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Address correspondence to
Dr Alexandre Henri-Bhargava,
Island Medical Program,
University of Victoria, PO Box 1700
STN CSC, Victoria, BC V8W 2Y2,
Canada, alexhb@uvic.ca.

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Dr Henri-Bhargava has received funding for clinical trials from AstraZeneca, Boehringer Ingelheim Ltd, Eli Lilly and Company, F. Hoffman-La Roche Ltd, and TauRx and has provided expert legal testimony in personal injury litigation in British Columbia. Dr Stuss serves on the advisory board of Spindle Strategy Corporation and has received personal compensation for speaking engagements for Bennett Jones LLP. Dr Stuss receives publishing royalties from Cambridge University Press. Dr Freedman serves as a trustee for the World Federation of Neurology and on the editorial boards of *Brain and Cognition* and *Journal of Parapsychology*; has received support from and served on an advisory board for Eli Lilly and Company Canada and receives publishing royalties from Oxford University Press; receives research/grant support from the Alzheimer Society of Canada, Brain Canada Foundation, Centre for Aging and Brain Health Innovation, Canadian Institutes of Health Research, and Westin Brain Institute; receives support from the Behavioural Neurology Physician Recognition Covenant Fund at Baycrest, the Morris Kerzner Memorial Fund, and the Saul A. Silverman Foundation as part of the Canada International Scientific Exchange Program project; and holds stock in companies producing or planning to produce medical marijuana and is listed on a provisional patent related to methods and kits for differential diagnosis of Alzheimer disease.

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Clinical Assessment of Prefrontal Lobe Functions

By Alexandre Henri-Bhargava, MDCM, MScCH, FRCPC;
Donald T. Stuss, OC, O Ont, PhD, FRSC, FCAHS, CPsych, ABPP-CN;
Morris Freedman, MD, FRCPC, FAAN

ABSTRACT

PURPOSE OF REVIEW: Whereas it was previously thought that there was a single overarching frontal lobe syndrome, it is now clear that several distinct cognitive and behavioral processes are mediated by the frontal lobes. This article reviews these processes and the underlying neuroanatomy and provides an approach to the assessment of prefrontal lobe functions at the bedside.

RECENT FINDINGS: Cognitive and behavioral frontal lobe functions are mediated by the prefrontal regions rather than the frontal lobes as a whole. At least five separate prefrontal functions have been defined: energization, task setting, monitoring, behavioral/emotional regulation, and metacognition. Energization is mediated by the superior medial prefrontal cortices bilaterally, task setting by the left lateral frontal cortex, monitoring by the right lateral prefrontal cortex, behavioral/emotional regulation by the orbitofrontal cortex, and metacognition by the frontal poles. Only task setting and monitoring are considered executive functions.

SUMMARY: Distinct cognitive and behavioral processes are mediated by different parts of the frontal lobe. Lesions in these areas result in characteristic clinical deficits that are discussed in this article. Key messages are that prefrontal regions mediate the higher cortical functions (as opposed to the frontal lobes in general) and that prefrontal functions are not equivalent to executive functions.

INTRODUCTION

Understanding the functions of the prefrontal lobes can be daunting at times, in part because varying terminology exists. In this article, the terminology used aims to be both accurate and useful for clinicians. The terms *frontal functions* and *prefrontal functions* are often used synonymously to mean the higher-order cognitive and social-emotional functions associated with the frontal lobes. However, parts of the frontal lobes, such as the motor cortices, supplementary motor areas, and frontal eye fields, are associated with more basic brain functions that are not usually considered to be higher-order cognitive or social-emotional functions;

therefore, these are not discussed in this article. The more precise term *prefrontal functions* is used in this article to avoid ambiguity.

The term *executive functions*, which is often associated with prefrontal lobe functions, also has myriad possible definitions. This article defines executive functions as a set of interrelated cognitive processes required for complex goal-directed activity, whose disruption is most often observed after damage to the lateral parts of the prefrontal cortex.¹ Although the terms *prefrontal functions* and *executive functions* are sometimes used synonymously, executive functions comprise only a subset of prefrontal functions. Prefrontal functions include cognitive and social-emotional processes in addition to those usually considered to be executive functions. Furthermore, some aspects of executive functions are dependent upon brain regions outside of the frontal lobes (FIGURE 2-1²).

ANATOMY OF THE PREFRONTAL CORTICES

As with all aspects of the neurologic examination, to understand the assessment of the prefrontal cortex, it is best to view it within the context of neuroanatomy. Models and concepts that are useful for the neurologic examination of prefrontal functions are presented here. Despite major advances in neuroscience, modern neurology remains rooted in the concepts of structural localization. Thus, localizing specific deficits to associated brain areas remains a useful clinical heuristic. However, it is increasingly recognized that most cognitive processes are not modular and are dependent on connectivity between large-scale networks in the brain. These networks are not discussed in detail here.

Structural Anatomy and Connectivity of the Frontal Lobes

Broadly speaking, the frontal lobes can be divided into three major regions defined by function and Brodmann architectonic (cellular) organization: primary motor cortex, premotor and supplementary motor cortices, and the association cortices comprising the prefrontal lobes. The prefrontal lobes can then be structurally divided in multiple ways, but this article focuses on four areas:

the superior medial prefrontal cortex, which includes the anterior cingulate cortex; the lateral prefrontal cortex; the orbitofrontal cortex; and the frontal poles.

The prefrontal cortices do not function as a single unit but are connected by several connection networks, including cortical, limbic, cerebellar, and subcortical. Best known are the cortico-striatal-pallidal-thalamic loops (often referred to as frontal-subcortical circuits), which help clarify the differentiation of function within the prefrontal lobes. Alexander and colleagues³ proposed a model with distinct, parallel frontal-subcortical loops that subserve different frontal lobe functions. With a few modifications, their model is generally accepted today (FIGURE 2-2). It is recognized that

KEY POINTS

- The terms *frontal functions* and *prefrontal functions* are often used synonymously to mean the higher-order cognitive and social-emotional functions associated with the frontal lobes. However, the more precise term is *prefrontal functions*.

- Although the terms *prefrontal functions* and *executive functions* are sometimes used synonymously, executive functions comprise only a subset of prefrontal functions.

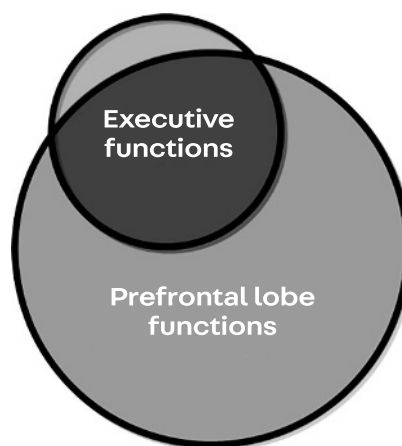


FIGURE 2-1

The relationship between prefrontal lobe functions and executive functions.

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loops are involved in basic motor function originating from the primary motor cortex and supplementary motor area as well as the frontal and supplementary eye fields. In addition, loops originating from the dorsolateral prefrontal cortex, lateral prefrontal cortex, orbitofrontal cortex, and anterior cingulate cortex subserve cognitive and social-emotional prefrontal functions.⁴ These frontal networks (and the fact that the functions associated with the prefrontal cortices tend to be less hard-wired and automatic) suggest that damage to the connections may sometimes result in a clinical profile that has similarities with dysfunction of the prefrontal cortex itself. For example, patients with lesions in the dorsomedial thalamus may exhibit symptoms of prefrontal lobe injury.⁵ However, careful analysis will likely show differentiation depending on the site of damage within such networks.⁶ In addition, by definition, complex tasks demand multiple processes in many brain regions. Here, the primary focus is on the prefrontal cortices themselves.

