EDITORIAL

Frontal Cortex and Behavior

Few subjects in neurology have been associated with as much enigma and paradox as the behavioral affiliations of prefrontal cortex. While some authors have attributed the highest integrative faculties of the human mind to this part of the brain [1, 4, 9], others have emphasized the surprising paucity of cognitive deficits in patients with substantial frontal lobe damage [11, 19]. At least two sources of difficulty are traditionally identified in this area of research: the nature of the clinical material, and the complexity of the behavioral deficits.

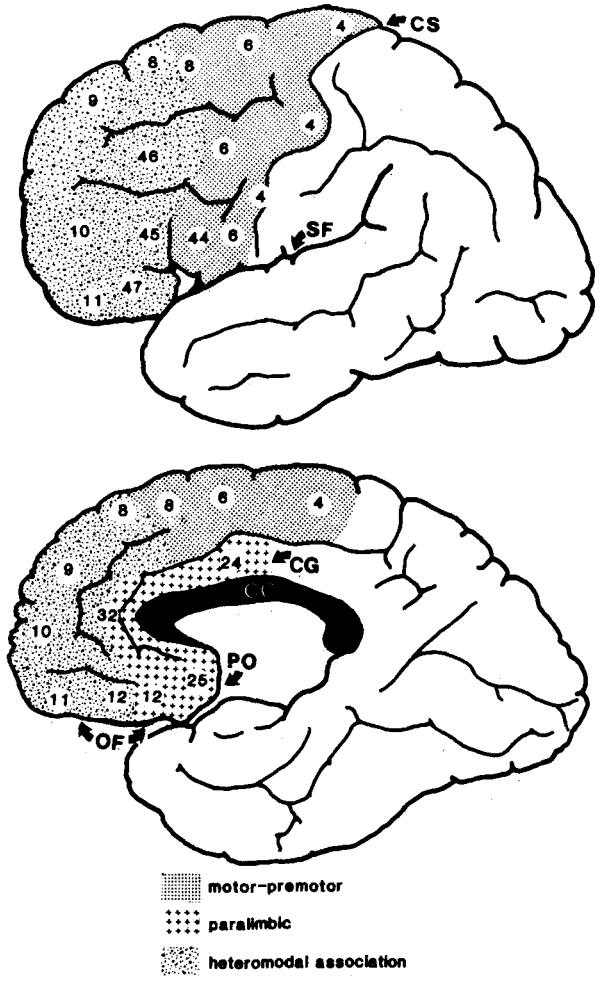
Much of the literature on prefrontal cortex, for example, has been based on patients with massive head trauma, slowly growing tumors, aneurysmal ruptures, or extensive surgical procedures performed to treat intractable seizures or severe psychiatric disease. The lesions are often bilateral and commonly extend beyond the frontal lobes. The pitfalls of basing brain–behavior correlations on this type of clinical material are considerable. It is not clear why patients with unilateral strokes confined to prefrontal cortex are so poorly represented in the literature. Either such cases are too infrequent, or the associated deficits continue to elude coherent description or perhaps even clinical detection.

The behavioral changes associated with frontal cortex damage introduce additional difficulties as they tend to be exceedingly complex, variable, difficult to define in technical terms, and almost impossible to quantitate by available tests. The recent work of Lhermitte [21, 22], while it suffers from the customary limitations with respect to patient material, introduces two important innovations: a novel behavioral correlate of frontal lobe damage and a colorful methodology for allowing such complex observations. Lhermitte's findings and his imaginative interpretation deserve to be analyzed within the larger context of contemporary research on the frontal lobes.

The frontal lobes occupy approximately one-third of the human cerebral hemispheres. The cortical surface of the frontal lobes is commonly divided into three components. The first is a *motor-premotor* component, which includes area 4, area 6, the supplementary motor area (medial aspect of area 6), parts of the frontal eye fields (caudal area 8), and parts of Broca's region (area 44). Depending on its exact location, damage to this component of the frontal lobe results in weakness, alteration of muscle tone, release of grasp reflexes, incontinence, akinesia, mutism, aprosody, apraxia, and some of the motor components in unilateral neglect and Broca's aphasia. The second component is located in the caudal-basal-medial part of the frontal lobe and contains the *paralimbic* cortex of the anterior cingulate, parolfactory, and caudal orbitofrontal regions. The third component is more rostral in location and contains the *heteromodal* (high-order) association cortex in areas 9, 10, 11, 12 (rostral), 45, 46, and 47 of Brodmann (see Figure) [24]. The terms "prefrontal cortex" and the associated "frontal lobe syndrome" generally refer only to the paralimbic and heteromodal components. These are the regions of the frontal lobe that will be emphasized in the following comments.

