Functions of the Prefrontal Cortex in the Human Brain

The prefrontal cortex of the human brain is affected by various pathological conditions, and for the apparent theoretical gains and clinical benefits, brain scientists and clinicians alike have for decades endeavored to understand the precise role of this region of the brain. Recent findings in electrophysiological and functional neuroimaging studies provide a better insight into the neuronal activities during various cognitive processes performed by the prefrontal cortex. Nevertheless, some of these findings are at odds with others, and the theorized roles of the prefrontal cortex remain largely under dispute. On the clinical side, a longer history of research provides a wealth of symptom descriptions on the multifaceted prefrontal dysfunction. In the midst of this abundance, however, there still exists a need for coherent categorization of these seemingly disparate symptoms. This task could be done based on the nature of affected cognitive processes and their putative neural substrates. With this view in mind, the present article selectively reviews major anatomical evidence and experimental data together with clinical observations on prefrontal patients in an attempt to integrate findings in science with behavioral data and ultimately to propose a model of functional organization within the prefrontal cortex.

Key Words: Prefrontal cortex, Dorsolateral, Ventrolateral, Executive function, Working memory, Frontal lobe symptoms, Positron emission tomography (PET), Functional magnetic resonance imaging (fMRI)

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INTRODUCTION

Unambiguously defining the functions of the prefrontal cortex poses a particular difficulty. The prefrontal cortex is the multimodal association cortex of the frontal lobe anterior to the Brodmann areas 6 (PMA, SMA) and 4 (MI). This region has extensive cortico-cortical and thalamo-frontal connections through which it receives inputs of various sensory modalities including vision, gustation, and olfaction (1-3). These connections also provide the prefrontal cortex with emotional and motivational information from the limbic system as well as input from the hypothalamus signaling the organism's internal state (1, 2, 4). The hypothalamus sends its projections to the magnocellular part of the mediodorsal nucleus of the thalamus, which in turn projects to the basal part of the prefrontal cortex (1, 4). The basal part of the prefrontal cortex, often called the orbitofrontal cortex, has reciprocal connections with the ventrolateral and dorsolateral areas of the prefrontal cortex (2). It is true that such massive connections complicate the task of isolating the exact functions of the prefrontal cortex from the posterior cortical and subcortical contributions in their interactions

with the prefrontal cortex. The convergence of inputs and the apparent need for substantial cross-communication indicated by many reciprocal interconnections, however, suggest that the prefrontal cortex is the most likely site for the final integrative processing prior to behavioral output, e.g. evaluation of multimodal inputs and selection of responses, and thus is the most promising candidate for the 'central executive (5)' or 'supervisory attentional (6)' site in the brain. This anatomically based conjecture is consistent with early clinical observations on patients with prefrontal damage. Prefrontal patients were clearly unimpaired in basic sensory motor tasks or conventional intelligence tests such as WAIS IQ test, yet they exhibited an array of symptoms which invariably indicated that what was affected is higher-order cognitive functions of executive nature, e.g. planning, attention shifting and the speed of mental processing, or another higher-order quality of psychological dimension, i.e. personality changes such as apathy often seen in dorsolateral patients and disinhibition as in patients with orbitofrontal damage. Precisely characterizing and defining the components of these 'executive functions' requires further investigation.

The foregoing clinical evidence is in line with the phylogenetic account that the largest expansion in the brains of higher species took place in the heteromodal association cortices (7). This may suggest that higher cognitive functions characteristic of higher species demand larger heteromodal association areas. One can take this a step further and postulate that of all the heteromodal association areas, the anterior heteromodal association cortex, namely the prefrontal cortex, would mediate the highest-order or integrative functions for it receives processed information from the posterior heteromodal areas of the temporoparietal cortex. Indeed, responses of the prefrontal cortex cells compared to cells in the posterior cortex are known to be less correlated with sensory-inputs and they are modulated by volition (8, 9). Frontal lesions disrupt only voluntary attention, but not involuntary attention or the orienting responses, which can be considered more reflex-like and rudimentary than volition and intentional actions (10). A positron emission tomography (PET) study demonstrated that frontal participation is required only for a newly learned motor activity while a well-practiced motor activity such as writing one's signature does not require frontal involvement (11). It has been suggested that for overlearned activities and in routinized situations, the posterior system including the basal ganglia is sufficient to maintain the activity (12).