Functional Anatomy of the Prefrontal Lobes

Understanding the functional neuroanatomy of the prefrontal cortex is challenging because different models exist of prefrontal functions. To some extent, these models are shaped by the methods used in the research that

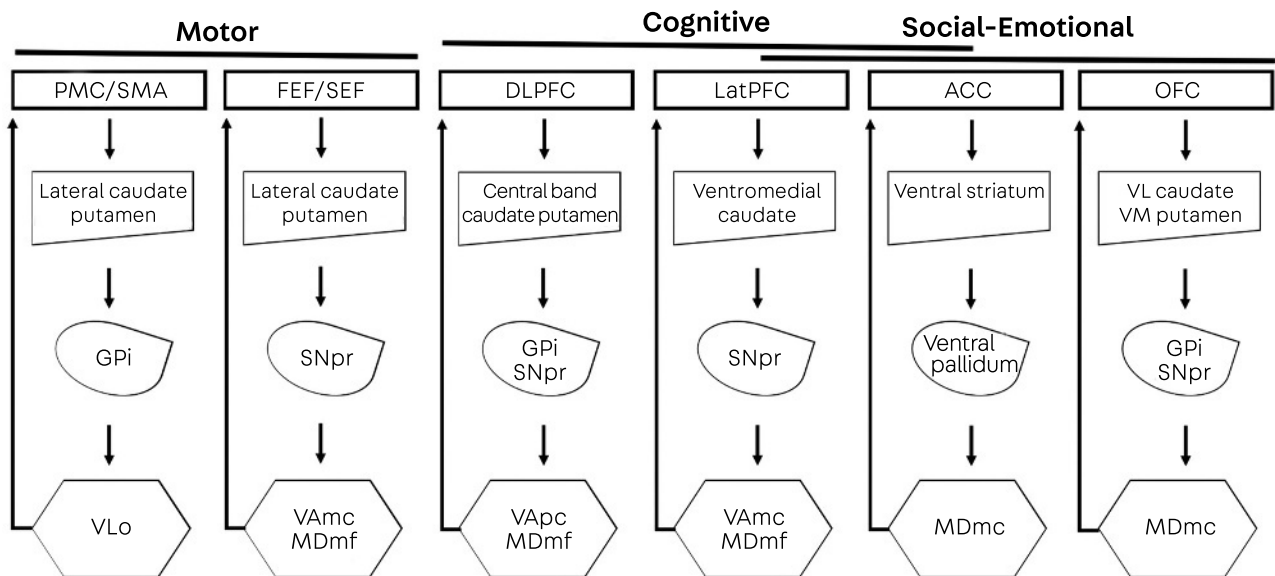


FIGURE 2-2

Frontal-subcortical circuits, based on 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. Multiple cortico-cortical and cortico-limbic connections also interconnect these loops. ACC = anterior cingulate cortex; DLPFC = dorsolateral prefrontal cortex; FEF = frontal eye fields; GPi = globus pallidus pars compacta; LatPFC = lateral prefrontal cortex; MDmc = medialis dorsalis, pars magnocellularis; MDmf = medialis dorsalis, pars multiformis; OFC = orbitofrontal cortex; PMC = premotor cortex; SEF = supplementary eye fields; SMA = supplemental motor area; SNpr = substantia nigra pars reticulata; VAmc = ventralis anterior, pars magnocellularis; VAp = ventralis anterior, pars parvocellularis; VL = ventrolateral; VLo = ventralis lateralis, pars oralis.

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developed them. This article relies upon the model of prefrontal function developed by Stuss and colleagues.⁷ This model is helpful for neurologists because it has been refined by examining neurologic patients with focal prefrontal lobe lesions.⁸ Starting from this model, five component processes have been identified as separate prefrontal lobe functions: energization, task setting, monitoring, behavioral/emotional regulation, and metacognition.

Energization is the process of initiating or sustaining any nonreflex response. Any activity that requires getting one's "mental clutch" out of the neutral position requires energization. In studies of patients with prefrontal lesions, deficits in energization were associated with bilateral damage in the superior medial prefrontal cortex, including the anterior cingulate gyrus.⁹

Task setting and monitoring are the two processes that fit the definition of executive functions. Task setting refers to developing and implementing a plan for carrying out activities such as paying bills. Monitoring is the process of checking that one remains on task over time, with adjustments in behavior as required for successful completion. In studies of patients with prefrontal lesions, deficits in task setting were associated with lesions in the left lateral frontal region, whereas deficits in monitoring were associated with lesions of the right lateral frontal area.⁹

Patients who have lesions in the orbitofrontal cortex exhibit difficulty with behavioral and emotional regulation. Damage to the frontal poles causes impairment of metacognitive processes, including self-awareness and the ability to attribute mental states to others, ie, theory of mind.^{8,10}

Linking Structural and Functional Anatomy

One reason the model of functional anatomy discussed here is clinically useful is that it can be linked to the anatomic frontal-subcortical circuits. The main function of the superior medial prefrontal cortex loop (FIGURE 2-2) is energization. The main functions of the left and right dorsolateral prefrontal cortex loops, respectively, are task setting and monitoring. An additional lateral prefrontal cortex loop has been argued to be involved in processes of inhibition.¹¹ Although growing evidence indicates that the concept of inhibition is useful and descriptive, most "inhibitory" tasks can be explained by the more fundamental energization and executive processes outlined above.^{9,12-14} The orbitofrontal cortex loop is involved in behavioral and emotional regulation. The frontal poles are involved in metacognitive processes but are not part of any frontal-subcortical circuit. Instead, it is believed that the frontal poles integrate information from diverse prefrontal cortices, but the mechanisms whereby this leads to metacognitive processes are poorly understood.¹⁵

CLINICAL ASSESSMENT OF PREFRONTAL FUNCTIONS

Prefrontal functions mediate cognitive activities and behaviors that may not be apparent in the artificially constrained environment of a clinical encounter and only manifest in the outside real world. Therefore, it is important to pay special attention to assessment of these functions if any clinical reason exists to think that they may be impaired. Many prefrontal functions are best assessed by carefully asking specific questions during history taking. For some functions, this can be supplemented by administering cognitive tests to patients.

Precursors to Assessing Prefrontal Functions

In assessing prefrontal function, the history is paramount and may be more important than the clinical examination. Many prefrontal functions are related to

KEY POINTS

- Five component processes have been identified as separate prefrontal lobe functions: energization, task setting, monitoring, behavioral/emotional regulation, and metacognition.
- Energization is the process of initiating or sustaining any nonreflex response. This is mediated by the superior medial frontal regions bilaterally.
- Task setting and monitoring are the two prefrontal lobe processes that fit the definition of executive functions.
- Task setting refers to developing and implementing a plan for carrying out activities such as paying bills. This is mediated by the left lateral frontal region.
- Monitoring is the process of checking that one remains on task over time, with adjustments in behavior as required for successful completion. This is mediated by the right lateral prefrontal region.
- Behavioral and emotional regulation is mediated by the orbitofrontal cortex, while metacognitive processes are mediated by the frontal poles.

behaviors, emotions, and social actions, all of which a patient may be unable to describe adequately or may even be unaware of. History from a collateral informant who knows the patient well is critical, but specific behaviors or symptoms must often be probed as collateral informants will not always intuitively relate behaviors that they have observed to the patient's problem. When possible, the collateral history should be obtained separately from the patient but with his or her consent, as this will allow collateral informants to more freely describe their observations without fear of retribution for divulging potentially embarrassing accounts. It should be stressed that "normal" human behavior spans a diverse range and not all abnormal behavior is due to neurologic disease; thus, it should be determined whether aberrant behaviors demonstrate a marked change from the patient's previous functioning.

