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Chapter 3

FUNCTION AND DYSFUNCTION OF THE PREFRONTAL LOBES IN NEURODEGENERATIVE DISEASES

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ABSTRACT

Clinical assessment of the functions of the prefrontal cortex in physiological and pathological states is dependent on one's model of prefrontal function. There is no overarching "frontal lobe syndrome"; rather, the prefrontal cortices are involved in a number of distinct cognitive and social-behavioural processes. Stuss, Shallice, Alexander and Picton studied patients with focal lesions. They found that damage to anterior cingulate and other superior medial prefrontal regions caused deficits in *energization*, which manifests clinically as a spectrum of disorders characterized by difficulty initiating and sustaining a response on cognitive testing and in daily behaviour. Damage to right dorsolateral prefrontal cortex (DLPFC) caused deficits in *monitoring*, and damage to left DLPFC caused deficits in *task setting*. Injury to ventromedial prefrontal cortex caused deficits in *emotional or behavioural self-regulation*; this may not be easily detected

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through bedside tests and requires careful history taking and observation for accurate diagnosis. Finally, damage to the frontal poles caused deficits in *metacognitive functions*. These different prefrontal areas participate in distinct cortico-striato-pallido-thalamo-cortical loops, but also form parts of larger scale frontal connectivity networks. Prefrontal dysfunction can be a symptom of the subcortical dementias, which include Parkinson's disease and vascular dementia among many others. Prefrontal dysfunction is also found in the frontotemporal dementias, and can also be present in the behavioural/dysexcutive variant of Alzheimer's disease. Bedside clinical tests and methods of observation are described that are sensitive to dysfunction of the prefrontal lobes.

TERMINOLOGY

Descriptions of prefrontal lobe functions have been associated with confusing terminology. In this chapter, terms are defined in a manner that will be useful for clinicians without sacrificing specificity. Strictly speaking, "frontal functions" include the functions of the primary and secondary motor cortices, as well as other areas such as the frontal eye fields. These will not be discussed. Instead the focus will be on higher order cognitive and social-emotional functions that rely heavily upon more anterior structures within the frontal lobes, and which are termed "prefrontal functions." It should be noted that many often use the term "frontal function" synonymously with "prefrontal function," even though these are technically not equivalent.

The term "executive function" is even more problematic; there are myriad definitions for this term. In this chapter executive functions are defined as a set of interrelated cognitive processes required for complex goal-directed activity, including processes such as planning, monitoring, goal-setting, etc. Disruption of these functions are most often observed after damage to the frontal lobes [1]. The terms "executive function" and "frontal or prefrontal lobe function" have often been used synonymously. However, the prefrontal lobes are involved in more than those cognitive functions usually considered to be "executive." Furthermore, regions outside the frontal lobes are involved in many executive functions [2]. In addition, executive functions refer to cognitive processes whereas the prefrontal lobes define an anatomical structure [3]. For these reasons, "executive functions" are not equivalent to "prefrontal functions," even though many executive functions are highly dependent upon the prefrontal cortices (Figure 1).

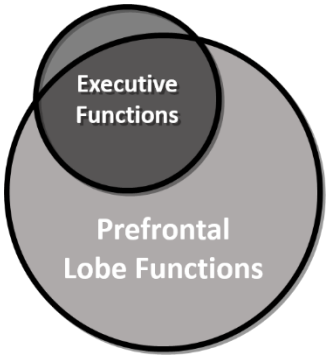

Figure 1. Relationship between prefrontal lobe functions and executive functions.

NEUROANATOMY OF PREFRONTAL FUNCTIONS

Stuss' Model of Prefrontal Function

There are different models of prefrontal function. Stuss, Shallice, Alexander and Picton, based on review of literature and a theoretical hypothesis, proposed that prefrontal lobe abilities consist of different functional categories interacting to achieve complex human behaviours [4]. To prove this, they examined patients with focal damage to specific frontal areas on theoretically derived experimental tests. The results indicated four anatomically segregated functions of the prefrontal lobes: energization, executive, behavioural/emotional self-regulation, and metacognition [3]. This model is an elaboration of the processes involved in the influential Supervisory System model of Norman and Shallice [5].

Deficits in *energization,* defined as "the process of initiating and sustaining any response," were secondary to damage to anterior cingulate and other superior medial prefrontal regions (SMPFC). Only two functions fit the classical definition of *executive functions*, and these were related to lateral frontal regions: right dorsolateral prefrontal cortex (DLPFC) - monitoring; left DLPFC - task setting, or planning. Monitoring is the process of checking a task over time and adjusting behaviour as needed for successful completion. Task Setting refers to putting in place a plan in response to a stimulus or demand, e.g., learning to drive a car, organizing the plan, and coordinating processes required to carry out the task such as putting the foot on the brake, as opposed to the gas pedal, when stopping the car [6].