The case of Phineas Gage (also known as the Boston Crowbar Case), described more than a century ago by Harlow [10], remains paradigmatic for research on the frontal lobes. Gage was a reliable and upright foreman who became profane, irascible, and irresponsible following an accident during which a tamping rod was blown through his frontal lobes. The many reports that have been published since Harlow's paper have provided additional support for the conclusions derived from the case of Phineas Gage, namely, that frontal lobe damage can lead to dramatic alterations of personality and conduct while leaving most cognitive and sensory–motor functions relatively intact.

Over the past 100 years, a remarkable spectrum of behavioral changes has been observed in patients with prefrontal lesions. Some of these patients become puerile, profane, slovenly, facetious, irresponsible, grandiose, and irascible; others lose spontaneity, curiosity, initiative, and develop an apathetic blunting of feeling, drive, mentation, and behavior (abulia); others show an erosion of foresight, judgment, and insight, lose the ability to delay gratification and often the capacity for remorse; still others show an impairment of abstract reasoning, creativity, problem solving, and mental flexibility, jump to premature conclusions, and become excessively concrete or stimulus-bound. The orderly planning and sequencing of complex behaviors, the ability to attend to several components simultaneously and then flexibly alter the focus of concentration, the capacity for grasping the context and gist of a complex situation, the resistance to distraction and interference, the ability to follow multistep instructions, the inhibition of immediate but inappropriate response tendencies, and the ability to sustain behavioral output without perseveration may each become markedly disrupted. Several common threads run through the behavior of these patients: a loss of attentive power, a sustained shallowness and impulsivity of thought and affect, and the preferential vulnera-



*The three cortical components in the frontal lobe. The numbers designate the location of the corresponding cytoarchitectonic regions of Brodmann. (*CC = *corpus callosum;* CG = *cingulate region;* CS = *central sulcus;* OF = *orbitofrontal region;* PO = *parolfactory (subcallosal) region; and* SF = *sylvian fissure.)*

bility of those behaviors that lack clear-cut external guidance.

Although the designation "frontal syndrome" is used as an umbrella term for the entire panoply of these behavioral changes, each patient may have a different distribution of the salient deficits; this distribution may even fluctuate from one examination to the next. This is one reason why the prefrontal syndrome appears so protean and heterogeneous. The specific pattern of the behavioral deficits in an individual patient is probably determined by the site, size, laterality, nature, and temporal course of the lesion and perhaps even by the past personality of the patient and age of onset. It is said that orbitofrontal and anteromedial lesions lead to affective disintegration while dorsolateral ones may lead to deficits of mental flexibility and reasoning [8, 25]. However, the evidence for such dichotomies is incomplete, especially since many of the lesions are often difficult to delineate precisely and the behavioral deficits too complex to fit a simple unified description. The more dramatic manifestations of frontal-lobe damage are seen after bilateral involvement. In contrast, the deficits associated with unilateral lesions can be quite subtle and often elusive.

Recent physiological observations complement the clinical experience. For example, it has been shown that there is a preferential prefrontal metabolic activation during the performance of attentional tasks, and during the initial solving of a reasoning test but not during its subsequent execution [30–32]. Furthermore, the P-300 wave elicited by the detection of novel or unexpected stimuli is lost in patients with prefrontal lesions [16]. These results are consistent with the loss of attentiveness, curiosity, and problem-solving ability seen in patients with frontal lobe lesions.