When performing a comprehensive neurologic assessment, the clinician must first determine that basic neurologic processes are intact before assessing more complex processes. In the assessment of prefrontal lobe functions, it is important to first determine that the patient is fully alert and not in a confusional state or delirium. For tests requiring motor responses, such as drawing, writing, or tapping, it is important to determine that basic sensorimotor functions are intact. Because many bedside tests of prefrontal functions rely on spoken instructions or verbal responses from the patient, it is important to determine whether the patient is aphasic. If language function is sufficiently impaired to make verbal responses or comprehension unreliable, the examiner should focus on tests that do not require language comprehension or a verbal response. If comprehension is significantly affected, most cognitive tasks (including prefrontal tasks) will be difficult to administer since the patient may not be able to follow instructions.

No single test can examine a specific cognitive function in total isolation, but rather certain tests are more or less reliant upon component functions. Many tests described here should not be conceived as tapping exclusively into a specific function but are more properly understood as being sensitive to a specific dysfunction.

Superior Medial Prefrontal Functions

Dysfunction of the superior medial prefrontal cortex leads to deficits in energization to various degrees. Initially, this is assessed by history and careful observation of the patient. At one extreme, a very severe deficit of energization will cause akinetic mutism, a total inability to initiate any internally derived activity but with intact basic sensory and motor functions and retained ability to react to external stimuli. Akinetic mutism is usually seen with lesions simultaneously affecting both hemispheres, either in bilateral medial prefrontal cortices¹⁶ or bilateral medial prefrontal-subcortical regions⁵ (**CASE 2-1**). Although it is not difficult to recognize that something is seriously wrong when patients exhibit akinetic mutism, this rare syndrome can be mistaken for locked-in syndrome or a psychiatric illness such as depression.

Less severe forms of energization deficit produce reduced initiation of motor, cognitive, or combined psychomotor responses despite preserved basic attention. The term *abulia* is often used to describe decreased initiation of cognitive responses, but it is a term that lacks precise definition.²⁰ *Apathy* is the term used to describe a less severe expression of lack of initiation. In the history, the patient will often be described as lacking motivation, and this may be misattributed to a psychological crisis, psychiatric illness such as depression, or

even general fatigue. Collateral informants may say, “I think she is depressed.” However, it is important to validate whether this is true directly with the patient. When the patient experiences a syndrome of decreased energization, during the history and physical examination, the examiner will observe that the patient’s eyes properly track the examiner and that the patient does not appear distracted, yet the patient either initiates speech or action less often than normal or is slow in initiation.

Phonemic word fluency (also known as lexical word fluency, the ability to generate words starting with a particular letter) can be a useful index of energization.²¹ To administer this task as an index of energization, it is important to first establish that the patient does not have aphasia. The patient is then asked to generate as many words that begin with a certain letter as possible within a defined time interval (generally 1 minute). Usually patients are asked to exclude proper nouns, numbers, and multiple versions of a single word (eg, *farm*, *farming*). If the patient generates significantly fewer words later in the time interval, this is particularly sensitive to dysfunction of the superior medial prefrontal region as opposed to other prefrontal regions.^{9,21} A popular version of this task is the FAS test, in which patients are asked to perform the task 3 times using each of the letters *F*, *A*, and *S*. Normative performance values are available for the FAS test.²²

The astute examiner will realize that patients with an energization deficit take longer to accomplish almost any task. They may run out of time when completing timed tasks, despite performing them properly.⁸ Computerized cognitive assessment tools can automatically record reaction times and the total time taken to perform a task.²³ This includes the electronic form of the popular Montreal Cognitive Assessment (MoCA)²⁴; however, direct correlation with timed performance on computerized tasks and medial prefrontal damage has not been adequately studied. At the bedside, it may be more useful to simply note that a patient is slow to perform cognitive tasks rather than to rely on any specific time cutoff. It is also important to allow patients time to complete the task to test the limits of abilities.

Apathy may, in some cases, represent the least severe form of energization deficit; however, different forms of apathy have been described that probably have different neural bases, and only some of these may be considered truly due to energization deficits.²⁵ Furthermore, the terms *apathy* and *abulia* are sometimes used interchangeably given that both are defined in various ways.²⁶ Apathy has been defined as an amotivational syndrome, and, indeed, lack of motivation will decrease speed of response; however, apathy may better be defined as a syndrome characterized by lack of initiation and drive, as it is clear that not all patients with abulia or apathy lack motivation in the sense of the will to act. Nevertheless, it is useful for the clinician to understand that apathy can stem from medial prefrontal cortex damage. The presence of apathy is usually determined by careful history taking; here again, care must be taken not to confuse apathy with depression. Specific rating scales, such as the Apathy Evaluation Scale, can provide helpful information in quantifying the degree of apathy. The Apathy Evaluation Scale is available in self-administered, informant-administered, and clinician-administered versions and is free and easy to use.²⁷

Although deficits in energization and the amotivational syndromes they produce have been classically described as arising from damage to the superior

KEY POINTS

- History from a collateral informant who knows the patient well is critical when assessing prefrontal function.
- Phonemic word fluency (also known as lexical word fluency) can be a useful index of energization.

medial prefrontal cortex and associated subcortical circuits, these syndromes can also develop with damage to other prefrontal-subcortical circuits. It appears that sufficiently decreased output from the basal ganglia within any of the frontal-subcortical circuits may produce deficits in energization.²⁸ This is frequently seen in extrapyramidal disorders such as Parkinson disease, in which slowed motor responses, cognitive responses, or both are a hallmark feature of the disease.²⁹

Lateral Prefrontal Functions

It has already been noted that different measures described for testing prefrontal functions may not be specific. In addition, some concern exists about sensitivity, since other factors (such as premorbid intelligence and experience) may mitigate against task performance in general. It is also important to note that many of bedside tests were first validated in patients with rather large lesions, which may

CASE 2-1

A 69-year-old retired physician was referred for a neurologic consultation. Four months before presentation, his wife had noticed that he was less interested in his usual activities. He did not initiate his usual summertime plans to golf or go on a trip. He reported feeling tired and nonspecifically unwell but denied any depression or other mood changes. As symptoms progressed, he stopped initiating conversations, and his physical movements became slowed and sparse. He spent his days literally doing nothing and just sat on the couch unless asked to do something. Four weeks before presentation, he also developed difficulty initiating gait, saying that his feet were stuck to the ground, and he walked with very small steps.

On examination, he had paratonic rigidity (inability to relax muscles during assessment of tone while conscious, often seen with dysfunction of frontal-subcortical circuits) in the lower limbs, but no tremor or abnormal movements. Muscle power was normal, although he did not move his limbs spontaneously unless asked. Tendon reflexes were brisk but without clonus. Plantar responses were flexor. Upper and lower limb tests of coordination were all performed quite slowly, but rhythmically, with normal amplitude and no past pointing. Sensation was normal. On examination of gait, he had a widened stance, significant retropulsion, and difficulty initiating a step. He was alert but sat passively in his wheelchair, looking at the examiner but otherwise not offering much spontaneous interaction. He answered questions in monosyllabic answers. He did not have much facial expression until one of his favorite childhood treats was presented to him, at which point his face brightened, he exclaimed "Humbugs!" and reached for a candy. He then told a story from his childhood in a few short, slow sentences.

