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The Human Frontal Lobes: Transcending the Default Mode through Contingent Encoding

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They said, "You have a blue guitar,
You do not play things as they are."
The man replied, "Things as they are
Are changed upon the blue guitar."
Wallace Stevens, The Man with the Blue Guitar

THE LEGACY OF PHINEAS GAGE

Contemporary research on the frontal lobes started at 4:30 P.M. on September 13, 1848, when an accidental explosion at a railroad construction site in Cavendish, Vermont hurled an iron tamping bar through the head of a 25-year-old foreman named Phineas Gage (Harlow, 1848). The tapered end of the 13.25 pound, 3.5 foot–long rod penetrated the head below the left zygomatic arch, passed behind the left eye, and exited through the calvarium, slightly right of the sagittal suture. The reconstruction of the trajectory, as published in 1868, showed that the bar must have pierced and carried away a substantial part of the frontal lobes (Fig. 2–1).

Dr. Edward H. Williams, who reached the scene 25–30 minutes after the accident, reported finding Phineas Gage spitting blood but in no apparent distress, and in the process of describing the event to incredulous bystanders who were amazed that he had walked away from such an accident (Bigelow, 1850). Joseph Adams, a local justice of the peace, submitted written testimony: "I saw him and conversed with him soon after the accident, and am of opinion that he was perfectly conscious" (Bigelow, 1850). Dr. John Harlow, summoned to attend to Gage, arrived approximately an hour later and, with Dr. Edwards' help, shaved the scalp and dressed the wound. The following day, Gage remained quite rational, and displayed an accurate recollection of the events related to the explosion. He subsequently developed a wound infection and lapsed into stupor and delirium for the next month. He then rapidly recuperated to the point where he was deemed physically and intellectually fit for work and, with the exception of blurred vision in the left eye and a slight left facial palsy, appeared none the worse for the wear.

Phineas Gage was examined by the Harvard surgeon Henry Jacob Bigelow in January 1850. Dr. Bigelow concluded that a considerable portion of the brain must have been destroyed and marveled at the sparing of function. Because of Bigelow's eminence in medical circles, Phineas Gage's condition became known as the Boston (rather than Cavendish) Crowbar Case, and the emphasis fell on the recovery. In fact, when the tamp-

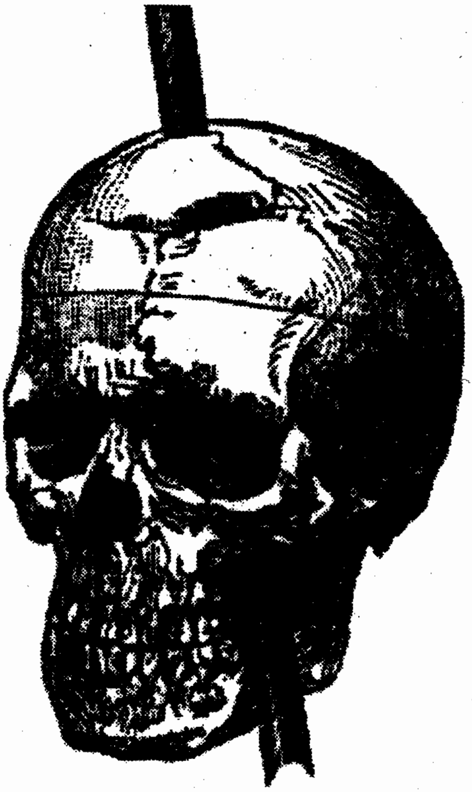

Figure 2–1. Passage of the bar through the skull of Phineas Gage, as reconstructed by Harlow in 1868 (Harlow, 1868).

ing iron was deposited to the museum at Harvard Medical School, it was beautifully engraved with the following inscription: "This is the bar that was shot through the head of M Phinehas P Gage at Cavendish Vermont Sept. 14, 1848. He fully recovered from the injuries."[1]

It appears, however, that Bigelow had been a bit premature in his pronouncements. The recovery might have been complete in the surgical sense, but not in the spiritual. Before the accident, "Gage was an ordinary sober Yankee, intelligent, a home-body, with no peculiar or bad habits."[2] The injury, however, led to a dramatic change, described in a passage that is now a classic in the annals of behavioral neurology (Harlow, 1868):

> His contractors, who regarded him as the most efficient and capable foreman in their employ previous to his injury, considered the change in his mind so marked that they could not give him his place again. The equilibrium or balance, so to speak, between his intellectual faculties and animal propensities, seems to have been destroyed. He is fitful, irreverent, indulging at times in the grossest profanity (which was not previously his custom), manifesting but little deference for his fellows, impatient of restraint or advice when it conflicts with his desires, at times pertinaceously obstinate, yet capricious and vacillating, devising many plans of future operation, which are no sooner arranged than they are abandoned in turn for others appearing more feasible.

Harlow added that, to his friends, his patient was "no longer Gage."

In time, Gage became increasingly erratic, moving from one odd job to another, the first being to sit at the entrance of the Boston Museum with the tamping bar between his knees.[3] He "worked" at Barnum where he was displayed as a curiosity. He then moved to Chile and drove a six-horse stagecoach in Valparaiso. All reports comment on his chaotic career and unprovoked profanity. His final destination was San Francisco, where he suffered a fatal epileptic fit in May of 1861, more than 12 years after the accident. Harlow, who had lost contact with Gage, eventually learned of Gage's death, contacted his mother and, with the help of the mayor of San Francisco, had the grave opened in 1868. The skull was removed and delivered to Harvard for safe keeping.[4]

THE SIGNS AND SYMPTOMS

Dozens of reports published since Harlow's 1868 paper have repeatedly confirmed the pivotal lesson taught by the case of Phineas Gage—namely, that massive damage to the frontal lobes can cause dramatic changes in personality and comportment while keeping sensation, movement, consciousness, and most cognitive faculties intact. This dissociation is largely responsible for the sense of enigma and paradox that has permeated research on the human frontal lobes. During the first half of the twentieth century, the "dilemma" of the frontal lobes unfolded in the form of a dialectic between those who considered it the seat of the highest integrative functions of the human mind (Brickner, 1934; Ackerly, 1935; Goldstein, 1936) and those who commented on the paucity of deficits associated with substantial frontal lobe damage (Hebb, 1945; Landis, 1949). This controversy was gradually resolved through the emergence of insightful clinical assessment methods, sophisticated neuropsychological instruments, and a willingness to acknowledge the neurological basis of emotion and personality. By the second half of the twentieth century, the literature on this subject started to reflect a surfeit rather than paucity of deficits linked to frontal lobe damage.

Mounting evidence from comprehensive case reports, for example, began to show that many patients with frontal lobe lesions became puerile, profane, slovenly, facetious, irresponsible, grandiose, and irascible, while others lost spontaneity, curiosity, initiative, and developed an apathetic blunting of feeling, drive, attentive power, and behavior. Frontal lobe damage came to be associated with an erosion of foresight, judgment, and insight, and an inability to delay gratification or experience remorse. Some patients tended to display an impairment of abstract reasoning, hypothesis generation, creativity, problem solving, and mental flexibility; jumped to premature conclusions; and became excessively literal. 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 could each become markedly disrupted following frontal lobe injury. (Mesulam, 1986).

In keeping with these clinical descriptions, neuropsychological testing of patients with prefrontal damage showed quantifiable deficits in tasks of concentration (as determined by digit span), sustained information retrieval (as determined by the F-A-S task of verbal fluency), and inhibition of inappropriate responses (as determined by the Stroop, go–no go, and Trail Making B tasks). Tests of motor sequencing (Luria), mental flexibility (the Visual-Verbal Test), and hypothesis formation (the Wisconsin Card Sorting Task) were also frequently impaired (Milner, 1963, 1982 Luria, 1966; Benton, 1968; Stuss & Benson, 1984; Leimkuhler & Mesulam, 1985; Weintraub & Mesulam, 1985). In contrast, most tests of perception, construction, language, and spatial attention remained intact. Explicit memory tended to be spared except for difficulties in the organization of retrieval and recall. Many patients displayed a "task difficulty effect," whereby performance in virtually all areas began to decline rapidly when the motivation required of the patient exceeded a certain level.