ANATOMICAL PRELIMINARIES

The surface of the human prefrontal cortex is conventionally divided into four regions: the dorsolateral area above the inferior frontal sulcus, the ventrolateral area below the sulcus, the frontal pole, and the basal part of the prefrontal cortex which is called the orbitofrontal cortex. The dorsolateral prefrontal cortex consists of the Brodmann areas 46 and 9, while the frontal pole refers to the area 10. Sometimes, the frontal eye field, area 8, is considered part of the posterior dorsolateral frontal cortex, but area 8 is usually distinguished from the dorsolateral area for its distinct role in voluntary eye movement and visual conditional association (13, 14). The ventrolateral prefrontal cortex includes areas 45 and 47/12 while the orbitofrontal cortex refers to areas 11, 12, 13, and 14. In view of the cytoarchitecture and the patterns of connectivity, however, two major trends emerge, i.e. the dorsal and the ventral (1, 2). According to this two-part division, the dorsal prefrontal cortex includes the frontal pole, and the orbitofrontal cortex is subsumed under the ventral prefrontal cortex. The dorsal prefrontal cortex receives substantial input from the parietal cortex and projects back to the parietal lobe, the superior temporal region, the cingulate cortex as well as the cerebel-

lum and the basal ganglia (1, 15). The ventral prefrontal cortex shares some parietal input with the dorsal area, but it has more notable connections with the temporal lobe and the limbic areas, e.g., the auditory association area of the superior temporal gyrus, multimodal areas of the superior temporal sulcus, the insular cortex, parahippocampal gyrus and the inferotemporal cortex, the last of which sends substantial projections to the amygdaloid complex (1, 2).

Of the dorsal prefrontal cortex, areas 46 and 9 have been much researched for their roles in working memory and other non-mnemonic executive functions. By contrast, the functions of area 10, the frontopolar cortex, in isolation have not been fully investigated. The anatomy of area 46 sets this region apart from the rest of the brain, for it receives input from virtually all parts of the brain and projects back to many of them. In line with this anatomical evidence, a wealth of experimental data indicates that area 46 is heavily implicated in executive functions which influence the overall cognitive processing, e.g. monitoring and managing/allocating attention. Area 46 is known to be activated in association with 'intrinsic', self-initiated activities (16). Area 9, on the other hand, has less extensive connections and its patterns of connection differ from those of area 46, although the two areas are often lumped together in functional studies. In a functional magnetic resonance imaging (fMRI) study using a face working memory task, the posterior middle frontal gyri, area 9, showed the most non-selective activities to visual stimuli and the least activity during delays while this pattern was reversed in the anterior middle frontal region, area 46, which is inferior and anterior to Petrides's mid-dorsolateral area, i.e., area 9/46 (8). These anatomical and physiological differences set the stage for further fractionation within the dorsolateral prefrontal cortex in terms of function. Functional neuroimaging studies reveal a modality division within the ventrolateral prefrontal cortex. The anterior ventrolateral area is consistently activated in non-spatial tasks, e.g., face and form, while more posterior region responds to spatial stimuli (17-19).

THEORETICAL CONSIDERATIONS ON THE FUNCTIONAL ORGANIZATION OF THE PREFRONTAL CORTEX

The majority of recent prefrontal research has been based on the concept of two visual streams proposed by Ungerleider and Mishkin (20). The ventral stream which refers to the occipitotemporal pathway is believed to subserve object and face recognition as well as foveal feature detection whereas the more dorsal, occipitoparie-

tal stream deals with spatial information. This concept has been carried forward to the anterior region of the brain by Goldman-Rakic who proposed that the dorsolateral region of the prefrontal cortex participates in spatial working memory tasks while the ventrolateral region of the prefrontal cortex is involved in object working memory tasks (21, 22). This model proposes that the distinction between the dorsal and ventral areas lies in the type of information they process, but not necessarily in their processing mechanisms. In fact, this model implies that both regions process different information by a unitary mechanism, namely working memory. Ungerleider and her collaborators reached a similar conclusion for humans using PET (17). This spatial vs non-spatial dichotomy, however, did not go undisputed. The continued preservation of the two separate streams was questioned in a number of studies. For example, Jonides et al. (18) observed a significant increase in blood flow in area 47 during a spatial working memory task and Rao et al. (23) demonstrated integration of information in the prefrontal cortex of monkey. The latter study found neurons which showed enhanced activities during the delay period in both "what" and "where" working memory tasks, and these neurons were diffusely distributed over the prefrontal region. This is in agreement with the previous discussion that information needs to come together somewhere prior to motor output in order for the organism to come up with the best plan of action. Anatomical data are in support of blurring the dorsal-ventral modality segregation within the prefrontal cortex. As discussed earlier, the prefrontal cortex is anatomically a site of convergence. For example, both dorsal and ventral regions receive direct input from the inferior parietal lobule where auditory, visual, and somatosensory afferents converge (1). Though the parietal input is heavier in the dorsal region compared to the ventral, they nevertheless share the parietal information which is primarily spatial by nature as opposed to object-oriented. In a similar vein, Petrides (24, 25) proposed a two-stage, process-specific model in which the dorsal and ventral areas differ in terms of their process mechanisms, not their modalities. In this model, the ventrolateral region executes comparisons of stimuli held in short term memory or organization of response sequences using the information consciously retrieved from posterior systems. The dorsolateral region, on the other hand, mediates monitoring and manipulation of information.