Brain MRI revealed a "butterfly" glioma compressing medial anterior structures including superior medial prefrontal cortices (FIGURE 2-3¹⁷). The patient and family elected for palliative care, and he succumbed to progressive neurologic deficits after 6 months.

include extension to nonfrontal regions. Thus, patients may not show deficits when lesions are smaller and confined to the frontal lobes. It is also important to look for consistency of impairment before concluding that frontal deficits are present. A complete neuropsychological examination using a series of standardized tests will assist in this regard.

Patients with damage to the lateral prefrontal cortex demonstrate deficits in task setting and monitoring, both of which are components of executive function. The lateral prefrontal lobes are also important for working memory, the ability to consciously retain and manipulate information in the short term.³⁰ Whether or not this can be explained by disruption of other executive functions or whether working memory is a distinct construct that is a more basic process of different integrated neuronal regions continues to be debated,^{31,32} but from a clinical perspective, it is useful to conceptualize this as a distinct aspect of prefrontal function that can be examined.

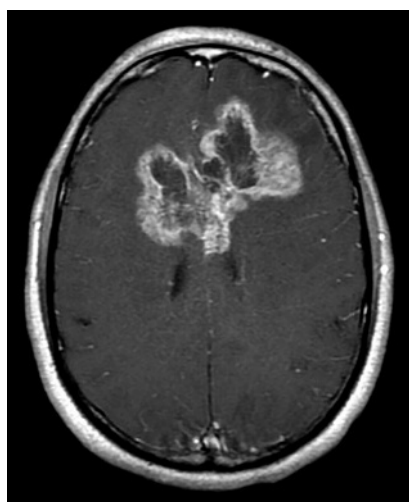


FIGURE 2-3
Butterfly glioma in the superior medial prefrontal cortex similar to the patient in **CASE 2-1**. Axial postcontrast T1-weighted brain MRI at the level of the centrum semiovale. A heterogeneously enhancing mass is seen in the region of the superior medial prefrontal cortex with mild mass effect as seen by effacement of the lateral ventricles. Radiologic diagnosis was consistent with a glioblastoma exhibiting a “butterfly” glioma shape. This diagnosis was confirmed pathologically.

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This case demonstrates several features of the superior medial prefrontal syndrome with progressive deficits in energization. The patient initially became passive and no longer initiated activity; however, he had no other obvious “neurologic” signs. At this stage, his symptoms could be called apathy or abulia, highlighting that these terms are often imprecise. The abulia became more pronounced, and he developed general psychomotor slowing, worsening to the point where he stopped initiating most internally generated goal-directed activity despite having the basic neurologic capacity to do so with intact sensorimotor function. When presented with an emotionally powerful external stimulus (his favorite childhood candy), he did interact. This degree of energization deficit usually requires the presence of a lesion affecting both superior medial prefrontal cortices, such as this patient’s tumor. Eventually, he had associated neurologic features that can be seen with medial prefrontal damage, including a fairly rapid progression of so-called apraxia of gait or frontal gait disorder^{18,19} as well as urinary incontinence.

COMMENT

The first clues that a patient has difficulty with task setting can be obtained with careful history taking. Such patients may be able to complete previously learned routines but will have difficulty in carrying out something novel. In more severe cases, completing even more familiar tasks in a logical manner can be impaired. If the onset of this symptom is insidious, the collateral informant may only come to realize its presence when specifically asked. For example, a patient may previously have been actively involved in planning family vacations, booking hotels, and researching travel routes, but now the spouse does all these tasks.

CASE 2-2

A 58-year-old man was referred for assessment of cognitive difficulties. He had been working as a successful real estate agent for over a decade, but 2 years before referral, he began not following through on arrangements, made seemingly impulsive decisions, and, ultimately could not sell properties. He took on simpler jobs but could not fill out his work schedule properly. He sought medical help, and, although he denied feeling depressed, he was prescribed antidepressants. He stopped assisting in grocery shopping and doing basic household chores, leading to marital discord, although the patient expressed remorse for the difficulty he was putting his wife through. He maintained personal decorum and social rules.

The patient had appropriate insight and concern into his difficulties. He could only name three words beginning with the letter *F* in 1 minute, and he named nine animals in 1 minute. He exhibited normal registration but mild difficulty with verbal and visual recall. His digit span was seven forward and three backward. He could not do serial subtractions of 7 from 100. He was concrete in assigning pairs of words to their superordinate category: he said that *train* and *bicycle* were alike "because they have wheels," *fork* and *knife* were alike because "you have them at dinner," and *man* and *tree* were alike because "a man can be in a tree." He could not perform the Luria hand sequences (palm, fist, edge) without the examiner doing them simultaneously. He made the performance errors on the tasks shown in [FIGURE 2-4](#), [FIGURE 2-5](#), [FIGURE 2-6](#), and [FIGURE 2-7](#). Brain MRI revealed widespread moderate supratentorial atrophy without any lobar predilection. Brain perfusion scanning revealed left parietal hypoperfusion.

A clinical diagnosis of the behavioral/dysexecutive variant of Alzheimer disease was made.³³ Over the next 5 years, his deficits progressed and broadened considerably; prominent amnesia and mild aphasia emerged within 18 months of consultation. He began to develop almost total dependence on his wife and became extremely anxious if she was not directly within his sight.

Patients who previously liked to try new recipes may begin to fall back on recipes they have memorized that have fewer steps and require less multitasking. Patients may also be described as needing to eliminate all distractions to accomplish tasks they could previously incorporate into a multitasked routine; for example, a patient may not be able to do the laundry without missing crucial steps if any distractions are present (CASE 2-2).

Further clues to the presence of lateral prefrontal cortex dysfunction can be obtained by listening to the patient's narrative discourse during history taking.



FIGURE 2-4

Abnormal performance on the alternating sequences task in the patient in CASE 2-2. The patient was given a page with an alternating square and triangle pattern (*dotted underline*) with the instructions "start here [end of dotted underlined section] and continue with the same design until you reach the end of the page." The patient made an initial task-setting error; instead of beginning with a square, he began with a triangle. He then continued to copy his initial incorrect "triangle-triangle-square" pattern instead of the correct "square-triangle" pattern (monitoring error).

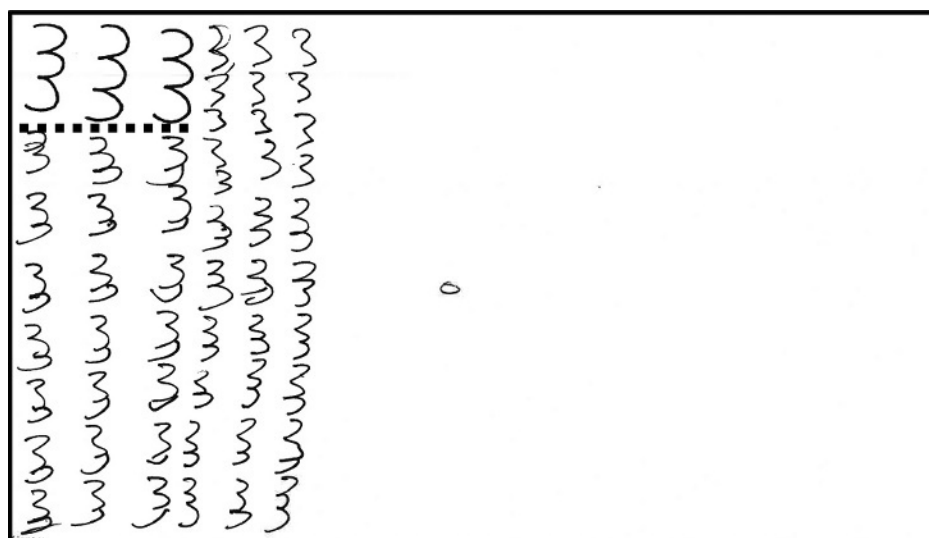


FIGURE 2-5

Abnormal performance on the multiple loops task in the patient in CASE 2-2. The patient was given a page with three triple loops in the top left corner (*dotted underline*) with the instructions "start here [end of dotted underlined section] and continue with the same design until you reach the end of the page." Despite multiple repeat instructions, the patient proceeded to copy the pattern down vertically instead of horizontally (task-setting error). On the fourth try (fourth column), the patient began to make monitoring errors: some of his triple loops are double loops that resemble the number 3.