Despite all these clinical findings, the dilemma of the frontal lobes appeared on the verge of being resurrected by reports of patients with sizeable frontal lobe lesions whose extensive neurological, behavioral, and neuropsychological examinations were quite unremarkable. Such cases started to lose much of their enigma, however, as it became clear that the same patient who gave exemplary answers to questions about social or moral conflicts during neuropsychological assessment could still act with a total lack of judgment when faced with the real situation, and that impeccable conduct in the office was not incompatible with major behavioral impairments in the unstructured setting of daily life.

Is there a unitary "frontal lobe syndrome" encompassing all of these signs and symptoms? Are there regional segregations of function within the frontal lobes? Is it possible to identify a potentially unifying principle of organization which cuts across the heterogeneous specializations attributed to the frontal lobes? The purpose of this review is to offer a very selective introduction to these questions.

SYNOPSIS OF BEHAVIORAL NEUROANATOMY

The 20 billion neurons of the human cerebral neocortex are spread over a surface area of 2–3 square meters which is then folded into the multiple gyri and sulci of the cerebral hemispheres (Tramo et al., 1995; Pakkenberg & Gundersen, 1997). Numerous cytoarchitectonic maps of the cerebral cortex have been published. They vary in complexity from Exner's map of more than 500 zones to the one of Bailey and von Bonin based on only 9 (Exner, 1881; Bailey & Bonin, 1951). The vast majority of investigators agree on the boundaries of primary sensory and motor cortices which, in turn, display a one-to-one correspondence between cytoarchitecture and function. Most investigators disagree on the location of boundaries within association cortex and find exceedingly few one-to-one correspondences between subregions of association cortex and specific behaviors. These are some of the reasons for espousing a functional rather than strictly cytoarchitectonic approach to the mapping of the cerebral cortex. Such an approach allows the subdivision of the cerebral cortex into five zones: primary sensory-motor, unimodal association, heteromodal association, paralimbic, and limbic (Mesulam, 2000b).

The *primary sensory-motor areas* of the cerebral cortex provide the most immediate interface with the extrapersonal environment, whereas the *limbic* areas receive almost no direct visual, auditory, or somatosensory inputs and have their most extensive affiliations with the hypothalamus and internal milieu. *Unimodal* areas provide a site for the modality-specific elaboration of sensory information, and *heteromodal* areas provide a site for the integration of inputs from more than one sensory modality. *Unimodal, heteromodal, and paralimbic* cortices serve as neural bridges between the internal and the external worlds so that the needs of the internal milieu can be discharged according to the opportunities and restrictions that prevail in the outside world. These three zones mediate the associative elaboration and encoding of sensory information, its linkage to motor strategies, and the integration of experience with drive, emotion, and visceral states.

The frontal lobes occupy almost a third of the cortical area in the human cerebral hemispheres. Each frontal lobe can be conceptualized as a pyramid containing an apex at the frontal pole, a base at the level of the central sulcus, and three external surfaces forming the lateral, medial, and orbital walls. All functional types of cortex are represented within the frontal lobes. Limbic cortex is represented in the form of an inconspicuous sliver of pyriform cortex at the most caudal end of the orbital surface; primary motor and motor association cortices are located on the lateral and dorsomedial surfaces; heteromodal cortex covers most of the lateral surface and the anterior parts of the medial and orbital surfaces; and paralimbic cortex is located on the caudal parts of the medial and orbital surfaces (Figure 2–2). The paralimbic component of the frontal lobe is continuous with the cingulate gyrus on the medial surface, and with the insula and temporal pole on the orbital surface.

The terms *prefrontal cortex* and *frontal lobe syndrome* refer almost exclusively to the paralimbic and heteromodal components of the frontal lobes. These are the only two components that will be addressed in this review. The *heteromodal* component of the frontal lobe is characterized by an isocortical architecture (high neuronal density, six layers, granular bands in layers 2 and 4). In contrast, the *paralimbic* component is characterized by a gradual architectonic transition from primitive allocortex to granular isocortex. It tends to have a lower neuronal density, less than six layers, and absent or rudimentary granular bands. The heteromodal component is known as *granular cortex* whereas the paralimbic component is known as *dysgranular* or *agranular cortex* (Mesulam, 2000b). The boundaries between these two components take the form of gradual transitions rather than abrupt shifts.

Orbitofrontal paralimbic cortex is extensively interconnected with the hypothalamus, amygdala, hippocampus, and also with other paralimbic cortices in the temporal pole, insula, parahippocampal gyrus, and cingulate gyrus (Morecraft et al., 1992; Öngür et al., 1998). The major connections of heteromodal prefrontal cortex are with the other heteromodal and unimodal cortices in the brain as well as with orbitofrontal and related paralimbic areas, especially the cingulate gyrus

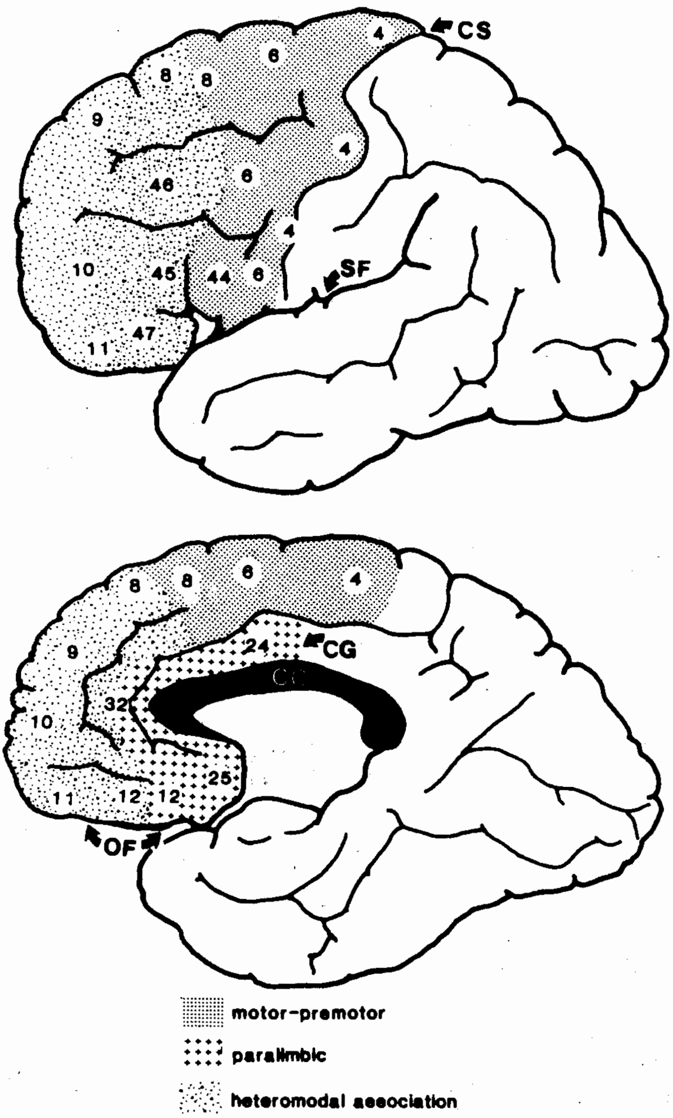

Figure 2–2. Lateral (*top*) and medial (*bottom*) views of the frontal lobes. The numbers refer to the Brodmann nomenclature (Brodmann, 1909). CC, corpus callosum; CG, cingulate gyrus; CS, central sulcus; OF, orbitofrontal surface; SF, Sylvian fissure.

(Chavis & Pandya, 1976; Barbas & Mesulam, 1985). Compared to other heteromodal cortices in the lateral temporal and posterior parietal lobes, prefrontal heteromodal cortex appears to have more pronounced paralimbic connections, a feature that may underlie its distinctive role in integrating extensively preprocessed sensory information with limbic and visceral states.

Prefrontal cortex is also characterized by prominent subcortical projections. Its heteromodal and paralimbic components send axonal projections to the head of the caudate nucleus. With respect to the thalamus, heteromodal prefrontal cortex is interconnected with the parvocellular part of the dorsomedial nucleus, whereas paralimbic orbitofrontal cortex is interconnected mostly with the magnocellular part of the same nucleus. Paralimbic as well as heteromodal components of prefrontal cortex also receive monoaminergic and cholinergic inputs. Interfering with dopaminergic or cholinergic neurotransmission in subregions of prefrontal cortex impairs the functions of the denervated areas, highlighting the importance of these transmitters for frontal lobe function (Brozoski et al., 1979; Dias et al., 1996).