The modality-specific model's assumption of strict segregation of the spatial and non-spatial information is not only at odds with the evidence for information convergence but also fails to accommodate all the functional differences between the dorsal and ventral prefrontal cortex and thus renders the model inadequate to

account for the dorsal vs ventral distinction. Despite this shortcoming, the spatial vs non-spatial model is useful, albeit limitedly, for understanding the functions of the prefrontal cortex in that the dorsal vs ventral differences in input types do seem to figure in the functional specialization. A model of the prefrontal functional specialization needs to reflect input type differences, provided that no commitment is made to the strict modality-specific conclusion. It is evident that a primary influence on the orbitofrontal and ventrolateral areas comes from the limbic system. This suggests that functions facilitated by the affective limbic input can be better subserved by the ventral area. Most visual stimuli, especially faces, have different emotional and motivational values attached to them. They trigger feelings associated with them, which in turn assist recognition and judgment as well as formulation of reactions to the stimuli. In addition to the limbic input, these functions, particularly recognition, require analysis of features and details. There are physiological findings which present the basis of such feature detector-like function of the ventral prefrontal cortex: the receptive fields of neurons in this area represent the fovea, a retinal region that analyzes details (21, 26, 27). Much like the primary visual system which has two systems, i.e., the parvocellular system associated with foveal vision which specializes in analysis of details and colors, and the magnocellular system specializing in detection of motion, it is conceivable that irrespective of the spatial vs non-spatial dichotomy, the ventral prefrontal cortex concerns details and the dorsal area concerns strategic action plans or the 'big picture' of matters.

Some clinical data seem to support this hypothesis. Patients with dorsolateral lesions show impoverishment of overall output (28) and exhibit symptoms attributable to poverty of alternatives (29). The orbitofrontal lesion patients, on the other hand, show deficits in analysis or problems due to ineffectual access to previously learned strategies material (30). Also orbitofrontal patients tend to confabulate (29), which can be seen as an activity done for the purpose of filling in the missing details. Both symptoms of ineffectual access to long term memory and confabulation can be related to the limbic aspects of the ventral prefrontal area. The former involves the hippocampocentric long term memory and the latter involves both long term memory and the emotional contribution of the amygdala. Confabulation is the evidence that the brain puts together bits and pieces of limited information with old items retrieved from the posterior part of the brain, in a way that makes sense. This process of "making sense" might be assisted by emotional and motivational input so that the made-up story appeals to and evokes the right feelings. Orbitofrontal patients must be impaired at this, as the product of their confabulation

is often preposterous.

The ventral prefrontal cortex, thus, adds limbic color of the amygdala concerning drives and emotions as well as previous knowledge retrieved from the posterior cortex. It seems to be involved in controlling these limbic elements, i.e., inhibition of drives (12, 62). The dorsal prefrontal cortex, on the other hand, is rather an objective and more impersonal side of the brain, separated from the emotional ventral prefrontal area. The evolutionary wisdom of separating these two streams until they finally meet before the motor output, seems to be the following. The dual structure of visual system, as indicated earlier in the article, consisting of both parvocellular and magnocellular systems enables an animal, depending on the situation, both to examine details when there is enough time and to escape quickly when, for instance, a moving shadow of a predator is detected. Analogous to this visual system, there is a need for two specialized yet well-interconnected systems in the prefrontal cortex to divide up the workload for efficiency and at the same time to maximize the effectiveness. If the occipitoparietal-dorsolateral stream were to concern itself primarily with the details of reacting to the external world by making moment-to-moment judgment based on affective information and past knowledge from the limbic system, it would not be able to deal with the 'big picture' such as getting actions to reflect intention and directing attention to things that need be done. An example may illustrate the reason for separating the limbic-colored ventral from the impersonal and 'rational' dorsal stream. A monkey that has witnessed a predator killing its mother and is being chased by another predator faces both emotional upheaval and urgency to escape. An effective dodging through a densely vegetated jungle involves a set of highly coordinated movements and requires certain strategy, in which case the dorsal prefrontal's facilitatory influence over structures like the cerebellum would be crucial. A fatal consequence might ensue if the onslaught of emotion from the amygdala could directly control the monkey's motor coordination. A more preferable design would be to screen out some of the emotional information in the ventral prefrontal area and to have a more toned-down, relevant version reach the dorsolateral cortex and the premotor cortex.

