Frontal Lobe Functions

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The frontal lobes constitute two thirds of the human brain, yet the functions performed by them remained mysterious for a long time. Apart from their well-known involvement in motor function and language, little was previously known about the functions of the frontal lobes. Recent advances have uncovered important roles for the frontal lobes in a multitude of cognitive processes, such as executive function, attention, memory, and language. The importance of the frontal lobes in processes underlying affect, mood, personality, self-awareness, as well as social and moral reasoning, is also a renewed area for research. This article focuses on recent advances in understanding frontal lobe functions.

Introduction

In 1848, a young construction foreman, Phineas Gage, suffered an unusual accident: a tamping iron was propelled through his face, skull and brain, damaging his left and right prefrontal cortices. This event dramatically changed his personality, but did not change his cognitive abilities and general neurologic function [1]. This relative preservation of cognition led to controversial views about the functions of the prefrontal lobes. Currently, multiple cognitive functions have been linked to the frontal lobes, and researchers continue to better delineate their role in personality and emotion. The importance of frontal dysfunction in numerous conditions, such as multiple sclerosis, stroke, and degenerative dementias, and its impact on rehabilitation outcome, as well as on the ability to maintain normal social roles, are active areas of research.

Frontal Lobe Versus Fronto-subcortical Systems

Anatomically, the frontal lobes are limited posteriorly by the central sulcus. They are divided into motor, premotor, and prefrontal regions. The anterior cingulate, classically a part of the limbic system, can also be considered an important subdivision of the frontal lobe. Whereas "frontal lobe functions" relate to the behaviors specifically associated with the frontal lobes, the integration of frontal cortical and subcortical connections, or the fronto-subcortical systems, has been proposed as a better physiologic substrate of frontal lobe functions [2]. There are five parallel frontal system circuits, each comprising a specific frontal region, its projections to the striatum, and connections with the globus pallidum and substantia nigra, and a return via the thalamus to the original frontal region. These circuits serve specific functions: a motor circuit involving the supplementary motor area, an oculomotor circuit involving the frontal eye fields, and three cognitive and affective circuits, namely the dorsolateral prefrontal, lateral orbital, and cingulate (medio-dorsal) circuits. Lesions anywhere along the axis of each circuit produce distinct behavioral disorders associated with that circuit (Table 1).

Cognitive Functions

The frontal lobes play a role in many processes, such as motor control, voiding, cognition, and neuropsychiatric function. We focus on recent advances in our understanding of the frontal lobes.

Attention

Deficits in attention are a hallmark of fronto-subcortical dysfunction. Attention involves a large network, including the reticular activating system, thalamus, anterior cingulate, frontal, and posterior parietal cortices. Attention can be separated into sustained, divided, and focused. Sustained attention is the ability to maintain attention over a prolonged period of time. Frontal lobe lesions, especially of the right hemisphere, have been shown to cause deficits of sustained attention [3]. Evidence suggests that the right lateral midprefrontal area, and to a lesser degree the inferior parietal lobule, are critical for maintaining good performance over time [4,5]. Divided attention, or the ability to simultaneously attend to different sources of information, relies more heavily on right frontal activation, whereas focused attention, the ability to inhibit irrelevant stimuli, may preferentially involve the orbitofrontal lobe [4,6].

Executive function

Executive function enables the performance of purposeful, goal-directed behaviors. Effective performance necessitates volition, planning, selection, sequential organization, and self-monitoring of actions [7]. Patients with frontal lobe dysfunction consequently perform