THE CANONICAL FRONTAL SYNDROMES: HETEROMODAL VERSUS PARALIMBIC

Although the literature tends to employ the term *frontal lobe syndrome* as if it referred to a unitary entity, the examination of patients with prefrontal lesions reveals numerous patterns. The specific clinical picture in an individual patient is likely to be influenced by the location of the lesion, its rate of progression, the age of onset, and perhaps even the past personality of the patient. However, two "canonical" subtypes of frontal lobe syndrome can also be identified. One is characterized by a loss of initiative, creativity, and concentration power, with a propensity for apathy and emotional blandness. This pattern can be identified as the *frontal abulic syndrome*. The second subtype is characterized by too much behavior, although the contents of behavior betray a lack of judgment, insight, and foresight. Despite intact retentive memory, patients with this second pattern of prefrontal syndrome do not seem to learn from experience and impulsively stumble from one disastrous situation into another. This can be called the *frontal disinhibition syndrome*. Patients with the *abulic syndrome* are occasionally misdiagnosed as being depressed and those with the *disinhibition syndrome* as being hypomanic.

These canonical syndromes can be illustrated with the help of two clinical vignettes. The magnetic resonance scan in Figure 2–3A belongs to a 50-year-old patent attorney of a Fortune 500 company. He complained of visual blurring and headaches. A left frontal glioma was discovered and removed. The surgery relieved the headaches and visual blurring. As he appeared fit in all physical and mental aspects, he decided to return to work. At work, he displayed his customary mastery of relevant knowledge but seemed to have lost his ability for focused concentration and concern for detail. He started to make careless errors, some of which proved very costly to his company. Reprimands were shrugged off and performance continued to be erratic. He was eventually forced to take early retirement,

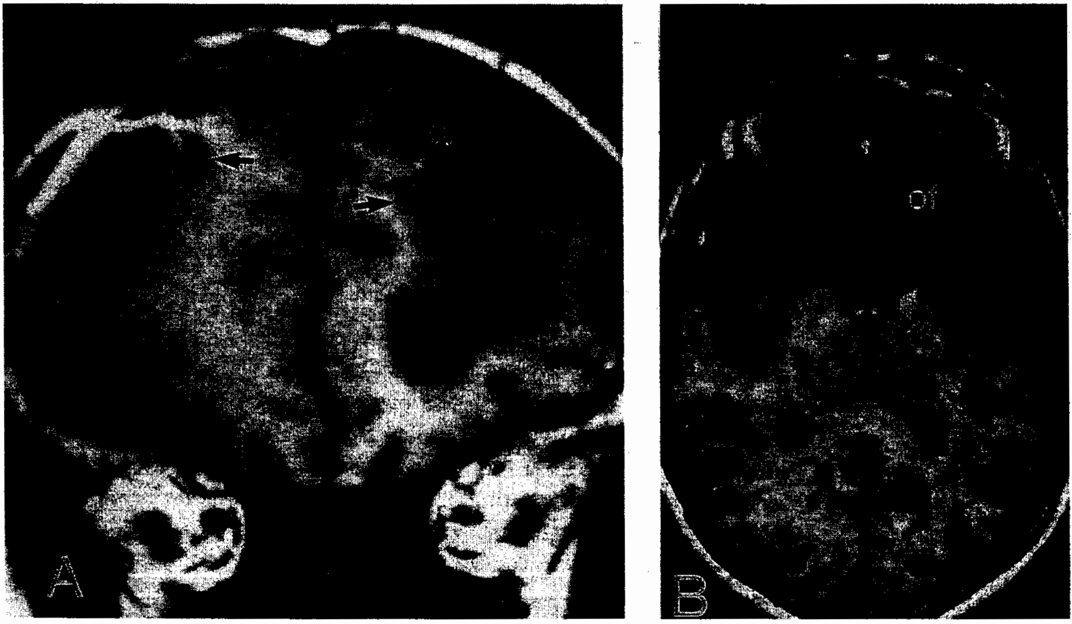

Figure 2–3. Magnetic resonance imaging scans of two patients. *A:* Coronal section through the anterior frontal lobe. The lesions (arrows) are predominantly in the heteromodal component of prefrontal cortex. *B:* Horizontal section through the orbital surface of the brain. The region that should have contained orbitofrontal cortex (of) is occupied by cerebrospinal fluid.

which he did without protesting, and seemed quite content to spend most of his time at home, watching television and helping his wife with household chores. When he last came to the clinic, he casually announced that his wife had just been diagnosed with metastatic breast cancer, but that he was not about to let this news bother him too much. This patient exemplifies the frontal abulic syndrome. His lesion was almost entirely confined to the anterior heteromodal part of the prefrontal cortex. The more posterior orbital and medial surfaces containing the paralimbic components remained quite intact, though undoubtedly disconnected from the damaged parts of heteromodal prefrontal cortex.[5]

A different clinical picture emerges in the case of a widowed woman, in her 50s, who also developed visual blurring (Figure 2–3B). An olfactory groove meningioma was discovered and removed. In the process of the neurosurgical procedure, the orbitofrontal region was extensively destroyed whereas the more dorsal heteromodal part of prefrontal cortex remained almost entirely intact. Prior to surgery, she was a conspicuously conventional woman who had been holding a steady job as an administrative assistant. After surgery, she showed very little neuropsychological impairment, even in "frontal" tests such as the Luria motor sequences, the Stroop Test, or the Wisconsin Card Sorting Test (Mesulam, 2000b). However, she started to encourage intimate encounters with perfect strangers, at least one of whom had just been released from jail. She admitted that her behavior was impulsive, and that it lacked "brakes," but neither the theft of her purse by one of her male guests nor a bout of sexually transmitted disease could curb these inappropriate impulsive behaviors. This patient displays the characteristic traits of the frontal disinhibition syndrome and shares many clinical features with Phineas Gage, whose brain injury must also have involved predominantly the orbital and medial parts of the frontal lobes (Figure 2–1).

These clinicopathological correlations are further supported by observations in nonhuman primates. Orbitofrontal lesions in monkeys, for example, lead to impulsivity and emotional hyperactivity whereas lateral frontal lesions in chimpanzees leave most basic neurological functions intact while inducing a pervasive state of apathy so that the animals spend most of the time in the middle of the cage in a state of indifference (Jacobsen, 1936; Butter & Snyder, 1972).

THE DEFAULT MODE: A STRAIGHT AND NARROW PATH FROM STIMULUS TO RESPONSE

Neither of the two canonical frontal lobe syndromes described above is associated with primary deficits of motility, sensation, or major cognitive domains, supporting the widely expressed contention that prefrontal cortex plays a predominantly "executive" rather than operational role in the control of neural function. Prefrontal lesions do not cause fixed and categorical impairments such as amnesia, prosopagnosia, or alexia. Instead, such lesions seem to promote the resurgence of behavioral tendencies that may occasionally surface in neurologically intact individuals, but that are prepotent only in developmentally more primitive stages of neural integration.

An example of such primitive behavioral tendencies is displayed by turkey hens with newly hatched broods. At this critical stage of motherhood, the hens develop an urge to attack all moving objects that fail to utter the characteristic peep of their chicks, a highly adaptive instinct for discouraging potential predators. If a turkey hen with new chicks is made deaf, however, she will attack her progeny and peck them to death. If a dominant male box turtle is placed before a mirror, it will attack its reflection and fight it from dawn to dusk or until the turtle (and its reflection) collapse from exhaustion. If a herring gull in confinement leaves her nest for momentary relief and her eggs are placed a few feet away on the sand, the returning gull will proceed to incubate the empty nest even though her eggs are in plain sight (Tinbergen, 1951; Schleidt & Schleidt, 1960; Harless, 1979). These three examples of reflexively triggered instinctive behaviors reveal the nature of a hypothetical *default mode*, a realm of neural function where inflexible stimulus-response linkages, sensitive predominantly to the internal milieu, remain impervious to modification by context or experience.