Deficits in processes involving *emotional or behavioural self-regulation* occurred in patients with injuries to ventromedial prefrontal cortex. Finally, patients with damage to the frontal poles (FPs) may have deficits in *metacognitive functions* such as self-awareness and ability to take the perspective of others, i.e., theory of mind (ToM) [3, 7].

Cortico-Striato-Pallido-Thalamo-Cortical Loops

The frontal lobes do not function as a single neuroanatomical unit. Early on, researchers identified neural projections from the frontal lobes to corpus striatum, from corpus striatum to globus pallidus, from globus pallidus to thalamus, and from thalamus back to the frontal lobes. These have been called cortico-striatal-pallidal-thalamic loops (also shortened to frontal-subcortical circuits). Research in the 1970's and 1980's, particularly through axonal tracer studies in primates, culminated in a model of these loops proposed by Alexander, Delong and Strick, and which continues to form the basis of our understanding of frontal lobe function and connectivity [8]. This model proposes distinct, parallel cortico-striato-pallido-thalamo-cortical loops, subserving distinct functions. Refinements to this model have revealed loops involved in motor function, cognitive function, and social-emotional processing [9]. These loops originate from primary motor cortex and supplementary motor area, frontal and supplementary eye fields, DLPFC, lateral prefrontal cortex (LatPFC), medial OFC, and anterior cingulate cortex (ACC) and frontal insular (FI) regions. They are illustrated in Figure 2.

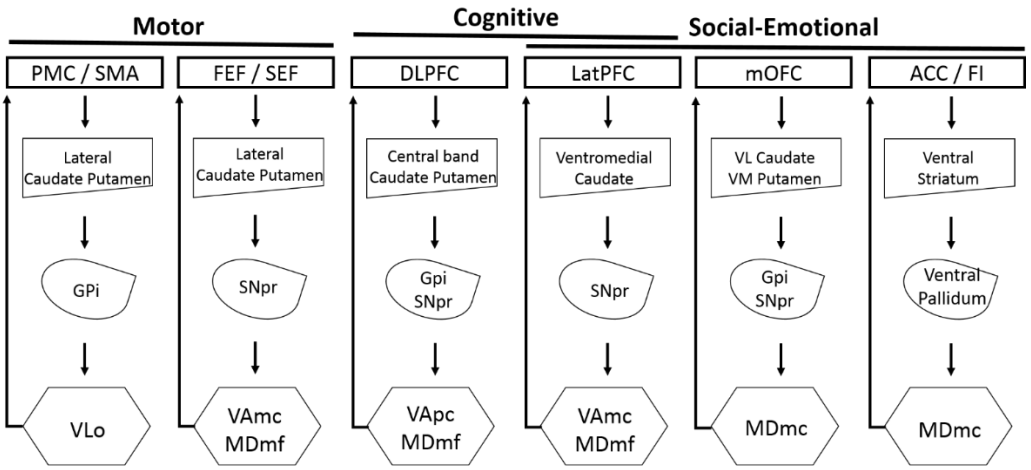

Figure 2. Frontal-Subcortical Circuits, based on Seeley's update of Alexander, Delong and Strick's model. Note that these loops are simplified; additional areas project to the striatum including areas outside of the frontal lobes. There are also myriad cortico-cortical and cortico-limbic connections that interconnect these loops. ACC = anterior cingulate cortex; DLPFC = dorsolateral prefrontal cortex; FEF = frontal eye fields; FI = frontal insula; GPi = globus pallidus pars compacta; LatPFC = lateral prefrontal cortex; MDmc = medialis dorsalis, pars magnocellularis; MDmf = medialis dorsalis, pars multiformis; mOFC = medial orbitofrontal cortex; SEF = supplementary eye fields; SMA = supplemental motor area; SNpr = subtantia nigra pars reticularis; VAmc = ventralis anterior, pars magnocellularis; VApc = ventralis anterior, pars parvocellularis; VL = ventrolateral; VLo = ventralis lateralis, pars oralis; VM = ventromedial.

Integration of the Two Models

Stuss' model has been mapped onto the cortico-striatal loop model [3]. The DLPFC loop is involved in cognitive functions including task setting and monitoring, lateralized to the left and right hemispheres, respectively [6]. However, there is an additional LatPFC loop that is not accounted for in Stuss' model. It has been argued that this prefrontal region is mainly involved in stopping, shifting, and inhibition of undesired responses, and is therefore at a crossroads between cognitive and social-emotional processes [9, 10]. In contrast, Stuss and colleagues did not find experimental evidence of an independent inhibitory function in lesion studies. Instead, based on parsimony they argued that inhibition was a psychological construct, the functions of which could be accounted for by more fundamental frontal lobe processes, either singularly or combination of energization, task setting and monitoring [6].