On neuropsychological investigation, patients with prefrontal damage show deficits in tasks of concentration (digit span), sustained behavioral output (the F-A-S and verbal fluency tasks), and inhibition of immediate but inappropriate response tendencies (the Stroop, Go–No Go, and Trail Making Part B tasks). Tests of motor sequencing (Luria), mental flexibility (the Visual-Verbal Test), and categorization (the Wisconsin Card Sort task) are also impaired, probably because of an underlying tendency for perseveration and for premature closure [2, 20, 23, 25, 26, 37]. In contrast, most tests of perception, construction, language, and directed spatial attention may be intact. Frontal lobe damage may also lead to a "task difficulty effect," whereby performance in virtually all areas begins to decline rapidly when the effort required of the patient exceeds a certain level. This indicates a motivational deficit rather than impairment of additional cognitive skills. Memory is usually preserved. Severe amnesias are rare and probably indicate deep extension of the lesion into the diencephalon and basal forebrain [34] or perhaps involvement of the most caudal and medial orbitofrontal-parolfactory regions [28]. Occasionally a secondary memory disturbance may emerge as a consequence of the inattention, poor motivation, and perseveration.

These quantifiable deficits in standard tests are not always impressive. In fact, some patients with sizable frontal lobe lesions may have routine neurological and neuropsychological examinations that are quite unremarkable. This creates a problem in the assessment of these patients, especially since the behavioral derangements—which sometimes constitute the only salient features—are also too complex to test in the office. This paucity of "objective" findings is sometimes responsible for overlooking the possibility of brain damage in some patients with frontal lesions. Even if some of the relevant behaviors could be reduced to testable, nontrivial components, there is reason to believe that

the performance in the office may not necessarily reflect daily behavior. It is not uncommon to find patients with a history of major behavioral difficulties who behave impeccably in the office. This is in keeping with the notion that these patients are most impaired under circumstances with minimal external control of behavior; the office setting may introduce sufficient external structure to suppress some of these behavioral tendencies. Furthermore, the same patient who gives perfect answers to questions about hypothetical social or moral dilemmas may act with a total lack of judgment when faced with the real situation. The clinical adage that judgment and complex comportment cannot be tested in the office is particularly pertinent to the evaluation of patients with frontal lobe damage.

In reaching his conclusions on the "environmental dependency syndrome," Lhermitte makes use of a less structured setting than is customarily used for neuropsychological assessment. The lack of specific instruction, the ambiguity of the context, and the method of open-ended observation allow the detection of behaviors at a level of complexity that is more commensurate with the specializations of the frontal lobes. This approach allows Lhermitte to show that patients with inferior prefrontal lesions display a remarkable tendency to imitate the examiner's gestures and behaviors even when no instruction has been given to do so, and even when this imitation entails considerable personal embarrassment. This tendency is descriptively labeled as "imitation behavior." Furthermore, the mere sight of an object may elicit the compulsion to use it, although the patient has not been asked to do so and the context is inappropriate—as in the case of the housewife who sees a tongue depressor and proceeds to give Professor Lhermitte a medical checkup. This is designated as "utilization behavior." There is also an excessive dependency on the immediate social environment, so that a certain setting elicits sterotyped responses that fit the setting but that ignore the incongruity of context. Lhermitte suggests that these behaviors, collectively designated as the "environmental dependency syndrome," stem from an excessive control of behavior by external stimuli at the expense of behavioral autonomy. This state of environmental dependency is in keeping with several other features of the frontal lobe syndrome, such as concreteness, stimulus-bound behavior, echopraxia, defective inhibition, and the inability to grasp context. It is conceivable that these more basic deficits collectively lead to the environmental dependency syndrome. Alternatively, the loss of behavioral autonomy could be considered as a primary event leading to the stimulus-bound and concrete behaviors, as well as to the difficulties in inhibition, foresight, and delay of gratification.