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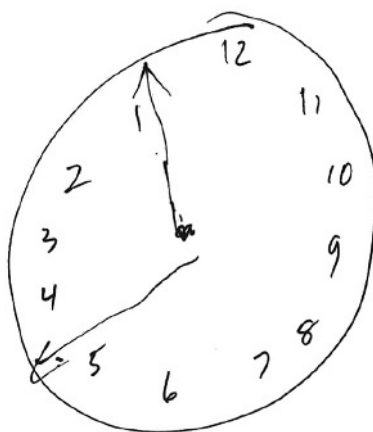


FIGURE 2-6

Abnormal performance on the clock drawing task in the patient in **CASE 2-2**. The patient was given a blank page and instructed "Draw a clock, put in the numbers and set the hands at ten past nine." He put the numbers in the counterclockwise order (monitoring error). He set the time at an irrelevant option and did not clearly indicate a longer minute hand (task-setting errors). He neglected to have the hands meet at the middle and escaped the boundaries of the clock with one of the hands (monitoring errors).

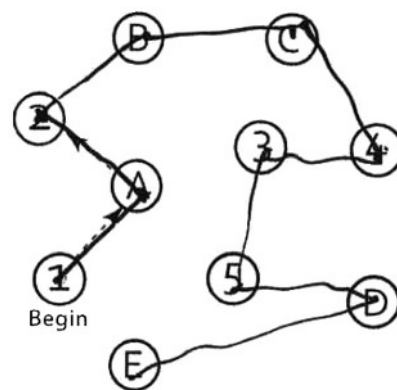


FIGURE 2-7

Abnormal performance on the Trail Making Test Part B in the patient in **CASE 2-2**. The patient was instructed "Please draw a line going from a number to a letter in ascending order. Begin here [1] and draw a line from 1 to A then to 2 and so on." The patient was not able to follow the sequence correctly, joining the letters C and D and the numbers 3 and 4 incorrectly without noticing his error (monitoring error). Basic visual scanning was intact as he was able to locate all of the circles.

COMMENT

This case illustrates several features of the dysexecutive syndrome typical of lateral prefrontal cortex dysfunction. As in many cases of problems with executive function, the patient was initially not specific about his descriptions of what was wrong because it was not immediately clear. Poor performance on several tasks pointed to lateral prefrontal cortex dysfunction.

In this case, prefrontal dysfunction was inferred from the patient's symptoms and cognitive examination, since a structural lesion was not seen. This suggested either a psychiatric or neurodegenerative etiology, and the history was more compatible with the latter. The differential diagnosis included behavioral variant frontotemporal degeneration (bvFTD) and the behavioral/dysexecutive variant of Alzheimer disease, with the latter being more probable according to diagnostic criteria.^{34,35} The case also serves as a reminder that the deficits seen early in bvFTD are usually (but not always) the behavioral and emotional dysregulation of orbitofrontal cortex dysfunction, which this patient did not have, rather than lateral prefrontal dysfunction.

Patients with lateral prefrontal lesions can have defective recruitment of procedures necessary for complex language assembly.³⁶ They may speak in grammatically correct sentences with normal syntax, but the content may be described as vague or confused. Such patients will be prototypical bad historians. If this pattern represents a substantial change from the previous mode of discourse, making note of this “frontal” speech pattern may provide the first clue to prefrontal lobe injury. Examiners could ask patients to discuss or write down examples of how they would go about planning something new and note the response. For example, the examiner could ask, “Suppose you were to make a career change and decide to open up a florist business. How would you go about this?” A patient with higher-order task-setting difficulties will answer in generalities or may skip important steps.

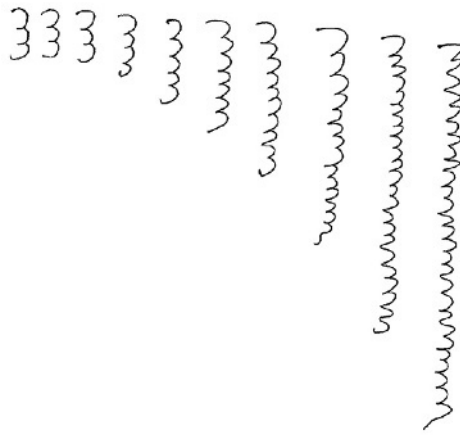
The digit span test is a simple test of working memory that is often used at the bedside. In this test, the patient is presented with progressively longer strings of digits and asked to repeat them back in the same order as they were presented. Usually the test involves allowing two attempts at a certain length of digits (albeit with different numbers used). Digit span backward involves the patient having to repeat the digits in the reverse order and may be more reliant on lateral prefrontal cortex processes.³⁷ In addition to taxing working memory, this test relies on intact task setting and monitoring. The difference between forward and backward digit span (usually two or less) may indicate the degree to which executive functions are impaired. When administering digit span tests, it is important for the examiner to present the digits at an even cadence approximately 1 second apart and to use consistent and neutral voice inflection, except for the last digit, for which the voice may be lowered to signal the end of the series of digits.

Some useful simple bedside tests that tap into lateral prefrontal cortex function were developed in the mid-20th century by Alexander Luria, including the Luria hand sequences.³⁸ In this test, patients are asked to place their hands on a table in a repeated palm, fist, edge sequence. Patients with basic difficulty in task setting will have difficulty repetitively and automatically performing this sequence correctly (although it has been shown that even neurologically healthy individuals may have initial difficulty).³⁹ Patients with basic monitoring difficulties will have difficulty maintaining this sequence over several repetitions and may perseverate (ie, repeat the same movement 2 or more times in a row without switching). A written equivalent that is commonly tested involves asking the patient to continue drawing a sequence of alternating connected square- and triangle-like sequences (FIGURE 2-4). The multiple loops task is a related task that is more sensitive to deficiencies of monitoring; patients are asked to repeatedly draw a series of three loops across a page.⁴⁰ Patients with monitoring difficulties may either draw the number 3 (FIGURE 2-5), which is a prepotent response (the action that has priority over others because of primacy during development, having been done recently, or having the greatest relevance) or will continue to draw more than three loops (FIGURE 2-8).

Another test developed by Luria that remains popular and easy to administer in various forms is the go/no-go task. In Luria’s description of the task, the patient must raise one finger in response to one tap (go) but must not make any movement in response to two taps (no-go). A nonrepeating sequence of single and double taps is presented, and the patient must respond appropriately throughout the sequence. Patients with difficulty in task setting will have

KEY POINTS

- The lateral prefrontal lobes are important for working memory, the ability to consciously retain and manipulate information in the short term.
- The digit span test is a simple test of working memory that is often used at the bedside.

