Provisional chapter

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

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Additional information is available at the end of the chapter

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.

2. 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**.

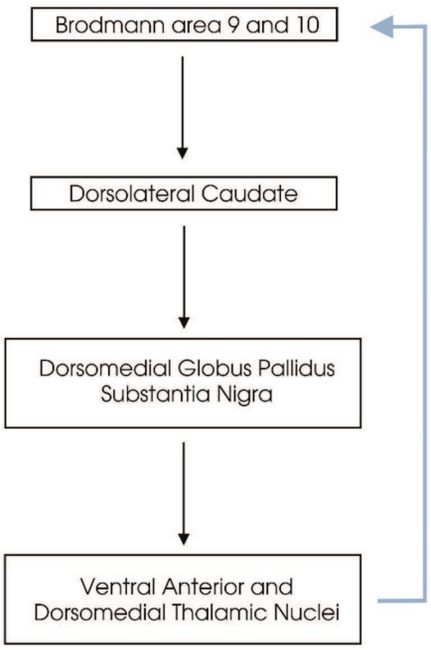

Figure 1. Basic schematic diagram of the direct pathway of the dorsolateral frontal circuitry (adapted from [9]).

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].

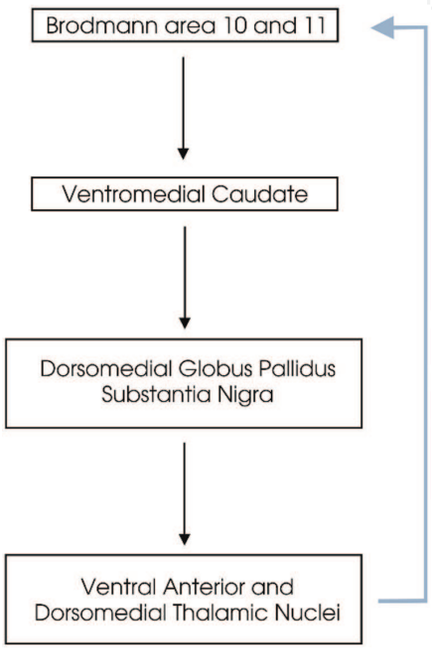

Figure 2. Basic schematic diagram of the direct pathway of the orbitofrontal circuitry (adapted from [9]).

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].

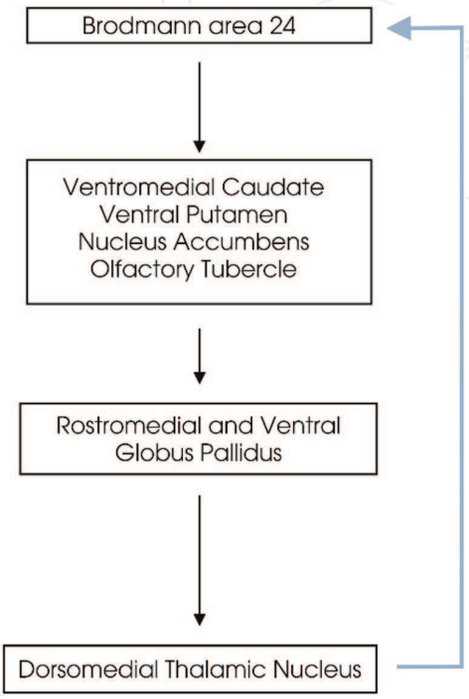

Figure 3. Basic schematic diagram of the direct pathway of the anterior cingulate circuitry (adapted from [9]).

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].

2.1. Brain's major fasciculi and frontal lobe tracts

The previous subsection 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, angular 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**.

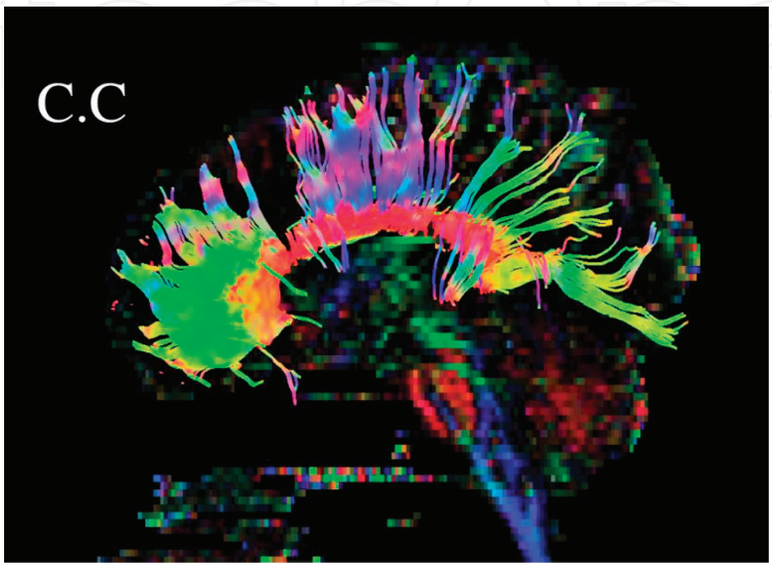

Figure 5. MRI tractography in sagittal view showing corpus callosum (C.C) fibers.