PREFRONTAL DYSFUNCTION IN VARIOUS PATHOLOGICAL CONDITIONS

More than a century ago, Hughlings Jackson proposed that the most recently evolved structures are more susceptible to disruption than older, phylogenically and ontogenetically more established structures (31). The pre-

frontal cortex, along with some heteromodal areas of temporoparietal cortex, is the most recently evolved and the last to undergo myelination. This notion, when taken together with the extensive interconnections which enable the prefrontal cortex to reflect changes in multiple regions of the brain, might indicate that the prefrontal area is perhaps the most sensitive area of the brain, whose structures are affected by many pathological conditions. Clinical observations point out that many age-related cognitive disorders as well as psychiatric and neurological disorders show symptoms similar to those of damage to the prefrontal cortex. In the aged population, frontal dysfunction is often observed (32). Patients with obsessive-compulsive disorder are impaired on the Object Alternation Test where the performance depends mostly on the integrity of the orbitofrontal cortex (33). Schizophrenics perform poorly on the Wisconsin Card-Sorting Test (WCST) known to be sensitive to the dysfunction of the dorsolateral prefrontal cortex (33, 34). They also perform poorly on spatial oculomotor working memory tasks (35). Patients with Parkinson's disease show, reminiscent of frontal patients, a lack of spontaneous facial expressions and are impaired on the WCST as well as other delayed response tasks (36, 37). Alcoholics with Korsakoff's disease are also found to be impaired on the WCST and delayed response spatial working memory tests (38).

These disorders may have different causes and symptomatology, but they all in one way or another appear to negatively affect the prefrontal function. Some investigators, in confirmation of the clinical evidence, found that these disorders indeed cause neurological changes in the prefrontal cortex. It has been reported that schizophrenics show abnormally low blood flow in the prefrontal cortex, particularly in the dorsolateral prefrontal cortex (4, 39). Likewise, in patients with obsessive-compulsive disorder, the orbital/ventromedial prefrontal areas which are heavily connected to the limbic system (40) are dysfunctional (30, 41-43). In another study, De Santi (44) measured the glucose metabolism by PET and reported age-related metabolic reductions in all frontal and temporal lobe regions with a much stronger age correlation in case of the frontal lobe, especially in the dorsolateral region of the prefrontal cortex. PET studies of Korsakoff patients (45, 46) indicate heavy involvement of the frontal lobe; after alcohol intoxication, the rate of frontal glucose metabolism decreased in the frontal cortex. During detoxification, regional glucose metabolism increased, and the glucose metabolism levels were greater in the frontal regions than other areas. Similarly, long term frontal metabolic changes were observed in cocaine abusers (47), in whom cocaine addiction appeared to underlie the decreased dopaminergic function (48). Given

that mesocortical dopaminergic projections from the ventral tegmental area heavily innervate the prefrontal cortex, decreased dopaminergic function would affect the proper functioning of the prefrontal cortex and this explains why frontal lobe symptoms are observed among cocaine addicts. The importance of dopamine for proper functioning of the prefrontal cortex was investigated in a longitudinal study of children with phenylketonuria (PKU) (49). In early and continuously treated PKU children, a decreased level of tyrosine, an amino acid which is a precursor of dopamine, affected the prefrontal cortex more than any other dopamine systems in the brain as the rapid firing rate of the prefrontal dopamine neurons led to a high dopamine turnover rate (50, 51). As a result, children with PKU showed deficits in tasks involving working memory and inhibitory control, two putative functions subserved by the prefrontal cortex.

The vulnerability of the prefrontal cortex may be the reflection of greater plasticity of this tissue in actuality. The prefrontal cortex might remain relatively plastic even in the adult brain. Myelogenetically, the multimodal association areas, which include the prefrontal cortex, are the last to myelinate after the primary and the unimodal association cortices mature. This late maturation means that structures are open to modulation for a longer period of time, which results in a prolonged critical period during development. The question then is whether there is any evidence for continuous plasticity of the prefrontal cortex even after development is completed. Molecular evidence of such nature has been shown by Benowitz and his collaborators who found that the neocortical association areas and the pyramidal cells in the hippocampus where Long-Term Potentiation (LTP) occurs had the highest concentrations of the Growth-Associated Protein-43 (GAP-43), a protein associated with growth and modulation of synapses (52, 53). Although their finding does not amount to an evidence that the GAP-43 is unique in the prefrontal cortex, it at least presents a molecular basis for plasticity in the association areas of the adult brain and makes another suggestion as to why the prefrontal cortex is susceptible to deterioration.