Table 1. Deficits in prefrontal cortico-subcortical circuits

Circuits	Cognitive effects	Psychiatric effects
Dorsolateral	Impaired set shifting (stuck-in set perseveration) Rigidity Concreteness Verbal-action dissociation Impersistence Verbal dysfluency (left) Design dysfluency (right) Poor problem-solving abilities Poor motor programming Poor planning Working memory deficits Spontaneous recall poorer than recognition	Depression
Orbitofrontal	Sensitivity to interference Poor decision making Theory of mind deficits Social and moral reasoning impairment Stuck-in-set perseveration (on object alternation)	Euphoria/mania Impulsiveness Disinhibition Jocularity Irresponsibility Inappropriateness Tactlessness Impaired social judgement Obsessive-compulsive disorder
Cingulate/medio-dorsal	Mutism Slowness Poor task maintenance Transcortical motor aphasia (left) Impaired generative cognition Poor humor appreciation (right)	Apathy Amotivation Abulia/decreased motor activity Aspontaneity Reduced affect Akinetic mutism (bilat) Gating zone for antidepressant response (?)

adequately in well-structured settings that place little demand on executive function, whereas impairment in routine daily life may be quite striking [8].

Volition refers to the ability of an individual to perceive his or her needs and to have the motivation to act on these needs. Impaired motivation has been associated with lesions of the anterior cingulate and dorsolateral prefrontal cortex. Akinetic mutism is the most severe form of amotivation and usually follows bilateral lesions of the anterior cingulate.

Planning requires the ability to look ahead in time, generate hypotheses for future events, select relevant actions according to the context, and sequence the actions needed to accomplish a specific goal. Moreover, facing novel situations requires the ability to change a plan. Patients with frontal lobe dysfunction have shown deficits in both planning and decision making [9–11]. Recent evidence suggests that isolated planning impairment on a complex multitasking test, the Greenwich Test, was associated with lesions of the right dorsolateral prefrontal cortex [12].

Carrying out a plan requires one to initiate, maintain, switch, and stop at the appropriate moment during a sequence of actions (self-monitoring). The ability to maintain, or to "stay on task" depends on focused attention, even in the face of interference. Interference can be internally generated (a thought) or externally generated (environmental stimulus). Patients with frontal lobe lesions are particularly sensitive to interference, and their performance on a memory task can be greatly impaired by the interposition of a distracting task [13]. Interference originating from the external environment can lead to stimulus-bound behavior, the patient being unable to inhibit automatic responses to environmental stimuli. This can lead to utilization and imitation behaviors, or to an "environment-dependency syndrome" [14]. Alternatively, previous responses or behaviors can interfere with subsequent behaviors within the context of an established set (recurrent perseveration). This type of perseveration is most common in aphasic patients, who tend to repeat a previously given response to a subsequent item on a confrontation naming task. This has been hypothesized to represent a failure of usual inhibition of memory traces. Recurrent perseveration seems particularly sensitive to left hemisphere lesions, especially in the temporoparietal region [15]. When the ability to switch and stop a behavior (or cognitive flexibility) is impaired, patients tend to perseverate into a certain set (stuck-in-set perseveration) or to inappropriately pursue a behavior (continuous perseveration). Stuck-in set perseveration is

found principally in fronto-subcortical dysfunction, and is common in Parkinson's disease. Inability to suppress stereotyped responses and to switch from an action to the other explain the occurrence of this type of perseveration [15]. Classically, the Wisconsin Card Sorting Test (WCST) is used for identifying deficits in shifting set. The subject is required to sort a series of cards according to three criteria (color, form, number) in response to the examiner's feedback. Failure to shift criteria according to the feedback received constitutes stuck-in-set perseveration. Abnormal performance on the WCST is associated with dorsolateral frontal lesions [16]. Stuck-in-set perseveration can also be interpreted as an inability to reverse a previously learned behavior. Freedman [17] adapted the object alternation task (OA) from animal models for use in humans. On OA, subjects are required to learn that the object under which a reward (penny) is located is alternated after each correct response. As a result, performance on OA necessitates the ability to shift set, as well as working, memory for objects. Lesions of the ventrolateral-orbitofrontal and medial frontal regions are associated with perseveration on OA in humans [18]. Alternatively, continuous perseveration can be explained by a failure to disengage attention from a current stimulus. Continuous perseveration is seen on graphomotor tasks such as drawing multiple loops. This type of perseveration is more frequent with right hemisphere lesions [15].