The OFC loop is involved in emotional and behavioural self-regulation [11]. This regulation, however, may occur through more basic cognitive processes in which the OFC plays a role. Some have argued for the division of the OFC into a ventral and medial portion, based on distinct connectivity patterns [12]. Ventral OFC receives multimodal sensory input, particularly from sensory modalities related to appetitive drives (e.g., taste and visceral afferents), whereas the medial OFC provides output to visceromotor structures in the brainstem and hypothalamus, in addition to its projections to ventral striatum [12]. The OFC is therefore well suited to its role in dynamically updating the value of available rewards or options in the context of the current internal state of the individual. Indeed, imaging studies

have demonstrated a role for the medial OFC in determining and updating the value of sensory stimuli and future outcomes. In keeping with this notion, patients with damage to orbitofrontal cortex are inconsistent when making basic preference choices [13].

The ACC circuit (SMPFC) is involved in *energization* in Stuss' model [3]. Functional neuroimaging studies suggest a role for error monitoring subserved by this circuit [14]. Some such studies have postulated a role for this area in determining and updating the value of future actions, although this observation may be biased by task specificity as differing experimental tasks require different levels of energization [15, 16].

The metacognitive processes putatively located in the FPs are not part of any of these loops. It is thought that the FPs integrate information from diverse prefrontal cortical regions, without themselves having direct subcortical connections. Because the frontal pole is connected to both OFC and SMPFC, it has been suggested that this region can integrate information about the value of future outcomes and of future actions [15, 17]. However, the precise mechanisms whereby this leads to metacognitive processes are unclear.

Larger-Scale Frontal Networks

Further insights into prefrontal function have been gained in the past decade by studying brain regions that are functionally connected. Using resting state functional MRI, Seeley and colleagues identified an executive control network (ECN), and a salience network (SN) [18]. The ECN demonstrates that the DLPFC is functionally connected with the dorsal caudate nucleus and anterior thalamus (confirming functional linkage of the anatomically linked frontal-subcortical loops), and also with parietal areas and other frontal areas. The SN consists of a functional linkage between the ACC and FI, as well as subcortical structures, limbic structures, and importantly the OFC. This demonstrates cross-connectivity between different frontal-subcortical loops at a functionally connected network level, even though their distinctness was highlighted earlier.

Zhou and Seeley postulated that the "frontoinsula represents the major afferent SN hub, representing subjective "feeling states" by integrating inputs from the interoceptive stream with those arriving from other networks, whereas the ACC serves as an efferent SN hub for mobilizing visceroautonomic, emotional, cognitive, and behavioral responses to the salience detected in the frontoinsula" [19]. Thus, whereas the ventral/medial OFC system is involved in the valuation of outcome or reward options, the SN mobilizes visceral/emotional responses to salience and weighs these outcome values to guide behavior.

CLINICAL ASSESSMENT OF PREFRONTAL FUNCTIONS

This chapter will focus mainly on so-called "bedside" tests of prefrontal function, meaning tests that can be easily administered in routine clinical settings without use of special equipment or test materials. There are many tests used to probe prefrontal lobe function that are more typically used by neuropsychologists than physicians, and these will only be briefly touched upon. However, the principles regarding testing prefrontal functions remain the same, whether one uses bedside tests or formal neuropsychological tests.

Interpreting performance on tests of prefrontal lobe function requires experience and skill. Failure is relative, not absolute, and performance may be inconsistent. Furthermore, inconsistent performance on cognitive tasks, in and of itself, is a symptom of prefrontal lobe dysfunction [20].

An important point to highlight is that, although tests may be sensitive to lesions in selective prefrontal brain regions, patients may be impaired on these measures for reasons unrelated to prefrontal functions. For example, even though tests of verbal fluency are sensitive to prefrontal lesions, patients with language deficits due to temporal or parietal lesions may also have reduced verbal fluency. Therefore, since patients may be impaired on a given cognitive test for different reasons, interpretation of the findings will depend upon the context in which the deficits occur, the nature of the errors, and the comparison of the performance on one test in relation to others.

Thus, there are no "true" tests of prefrontal functions. Instead, there are tests that tap into one or more of the processes related to specific frontal regions. The same applies to executive function. Deficits in executive function detected by cognitive tasks are identified by the nature of the errors, and not simply by poor overall performance on a given test. For example, on a test of list learning, false positive errors suggest a task setting deficit with failure of setting a criterion to respond by only producing words on the list. In contrast, recalling the same word twice suggests poor monitoring of previously recalled words. Thus, it is not the list learning task itself that is a measure of executive function but the component processes of task setting and monitoring involved in completing the task. It should also be noted that there are not many validity studies of many of these tests in patients with focal lesions, and there are still questions of sensitivity and specificity.