SYMPTOMS OF PREFRONTAL PATIENTS AND CONJECTURES ON CAUSES

Mental inflexibility/perseveration

One of the major deficits of prefrontal patients is a group of symptoms that can be characterized as mental inflexibility or perseveration. This can be well demonstrated in the Wisconsin Card-Sorting Test (WCST) where subjects are to sort the cards according to criteria

which change in the course of a test session, e.g., sorting cards by color and then by pattern. Patients with even small dorsolateral removals show severely impaired post-operative performance on this task in comparison to patients with orbitofrontal or other posterior removals (37, 54). Corroborating evidence comes from a PET study in which the most robust and sustained activation during the WCST was located in the dorsolateral prefrontal cortex among the activation foci distributed over various regions including the orbitofrontal area, the inferior parietal lobule and the inferior temporal cortex (34). Successful performance on the WCST requires completion of three steps that would mainly tax working memory and executive functions of the dorsolateral prefrontal cortex. First, based on the examiner's feedback, the subject should be able to figure out the sorting criterion by trial and error. Efficiency of this process depends on the subject's ability to keep track of the criteria that he had already tried and then to infer a new sorting criterion in precise terms. Secondly, when the examiner switches from one criterion to another without explicitly informing the subject of the change, the subject should quickly detect that sorting by the first criterion no longer produces desirable results and should see the need to find a new criterion rather than continuing to sort cards by the previous one. Thirdly, once the subject figures out the new criterion, it would help him for the first few trials to keep reminding himself of the new criterion, until he becomes accustomed to it. Unless the subject pays attention like this, he would easily make the mistake of sorting the cards by the previous criterion or be distracted by, other prepotent features of the cards, e.g., color which is inherently prepotent compared to others. Poor performance could be a result of stumbling at any of these three stages.

Prepotent response tendency and perseveration is the nature of deficit that prefrontal patients exhibit. They can maintain their action following the initial sorting criterion, but cannot easily switch gears, failing to start sorting by a new criterion. Similar inability to switch from one type of calculation to another was reported by Luria (10). It is interesting to note, however, that the prefrontal patients' performance on these tasks improves when a warning of possible change in criteria is given at the beginning of the test (54, 55). This positive effect of pre-warning reveals one possible cause of perseveration. The pre-warning removes novelty and introduces an element of expectation. Such an external cue obviates self-initiated detection of changes in sorting criteria by compromising step two of the task performance discussed in the preceding paragraph. Now that detection of changes is part of the instructed task, patients who would otherwise be confused in an unexpected situation

can better manage the task. Another insightful observation on the nature of perseveration is that the patients can sometimes tell the examiner at least an abstract description of the correct criterion but continue to sort the cards by the previous criterion (37). This is often taken as an indication that the subject knows what to do, yet he fails to inhibit the old, entrenched sorting criterion. Attributing prepotent response tendency to failed inhibition can be a quick post-hoc explanation, but it does not mean much unless the causes leading to the failed inhibition are identified. One possible interpretation of the dissociation between knowledge and action is to view it simply as a disconnection syndrome. The updated knowledge would have no effect on the behavior if the dorsolateral area (or its connections to other motor-related areas) which would normally instruct the motor system to reflect the revised plan is damaged. Similar inability has been reported among early and continuously treated PKU children. They have difficulty acting according to their intention, and this often earns them a reputation as 'willfully bad' children. Their inability stems mainly from dysfunction of the dopamine circuitry in the dorsolateral prefrontal cortex (49). For an alternative interpretation, the inability to infer a general yet precise rule can result in the same failure of inhibiting the prepotent response. Abstract and imprecise internal definition of a new sorting criterion is less enforceable than the salient plan, i.e., previous sorting criterion still prepotent in working memory or salient external features, e.g., color. The more abstract the internal definition is, the more these salient features would win out and dictate the subject's response.