Many conceptual frameworks of executive function have been proposed in the literature. For example, the schema used above (volition, planning, execution, and self-monitoring) was suggested by Luria [7] based on clinical observation. Shallice [19] suggested that a supervisory attentional system located in the frontal lobes modulates the largely automatic and overlearned abilities under the influence of posterior sensorimotor areas. Another view is that there are many frontal functions divided according to their hierarchical level and interacting with postero-basal functions [20,21••]. An ongoing debate is whether executive function should be considered in a unitary or diverse fashion. For example, some authors have considered the supervisory function of the prefrontal lobes in a more unitary manner as a function of "general intelligence." Reviewing the pattern of activation from functional neuroimaging studies of five different cognitive demands, Duncan and Owen [22] suggested that a specific network within the prefrontal lobes could be recruited to solve diverse cognitive demands. This network is suggested by the simultaneous activation within three regions during the performance on different tasks: 1) the dorsal part of anterior cingulate, 2) a mid-dorsolateral focus including the middle and inferior part of the inferior frontal sulcus, and 3) a ventral focus, dorsal and anterior to the Sylvian fissure along the frontal operculum up to the anterior insula. Alternatively, many theorists suggest that there are many frontal functions interacting within a hierarchical structure [21••].

Memory

The executive functions mediated by the prefrontal lobes are also involved in memory. Although there is no frontal amnesia per se, impaired executive control over the memory system can lead to significant deficits when testing memory function. Memory is not a unitary process and can be divided into different components: immediate (short-term), long-term, remote, working memory, prospective memory, etc. It also differs according to type of material to be remembered (*eg*, verbal, spatial, object). Immediate memory, classically assessed with span tests, is usually unaffected by frontal lesions. However, working memory, the temporary holding of information that is currently being processed, relies on the function of the dorsolateral prefrontal cortices, and as a result is impaired following lesions of those areas [23]. Deficits in learning and long-term memory are also following frontal lobe lesions, with severity varying according to task demands. Tests that require planning and organizational strategies either at encoding or retrieval, such as word-list learning or recall of remote memories, are affected by frontal deficits [24]. Free and cued recalls are impaired, whereas performance tends to improve with recognition. Patients may also demonstrate a non-graded retrograde amnesia, which contrasts with the temporally graded retrograde amnesia seen after mediotemporal lobe lesions [25]. The selection, monitoring, and verification of the information retrieved from the memory store may be impaired, most often after damage to the right prefrontal lobe or orbito-medial cortices, leading to repetition and confabulation [24,26]. Functional imaging studies have suggested that left prefrontal regions are more involved in encoding of novel events in episodic memory, whereas retrieval of episodic information is mediated bilaterally but with a right hemispheric bias [27]. Left prefrontal cortex is also involved in retrieval of information from semantic memory. This asymmetric activation of the prefrontal cortices on functional imaging has lead to the development of the HERA (hemispheric encoding/retrieval asymmetry) model [28].

The frontal lobes are also involved in retrieving the spatio-temporal context of events. Frontal lobe patients might recall specific information without remembering the relevant contextual details. Location information retrieval may be handled predominantly by the left-middle frontal gyrus, whereas the medial frontal lobes may mediate temporal information [29]. Finally, the frontal lobes have also been shown to play a role in prospective memory (the ability to remember to do things in future) [30]. The left medial prefrontal cortex may have a predominant role in prospective memory [12].