Dorsolateral Prefrontal Functions

Clinical tests of prefrontal function have been developed over the last half-century, beginning with the work of Alexandre Luria, whose tests are still often used in routine clinical practice [21]. The vast majority of these tests tap into DLPFC functions. They examine distinct components of cognitive functions, and often are not all impaired in the same patient. This gives further support to the concept that functions of the frontal lobes are subserved by distinct sub-component processes.

A number of tests of DLPFC function require special materials for administration that are often not readily available in a physician's office or at the bedside. These tests are typically administered by neuropsychologists. Only one such popular test will be discussed, i.e., the Wisconsin Card Sorting Test (WCST). In contrast, many other tests can be readily administered in an office or "bedside" setting using only pencil and paper. An exhaustive description of all available tests is beyond the scope of this chapter, but some of the more commonly used tests will be discussed.

The *Wisconsin Card Sorting Test* (WCST) is used widely in experimental psychology and for clinical neuropsychological assessment, and is sensitive to deficits in executive function. A standard approach involves presenting patients with cards that can be sorted according to different criteria (colour, form, number). Patients are required to discover the sorting rules based upon feedback from the examiner. The first rule is to sort the cards by "colour." After 10 correct sorts, the criteria are changed to "form" without warning. After 10

correct sorts to "form," the criteria are then changed to "number," and then back to "colour" with the sequence being repeated until 6 sorts have been completed or 128 cards have been used up. Thus patients must discover the rule of sorting to colour, maintain this set, and then shift set after the sorting rule changes [22]. The WCST measures executive functions of task setting (discovering the sorting rule) and monitoring (maintaining the rule until it changes). A deficit in the process of task setting suggests a left DLPFC lesion whereas a deficit in monitoring suggests right DLPFC damage. This is most apparent by analyzing an individual's reaction to instructions: The first administration of the test will stress more an individual's ability to analyze and plan response, being more sensitive to left DLPFC damage; if errors are made after instructions are given, the problems are most likely sensitive to monitoring [23]. It is important to determine which version of the card sorting test has been used, since a version commonly used in the U.S. provides more details about the rules in an attempt to eliminate confusion, and in so doing potentially stresses more the process of monitoring rather than task setting or planning [24]. The requirement for a deck of stimulus cards precludes its widespread use as a standard bedside test.

Digit span backwards is commonly used as a bedside test of working memory due to DLPFC function [25]. It is generally administered after digit span forwards, a test of working memory that simply consists of determining the longest string of digits that a patient can repeat back. The backwards digit span test requires the patient to repeat the string in reverse order. This involves working memory as well as the executive functions of task setting, i.e., repeating the digits in reverse order as opposed to forwards, and monitoring, i.e., repeating the digits only once. Scoring options include noting the longest string of numbers that can be successfully repeated backward, and a discrepancy score between the forward and reverse digit span. This test is easy to administer at the bedside, but lacks specificity.

Due to impaired monitoring and task setting, patients with DLPFC damage may have difficulty performing tasks requiring sequencing of successive motor actions. Such tasks were initially developed by Luria and are easy to administer at the bedside [21]. These include a motor task known as the *Luria hand sequences*, in which patients are required to repetitively place their hand on the table in a "fist – edge – palm" sequence. A written equivalent of this task involves asking a patient to copy and continue drawing a sequence of alternating square-like and triangular figures. A related task that is more sensitive to deficiencies of monitoring is the multiple loops task in which patients are required to repetitively draw three loops without perseverating by drawing more than three loops [26]. Task setting is required for acquiring the set necessary to carry out the task. Monitoring is required to determine when to shift from one aspect of the task to another, such as stopping after drawing three loops and shifting to draw another figure with three loops. Patients who had undergone prefrontal leucotomies, which spares the DLPFC, are not impaired on these tests [27].

Various versions of the *go/no-go* task are popularly used to test DLPFC function, although patients may be impaired on these measures following medial frontal lesions [25]. Luria's original task involves raising one finger in response to one tap ("go") but making no movement in response to two taps ("no-go"). A modification of this task involves instructions to raise one finger in response to two taps and two fingers in response to one tap. This test involves executive functions of task setting, i.e., learning the target responses, and monitoring the stimuli to determine which response to make.