The default mode has several major characteristics. The preferred path from stimulus to response is straight and narrow, triggering automatic reactions and immediate gratification. Options for alternative interpretations or actions are not encouraged, minimizing choice or improvisation. The horizon of consciousness is confined to the here-and-now, leaving little room for hindsight or foresight. Repetitive displays of hard-wired responses are promoted even when they do not fit the prevailing context. Appearance cannot be differentiated from significance: whatever glitters *is* gold. Although the default mode is most conspicuous in submammalian species, the laws of evolution suggest that it should remain represented, perhaps in latent form, in the central nervous system (CNS) of more advanced species as well.

The rest of this review will attempt to show that frontal lobe damage allows a resurgence of the default mode and that the principal physiological function of prefrontal cortex is to suppress and transcend this mode by enabling neuronal responses to become contingent rather than obligatory. This influence of prefrontal cortex is manifested through five core functions: 1) working memory and related attentional processes; 2) the inhibition of distractibility, perseveration and immediate gratification 3) The active pursuit of choice and novelty; 4) the conditional mapping of emotional significance; and 5) the encoding of context, perspective, and mental relativism.

WORKING MEMORY: SELECTIVE EXPANSION OF CONSCIOUSNESS BEYOND THE HERE-AND-NOW

The flow of ambient information greatly exceeds the real-time processing capacity of any CNS (Broadbent, 1958; Baddeley, 1996). It is therefore necessary to postulate the existence of neural systems that selectively focus awareness on behaviorally relevant events while holding potentially distracting stimuli at bay. *Attention* is a generic term used to designate the entire family of neural operations serving this purpose (Mesulam, 2000a). Experiments in monkeys and humans indicate that prefrontal cortex plays a critical role in nearly all such functions, including divided attention, sustained attention, and especially working memory (Pardo et al., 1991; Johannsen et al., 1997; Mesulam, 2000a). *Working memory* constitutes one of the most distinctive specializations of prefrontal cortex. It is an attentional function that enables the on-line holding and mental manipulation of information. Working memory transforms information access from a sequential and disjunctive process, where only one event cluster can be heeded at any given instant, to a conjunctive pattern where several selected clusters can become incorporated into the stream of consciousness (Fig. 2–4).

The critical relevance of the primate prefrontal cortex to working memory was first demonstrated in the course of *delayed-response tasks*. In these experiments, the animal watches food being placed under one of two cups. An opaque screen is then lowered and held there for an interval of seconds to minutes during which the animal has to keep the relevant information in working memory so that it can choose the correct cup when the screen is lifted. Chimpanzees and monkeys with dorsolateral prefrontal lesions are severely impaired in this task (Jacobsen, 1936; Goldman & Rosvold, 1970). In a variant of this task, known as the *delayed matching to sample test,* a monkey is first shown a sample stimulus, exposed to a variable delay, and rewarded for responding to a test stimulus only if it matches the sample. The crucial component is the delay period (up to 20 seconds in these experiments), during which the animal has to maintain a mental, on-line representation of a stimulus that is behaviorally relevant but no longer part of ambient reality. Lateral prefrontal neurons emit sustained responses during delay periods as if prolonging the impact of the stimulus or anticipating its reappearance (Desimone, 1996). These neurons also participate in the on-line maintenance of *convergent* information belonging to different modalities.

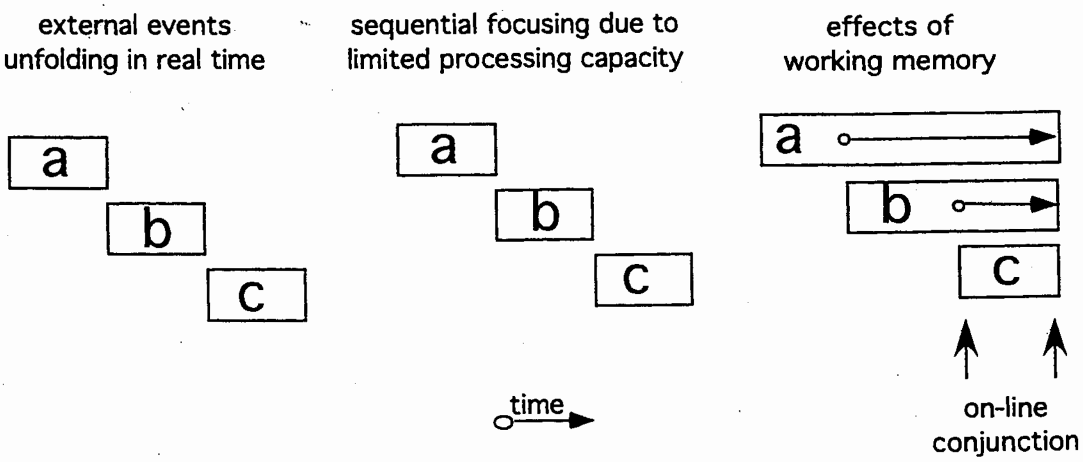

Figure 2–4. Diagrammatic illustration of working memory. The column on the *left* illustrates the real-time unfolding of three events. The *middle* column shows what would have happened to the mental representation of these three events in the absence of working memory. The column on the *right* depicts the contribution of working memory. The horizontal arrows reflect the on-line holding of information.

In one experiment, for example, monkeys were required to retain first the identity of an object and then its location. After having retained object information in the initial delay, many prefrontal neurons switched modes and conveyed spatial information in the second delay (Rao et al., 1997). Prefrontal lesions can disrupt delay activity in the sensory association area corresponding to the modality of stimulus presentation, indicating that prefrontal cortex exerts a top-down (executive) influence on working memory in other parts of the brain (Fuster et al., 1985; Desimone, 1996).

The relevance of the human prefrontal cortex to working memory was confirmed by functional imaging in 1973 when Risberg and Ingvar found that digit span tasks yielded hemodynamic activations in the lateral frontal lobes (Risberg & Ingvar, 1973). Since then, numerous imaging studies have reported lateral prefrontal activation during working memory tasks based on verbal, perceptual, and spatial stimuli (Petrides et al., 1993; D'Esposito et al., 1995; Cohen et al., 1997; LaBar et al., 1999). In the *2-back task*, for example, the subject is shown a string of letters, one letter at a time, and is asked to press a button if the letter is identical to the one that came before the immediately preceding one. This is a demanding task and requires the on-line holding of at least two bits of information at any given time. Successful performance in this task leads to robust activation in lateral heteromodal prefrontal cortex with a center of gravity in the middle frontal gyrus (LaBar et al., 1999). An even more demanding task, based on the ability to keep one goal in mind while pursuing another, also leads to selective activation within lateral heteromodal prefrontal cortex (Koechlin et al., 1999). As in the case of the monkey, the human lateral prefrontal cortex has also been shown to mediate the convergent on-line holding of multimodal information (Prabhakaran et al., 2000). In keeping with these findings based on functional imaging, patients with lateral prefrontal lesions show profound impairments of working memory—they are impaired in tasks of delayed response (Freedman & Oscar-Berman, 1986), they cannot hold information on-line, and they have difficulty maintaining a coherent stream of thought.

Daily activities that range from keeping a telephone number in mind to considering alternative facets of a moral dilemma rely on working memory. In the clinic, working memory is most readily tested with the *digit span task*. In this task, the ability to hear and then repeat a string of numbers requires the on-line holding of information, while the ability to repeat the numbers in reverse requires a manipulation of the internalized information. The "on-line holding" aspect of working memory is likely to play an important role in shifting the focus of attention from external events to their internal representations. This is an essential ingredient of the phenomenon commonly identified as thinking. The other aspect of working memory, the "manipulation" of the on-line information, is likely to play an important role in the volitional scanning and reorganization of mental content, explaining why patients with prefrontal lesions have prominent difficulties in tasks of verbal fluency and memory retrieval. These two aspects of working memory collectively enable the contents of consciousness to be selected deliberately rather than set reflexively (in a stimulus-bound mode) by events in the environment.