This type of perseveration could lead to fatal consequences for mountain climbers, who may persist in their plan to reach the top of the mountain even in inclement weather. In May 1997, a group of mountain climbers died on Mt. Everest after they began their final ascent later than they had originally planned despite the warnings of a coming storm. It was reported that they were all experienced climbers. At a high altitude, they were likely to suffer from oxygen deficiency, which is known to induce changes in chemistry and neuronal activity particularly in the prefrontal cortex as well as in the hippocampus (56, 57). In addition to oxygen deficiency, the effects of the fatigue from the journey and possibly lowered serum glucose level must have been most pronounced when the climbers reached near the top of the mountain. These adverse conditions could lead to depressed activities in the prefrontal cortex, particularly in the stress responding neurons of the prefrontal cortex (58-61). It has indeed been reported that climbers at a high altitude usually become muddle-headed and lack a sense of good judgment. They fail to revise their plan

or construct a new strategy to best suit the changed situation when adverse weather arises. An underlying cause of the problem seems to be the inability to consider alternative plans and to show flexibility in decision-making. This possible account is consistent with Luria's view on the frontal lobe's participation in voluntary actions. Without the prefrontal involvement, mountain climbers would have difficulty self-initiating new plans. Consequently, they have no choice but to resort to what is already in operation, either the pre-existing plan or established habits. Revision of the action plan can result only from a conclusion that an alternative plan better suits the present situation. The prefrontal cortex seems to make such a decision through a process of reassessing the situation and comparing multiple options, and this process demands working memory as well as executive functions of the dorsolateral area in particular. Executing revision of action plans requires some modulatory system, most likely the prefrontal cortex, to intervene first and inhibit the old plan before executing the new one. Unless there is a need for revision of the action, however, the modulatory system would not intervene and the old plans and firmly entrenched memories, presumably provided by the posterior association cortex, would be sent to the frontal lobe and executed by default in the absence of dorsolateral's new agenda. Thus, the motor perseveration observed among the prefrontal patients can be seen as inappropriate adherence to the old strategy, a type of cognitive rigidity due to unavailability of alternatives.

Disinhibition and distractibility

Disinhibition

The habit-driven nature of the prefrontal symptoms was discussed in the preceding section. Another deficit that prefrontal patients exhibit can be characterized as disinhibition. Prefrontal patients are noted for their inability to choose which external cues or internal urges to respond to and which to suppress. Their disinhibitory behavior is marked by a lack of control and shows evidence of reflex-like responses to all the cues of the moment. Such behavior is often interpreted as 'rule-breaking', especially in a social context, and ranges from mild to socially disastrous. As an example, prefrontal patients often behave as if they break a rule that disallows such behavior (12). When instructed not to flip cards, these patients cannot resist turning the cards at the first sight even though they perfectly understand the instruction and can even verbally repeat it. Another example is a corporate executive with massive frontal damage who urinated in the corner of an office while a meeting was in progress. The well-publicized case of Phineas Gage is described by Blumer and Benson as

follows: After an injury which mainly affected the left frontal lobe from the medial orbital region upward to the precentral gyrus, he indulged in the 'grossest profanity' and exhibited 'the animal passions of a strong man' (62).

Such social and sexual disinhibition is most commonly observed among orbitofrontal patients. The basic and self-preserving urges to urinate, eat, mate, escape and the like must come primarily from the hypothalamus and the limbic system, especially from the amygdaloid complex which is closely connected with the orbitofrontal cortex (1). In addition, the orbitofrontal cortex has strong connection with the piriform cortex as the piriform cortex sends projections to the posterior orbitofrontal cortex directly or to the mediodorsal nucleus of the thalamus, which then projects to the orbitofrontal cortex (63). Olfaction sheds some additional light on the role of the orbitofrontal cortex. Olfaction is closely associated with many motivational drives such as eating, escaping and mating. This is evident in rodents in particular whose olfaction plays a major role in mating and other self-preservation behavior such as food searching. Just as such behavior concerns things of immediate relevance, olfactory cues relate to the immediate environment. The smell of a dangerous predator or of food presents data of more immediate sort than, say, visual cues, i.e., sight of either some distance away. Given that the input of immediate concern together with the affective limbic input reaches the orbitofrontal cortex, failure to dismiss external cues or to inhibit internal urges is probably a consequence of the orbitofrontal area being damaged. If this ventral/orbital region acts as an inhibitory filter of emotional cues coming from the limbic system, removal of such a selection/suppression mechanism due to damage in the ventral prefrontal area would result in behavioral manifestation of responses to all cues, appropriate or inappropriate. A worse form of disinhibition would be observed if, as in the Phineas Gage case, the ventral removal is coupled with dorsal dysfunction and, as a result, ventral symptoms dictate the person's behavior in the absence of the dorsolateral's agenda. This model of the orbitofrontal cortex with an inhibitory control over the input from the posterior limbic system can explain many of the well-documented orbitofrontal symptoms such as reactivity, fluctuation of emotion, and lack of insight all of which are none other than the reputation one earns by rash, emotion-driven behavior.