Tests of abstract thinking have long been used as tests of executive function. Popular among these is the *similarities test* wherein subjects are presented with two stimuli (words or

objects) and asked in what way they are alike. Correct answers require mentally placing both stimuli into the same superordinate taxonomic categorization (task setting). This "consists of grouping objects or words according to their common features at a high level of generality" and has been shown to activate left peri-Sylvian prefrontal regions on PET scanning [28, 29]. Interpretation of proverbs has been proposed as an equivalent test of abstract thinking. However, the correct interpretation of a proverb may have more to do with having access to previously-learned semantic knowledge of the proverb's meaning, and therefore may be more a test of semantic memory [30]. Thus testing similarities may be preferable to proverbs, but even here familiarity may affect performance.

Lexical (phonemic) word-list generation is another common measure of executive function [31]. Patients are asked to name as many words beginning with a certain letter as possible in one minute, excluding proper names. A popular version of this test is the *FAS test*, where patients are asked to perform the task three times using each of the letters "F," "A," and "S." Normative values for performance on this task are available [32]. This task has been shown to be most impaired in patients with left DLPFC damage, although patients with medial frontal lesions can also be impaired due to deficits in energization [6, 33]. This test taps into multiple component sub-processes of the brain including retrieval, updating, shifting, inhibition, and energization [6, 34]. Task setting is required to generate as many different words as possible without false positive errors such as listing proper names. Monitoring is required to avoid repeating the same word.

Design fluency is the non-verbal homologue of lexical word-list generation. There are various versions of this task. At its most simple level, patients can be asked to draw as many unique figures as possible in a limited amount of time. This task was shown to be most impaired in patients with right DLPFC lesions [35]. In a more standardized version, patients are shown a matrix of five dots and asked to make as many unique figures as possible by joining the dots using straight lines, in one minute [36]. Various more complex versions of this task are available but become more cumbersome to use at the bedside and may be best used in the context of neuropsychological assessment [37].

Whereas word and design fluency tap into multiple components of DLPFC function, other tasks may tap into more basic components. The *Trail-making Test* (TMT) is employed as a popular test of DLPFC function [38]. Patients are presented with a sheet of paper with 25 circles. In *Part A*, the circles contain the numbers 1 to 25, and patients must connect the circles in ascending order by number as quickly as possible without making errors; thus testing basic visuomotor attention and scanning, as well as motor and visual search speed. In *Part B*, the circles contain the letters A to L and the numbers 1 to 13. Patients must alternate from number to letter in increasing order as quickly as possible without making errors. TMT Part B relies more heavily on task setting and monitoring, as compared to Part A. The TMT is easily administered at the bedside [39]. It should be noted that dysfunction outside of the DLPFC can cause impairment on the TMT, thus making it sensitive for prefrontal dysfunction but not always specific for DLPFC dysfunction [40].

The *clock drawing* test is easy and quick to administer at the bedside. Several processes are involved in *clock drawing* and include planning, monitoring, visuospatial function, and abstraction. Choosing the time setting is important for sensitivity of clock drawing as a cognitive assessment tool. Setting the time at 10 after 11 is one of the more sensitive times and illustrates the role of abstraction on the clock drawing task. For this time setting, the "10" must be mentally recoded so that the minute hand is set on the number "2." Patients with

frontal lobe lesions who are impaired in abstract thinking tend to make stimulus-bound errors and process the "10" in a perceptual fashion rather than at a semantic level. Consequently they tend to place the minute hand on the "10' rather than the "2." [41] Executive functions required for clock drawing include task setting to plan the layout of the clock including the size and shape of the contour, placement of the numbers, and setting the time. Monitoring is required to avoid duplicating numbers and drawing extra hands, as well as self-correcting errors such as poor number placement.

Test batteries exist that incorporate several of the above tests. The *Executive Interview (EXIT-25)* is a widely-available 25-item assessment battery that incorporates a wide array of bedside tests, including many of those discussed above. It takes 15 minutes or more to administer and requires a freely-obtainable stimulus booklet [42]. Another popular battery is the *Frontal Assessment Battery (FAB),* which incorporates lexical word fluency, similarities, conflicting instructions, go/no-go, Luria hand sequences, and a measure of environmental dependency [43]. Scores less than 14/18 are considered suggestive of "frontal impairment," although strictly speaking, this battery mainly tests DLPFC functions. Of particular interest to clinicians, this battery was initially validated as a method for distinguishing non-Alzheimer dementias with primarily prefrontal dysfunction from the more typical amnestic syndrome of Alzheimer's disease (AD). The EXIT-25 and the FAB have been found to correlate quite closely, with the FAB being shorter and easier to administer [44].