**FIGURE 2-8**

Abnormal performance on the multiple loops task in a patient with dorsolateral prefrontal cortex dysfunction. The patient was given a page with three triple loops in the top left corner with the instructions “start here [end of first three triple loops] and continue with the same design until you reach the end of the page.” Instead of drawing only three loops for every set, the patient perseverated, drawing progressively longer sets of loops. This demonstrates an error in task monitoring.

difficulty in completing the task despite multiple instructions. Those with difficulty in monitoring will make errors. The conflicting instructions task is a modification of the go/no-go task that is often administered in addition to it. In this task, the patient must raise two fingers in response to one tap and one finger in response to two taps.

The Trail Making Test is a popular test with myriad versions and is thought to be a sensitive measure of executive function and lateral prefrontal cortex damage.⁴¹ In the most popular form, patients are first presented a sheet of paper with 25 circles, with the numbers 1 through 25 printed inside the circles. This is Part A of the test. Patients must connect the circles in the correct order as quickly as possible without errors and are timed.

Part A is particularly sensitive to energization deficits (specifically basic motor speed and visual search speed), but this also tests basic visuomotor attention and scanning. In Part B, the 25 circles contain the numbers 1 to 13 and the letters A to L. Patients must alternate numbers and letters in ascending order as quickly as possible without errors (FIGURE 2-7). Thus, Part B relies more on task setting (remembering to shift mental set) and monitoring of errors than does Part A. Although this test is widely interpreted as sensitive to lateral prefrontal cortex damage, careful analysis indicates that it is a multifactorial test and affected by damage to many brain regions; controlling for these factors has pointed to the influence of the superior medial frontal region.⁴²

Phonemic (lexical) word fluency has already been discussed as a task that can be sensitive to medial frontal damage due to decreased energization, resulting in reduced initiation and production of responses. However, successful completion of this task also requires planning and searching, as well as language processing. In fact, impairment in phonemic fluency is greatest in patients with left lateral prefrontal cortex damage.²¹ A notable discrepancy from the better performance on semantic fluency (generation of words within a defined category, such as animals) is often seen. Design fluency is the analogous nonverbal generation task. In its simplest form, patients can be asked to draw as many unique figures as possible in a given amount of time.⁴³ More systematized versions place some constraints. In one popular version of the task, patients are shown an array of dots and asked to make as many unique figures as possible in 1 minute by using straight lines to join the dots.⁴⁴ Design fluency is most impaired in patients with right lateral prefrontal cortex damage.⁴⁵ In sum, fluency tasks are good tests of

component executive functions and are sensitive to lateralized lateral prefrontal cortex damage.

Tests of abstract thinking are used to test executive function and tap into task-setting functions. Interpretation of proverbs are often proposed as such⁴⁶; however, the correct interpretation of a proverb more likely depends upon recall of previously learned knowledge regarding the proverb's semantic meaning rather than the generation of a novel abstract idea.⁴⁷ Many people with normal prefrontal function will not be able to correctly interpret a proverb they have never heard; thus, proverbs are not a reliable test of prefrontal functions. Another task that may also depend upon semantics, albeit less so, is the similarities test. Patients are presented with a pair of stimuli (words or pictures) and asked in which way they are alike. The correct answer requires the patient to place the stimuli into the same superordinate category (ie, the category to which both stimuli belong, such as *fork* and *knife* both belong to the category *utensils* and *song* and *painting* both belong to the category *art*). Performance on this test activates left perisylvian prefrontal regions.⁴⁸ Reliance on semantics may be reduced by giving clear instructions; rather than asking "How are these two things alike?" the examiner can say "I will give you two words, and I would like you to tell me to what category they belong."⁴⁹

Visuospatial function involves multiple top-down visual processing aspects that involve the lateral prefrontal cortex.⁵⁰ Many of these involve task-setting functions that can be assessed by asking patients to draw a particular item without a model to copy (eg, asking them to draw a three-dimensional cube without showing them a drawing of a cube). If patients have difficulty executing the task, it must subsequently be determined whether they possess basic bottom-up visual processing that does not employ the prefrontal cortices. This can be done by asking the patient to trace or copy the figure in question. If the patient can copy the figure but is not able to draw it from command, it may suggest difficulty with task setting.

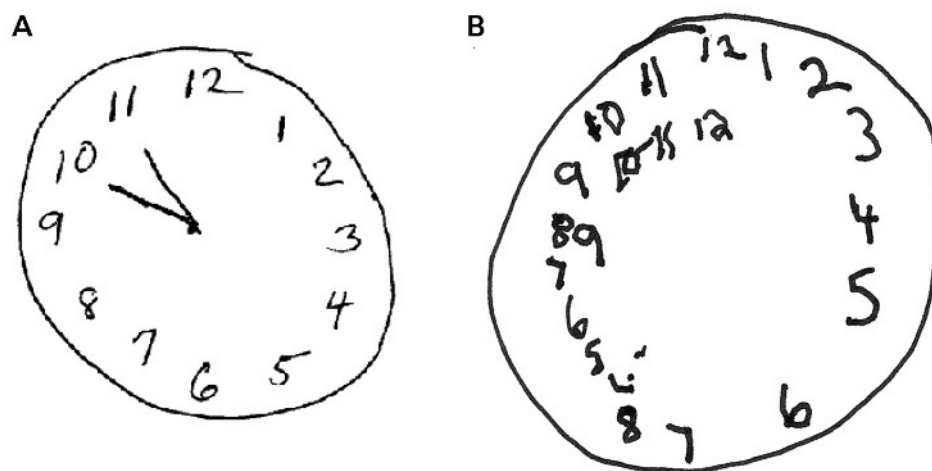
Clock drawing is a popular bedside cognitive test that expands on drawing to command.⁵¹ Although successful clock drawing requires multiple cognitive processes including visuospatial abilities, it can be sensitive to prefrontal damage with respect to execution of the task, including processes that involve planning and monitoring. Most variations of this test involve instructions such as "Draw the face of a clock, put in the numbers, and set the hands at [a particular time]." The time chosen is important; for maximum sensitivity, it should involve a time where the correct positioning of the hands on the clock requires the patient to overcome prepotent responses. "Ten past eleven" and "five past four" are good choices. Patients who lack adequate task setting or monitoring and adopt literal responses will place the hands at 10 and 11 (9:55 or 10:50) instead of 11 and 2 in the former, and at 5 and 4 (4:25 or 5:20) instead of 5 and 1 in the latter. They may also duplicate numbers, draw extra hands, or fail to self-correct. Patients with significant difficulty with task setting may become stuck and not know how to approach drawing the contour, placing the numbers, or setting the time on the clock (FIGURE 2-6 and FIGURE 2-9⁵²).

Orbitofrontal Functions

Behavioral disinhibition, emotional dysregulation, and altered social cognition are seen in patients with orbitofrontal cortex lesions. These can include

KEY POINTS

- Tests of abstract thinking are used to test executive function and tap into task-setting functions.
- Clock drawing is a very popular bedside cognitive test that taps into prefrontal function.
- Behavioral disinhibition, emotional dysregulation, and altered social cognition are seen in patients with orbitofrontal cortex lesions.

**FIGURE 2-9**

Frontal errors in the clock drawing task. In both instances, the patient was asked to draw a clock and set the hands to 10 past 11. **A**, The patient planned the clock face properly, including numbers, but made a monitoring error and was pulled to a prepotent response (the numbers 10 and 11) when setting the time. An additional monitoring error was failing to differentiate the short hour hand from the long minute hand. **B**, Another patient had more severe task-setting and monitoring difficulties. They placed the numbers incorrectly, originally in the wrong place, then perseverated. They were not able to initiate the task of setting the hands and instead wrote “10-11” inside the clock face.

