactions need in a continuous way to adjust their behavior and regulate distress, implicating in this fashion a great need for establishing psychological interventions aimed at improving their metacognitive and mentalizing capabilities. Our paper clearly addresses this need by providing more comprehensive cognitive explanations of complex mental health problem as well as offering a new path toward understanding symptom expression of metacognitive and mindreading disturbances. The vital point in this paper is to demonstrate that phenomenology of social interactions as well as symptom expression in severe psychological and mental disorders can be described by adapting an interactionist approach that combines access consciousness mechanisms with mental capacities of mindreading and metacognition in a complex unit. According to this view, social cognition can be driven by a set of independent mental functions in the brain that interact with each other [12, 24, 25], and as a matter of fact each element underlying this interaction may be a subject of selective impairment. On the other hand, the interactionist model undoubtedly maximizes a role of individual within the process of psychotherapeutic intervention by emphasizing his/her conscious efforts. For instance, given the interactionist view on global access and both forms of mentalization, we can also efficiently explain the way the therapy based on metacognitive training provides promising results in treating severe psychiatric disorders [27]. Indeed, the interactionist approach suggests that the individual can consciously correct his/her theories and interpretations about oneself and others, since access consciousness mediates the effective interaction between the sets of independent mental capacities. Moreover, interactionist perspective assumes that consciousness mechanisms by its mediating and integrating functions improve social cognition including metacognitive and mentalizing skills. Therefore, future studies should seek for effects of consciousness on improving both metacognition and mindreading skills either in clinical or in nonclinical population samples.

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Conflict of interest

Authors Małgorzata Gakis, Ewelina Cichoń, Tomasz Cyrkot, and Tomasz Cyrkot declare that they have no conflict of interest.

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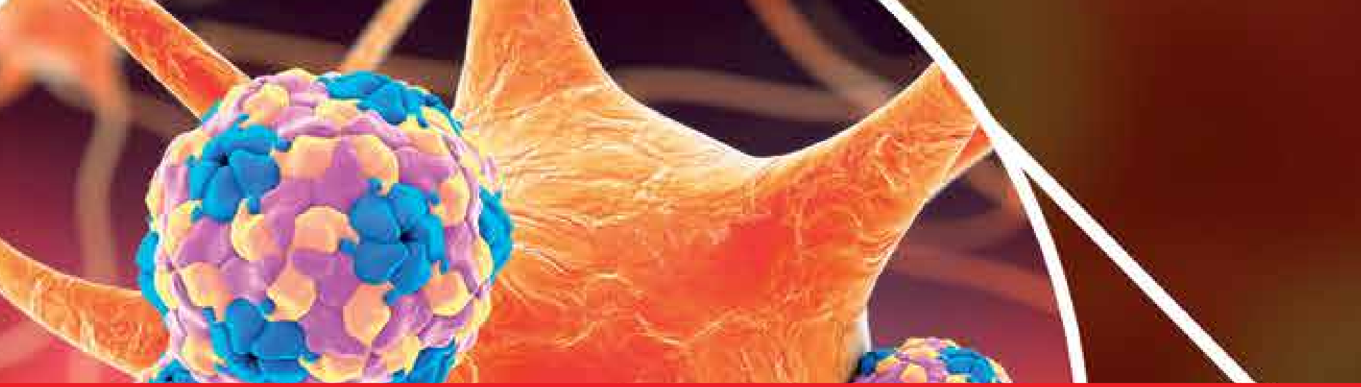

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The prefrontal cortex reaches its greatest development in the human brain, making up nearly one third of the neocortex. Due to its remarkable evolution, the prefrontal cortex plays an important role in higher integrative functions such as information processing, thinking, understanding, attention, behavior, motivation, emotions, working memory, and analysis. This book brings together theoretical and technical research advances on the prefrontal cortex, from the basic explanations of the neuronal architecture of the prefrontal cortex and its anatomy, presenting it as a morphological substrate for many psychological conditions, through normal and altered connectivity and its manifestation in different behavior and identification of organizational levels inside the prefrontal cortex through different neuroimaging methods. It also provides an interdisciplinary view of the prefrontal cortex and its issues and discovers the main role of this part of brain in psychosocial, economic, and cultural adaptation.

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