Medial Prefrontal Functions

As discussed above, the SMPFC, and in particular the ACC, is involved in monitoring the value of future actions in response to internal states [15]. Therefore, dysfunction of this area leads to difficulties in initiating internally-driven actions. At the moderate and severe ends of the spectrum, this type of dysfunction is usually apparent from the patient history and behavioural observations. Deficits can range from apathy, a mild quantitative reduction in internally-generated behaviour, to a more significant reduction, termed abulia, or at the most severe extreme, akinetic mutism, in which there is a severe loss of all internally-generated behaviour [45, 46]. Different forms of apathy can be described which probably have differing neural bases [47]. Only some types of apathy can be considered amotivational. Furthermore, the terms apathy and abulia are at times used interchangeably in clinical settings [48].

Apart from careful clinical observation, bedside tests are rarely used to determine the presence or severity of an apathy syndrome. However, there are several rating scales that can be used to supplement clinical observation. The *Apathy Evaluation Scale* (AES) is a validated 18-item scale that is freely accessible, easy to administer, and comes in self-administered, informant-administered, and clinician-administered versions [49].

Some of the bedside tests of DLPFC function described earlier likely also tap into SMPFC function. Lexical word fluency was described above as a test of DLPFC function. However, in their experiments with patients who had lesions to SMPFC, Stuss and colleagues found deficiencies on this task as well [33]. More specifically, patients with SMPFC lesions named fewer words in the latter portion of the naming task, indicating that they had difficulty sustaining their effort due to poor energization. Patients with SMPFC damage also perform poorly on tasks requiring speeded responses [3]. Thus it should be expected that general psychomotor speed will be reduced in patients with superior medial damage. Psychomotor

speed is not typically measured at the bedside, but usually commented upon in behavioural observations. Another cognitive task that is sensitive to medial frontal lesions is the *object alternation test* [50, 51, 52]. This test is also sensitive to orbitofrontal lesions and is described in the next section below.

Although apathy and amotivational syndromes are classically described as the hallmark of damage to the SMPFC, as well as the associated circuitry involving the ventral striatum (in particular the nucleus accumbens) and ventral pallidum (see Figure 2), such syndromes can develop with frontal and subcortical damage outside these areas. In fact, the driving mechanism producing some of these syndromes may often hinge on reduced output from the basal ganglia to any of the frontal-subcortical loops [53]. Amotivational syndromes, apathy, or other forms of reduced response to internal stimuli may therefore also be seen with dysfunction of the SMPFC or the basal ganglia.

In summary, behavioural observations for reduced psychomotor speed, apathy, abulia, or in extreme cases akinetic mutism, form the cornerstone of "testing" for SMPFC. Clinical rating scales can be used to bolster these observations. Reduced performance on speeded cognitive tasks or failure to maintain performance may also provide clues to the presence of SMPFC or basal ganglia dysfunction.

Orbitofrontal Functions

Dysfunction of the orbitofrontal areas produces changes in behaviour, emotion, appetite regulation, and social cognition. Seemingly unrelated behavioural disturbances may arise from a central problem in the evaluation of outcomes (including rewards) and options for action. These can include hyperphagia or altered food preferences, sexually inappropriate behaviour, loss of social decorum, jocularity, argumentativeness, capriciousness, narrowed or inappropriate preoccupations, and even criminal behaviour. When dysfunction is restricted to the orbitofrontal area of the brain, performance on tests of DLPFC function described above may be normal. The only clinical signs of OFC dysfunction may be evident from careful history taking or clinical observation of aberrant behaviour. However, formal clinical assessment scales may be helpful. For example, the *Frontal Behavioral Inventory* (FBI) is a clinician-administered assessment scale given to caregivers to aid in the diagnosis of behavioural variant frontotemporal dementia (bvFTD), and captures many of the abnormal behaviours that can be seen with OFC dysfunction. The FBI has also been used to demonstrate OFC dysfunction in neurological diseases other than bvFTD, and in traumatic brain injury [54, 55].

It can be difficult to distinguish aberrant behaviour in a neurologically intact individual with an unusual personality from early or mild signs of OFC dysfunction. Because standard bedside cognitive tests and clinical neuropsychological measures are relatively insensitive to OFC dysfunction, there is a need for development of cognitive tests of OFC function. One candidate is the *object alternation test*, a task adopted from the non-human animal literature to study cognitive function in humans and which has been shown by Freedman and colleagues to be sensitive to ventrolateral-orbitofrontal and medial frontal dysfunction in humans [50, 51]. During this task, a penny is placed under one of two objects. Subjects are required to learn that the object under which a penny is located is being alternated after each correct response. Freedman et al. showed the object alternation test is a highly sensitive

measure of medial frontal function in bvFTD [52]. A limitation of the object alternation test for bedside use is that a test apparatus or computer program is required.

A battery of tests termed the *Executive and Social Cognition Battery* (ESCB) has been proposed as a sensitive measure of OFC dysfunction in bvFTD [56]. The components of the ESCB are derived from the experimental psychology literature and are thought to be tests of day-to-day activities in a "real-life" environment. These tests require specific stimuli including card decks, which restrict the utility of the ESCB as a bedside test; however, this battery may find utility within a more lengthy neuropsychological assessment.