Working memory can be said to enrich the texture of consciousness by prolonging the impact of selected components of experience beyond the here-and-now. It would also seem to play a major role in determining how many channels of information can be handled in parallel. The span of working memory could be likened to the number of balls that a juggler can hold in the air. Simple nervous systems based on the default mode of neural functioning can handle only one ball at a time, and even that one is not thrown very far. In contrast, the working memory capacity of the human brain allows multiple balls to be held up in the air at any given time so that thought can reflect the contributions of multiple processing streams. There are undoubtedly great interindividual variations in the capacity for working memory. A most remarkable example is provided by Julius Caesar, who is said to have had the ability to dictate on different topics to three scribes at the same time (Tucker, 1765).

DISTRACTIBILITY, PERSEVERATION AND DISINHIBITION

An automatic orientation toward salient events, regardless of their relevance to current goals, and a tendency to repeat the same responses even when they have outlived their usefulness are two characteristic features of the default mode. The resultant distractibility and perseveration are ubiquitous in the behavior of animals, children, and adults with brain disease. The inhibition of distractibility and perseveration, appears to require the integrity of prefrontal cortex.

In a delayed matching-to-sample A●B●C●D●A paradigm of working memory, for example, a prefrontal neuron known to emit a selective delay activity following the presentation of A, continues to show high delay activity after B, C, and D and maintains it until the reappearance of A (Desimone, 1996). Prefrontal neurons may therefore play a critical role in protecting on-line information from interference by distractors. In human subjects, the requirement to ignore distractors during target detection leads to the activation of the anterior cingulate, medial prefrontal, and lateral prefrontal cortices (Coull, 1998). Nearly identical areas are activated by the *Stroop Test*, when subjects must state the color in which the word is written while suppressing the distracting tendency to read the word itself (Brown et al., 1999). In keeping with these functional imaging experiments, patients with frontal lobe lesions display a marked increase in distractibility (Chao & Knight, 1995).

The vulnerability to perseveration can be probed through the *go no-go task*, where the subject is asked to respond to one type of stimulus while suppressing responses to another. Tumors in the medial prefrontal region interfere with the inhibition of inappropriate responses during no-go trials, a deficit that can be reversed upon removal of the tumor (Leimkuhler & Mesulam, 1985). Functional imaging in neurologically intact subjects shows that response inhibition in the no go trials is associated with activation in the medial prefrontal cortex as well as in the heteromodal prefrontal cortex of the inferior frontal sulcus (Konishi et al., 1999). This multifocal distribution of activation helps to explain why so many different kinds of prefrontal lesions lead to disinhibition and perseveration. Perseverative tendencies in patients with prefrontal lesions interfere with the acquisition of nonrepetitive sequential behaviors such as those required by the "palm-fist-edge" task of Luria. In other patients, disinhibition undermines the ability to suppress inappropriate behaviors that lead to immediate gratification. In monkeys, inferofrontal/orbitofrontal lesions lead to errors of commission in go–no go tasks and to perseverative errors during reversal learning when previously rewarded and neutral stimuli switch contingencies (Iversen & Mishkin, 1970). In keeping with these results, the suppression of the perseverative tendency to look at a distracting stimulus during an anti-saccade task is associated with lateral prefrontal neuronal activity (Funahashi et al., 1993).

The area of lateral prefrontal cortex activated during the inhibition of responses on no-go trials overlaps with the area activated during category shifts in the Wisconsin Card Sorting Test (Konishi et al., 1999). This finding implies that category shifts may be dependent upon the suppression of perseverative responses so that new hypotheses can be explored. This is in keeping with clinical experience in which patients with prefrontal lesions display major impairments in the Wisconsin Card Sorting Test, mostly because of perseveration and lack of mental flexibility in exploring new sorting criteria (Milner, 1963). This impairment of mental flexibility may also be responsible for the poor performance of such patients in the *Visual–Verbal Test,* where a previously successful sorting strategy must be relinquished and replaced by a partially overlapping alternative.

The relationship of prefrontal cortex to working memory, inhibition, and hypothesis testing underscores the importance of this region for complex reasoning processes such as those that can be probed with *Kuhn's plant problem* (Kuhn & Brannock, 1977). In this problem, the subject is shown pictures of four plants, two of which look healthy and two unhealthy. Each plant has been cared for with one of two different regimens of plant food, watering, and leaf lotion. The goal is to identify which of the three variables is critical for growing a healthy plant. A successful resolution of the problem requires working memory, hypothesis generation, the parallel consideration of multiple variables, the suppression of perseverative inferences, and the inhibition of distractibility by irrelevant cues. Patients with bifrontal lesions acquired early in life have considerable difficulties solving this problem (Price et al., 1990).

NOVELTY, UNCERTAINTY, AND CHOICE

A preference for sameness and uniformity is a property of the default mode and promotes behaviors that can be described as stimulus-bound or stereotyped. The antitheses of this tendency, novelty seeking and playfulness, are inconspicuous in amphibians and reptiles, emerge in birds, and reach their most exuberant expression in advanced mammals, especially primates. Monkeys will work hard in a setting where the only reward is a brief peek through a window, and human subjects who are given a choice between familiar and novel patterns will consistently spend more time viewing the latter (Butler, 1953; Berlyne, 1960). Prefrontal cortex seems to play an essential role in novelty seeking. The P300 elicited by novel, changing, or deviant stimuli, for example, is critically dependent on the integrity of prefrontal cortex, and an N200–P300 response that is maximal over prefrontal cortex appears to determine the attentional resources that will voluntarily be allocated to novel events (Knight, 1984; Daffner et al., 2000). In keeping with these relationships, task-related prefrontal activation decreases significantly as the task becomes more familiar (Raichle et al., 1994). These aspects of frontal lobe function may help to explain why prefrontal lesions lead to apathy and also why patients with such lesions are disproportionately impaired when facing novel situations (Godefroy & Rousseaux, 1997; Daffner et al., 2000).

The default mode of neural function does not tolerate much choice or uncertainty. Prefrontal neurons are sensitive to both of these behavioral parameters. In the monkey, for example, lateral prefrontal neurons can encode the certainty (or uncertainty) with which a cue predicts the outcome of a subsequent response (Quintana & Fuster, 1999). In humans, guessing behaviors, where stimulus–response linkages are maximally unconstrained and where choice and doubt are accentuated, give rise to prominent orbitofrontal activation (Elliott et al., 1999). Furthermore, greater activation of lateral prefrontal cortex has been reported when actions are selected by voluntary choice than when externally specified (Rowe et al., 2000).

These relationships to novelty seeking and choice suggest that prefrontal cortex belongs to a neural circuit that transcends the one-to-one relationship between stimulus and response in favor of a one-to-many setting that tolerates a greater diversity of outcome. In almost all other animals, genetic factors constrain behavioral domains such as those involved in dietary preferences, methods of communication, courting displays, and affiliative interactions. The situation is drastically different in humans, where thousands of languages have been invented to express the same thoughts, thousands of cuisines to satisfy the same hunger, and thousands of diversions to dissipate the same boredom. An ability to tolerate and seek novelty underlies this uniquely human aptitude for discovering multiple solutions to similar problems, a faculty that greatly accelerates adaptation to rapidly changing circumstances (Mesulam, 2000c).

EMOTIONAL COLORING OF ACTION, EXPERIENCE, AND DECISION MAKING

In the reptilian and amphibian CNS, sensory areas are monosynaptically interconnected with the limbic system so that perception becomes colored with emotion at the very initial stages of neural processing. A byproduct of this arrangement, and a chief characteristic of the default mode, is to promote rigid stimulus–response linkages where the salient sensory features of a primary reinforcer trigger automatic responses energized by the prevailing motivational state. The primate CNS introduces a greater degree of flexibility by inserting intervening synapses between sensory and limbic areas, as if to prevent actions from being dominated by limbic imperatives, but then resorts to very complicated multisynaptic circuitry for integrating experience with emotion, ensuring, however, that one is not overwhelmed by the other (Mesulam, 1998).

Prefrontal cortex appears to play a principal role in this multisynaptic integration of emotion with action and experience. Although all of prefrontal cortex participates in this process, its paralimbic components display a closer affiliation with emotion and related aspects of visceral function. In functional imaging experiments, for example, neural activity in orbitofrontal cortex varies according to the hedonic valence of sensory experience and the magnitude of reward or punishment (Blair et al., 1999; Rolls, 2000). The lateral part of orbitofrontal cortex seems more closely related to punishment whereas its medial part seems more closely related to reward (O'Doherty et al., 2001; Small et al., 2001). Furthermore, attending to the attractiveness or emotional expressiveness of faces yields a relatively selective activation of inferior frontal and orbitofrontal cortex (Nakamura et al., 1999).