Panel B reprinted with permission from Henri-Bhargava A, Freedman M, CMAJ.⁵²
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environmental dependency (the need to touch and feel things), hyperphagia or altered food preferences, sexually inappropriate behavior, inappropriate jocularity, loss of social decorum, argumentativeness, capriciousness, narrowed preoccupations, and even criminal behavior. These apparently loosely related behavioral disturbances may all stem from a more basic disturbance in the evaluation of outcomes and options for action.⁵³

The clinical examination of patients with orbitofrontal cortex lesions can be challenging; if their deficits are circumscribed, they will perform normally on most tests of executive function described earlier in this article. Therefore, clues to the presence of orbitofrontal cortex dysfunction usually arise in careful history taking from informants. Aberrant behavior must be specifically asked about and examples elucidated. In progressive disease, such as dementia, informants may initially find plausible excuses to explain the patient's behavior, and it is only with time that a pattern of aberrant behavior diverging from previous behavior becomes clearly apparent (**CASE 2-3**). Formal clinical scales can be helpful to guide history taking. The Neuropsychiatric Inventory (NPI)⁵⁴ can be used to elucidate many types of behavioral impairment, although these are not specific to the behavioral derangements seen in orbitofrontal cortex dysfunction. The Frontal Behavioral Inventory⁵⁵ is another assessment questionnaire that a clinician can administer to an informant to probe the spectrum of behaviors seen in behavioral variant frontotemporal dementia (bvFTD), a disease in which the degeneration includes the orbitofrontal cortex. Key questions asked on the Frontal Behavioral Inventory that are particularly pertinent to orbitofrontal cortex dysfunction include questions regarding patient personal neglect,

perseveration and obsession, hoarding, socially inappropriate behavior, excess jocularity, poor judgment and impulsivity, aggression, hyperorality, hypersexuality, and environmental dependency (the tendency to automatically touch, grab, and use objects in one's own immediate environment). Other questions on the Frontal Behavioral Inventory are more pertinent to lateral prefrontal cortex, superior medial prefrontal cortex, or frontal pole dysfunction, so looking at the pattern of responses is important. The Frontal Behavioral Inventory has been shown to be sensitive to orbitofrontal cortex injury in traumatic brain injury.⁵⁶

Frontal Pole Functions

The frontal poles integrate information from other prefrontal regions and are involved in metacognitive functions, such as being able to take the perspective of others and self-awareness. This includes perceiving one's own and others' emotional states. The ability to be aware of one's own state of mind and that of others is called theory of mind.⁵⁷ Some researchers have proposed distinguishing cognitive theory of mind (understanding what others think), affective theory of mind (understanding what others feel), and conative theory of mind (being able to influence others' mental states based on one's own understanding of them). The frontal poles may be variably involved in all of these.⁵⁸

It is, therefore, important to pose questions to collateral informants about whether the patient demonstrates preserved sympathy, which is the ability to generate an emotion in reaction to another's emotional state, as well as preserved empathy, which is the ability to recognize others' emotional states. Spouses, close friends, and relatives will usually be the best informants but may not think to volunteer information about the patient's emotional state and responses unless they are specifically asked about them. Patients with frontal pole dysfunction and reduced theory of mind may often have behavioral/emotional dysregulation due to orbitofrontal cortex dysfunction given the proximity of these two regions and the fact that these two regions may often be injured or degenerate simultaneously in various conditions.

Theory of mind is not routinely tested in the neurologic mental status examination, and the practical application of research-oriented tests of theory of mind from neuropsychological experiments to routine clinical practice remains underexplored. One test that could be used to assess theory of mind is the false belief task, commonly administered as the "Sally-Anne test,"⁵⁹ in which a story or skit is presented to the patient as follows. Sally hides a ball in the presence of Anne and then leaves the room. While Sally is out of the room, Anne moves the ball to a different location. Sally returns into the room. The participant is then asked where Sally believes the ball is. They must understand that Sally believes that the ball is still in its original location. This test specifically examines cognitive aspects of theory of mind, as do asking the patient to explain humor in cartoons or to demonstrate comprehension of stories that require the reader to understand a mind state.⁶⁰ Tasks that require the participant to identify facial expressions corresponding to emotions of the subjects in a story could be used to assess affective aspects of theory of mind.⁶¹

Patients with focal injury to the frontal poles may demonstrate deficiency in theory of mind.⁶² Deficits in theory of mind have also been demonstrated in degenerative diseases that affect the frontal poles or the connections to them, including Parkinson disease,⁶³ Alzheimer disease,⁶⁴ and bvFTD.^{63,64} This is usually inferred from the patient's history (**CASE 2-3**).

KEY POINT

● The frontal poles integrate information from other prefrontal regions and are involved in metacognitive functions such as theory of mind, (ie, being able to take the perspective of others and self-awareness).

CASE 2-3

A 72-year-old retired university department head was assessed at the request of his family, who reported a 4-year history of progressively odd behavior. First, his son had recently gained access to his emails and discovered that his father had engaged in extensive correspondence with scammers and had given away \$200,000 in payments to them. This was totally uncharacteristic of a man who would have previously been described as no-nonsense and very frugal. Surprisingly, the patient was unable to understand why his family was upset and that the scenarios presented by the scammers were unrealistic. He could not see irony in the fact that he seemed to care more about unrealistic hypothetical kidnapping victims than his own family. Decreased emotional responsiveness worsened, and he became cold and distant in all everyday matters. He no longer comforted his wife when she was upset, although he became very emotional about football scores. He began to openly consume large amounts of Internet pornography. He developed binge eating and would consume an entire carton of ice cream at one sitting.

When directly questioned, the patient denied, minimized, or confabulated about many of the behaviors. He could answer direct questions fluently but would often wander from topic to topic and give empty responses.

His neurologic examination was normal, including a score of 29/30 on the Montreal Cognitive Assessment (MoCA). Brain MRI showed atrophy of the prefrontal cortices, particularly the orbitofrontal cortex and frontal insula (FIGURE 2-10A, 2-10B, and 2-10C). Brain perfusion scanning demonstrated frontotemporal hypoperfusion (FIGURE 2-10D and 2-10E).

The patient met consensus criteria³⁵ for probable behavioral variant frontotemporal dementia. His behaviors were treated unsuccessfully with trials of multiple agents, including benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), trazodone, and antipsychotics. He was actively followed by a multidisciplinary health team to minimize the consequences of his behaviors while he continued to live at home.

COMMENT

The patient in this case presented with prominent symptoms of prefrontal lobe dysfunction, particularly the behavioral and emotional dysregulation of orbitofrontal cortex dysfunction, the metacognitive deficits of frontal pole dysfunction, and, to a lesser extent, some passivity suggesting decreased or aberrant energization as seen in superior medial prefrontal cortex dysfunction. The case highlights several important points regarding assessment of these symptoms. First, the general neurologic examination and office cognitive assessment, including basic tests of executive function, were normal, and the diagnosis of prefrontal lobe dysfunction relied on facts obtained during a careful history. Healthy people may have difficulty describing their behavior, and when insight and other metacognitive functions are impaired (as in this case), it is very unlikely that patients will be able to give an accurate account of their behavior. Collateral history is, therefore, essential for diagnosis.