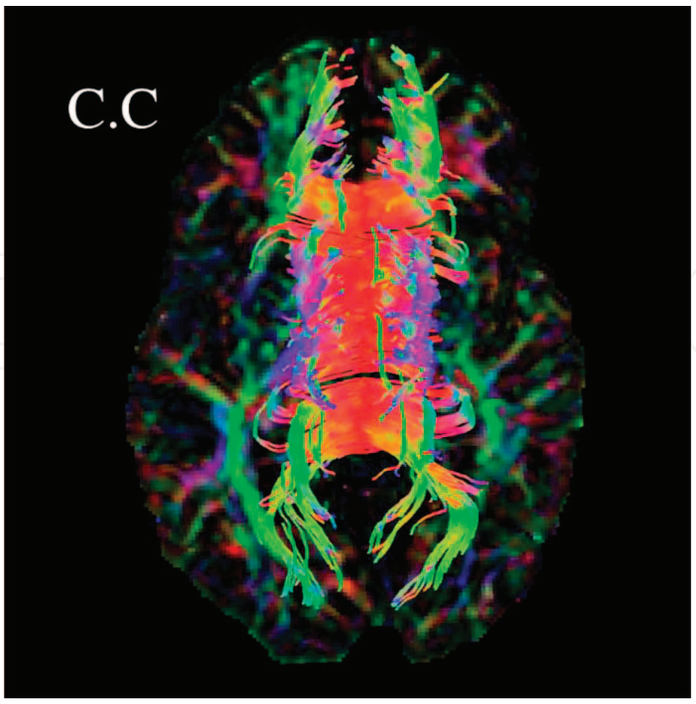

Figure 6. MRI tractography in axial view showing corpus callosum (C.C) fibers.

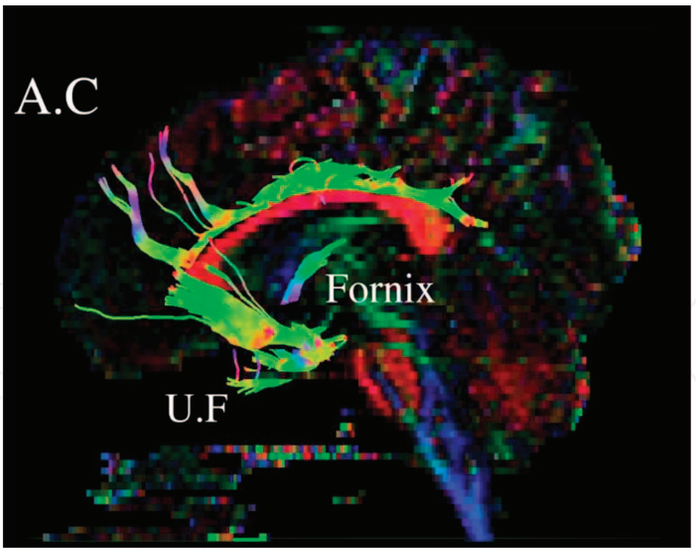

Figure 7. MRI tractography in sagittal view showing anterior cingulate (A.C) fibers, fornix and uncinate fasciculus (U.F) fibers.

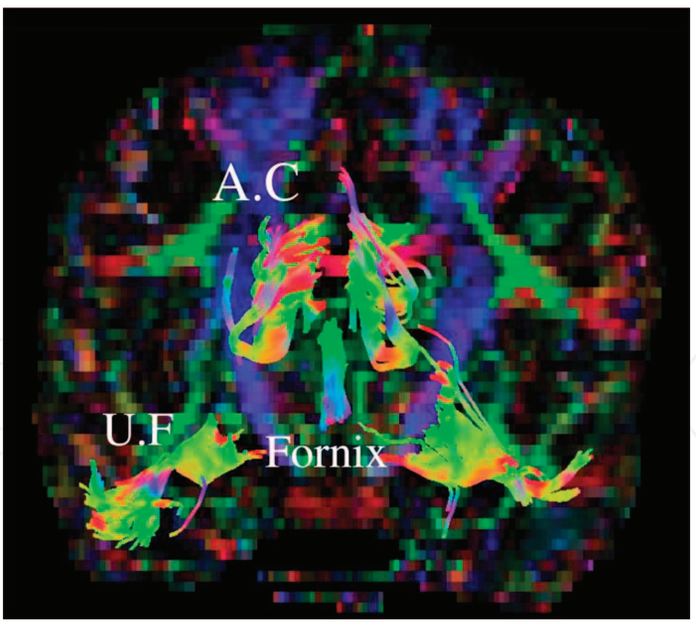

Figure 8. MRI tractography in coronal view showing anterior cingulate (A.C) fibers, fornix and uncinate fasciculus (U.F) fibers.