In the monkey, single-unit recordings show that the majority of orbitofrontal neurons are sensitive to reward (Hikosaka & Watanabe, 2000). The anticipation of a raisin, for example, elicited brisk orbitofrontal activation during the delay period on trials in which the animal subsequently consumed the reward but not on trials where satiety led to the refusal of the raisin (Hikosaka & Watanabe, 2000). These neurons are thus more responsive to the motivational valence of an anticipated reward than to its identity. In contrast, lateral heteromodal prefrontal cortex contains neurons that are also sensitive to the identity of the reward and the cues with which they have become associated (Watanabe, 1996). It appears, therefore, that orbitofrontal neurons encode the hedonic valence of anticipated experiences, whereas the lateral prefrontal neurons may also encode the cognitive categorization of such experiences and their arbitrary associations (Hikosaka & Watanabe, 2000).

Through its amygdaloid and hypothalamic connections, orbitofrontal cortex can modulate the visceral correlates of emotion. Electrical stimulation of orbitofrontal cortex, for example, causes major changes in blood pressure, heart rate, vascular tone, gastric secretions, and respiratory rate (Kaada et al., 1949; Pool & Ransohoff, 1949; Kaada, 1960; Oppenheimer et al., 1992). These visceral manifestations can mediate the influence of emotions upon thought, experience and action (Mandler, 1962). Patients with damage to the ventromedial components of prefrontal cortex, for example, fail to produce an anticipatory visceral response just prior to making risky decisions in a task in which the winning long-term strategy is based on resisting oversized short-term gains (Bechara et al., 1997). The absence of the anticipatory visceral activation in these patients is associated with a perseverative impulse to seek immediate gratification even when subsequent questioning reveals that they realize this to be a disadvantageous strategy (Bechara et al., 1997). The ventromedial prefrontal damage in these patients presumably disengages decision making from the restraining influence of the anticipatory visceral reaction or "gut feeling." This disengagement seems to allow the short-term imperatives of the default mode to preempt adaptive long-term planning.

Prefrontal damage tends to disrupt the contingent rather than constitutive aspects of emotion and motivation. Thus, patients with frontal lobe damage have no major change in appetite but may become less discriminating in their food preferences; prefrontal lobotomy does not alter the threshold for withdrawing from painful stimuli but blunts the concern for the pain. In monkeys, orbitofrontal or anterior cingulate lesions result in marked alterations of emotional responsivity: the animals do not lose the capacity for the emotion but lose the ability to match its intensity to the significance of the triggering event (Smith, 1944; Butter & Snyder, 1972).

As noted above, heteromodal prefrontal cortex plays a critical role in working memory. The object of working memory need not be confined to numbers, places, or words. Emotion itself could conceivably become the object of working memory for on-line holding and manipulation, allowing the emotional impact of an event to be extended beyond its real-time evolution. Such on-line holding and mental manipulation of an emotion would increase its associative depth and synaptic reverberation. Through such processes, prefrontal cortex would be expected to play an important role in the genesis of complex moral and civic emotions. Prefrontal lesions on the other hand, would be expected to promote a state of emotional shallowness interpersed with stimulus-bound emotional outbursts.

SIGNIFICANCE, CONTEXT AND AMBIGUITY

The behavioral repertoire of primates requires an adaptation to a complex reality where the same cue may signal reward in one context but not in another and where the same stimulus may elicit one response in one setting but a different one in another. This aspect of behavioral flexibility requires neural mechanisms that can encode arbitrary stimulus-response contingencies and their experience-dependent temporal fluctuations. Two pivotal experiments illustrate the relevance of prefrontal cortex to these aspects of encoding.

In one of these, a monkey was first taught to respond to red objects (circles or crosses), but to withhold responding to green objects (circles or crosses). At this stage, some lateral prefrontal neurons gave a much brisker response to the green circles and crosses. The animal was subsequently taught a different contingency in which it had to respond to circles (green or red), but withhold responding to crosses (green or red). At this second stage, the same lateral prefrontal neurons that had previously given a muted response to the red cross (when it was the go signal) gave vigorous responses to the identical cue, now that it had become the no-go signal (Sagakami & Niki, 1994). It appears, therefore, that the primate prefrontal cortex contains the sort of neuron that would be necessary for differentiating appearance from significance, and for realizing that glitter and gold need not overlap. Through the intercession of such neurons, the control of behavior could be liberated from a small set of genetically determined primary reinforcers and transferred to a much larger set of higher-order markers whose relationship to the primary reinforcers can undergo experience-induced modifications.

In another experiment, distinctive visual patterns predicted the delivery of raisin, apple, or cereal rewards. During any given session, the monkey could be receiving one of two types of reward (raisin versus apple or apple versus cereal), each reward being signaled by a specific visual cue. In one animal that fancied raisins the most and cereal the least, the cue that predicted a piece of apple elicited a much brisker response from the same orbitofrontal neuron when the apple reward was paired with the cereal reward than when it was paired with the raisin reward (Tremblay & Schultz, 1999). This sort of neuron appears to encode the way in which context alters the relative significance of a secondary reinforcer, even when its linkage to the primary reinforcer remains unchanged.

An elegant experiment reported in 1974 had already demonstrated the role of the human prefrontal cortex in encoding the influence of context. In this experiment, subjects were shown a set of either three letters or three numbers and were asked to read the members of each set as rapidly as possible. The font was chosen so that one of the stimuli was ambiguous and could be read either as a "B" when it was presented as a letter or as "13" when it was presented as a number. This same stimulus was found to elicit differential evoked potentials in the frontal lobe when it was read as a letter as opposed to a number (Johnston & Chesney, 1974). In contrast, visual cortex in the occipital lobe gave identical responses to this stimulus, regardless of how it was being read. This notable result indicates that occipital cortex is sensitive to the surface sensory properties of visual stimuli, whereas prefrontal cortex is also sensitive to the way in which context alters their meaning.

The encoding of context necessitates the parallel processing of multiple considerations related to the target event and its background. This sort of process becomes particularly critical in guiding behavior under "ambiguous" conditions where there are no absolutely correct choices; When shown "ambiguous" advertisements that contained literal as well as implied messages, for example, patients with prefrontal lesions could not infer the less obvious nonliteral meaning (Pearce et al., 1998). Furthermore, patients with frontal lobe lesions performed more poorly than control subjects in realworld financial planning tasks in which there were no absolute right or wrong answers and numerous ambiguous variables needed to be considered in concert (Goel et al., 1997). The impairment of humor appreciation that has been described in patients with frontal lobe lesions (Shammi & Stuss, 1999) may also reflect, at least in part, the inability to detect nonliteral inferences and contextual incongruities. Furthermore, certain types of prefrontal lesions can lead to florid confabulations (Moscovitch, 1995), probably because they interfere with the ability to determine contextual plausibility during memory retrieval.

The experiments described in this section also suggest that prefrontal cortex is likely to play a crucial role in abstract thinking in which a literal (stimulus-bound) association needs to be resisted in favor of a less obvious inference implied by the context. Prefrontal damage frequently triggers a stimulus-bound state in which thinking becomes concrete and behavior is guided by the surface properties of events in the environment. One of our patients, for example, slavishly complied with solicitations for magazine subscription she received in the mail, and felt compelled to read aloud all signs and billboards she encountered in the streets. Such stimulus-bound behaviors lead to a phenomenon that has been termed the *environmental dependency syndrome* by Lhermitte (Lhermitte, 1986; Lhermitte et al., 1986). In eliciting the manifestations of this syndrome, Lhermitte employed 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 allowed him to show that patients with large prefrontal lesions display a remarkable stimulus-bound tendency to imitate the examiner's gestures and behaviors even when no instruction had been given to do so, and even when this imitation entailed considerable personal embarrassment. Furthermore, the mere sight of an object was shown to elicit the compulsion to use it, although the patient had not been asked to do so and the context was inappropriate—as in the case of the housewife who saw a tongue depressor and proceeded to give Professor Lhermitte a medical checkup. In these patients, an excessive dependency on the immediate environment led to stereotyped responses that ignored the incongruity of context. Prefrontal lesions can thus cause thoughts and actions to fall under the control of external stimuli in ways that interfere with behavioral flexibility and individual autonomy (free will).