Frontal Polar Functions

The FPs appear to be involved in metacognitive tasks such as perceiving one's own emotional state, perceiving emotional states of others, and understanding what another person may be thinking. The abilities to impute the mental states of oneself and others are referred to as theory of mind (ToM) [57]. ToM can be assessed using experimental tests such as the *false belief tasks* [58, 59, 60]. For example, on first order false belief tasks, stories are presented to a subject in which someone (Person A) puts an object away in the presence of another individual (Person B) and then leaves the room. Person B then moves the object to a different location while Person A is away. Person A returns and the subject is asked a belief question, i.e., "Where does Person A think that the object is?" Correctly answering this question requires the subject to take the mental perspective of Person A. Other ToM tasks involve recognition of humour from cartoons and stories which require the reader to understand a mind state [61]. ToM deficits have been demonstrated in patients with focal frontal lobe lesions, Parkinson's disease, AD, and bvFTD [59, 60, 62]. However, ToM is not routinely tested in clinical practice, although it certainly could be. Usually, deficits in ToM are imputed from the patient's history, for example when deficits in empathy are reported. The application of experimental ToM tasks to routine clinical practice is an untapped area of research.

DISORDERS OF PREFRONTAL FUNCTIONS IN NEURODEGENERATIVE DISEASES

There is a vast and interesting literature pertaining to disordered frontal lobe function in psychiatric disease and acquired neurological brain injury. However, this chapter will focus on disorders of the prefrontal lobes in neurodegenerative diseases. When dealing with neurodegenerative diseases affecting the prefrontal lobes, a useful heuristic has been to divide disorders between so-called "subcortical" and "cortical" dementias. The characteristic features of each are discussed below.

Subcortical Dementias

The term subcortical dementia was first used to describe cognitive deficits associated with progressive supranuclear palsy and Huntington's disease [63, 64]. It is now used to

describe a syndrome associated with dysfunction of the frontal-subcortical loops and often involves damage to both cortical and subcortical structures pathologically [65]. A preferable term may be fronto-subcortical dementia since the neuropsychological deficits associated with subcortical dementia are often related to frontal system dysfunction [66]. In fact, these terms are often used interchangeably. In contrast to the subcortical dementias, the cortical dementias are syndromes in which disorders of memory, language, perception and praxis are prominent [67].

Clinically, patients with subcortical dementia tend to demonstrate features of SMPFC and DLPFC dysfunction. The classical profile of patients with subcortical dementia is characterized by forgetfulness, impaired manipulation of acquired knowledge (e.g., calculating and abstracting ability), personality changes marked by apathy or depression with occasional episodes of irritability, and slowed thought processes [63]. Patients usually demonstrate deficits in energization, performing poorly on speeded tasks. Memory encoding, a medial temporal function, is largely intact. However, retrieval, which relies on frontal-subcortical systems, may be impaired. Working memory may also be impaired. For example, patients may perform poorly on the reverse digit span task [68]. Patients may also be impaired on experimental measures of DLPFC functions, as well as clinical measures such as the TMT [69]. In addition, word list generation may be impaired. Aphasia is uncommon, although patients often have slow speech and dysarthria.

Subcortical dementias are caused by disorders affecting the subcortical grey matter structures, such as Parkinson's disease, Huntington's disease, progressive supranuclear palsy, thalamic degeneration, and AIDS dementia complex, or by disorders of the white matter connections between the prefrontal lobes and the subcortical grey matter structures, such as subcortical vascular cognitive impairment, idiopathic normal pressure hydrocephalus, or multiple sclerosis. In addition, frontal cortex may be affected [65]. It is likely that the specific characteristic of a subcortical dementia may relate to the specific frontal-subcortical pathway involved.

Behavioural Variant Frontotemporal Dementia (bvFTD)

Arnold Pick first described forms of dementia with focal atrophy, particularly in the frontal and temporal lobes [70]. These are now considered part of the spectrum of frontotemporal lobar degeneration (FTLD), which is a group of related but pathologically diverse neurodegenerative diseases that preferentially affect the frontal and temporal lobes. FTLD presents with a number of phenotypes determined by the anatomical sites of maximal involvement. The most common phenotype of FTLD is bvFTD [71].