Distractibility

Phineas Gage showed signs of another type of impaired inhibition and selection which can be termed distractibility (62, 64, 65). Distractibility refers to the fact that prefrontal patients are very easily distractible, which may mean that they are unable to focus on a

single plan that can override other thoughts triggered by transient sensory input. Phineas Gage was able to devise several plans of operation, not necessarily all at once. He differed from normal persons in that he would soon abandon these plans and he discarded them because others began to appear more feasible to him (62). In other words, he was distracted by other plans as he was unable to think in order of relative importance. Making an informed decision about the order of importance would no doubt require the orbitofrontal/ventral input on the motivational and other practical aspects of the plan and this ventral's bias would facilitate the final decision. Thinking in the order of importance and ruling out alternative thoughts as they come to mind, however, necessitates some second-order executive control beyond the on-the-spot judgment or the first-order binary selection, i.e., inhibition or not. One needs to weigh pros and cons of competing plans and prioritize them both conceptually and temporally in terms of factors like urgency/timeliness, magnitude of consequences, and feasibility, i.e., the individual's current condition as well as external circumstances. By the end of this process, the person would be equipped with a list of guidelines and criteria by which other later irrelevant thoughts could be easily ruled out. The minimum prerequisite for the whole process would be working memory to hold all the relevant items in mind and manipulate them. Inability to complete this mental process would lead to discarding all plans of operation, which would make an individual appear indecisive and less initiative. Distractibility resulting in abandoning all plans is distinguished from disinhibitory distraction discussed earlier which leads to responding to all external and internal cues irrespective of propriety. From the behavioral point of view, responding to external stimuli or internal urges as in the case of flipping cards against the instruction or urinating at the meeting can be easily executed whereas responding to different plans by prioritizing them on the basis of criteria such as order of importance requires complex mental organization prior to behavioral execution. The former is reactive while the latter involves proactively organizing thoughts in the internal, cognitive realm. It is possible that disinhibition manifested in failure of suppression is mainly caused by dysfunction of the orbitofrontal/ventral prefrontal cortex whereas distractibility manifested in indecisiveness and decreased self-initiated activities can be primarily attributed to the dorsolateral prefrontal dysfunction.

Symptom of jumping to conclusions

Prefrontal patients are impaired on another neuropsychological test known as the thematic picture task

(10) where patients are presented with a thematic picture with many details from which they are to figure out the overall theme. Prefrontal patients tend to focus on one random detail and jump to conclusions; for instance, they, at the sight of a sign, "danger", immediately guess that it is a picture of high-voltage cables or an infected area or a zoo when in fact the actual picture shows the 'danger' notice standing next to a person shouting for help in a hole of a frozen pond (10). Because they randomly pick a particular detail, they literally cannot see the big picture just as someone who does not step back from a pointillist painting has no hope of appreciating its overall pattern. Luria's account does not include which region of the frontal cortex was ablated in the patients who showed impairment on the thematic picture task. Jumping to conclusions is highly reminiscent of orbitofrontal patients who exhibit lack of insight in their rash behavior. Given that orbital patients are so reactive and so easily distractible that a single cue is sufficient to trigger a response, one salient feature like 'danger' could elicit a rash conclusion on the theme of the picture. In such responses, the patients fail to see that their choice does not fit the overall context. Similar inability to consider the overall contextual information exists in the verbal domain. Prefrontal patients, when asked to interpret proverbs, come up with a literal or restrictive interpretation rather than a contextual interpretation. One patient is reported to have told the experimenter that the proverb, "strike while the iron's hot", means that he needs to start ironing his shirt when the iron is warmed up (66).

Dorsal participation in the thematic picture is suggested by one line of evidence. Luria, using the method of Yarus or Vladimirov, recorded eye movements while patients and normal control subjects examined the thematic picture (10). One of the things that this thematic task required was figuring out the ages of the characters in the picture. The normal control subjects moved eyes around, extracting relevant features from all over the picture while the patients' eye movements were much restricted to the point of their first fixation. From these data, at least two interpretations are possible. The deficit might have been caused by direct damage to area 8, the frontal eye field, which is known to mediate voluntary eye movements. Or equally likely, it could have been caused by the subject's overall deficiency of executive functions, e.g., lack of a search strategy due to the damage to area 46. Damage to area 46 and its efferent projections would cause failure to transmit proper commands to area 8 for initiating the search. One needs to actively construct plans of operation, e.g. which details to look for, in order to guess how old a character might be in the picture. This process, among others, requires

integrative thinking with the extracted information within working memory and hierarchically organizing the information by their relevance to problem-solving. After the plans of operation are formed and the actual examination of the picture begins, the plans must be revised according to the recent input about the picture. One can either confirm or reject his hypothesis on the characters' ages based on the newly acquired information on the picture, and can resume further analysis if necessary. Dorsal prefrontal participation seems critical given that the task demands are on working memory and strategic executive control. Ventral prefrontal cortex may play a facilitatory role in judging relevance of picture details by providing the dorsal region with necessary affective and experience-based information from the limbic system.