SWITCHING PERSPECTIVES AND MENTAL RELATIVISM

In the default mode, events tend to be assessed from an egocentric perspective so that the horizon of consciousness does not extend beyond the here-and-now and the self is the center around which other events revolve. One way to transcend the default mode would be to transpose the effective reference point from self to other, from here to there, and from now to then, so that the same event can be apprehended from multiple vantage points, each generating its own set of considerations. Prefrontal cortex may play a pivotal role in these hypothetical transformations. In *Flavell's role-taking task,* for example, a subject is shown a map and asked to detect ambiguities in directions being given to a fictitious traveler who is trying to reach a specific house on the map (Flavell, 1968). In the first phase of the test, the fictitious traveler and the subject share an identical spatial perspective. In the second, the traveler has a different initial location so that the subject needs to assume the spatial perspective of the traveler. Patients with early-acquired frontal lobe disease do well in the first phase but not in the second, suggesting that the ability to apprehend events from a non-egocentric spatial perspective may be impaired (Price et al., 1990).

Prefrontal cortex could conceivably also mediate shifts in time, rather than space, so that intended actions and their consequences can be apprehended from a vantage point in the future. As noted above, prefrontal neurons in monkeys fire in anticipation of reward, as if a future reality were being previewed (Hikosaka & Watanabe, 2000). In humans, functional imaging shows that premotor (and perhaps prefrontal) cortex participates in the estimation of temporal intervals (Coull & Nobre, 1998), suggesting that this part of the brain may shift awareness into an inferred future. The ability to shift vantage points into the future so as to predict potential consequences of contemplated behaviors would provide the essential ingredients for planning, sequencing, and foresight, faculties that become severely impaired in patients with prefrontal damage.

A third sort of putative shift of perspective entails the ability to enter someone else's shoes and to surmise what that other person might think and feel in response to specific events and actions.[6] Circumstantial evidence implicates prefrontal cortex in the mediation of these "psychological" shifts of perspective as well. For example, the ability to read others' minds or to infer their reactions, intentions, and feelings becomes impaired by prefrontal lesions whereas tasks that require such inferences lead to the activation of medial prefrontal cortex (Stone et al., 1998; Blair & Cipolotti, 2000; Castelli et al., 2000; Gallagher et al., 2000). Interpersonal skills, judgment, socially appropriate comportment, and moral conduct are at least partially dependent on the ability to transcend an egocentric point of view and to regulate behaviors according to their inferred impact on the feelings and reactions of significant others. In the absence of this faculty, compassion, empathy, and conscience may fail to develop, giving rise to the characteristic insensitive behaviors, callous amorality, and sociopathic behaviors of patients with prefrontal disease. Such deficits are particularly pronounced if prefrontal damage is acquired early in life or centered in orbitofrontal cortex (Price et al., 1990; Anderson et al., 1999; Blair & Cipolotti, 2000).

The neural computations that are likely to mediate perspective shifts would be expected to depend on a state of mental relativism where multiple representations of the same event can be tolerated. The capacity for realizing that such multiple representations (for example, the self and its reflection in the mirror) constitute alternative manifestations of the same basic phenomenon is not automatic. Turtles, for example, will attack their own reflection in the mirror; only specially trained monkeys give any sign of rudimentary self-recognition in front of a mirror; and many demented patients will react to their reflections as if they were intruders (Ajuriaguerra et al., 1963; Harless, 1979; Gallup et al., 1980; Hauser et al., 1995). The tolerance of multiple representations may have necessitated the evolution of a critical mass of neurons, such as those in prefrontal cortex, with no obligatory role in routine sensory, skeletomotor, or autonomic function. These neurons would have developed the sort of flexible (discretionary) firing contingencies that could mediate the encoding of multiple representations. One by-product of such a development would be the emergence of an observing self who becomes differentiated from the sensory flux of ambient events and who can therefore intentionally reflect on experience (Mesulam, 1998). Such a capacity for introspection may have generated first the sense of a "commenting self" separate from the experiencing body, then the belief that others also have commenting selves, and, ultimately, that these other commenting selves believe that others also have commenting selves. This is the sort of representational amplification that would be necessary to sustain the shifts of perspective described above, especially those that mediate the ability to experience the world through the eyes, thoughts, and feelings of others.

Is it possible to identify shifts of psychological perspective in nonhuman primates? The premotor cortex of monkeys contains "mirror neurons" that respond both when the animal performs a particular action and when it observes the same action being performed by another animal. The suggestion has been made that these neurons provide precursors of the neural circuitry that allows the reading of other minds (Gallese & Goldman, 1998).

Monkeys are social animals. Their interactions rely on token aggressive and submissive displays, mutual grooming behaviors, and vocalizations. Social success depends on directing the proper behavior to the proper individual in the proper context, presumably based on some awareness of how these behaviors influence conspecifics. Monkeys with orbitofrontal lesions show a severe disruption of these affiliative behaviors and eventually become ostracized into social isolation (Kling & Steklis, 1976). Careful observation in a naturalistic setting is necessary for detecting such alterations since these animals may show few, if any, abnormalities in the structured setting of the laboratory. These experiments provide an animal model for the socially maladaptive behaviors seen after frontal lobe damage and support the contention that these aberrant behaviors are more likely to emerge after damage to the paralimbic component of the frontal lobe. These experiments also support the clinical adage that the consequences of prefrontal lesions become particularly conspicuous in naturalistic settings where behavioral guidelines are ambiguous.

FRONTAL LOBE VERSUS FRONTAL NETWORK SYNDROME

Dorsolateral prefrontal cortex belongs to a neural circuit that includes posterior parietal cortex, the head of the caudate nucleus, and the dorsomedial thalamic nucleus. Orbitofrontal cortex, on the other hand, functions as a component of a paralimbic ring that includes the cingulate gyrus, parahippocampal cortex, the temporal pole, and the insula. Prefrontal cortex could thus be conceptualized as a site of confluence for two partially overlapping and interconnected networks—a ventromedially located limbic system with its well-known relationships to emotion, motivation, memory, and visceral function; and a more dorsolateral frontoparietal system subserving working memory and related cognitive processes.

All complex behavioral domains are coordinated by large-scale distributed networks. The performance of a relevant task engages all components of the pertinent network, and damage to any network component can impair behavior in the relevant domain (Mesulam, 1990). The prefrontal networks follow these principles of organization. In addition to dorsolateral prefrontal cortex, for example, the *N*-back working memory task also leads to the activation of posterior parietal cortex, the caudate nucleus and the dorsomedial thalamic nucleus (LaBar et al., 1999). Furthermore, working memory tasks modulate the coherence between prefrontal and parietal activity, suggesting that the collaboration of these two areas is essential for performance (Diwadkar et al., 2000). In keeping with this organization, the manifestations of the frontal lobe syndrome, especially those aspects related to abulia, working memory, and other executive functions, can also arise after damage either to the caudate nucleus or to the dorsomedial thalamic nucleus (Richfield et al., 1987; Mendez et al., 1989; Sandson et al., 1991). Although these same signs and symptoms can also result from posterior parietal lesions, the verbal and visuospatial impairments of the parietal syndrome dominate the clinical picture of such patients.

A circumstance of considerable interest is the emergence of the frontal lobe syndrome as a consequence of multifocal white matter disease or metabolic encephalopathy (Wolfe et al., 1990; Mesulam, 2000a). Assuming that a major physiological function of the frontal lobe is the top-down or executive modulation of other networks, the emergence of the frontal lobe syndrome should come as no surprise in these cases, where multifocal partial lesions (none of which are individually severe enough to disrupt specific cognitive domains such as language or memory) collectively undermine internetwork coordination. In clinical practice, multifocal lesions and toxic–metabolic encephalopathies are more frequently encountered causes of the frontal lobe syndrome than lesions directly involving prefrontal cortex. A diagnosis of "frontal network syndrome" rather than "frontal lobe syndrome" may therefore prevent considerable confusion by acknowledging that the responsible lesion could be located anywhere within this distributed network.