Language

Two classic aphasia syndromes have been associated with dysfunction of the frontal lobe: Broca's aphasia and transcortical motor aphasia (TCMA), which highlight the role of the dominant frontal lobe in language. The left inferior

frontal gyrus and operculum (Broca's area) are involved in the assembly of phonemes into words and words into sentences, as well as in the grammatical structure of sentences. Lesions of these regions lead to distortion, or improper articulation, of phonemes, agrammatism, and reduced fluency. Impaired retrieval of words, predominantly verbs, also leads to anomia. As a result, the characteristics of Broca's aphasia are nonfluent, effortful output with word-finding difficulties, impaired repetition, but relatively preserved comprehension [31]. TCMA occurs with lesions involving the supplementary motor area, or its connection with the frontal perisylvian speech area. The supplementary motor area is involved in the driving mechanism of speech. Consequently, transient mutism may be seen in TCMA, followed by impaired initiation of speech, prolonged response latency, and reduced verbal output but normal fluency paired with normal repetition and comprehension [32].

In addition, the frontal lobes are also implicated in other aspects of language. In particular, the right hemisphere has a predominant role in the modulation of prosody, the attitudinal and emotional melody carried by normal speech, and the elaboration of gestures accompanying discourse. Lesions of the right posterior inferior frontal region (a region analogous to Broca's area on the left) impair spontaneous affective prosody of speech, the ability to repeat the prosody given to a declarative sentence free of emotional words, as well as the production of gestures of the face and limbs that are normally associated with the discourse. However, comprehension of prosody and gestures are preserved [33••]. Ross *et al.* [33••,34] have proposed a classification of aprosodia that parallels the classification of aphasia.

Prefrontal lesions, either right or left, are associated with impaired verbal self-regulation and impairment in organization and planning of the verbal output. Left prefrontal lesions are associated with a decreased number of themes in the discourse, reduction in total verbal output (laconicism), a restricted range of sentence structures, and a tendency to repeat structures, but a preserved coherence of speech. Alternatively, right prefrontal lesions are associated with decreased coherence of speech, inclusion of themes unrelated to the discourse, impaired veracity of discourse, and verbal social inappropriateness (dysdecorum). Patients with right prefrontal lesions also have a reduced ability to make use of analogy and irony. They are excessively literal and direct, suggesting a difficulty constructing indirect or inferential statements [35].

The social and emotional brain

The fine interaction of cognition, emotion, and learned social contingencies affects our ability to produce an appropriate emotional and social response in a given context (*ie*, our behavior). Neuropsychiatric manifestations associated with fronto-subcortical dysfunction have long been recognized. However, research in this area has been limited by problems, such as the difficulty to operationally define concepts such as affect, mood, insight, or personality [36]. However, a renewed interest in neuropsychiatry and the frontal lobes has recently emerged.

Affect and mood

Dysfunction of the frontal lobes may increase susceptibility to psychiatric syndromes such as depression, mania, apathy, and obsessive-compulsive disorder. Recent advances have been made in understanding depression and its response to treatment. Mayberg *et al.* [37•] proposed a model where both limbic and neocortical regions are reciprocally related. Patients suffering from depression, as well as subjects with induced sadness, showed increased regional cerebral blood flow (rCBF) in the subgenual area, and decreased rCBF in right prefrontal area, and, less significantly, in the inferior parietal area and dorsal anterior cingulate. Both the inhibition of overactive ventral regions and normalization of frontodorsal hypofunction are needed for recovery from depression. Patients who did not respond to fluoxetine failed to show these findings, and by its connections with the dorsal anterior and subgenual cingulate, the rostral cingulate may play a key role in the ability to induce these changes [38••].

The right frontal lobe may also be implicated in humor appreciation. In a recent study, subjects with superior right frontal polar/medial lesions did not appreciate verbal and nonverbal humor even when they recognized its existence, suggesting a lack of convergence of cognition and affect necessary for appreciation of humor [39].