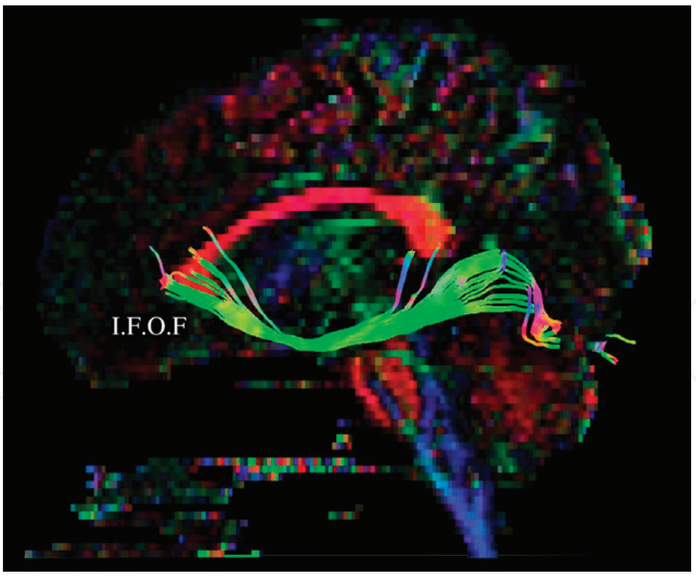

Figure 9. MRI tractography in sagittal view showing inferior fronto-occipital fasciculus (I.F.O.F) fibers.

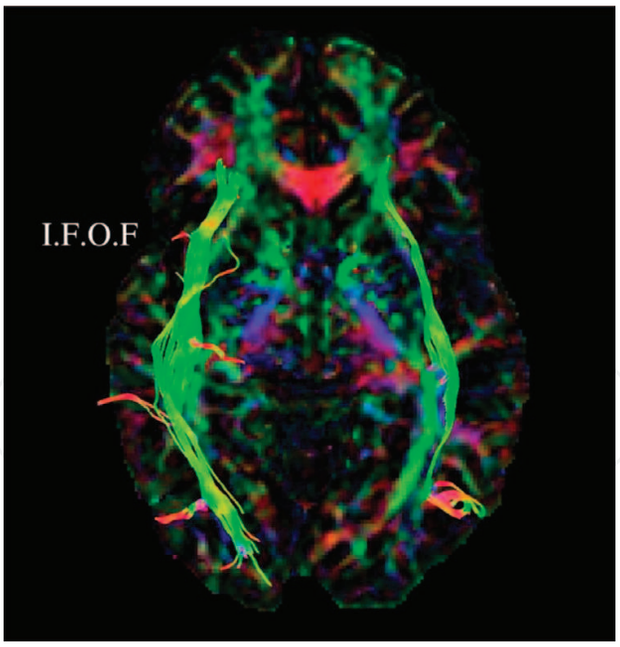

Figure 10. MRI tractography in axial view showing inferior fronto-occipital fasciculus (I.F.O.F) fibers.

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.

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 Louis 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].

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].

3.2. Illustrative case 2

In 1839, Louis 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 Paul Broca, 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].

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 based on functional MRI studies showed that the abnormalities were compatible with the damage to most of the fasciculi involved in the computed structural reconstruction [2].

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].

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].

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 regions, 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].

4.3. Illustrative case 6

A 56-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 perseveration, 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 cognitive deficits persisted [15].

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 onset 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].

5. Appendix: cerebellar cognitive-affective syndrome (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 transporter 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].

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.

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 43-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 expressive 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

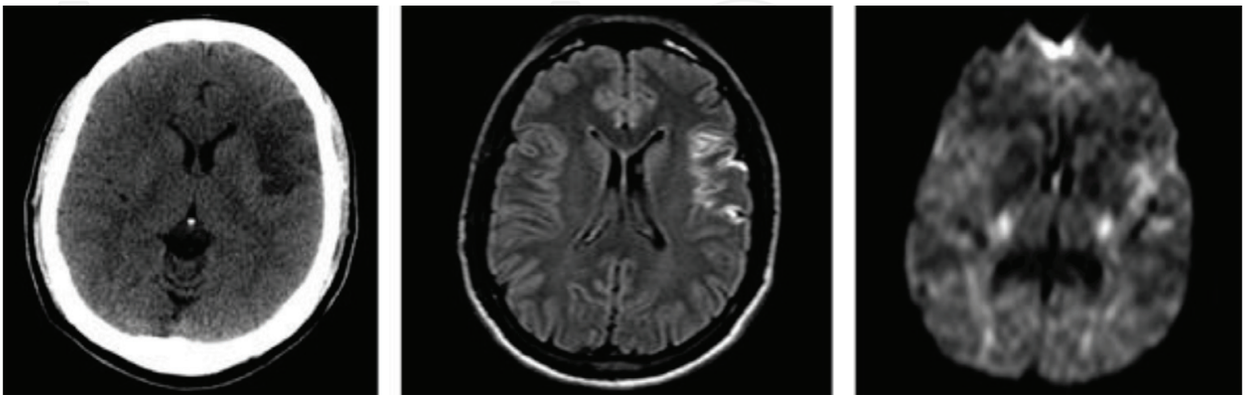

Figure 11. Cranial computed tomography, brain MRI (FLAIR-weighted), and brain diffusion MRi (DWI) showing, respectively, hypodense area in the left inferior frontal gyrus, hypersignal in the left anterior and posterior insular cortex, and restricted diffusion in the cortical region of the left insular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

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].

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].

7. 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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