OVERVIEW AND SUMMARY

Prefrontal cortex enjoys an exalted ontogenetic and phylogenetic status. It is nearly unidentifiable in subprimate species and reaches its greatest relative size in the human. Even in the human, prefrontal cortex does not fully mature, either physiologically or structurally, until approximately mid-adolescence (Diamond & Doar, 1989; Huttenlocher & Dabholkar, 1997; Luciana & Nelson, 1998). In keeping with these developmental patterns, prefrontal cortex appears to sit at the apex of behavioral hierarchies. Phineas Gage, for example, showed that prefrontal cortex is not all that necessary for enjoying the circus, driving a stagecoach, circumnavigating the globe, recalling yesterday's events, or communicating with others. It would seem that prefrontal cortex assumes a critical role only for behaviors that require the highest levels of mental integration.

Many cortical areas in the human brain are devoted to the modality-specific representation of events, faces, words, and locations. Others mediate the transmodal binding of these representations so that faces can lead to recognition, words to comprehension, intentions to actions, events to memories (Mesulam, 1998). Focal brain lesions that interfere with these processing streams lead to disconnection syndromes such as apraxia, prosopagnosia, color anomia, amnesia, and so on (Geschwind, 1965; Mesulam, 2000b). Prefrontal cortex is not essential for encoding any of these representations and is not implicated in the pathogenesis of any traditional disconnection syndrome. Damage to prefrontal cortex leads to a distinctive set of impairments that are context-dependent (contingent) rather than categorical. The manifestations of prefrontal damage become particularly prominent when the environment contains distractors; when ambiguity and conflict are high; when appearance and significance are at odds; when events must be interpreted in light of contextual peculiarities; when prepotent response tendencies must be restrained for some long-term purpose; when decision trees have multiple branches; and when the egocentric point of view must be transcended.

Prefrontal cortex regulates the selection, timing, monitoring, and interpretation of behavior rather than the formation of the constituent percepts and movements. Prefrontal cortex is consequently said to provide the critical substrate for executive functions through the top-down modulation of other neural systems in the brain. This top-down modulation is exerted through widespread prefrontal connections that are in a position to activate a given network, inhibit another, influence network combinations, and perhaps even allow anticipatory readouts of contemplated actions. Prefrontal cortex could thus enable the highest level of internal representation (of networks rather than of sensory data or motor programs) and provide an arena for the various networks to play out different scenarios.

In most other parts of the brain, regional specializations can be designated by single terms such as *language, vision, spatial attention, face perception,* and so on. No single term is yet available to encompass all the specializations attributed to prefrontal cortex. Perhaps the problem lies in the fact that prefrontal cortex contains different subareas with different specializations; perhaps a unitary functional designation will emerge with more research; or perhaps no unitary designation will be established, even for individual cytoarchitectonic subsectors or topographical regions of prefrontal cortex.

This review has resorted to the pedagogical practice of proposing a unified functional specialization for prefrontal cortex by contrasting it to a hypothetical antithesis designated the *default mode.* The influence of the default mode, as defined in this review, becomes prominent in species that lack prefrontal cortex, during infancy when prefrontal cortex is not yet fully developed, and in adult primates with prefrontal lesions. In this mode of neural function, the path from stimulus to response is short, appearance and significance overlap, familiarity and repetition are promoted, and the horizon of consciousness is confined to the here-and-now of an egocentric perspective. Events in the default mode lead to automatic, predetermined, and obligatory responses without allowing much neuronal space for thought, foresight, choice, innovation, or interpretation.

Nearly all functional affiliations attributed to prefrontal cortex can be conceptualized as attempts to constrain or transcend the influence of the default mode and its stimulus-bound style of responding to the environment. Working memory allows the contents of awareness to be chosen deliberately rather than set reflexively by ambient events; voluntary shifts of perspective allow the horizon of consciousness to transcend the egocentric vantage point; the suppression of perseveration promotes choice, improvisation, and hypothesis generation; the arbitrary and reversible linkage of emotional valence to secondary reinforcers allows a differentiation of appearance from significance; the ability to inhibit prepotent tendencies helps to establish a state in which the translation of emotions into action and of thoughts into words can be restrained when necessary; and the capacity for the parallel processing of multiple variables enables the encoding of contextual relativity and the realization that things are not always what they seem to be.

One common denominator, if one can be found, is the insertion of a neural buffer between stimulus and response in a way that delays closure so that weaker associations and alternative responses can be considered. The outcome is a mental relativism in which each event can evoke multiple scripts and scenarios that can then compete for access to thought and behavior. These processes rely on contingent rather than obligatory encoding so as to promote the inferential, pragmatic, and interpretive aspects of mental function.

Despite considerable advances in this field of research, it is difficult to dismiss the sense of uniqueness associated with frontal lobe function. It is quite remarkable, for example, that sizeable frontal lobe lesions can remain clinically silent for many years. Even after massive bifrontal lesions in monkeys, chimpanzees, and humans, 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, immoral, 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. This is in keeping with the contention that 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.

There have been numerous attempts to capture the astounding feats of the human brain in comparison to technological artifacts. Hydraulics, switchboards, servo-mechanisms, silicone chips, and massively parallel supercomputer networks have each been invoked to model brain activity. Some of these analogies have been quite helpful in shaping the investigation of movement, perception, attention, language, memory, and even chess playing. Prefrontal cortex has been more resistant to this sort of analysis. With the exception of working memory (where the linkage to random access memory has been made), it is hard to find an adequate technological tool that can model the functions of prefrontal cortex. In the absence of such a model, one could invoke a somewhat fanciful analogy from the field of sculpture. Statues can start either as mounds of clay that are molded into the desired shape or as blocks of marble that change shape as the pieces that occlude the desired form are chipped away. The posterior cortices of the human brain serve the first approach as they synthesize veridical templates of external reality; prefrontal cortex promotes the second approach by chipping away at surface appearance until a deeper "meaning" is uncovered. In a figurative sense, it could be suggested that the dialectic tension between these representative and interpretive approaches to neural encoding help to set the tone of human consciousness.

The phylogenetic emergence of prefrontal cortex may have introduced the capacity for choice, change, and reflection but has not specified the nature of the choices, the contents of the reflections, or the direction of the changes. The mental faculties promoted by prefrontal cortex are thus as likely to lead to the greatest feats of culture and civilization as they are to Hiroshima and Auschwitz. The mechanisms that shape the course of individual actions are currently beyond the scope of neurological analysis. Perhaps this will become possible when a new science is developed for analyzing not only how a single brain reacts to experience but also how brains (and their owners) interact with each other to form social matrices which then influence individual decisions. Such an analysis is likely to show that prefrontal cortex plays a pivotal role in these aspects of social neurology as well.

It is fair to conclude that the sense of enigma surrounding the case of Phineas Gage is rapidly vanishing. It is also clear, however, that much more work needs to be done so that the speculations and metaphors linked to prefrontal cortex can yield to facts and mechanisms. Considering what has already been achieved during the first 150 years of research on the frontal lobes, it would be safe to predict that this field will continue to generate fertile insights into the uniquely human aspects of neural function and mental integration.

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NOTES

1. The discrepancy in the date has not been explained. The event definitely occured on September 13.
2. From a 1928 letter, now at the Warren Museum of Harvard Medical School, from Dr. Edward Williams' son, Edward H. Williams, Jr.
3. He became very attached to the iron bar and seems to have kept it until he died.

4. It is now part of the Warren Museum collection at Harvard Medical School.
5. A prototypical example of the frontal abulic syndrome had been reported by Wilder Penfield. He published the effects of a right prefrontal removal (affecting mostly heteromodal cortex) he had performed on his own sister for the treatment of a slowly growing oligodendroglioma. Following the acute postoperative period, Penfield noted that his sister's judgment, insight, social graces, and major cognitive abilities had remained intact. When visiting her home as a dinner guest, however, Penfield noted a diminished capacity for the planning and administration of the meal, decreased initiative, and a slowing of thinking (Penfield & Evans, 1935).
6. This is the mental faculty that is also known by the cumbersome term *theory of mind.*

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