Distinct histopathological forms of FTLD exist, involving different patterns of accumulations of one of two major proteins in most cases, Tau and TDP-43. In inherited forms, there may be mutations in one of several genes. However, the most common mutations involve the C9orf72, tau (MAPT) and progranulin (GRN) genes [71]. Yet almost every one of these histopathologic and genetic variants can lead to the clinical bvFTD phenotype. For the most part, the phenotype is dictated by the brain regions affected rather than the pathology itself. In most cases of bvFTD, neurodegeneration affects the VMPFC, ACC, and FI preferentially [72]. These are the major nodes of the SN, and it has therefore been argued that bvFTD is a disease of the SN [73]. These nodes of the SN are also brain regions that contain a

distinct type of neuron called von Economo neurons (VENs), which are only found in highly-evolved primates (including humans), certain cetaecans, and African elephants. VENs appear to be the early victims of neurodegeneration in bvFTD [74]. It appears that VENs are particularly sensitive to the pathogenic processes occurring in FTLD, although the mechanisms are unknown. This results in degeneration of the VEN-rich brain areas that form the SN. The degeneration and subsequent dysfunction of the SN leads to signs of bvFTD.

As would be predicted from degeneration of the SN, the clinical features of bvFTD are those of OFC and SMPFC dysfunction [75]. Patients present with early apathy and inertia (SMPFC signs), as well as socially inappropriate behaviour (OFC signs) [76]. Usually there is also a significant loss of empathy and lack of insight, which may reflect involvement of the FI in the SN.

As the disease progresses, degeneration in bvFTD affects other parts of the prefrontal cortex. In more moderate stages of the illness, symptoms of EN dysfunction may emerge, concurrent with atrophy of the DLPFC. It is at this point that patients with bvFTD may become impaired on tests of DLPFC function that were mentioned above; although early on in the disease they may perform such tasks normally.

Behavioural/Dysexecutive Variant of Alzheimer's Disease

Alzheimer's disease (AD) is the prototypical example of cortical dementia and usually presents as an amnestic syndrome. However, there may be an atypical presentation with primarily prefrontal features. Johnson and colleagues identified a subset of patients with pathologically-proven AD, whose early predominant clinical presentation reflected a disturbance of executive function [77]. They termed this the "frontal variant of Alzheimer's" and demonstrated an aberrant pattern of neurofibrillary tangle deposition, more concentrated in the prefrontal cortices. In contrast, these are more concentrated in mesial temporal structures in typical AD. Subsequent studies have refined this concept and identified patients with AD and predominant executive dysfunction, such as that described by Johnson and colleagues, as well as patients with prominent bvFTD-like behavioural disturbances [77, 78]. The term behavioural/dysexecutive variant of AD has been proposed for this presentation. Interestingly, on neuroimaging, patients with the behavioural/dysexecutive variant of AD demonstrate more prominent atrophy in the parietotemporal areas bilaterally, similar to typical AD patients, and much less atrophy of the frontal regions than is seen in patients with bvFTD [78]. Therefore, disease preferentially affecting the prefrontal cortices may not necessarily account for the symptoms of the behavioural/dysexecutive variant, and additional mechanisms may be in play whereby a minority of patients with AD show symptoms of DLPFC or of SMPFC/OFC dysfunction.

CONCLUSION

This chapter has discussed the cognitive and social-behavioural functions of the prefrontal regions of the brain. It is no longer thought that there is a single overarching "frontal lobe syndrome." Rather, the prefrontal cortices are involved in a number of distinct

cognitive and social-behavioural processes. As a useful heuristic, three main syndromes can be discussed, which appear to have distinct anatomical substrates. DLPFC dysfunction causes mainly executive function difficulties that can be identified using bedside tests. OFC dysfunction causes impairments of interpersonal conduct that cannot easily be detected using bedside cognitive tests and that require careful history taking and behavioural observations to identify. SMPFC dysfunction causes difficulty with energization which may manifest clinically as a spectrum of disorders characterized by difficulty initiating and sustaining a response on cognitive testing and in daily behaviour. The FPs are involved in metacognitive processes.

The discovery of functionally connected networks of brain activity, such as the EN and SN provide an alternate way of viewing prefrontal function, and in particular illustrate how function of the OFC and SMPFC are connected. Early on in bvFTD, the SN is preferentially affected, giving rise to aberrant interpersonal conduct, loss of empathy, and poor insight with spared cognitive functions. Later on in the course of bvFTD, the EN is affected and patients demonstrate executive function difficulties.

Neurodegenerative diseases affecting the frontal lobes can generally be divided into subcortical and cortical dementias. Subcortical dementias manifest with deficiencies of energization, amotivational syndromes, and executive function difficulties. AD is the prototypical cortical dementia and usually presents as an amnestic syndrome associated with prominent parietotemporal pathology. However, a behavioural/dysexecutive variant of AD may represent an additional prefrontal dementia, although in this condition the neurodegeneration is more widespread, and the reasons why primarily prefrontal functions are affected remains to be elucidated.

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