Personality

"Gage was no longer Gage." This statement made by friends of Phineas Gage exemplifies the extent of the potential effect on personality of a frontal lobe lesion. The alteration of personality and social function appears to be especially profound in patients with acquired ventromedial prefrontal cortex (VMPC) lesions. A syndrome of "acquired sociopathy," characterized by dampened emotional experience and emotional dysregulation, as well as disturbances in decision making, goal-directed behavior, social behavior, and insight, is associated with bilateral VMPC dysfunction. Emotional blunting, behavioral rigidity, poor frustration tolerance, and lability are paired with poor judgement, indecisiveness, impersistence, and poor planning [40]. The poor decision making of these patients has been experimentally assessed with a gambling task reproducing real-life decisions. Poor performance on this task may be at least partially due to insensitivity to future consequences, positive or negative, and a propensity to act upon immediate prospects [41]. Patients sustaining bilateral VMPC injury early in life were also found to demonstrate the syndrome of acquired sociopathy, but unlike adult-onset patients, they also show defective social and moral reasoning [42]. VMPC appears to play an essential function in the acquisition of complex social conventions and moral rules, both at a semantic level and for the application of those rules into our behaviors.

Self-awareness

In the hierarchical model of frontal lobe functions, the highest level of function is the one of self-awareness [21••,43] and theory of mind [44,45]. The sense of self as an entity across time necessitates the convergence of both memory and emotion. The Capgras syndrome, the belief that a significant other has been replaced by an imposter, is an example of failure of this convergence. Alexander *et al.* [46] reported such a phenomenon in a patient who had sustained bilateral frontal lobe damage, more extensive on the right, and who was convinced that a new, identical second family had replaced his first family. The knowledge with respect to his family members was not accompanied by the emotional experience and the sense of warmth and intimacy that should have triggered those memories. Knowing who we are is an essential step in the process of projecting who we want to be. The right prefrontal lobe has been suggested as a key area for recollection of past events with their associated emotions and connecting those with plans and expectations with the future [47].

Theory of mind

Theory of mind refers to the ability to be aware of the thoughts and feelings of others and to make inferences about the mental states of others. Deficits in theory of mind have been associated with frontal lobe lesions [44,45]. Moreover, different regions within the frontal lobe may mediate different aspects of the theory of mind. Recently, Stuss *et al.* [45] examined the roles of frontal and nonfrontal regions in theory of mind. Patients with lesions throughout the frontal lobes were more impaired on their ability to represent another's perceptions based on their own experiences. However, the ability to infer that a person is deceiving them was impaired in patients with bilateral, particularly right, orbito-medial lesions [45].

Bedside Frontal Lobe Scales

Ettlin *et al.* [48] developed a bedside mental status examination to assess frontal lobe functions: the Frontal Lobe Score (FLS). This scale screens both cognitive and behavioral effects of frontal lobe dysfunction. The authors suggest a cut-off score of 12 or higher as indicative of such dysfunction, which leads to a sensitivity of 92.3% and a specificity (from nonfrontal lesions) of 75.0% in a clinical setting [49]. The FLS takes 20 to 45 minutes to complete, depending on the severity of impairment. Dubois *et al.* [50•] elaborated a short battery amenable to bedside assessment, the Frontal Assessment Battery (FAB). The FAB consists of six subtests exploring conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy. Although it was found to have a good concurrent validity with other frontal lobe measures, the discriminant sensitivity and specificity from nonfrontal lesions have not yet been established [50•].

Assessment batteries were also created to detect behavioral changes occurring with frontal lobe diseases, mainly frontotemporal dementia (FTD). Kertesz *et al.* [51] proposed a caregiver questionnaire to operationalize behavioral criteria of FTD. The Frontal Behavior Inventory (FBI) takes 10 to 15 minutes to complete. It comprises 24 items that are scored with a 4-level quantitative scale. It has a high inter-rater reliability and content validity. A cut-off score of 30 or higher leads to 88.5% sensitivity and 96.3% specificity for FTD (from other etiologies of dementia, including vascular, Alzheimer's disease, primary progressive aphasia, and dementia syndrome of depression) [52]. All false-positive patients had a diagnosis of vascular dementia that may have a frontal-type symptomatology and neuropsyhcologic deficits [53].

Conclusions

The frontal lobes and their influence in numerous behaviors are the center of very dynamic research. Recent advances allow a better understanding of the complex interactions between brain and mind.

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