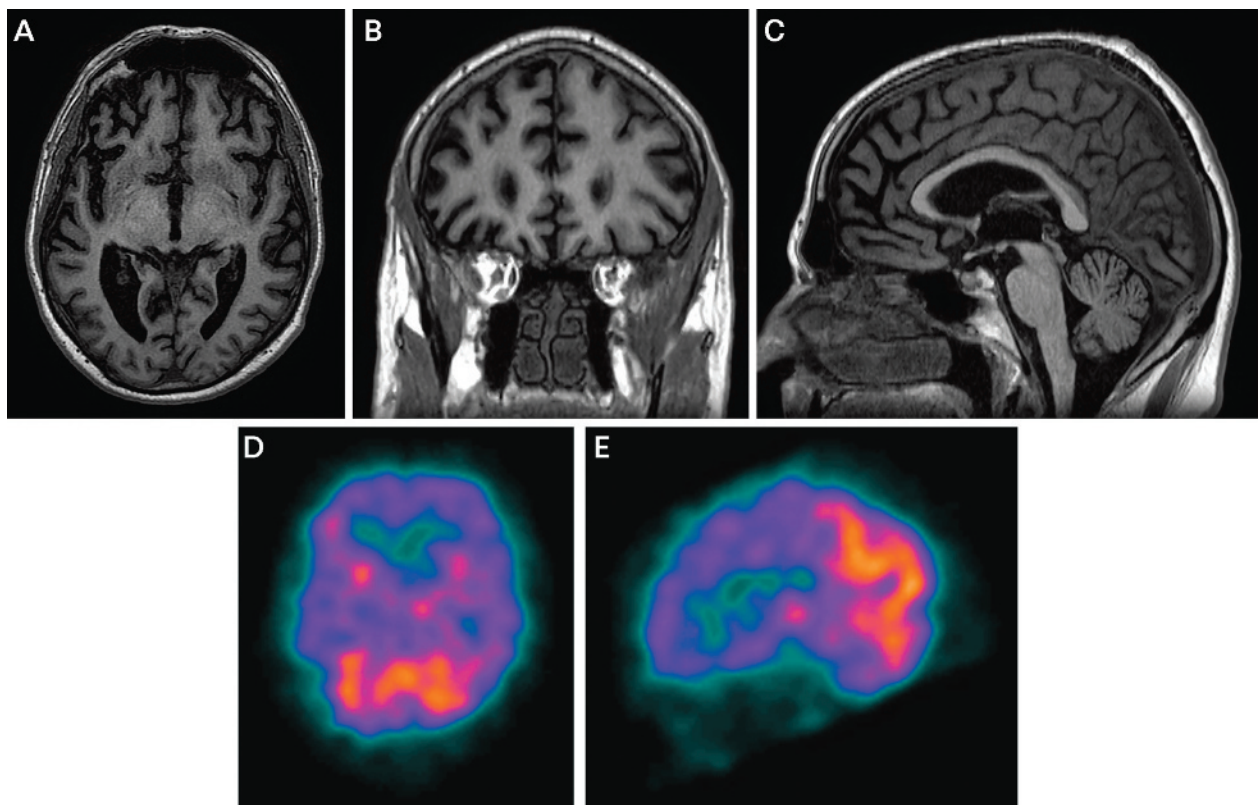


FIGURE 2-10

Neuroimaging of the patient in **CASE 2-3**. Axial (A), coronal (B), and sagittal (C) T1-weighted brain MRI sequences demonstrating focal atrophy of the prefrontal cortex bilaterally, right greater than left, in behavioral variant frontotemporal dementia. Axial (D) and sagittal (E) sections of hexamethylpropyleneamine oxime (HMPAO)–single-photon emission computed tomography (SPECT) brain perfusion scan. Normal perfusion (*orange*) is seen in the cerebellum and occipitoparietal regions, whereas frontotemporal areas demonstrate marked reduction in perfusion (*purple*).

TEST BATTERIES

Because there are many ways to test cognitive functions, neurologists often like to rely on test batteries that can assist in remembering tests to be used and allow for standardized repeated measurement. The Mini-Mental State Examination (MMSE)⁶⁵ is one such test that is very widely used, but one of its major drawbacks is that it is not sensitive to prefrontal cortex dysfunction. However, cognitive test batteries that are useful for examining prefrontal functions have been developed, although many of the tests in these batteries are primarily sensitive to lateral prefrontal cortex functions (TABLE 2-1⁶⁶⁻⁷⁰). The Executive Interview (EXIT-25) is a 25-item battery that was developed specifically to address the need to assess executive functions in patients with dementia. It does not require any special equipment apart from a freely available stimulus booklet, and it can be administered in a clinical office setting.⁶⁶ It focuses on tasks that require task setting and maintenance at a very basic level and therefore mainly assesses lateral prefrontal cortex function. The Frontal Assessment Battery is a similar battery that is shorter and easier to administer, yet correlates with the EXIT-25^{67,68}; it regroups many tests discussed earlier, including the similarities test, phonemic word fluency task, Luria hand sequences, go/no-go and conflicting instructions tasks, and a test of environmental dependency, which asks the patient not to touch the examiner's outstretched hands. The MoCA is a freely available and popular tool for testing cognitive function that aims to test a variety of cognitive domains.⁶⁹ This includes tests of executive function, such as the modified Trail Making Test Part B (FIGURE 2-7), clock drawing, similarities, and phonemic word fluency.⁷¹ These batteries may all be helpful in detecting basic impairments of task setting and monitoring and so may be most useful for

TABLE 2-1

Test Batteries for Office Assessment of Prefrontal Functions

Test Battery Name	Approximate Time to Administer	Focus	Advantages	Disadvantages
Executive Interview (EXIT-25) ⁶⁶	15 min	Lateral prefrontal functions	Tests executive functions in several ways	May be overly lengthy and complex to administer ⁶⁷
Frontal Assessment Battery (FAB) ⁶⁸	5 min	Lateral prefrontal functions	Relatively easy to learn and administer; feasible assessment of prefrontal function in diverse populations	Not sensitive to mild dysfunction
Montreal Cognitive Assessment (MoCA) ⁶⁹	10 min	Various cognitive domains, including lateral prefrontal functions	Widely used; easy to administer	Components of the test that focus on prefrontal functions are not all grouped together; not sensitive to mild dysfunction
Executive and Social Cognition Battery (ESCB) ⁷⁰	30 min	Lateral prefrontal and orbitofrontal functions	More sensitive to orbitofrontal cortex dysfunction	Not widely used; requires special stimuli and training to administer

detecting lateral prefrontal cortex dysfunction. Patients with energization deficits due to superior medial prefrontal dysfunction may be slow in performing the tasks on these batteries as in all other cognitive tasks. However, patients with the significant metacognitive deficits typical of frontal pole dysfunction or the emotional and behavioral dysregulation typical of orbitofrontal cortex dysfunction may still perform normally on these batteries. Such test batteries, therefore, lack sensitivity for some types of prefrontal dysfunction.

Few office tests are commonly used that are sensitive to orbitofrontal cortex and frontal pole dysfunction. The Executive and Social Cognition Battery (ESCB) has been developed to try to test prefrontal dysfunction in a real-life environment, specifically in the context of bvFTD.⁷⁰ However, this battery may be more useful for neuropsychologists than neurologists as it requires specific stimuli, including specialized card decks that may not be readily obtainable.

The validity of standard prefrontal cortex neuropsychological tests has been completed in a series of studies.⁷² They are excellent examples of the complexity of administering and interpreting these tests in the context of the individual's neurologic, medical, and social history.

CONCLUSION

Lesions in the prefrontal regions of the frontal lobes may result in distinct cognitive and behavioral deficits depending on the site of the damage. Cognitive processes affected include energization, task setting, and monitoring, of which only task setting and monitoring are considered executive functions. These processes can easily be tested at the bedside. Other prefrontal processes include behavioral/emotional regulation, which is best assessed by careful history. Metacognition, which includes theory of mind, is another important prefrontal process. However, a need remains to develop easy-to-administer tests to assess metacognition at the bedside.

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