It is suggested that the environmental dependency syndrome results from a loss of frontal inhibition and the resultant overactivity of the parietal lobes. The reciprocal inhibition between these two cerebral regions is an established concept. Denny-Brown and Chambers [4a] emphasized that the grasp reflex in patients with frontal damage reflects the unopposed activity of the parietal lobes and that, in turn, patients with parietal lobe lesions display an opposite tactual avoidance response that reflects the uninhibited influence of the frontal lobes. These observations contain the seeds of an approach–avoidance equilibrium, based on the reciprocal inhibition between the frontal lobes, which promote distance from the environment, and the parietal lobes, which foster approach. In an analogous but much more complex sense, Lhermitte suggests that the lack of environmental autonomy in patients with frontal lobe damage reflects the activity of the parietal lobes unopposed by the customary frontal inhibition. This formulation carries the implication that a behavioral deficit of opposite polarity with respect to the environment should result from parietal lobe lesions. Indeed, it could be suggested that the unilateral neglect of extrapersonal events that emerges after damage to the posterior parietal region (or to any component of the posterior parietal–frontal eye field–cingulate network) represents such an excessive withdrawal (or autonomy) from the environment. Perhaps the proper psychological distance from the environment reflects the balance of reciprocal inhibition between prefrontal cortex and the posterior parietal network. According to this hypothesis, prefrontal lesions could promote not only an excessive approach to the environment, leading to distractibility and concreteness, but perhaps also an excessive distance from the intrapsychic processes necessary for insight, foresight, and abstraction. In contrast, lesions in the parietal network could promote an avoidance of the extrapersonal world and perhaps an excessive reliance on intrapsychic data, even when these are in conflict with external reality. This state could lead to the anosognosia and psychotic hallucinations that emerge in conjunction with parietal lesions [29]. This janusian view of frontoparietal interactions with one face, under frontal control, directed inward and the other, under parietal influence, directed outward may have considerable value for investigating the physiological foundations of complex psychological states, especially those related to self-awareness.

Results derived from animal experimentation help to place the clinical observations in perspective. The prefrontal cortex of subhuman primates is also composed of paralimbic and heteromodal components situated along a plan of organization almost identical to that seen in humans. Morphologically, the paralimbic component of the frontal lobe (the anterior cingulate, parolfactory, and caudal orbitofrontal regions) is characterized by an architecture that is transitional from

simple allocortex to granular isocortex. Pathway tracing experiments in monkeys show that these areas receive major inputs from the amygdala and from several association areas, especially those in the heteromodal part of prefrontal cortex [24]. Hence, the paralimbic regions provide a site of interaction between limbic inputs and extensively preprocessed sensory information, an arrangement which suggests that these areas should be of crucial importance for channeling drive and emotion to appropriate targets in the environment. In keeping with these expectations, it has been shown that orbitofrontal or anterior cingulate ablations in monkeys result in marked alterations of emotional responses to stimuli: the animals do not lose the capacity for the emotion but they lose the ability to modulate the intensity of affect in ways that are commensurate with the significance of the environmental event [3, 35]. Experimental lesions in the paralimbic component of the frontal lobe also interfere with social interactions. In social animals such as monkeys, group bonds heavily rely on specific aggressive and submissive displays, grooming behavior, and vocalizations. Success depends on directing the proper behavior to the proper individual in the proper context. Animals with orbitofrontal lesions show a severe disruption of these conspecific affective and affiliative behaviors and eventually experience social isolation [15]. Careful observation in a naturalistic setting is necessary for detecting these alterations. In the laboratory these animals may show few, if any, deficits on tests of attention, perception, motor skill, or even problem solving. These experiments provide a model for the socially maladaptive and emotionally inappropriate behaviors seen after frontal lobe damage and support the contention that these behaviors emerge after involvement of the paralimbic component in the frontal lobe.

The largest part of prefrontal cortex in all advanced primates consists of granular heteromodal isocortex. The major cortical inputs into this part of the brain come from modality-specific association areas, from other heteromodal areas (especially in the parietal lobe), and from paralimbic regions, especially those in the orbitofrontal and cingulate regions [24]. Thus, the heteromodal prefrontal cortex provides a template for the cross correlation of sensory experience and its initial integration with paralimbic input. Bilateral lesions in the most anterior heteromodal parts of prefrontal cortex in monkeys and chimpanzees lead to inattentiveness, distractibility, apathy, emotional blunting, and a lack of curiosity and interest in the environment [5, 6]. More caudal lesions in dorsolateral and inferior heteromodal cortex lead to perseveration, vulnerability to interference, the inability to inhibit inappropriate responses, and a curious difficulty in the retention of spatial cues [13, 14, 27]. Except for the last deficit, which has not yet been elicited in humans, these observations are of marked clinical relevance and suggest that the analogous deficits in patients with frontal lobe lesions may be linked to damage of the heteromodal component in this part of the brain.

Single-unit recordings in the heteromodal prefrontal cortex of awake and behaving monkeys show that some of the constituent neurons are selectively active during delay periods when the animal has to inhibit responding or during periods of attentive concentration [7, 18]. These units provide a cellular substrate for the role of prefrontal cortex in inhibition and attention. Most of the heteromodal prefrontal neurons readily respond to sensory input, some in a single preferred modality, others in several modalities [12]. However, these neurons are far less responsive to the specific physical dimensions of the sensory stimulus than are neurons in the modality-specific areas of the brain. For example, a striate (area 17) neuron sensitive to a certain stimulus orientation will always fire when an object in that orientation enters its receptive field. In contrast, many of the visually responsive neurons in the heteromodal and probably also in the paralimbic components of the frontal lobe have no specificity for color, size, orientation, or movement. Instead these neurons are very sensitive to the *behavioral relevance* of the environmental event. Thus a neuron that responds briskly to a stimulus associated with reward may drastically alter its response to the same visual stimulus when it becomes associated with an aversive or neutral outcome [17, 36]. These neurons provide a mechanism whereby identical physical stimuli may elicit different reactions depending on the context and past experience. It could be suggested that this sensitivity to the behavioral relevance, rather than to the physical dimensions of stimuli, provides the neural substrate for realizing that "not all that glitters is gold." Without this type of neuron, neither autonomy from the environment nor abstract thinking would be possible, since a given stimulus would automatically call up a predetermined response regardless of context. Indeed, this excessive dependency on environmental stimuli, based on rigid stimulus–response linkages, is the very hallmark of instinctual behavior in lower species. For example, a turkey hen with a newly hatched brood will treat every moving object within the nest as an enemy unless it utters the specific peep of her chicks. If a hen is experimentally made deaf, it will kill its own progeny soon after hatching [33]. The behavioral repertoire of higher species is characterized by a far greater autonomy from the environment. This autonomy and the associated behavioral flexibility appear very much linked to the development of heteromodal and paralimbic regions in the brain, especially in the frontal lobes. With respect to mechanism, the frontal lobe neurons that are selectively responsive to shifts in be-

havioral relevance could provide modules that are analogous to *and-gates* and *or-gates* on a programming board [24]. The insertion of these modules between stimulus and response could lead to the dissolution of rigid linkages in a way that establishes a cellular basis for choice, change, and flexibility.

Despite considerable advances in this area of research, it is difficult to dismiss the sense of uniqueness associated with frontal lobe function. It is quite remarkable, for example, that sizable frontal lobe lesions can remain clinically silent for many years. Even after massive bifrontal lesions in monkeys, chimpanzees, and human beings, change can often be detected only in comparison with the previous personality of that individual rather than in reference to any set of absolute behavioral standards. In fact, many of the alterations associated with prefrontal lesions appear to overlap with the range of normal human behavior. For example, while similar behaviors do emerge after frontal lobe lesions, there is also a vast number of improvident, irresponsible, inappropriate, and facetious individuals who have no evidence of demonstrable brain damage. In contrast, the lack of visible damage to the pertinent cerebral area is a rare occurrence in individuals with aphasia, amnesia, apraxia, or unilateral neglect. Perhaps this means that the prefrontal cortex underlies functions that are much less "hard wired" and that it acts predominantly as an orchestrator for integrating other cortical areas and for calling up behavior programs that are appropriate for context. Damage to this part of the brain would thus result in behavioral deficits that are context dependent rather than static. Hence, the fact that prefrontal lesions lead to marked difficulties of complex comportment in patients whose basic perceptual and cognitive machinery is intact loses much of its paradox. Lhermitte's methodology and his observations are in keeping with these dynamic behavioral affiliations of the frontal lobes. Hopefully these papers will stimulate additional research on the anatomical and physiological principles that link the frontal lobes to such complex aspects of human behavior.

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M.-Marsel Mesulam, MD
The Bullard and Denny-Brown Laboratories
Division of Neuroscience and Behavioral Neurology
Harvard Medical School Department of Neurology
Dana Research Institute
Beth Israel Hospital
Boston, MA 02215

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