It is not clear that the type of problem revealed in the thematic picture task is a difficulty with integration of multiple features or difficulty with disengaging attention, i.e., being stuck with a detail before integrative process can even occur. In the recording of the eye movements, frontal patients certainly made fewer eye movements and they were more restricted than those of normal subjects, indicating some inertia in disengaging attention. But even with the fewer features extracted by a limited examination, patients tend not to make full use of them, indicating an integration problem. Parietal lobe patients often show similar difficulty with disengaging attention and integration. Parietal patients, for instance, may see a nose or a pair of glasses alone, but cannot see a person with the nose wearing the glasses. The close interconnections between the prefrontal and the posterior parietal lobe might account for the similarities in deficits. Quintana and Fuster (67), however, showed clear dissociation of the prefrontal functions from the parietal functions. Rhesus monkeys with a reversible lesion (by cooling) of dorsolateral prefrontal or posterior parietal cortex performed on a cognitive visuomotor integration task. The task required short term retention of some spatial and some non-spatial information. Both prefrontal and parietal cooling increased response time, but prefrontal cooling resulted in poor performance on the task irrespective of spatial demands while the parietal cooling impaired ability to process and retain spatial information only. The impairment due to the prefrontal cooling was worsened as the delay was increased whereas the impairment caused by the parietal cooling was unrelated to the delay. It is assumed that since monkeys need to hold the information during the delay, the activity during the delay is the index of working memory. Given this assumption, the results suggest that the posterior parietal area processes spatial information and it is part of the distributed neural system for spatial working memory, but its role is more of contribution to rather than media-

tion of working memory itself. The dorsolateral prefrontal cortex, on the other hand, participates in the spatial working memory because it mediates overall working memory.

HYPOTHESIZING A MODEL OF DORSAL VS. VENTRAL FUNCTIONAL SPECIALIZATION

One interesting implication of the foregoing functional specialization is that the dorsolateral region does not exercise control over all plans of action and it may not be the final check point for every motor output. Some motor output such as the inappropriate behavior exhibited by most orbitofrontal patients are executed uncensored. This type of responses to internal or external cues might be taken care of on the spot by the ventral cortex, which in consultation with the limbic regions, selects what feels appropriate on the basis of the affective information and what seems right on the basis of past experience and associations. Even if the ventral cortex is dysfunctional and fails to selectively screen out inappropriate cues, the dorsal prefrontal cortex does not seem to get involved at the level of inhibiting specific reactions. Rather than mediating such outbursts of discrete reactions, the dorsal prefrontal cortex may be called upon only for overall regulation such as deciding the time table of multiple activities for integrated behavior. Understanding the dorsal vs ventral functional specialization within the prefrontal cortex may in a sense be assisted by drawing an analogy between the dorsal area and a chief executive officer (CEO) who is at the top of company's managerial hierarchy. A CEO makes decisions relevant to the overall direction and strategies for the company as well as decisions on cross-departmental issues while the majority of day-to-day operational decisions are made by managers in the relevant departments within the general framework set by the CEO. This is how top management officer exerts influence over all parts of the company without having direct interaction with every single member within it. The dorsolateral may work in a similar fashion, for it seems to play a major role in overall efficiency, e.g. reduced response time, sustained attention, and other attention management as to how much attention should be allocated to perform a particular task in a multiple task paradigm. The dorsolateral cortex then projects back to different sensory and motor regions of the brain at various processing levels in order to bias and modulate their processing (1, 9).

The CEO analogy may be useful in another respect. Although the nature and scope of control is different, both the CEO and managers are involved in decision-making and good working relationship between the two

is critical to the normal functioning of each and to the company's overall performance. Likewise, the dorsal and ventral prefrontal areas share executive functions, although the kind and level of decision-making is different, and the two areas are closely connected so that dysfunction of one would affect the other. Assuming that the hierarchical model applies to the dorsal and ventral prefrontal areas, the dorsolateral cortex would be as much affected as it relies on the ventral input; it would make partially uninformed decisions without the ventral input. It is also possible that with the dysfunctional ventral inhibitory filter, the dorsal workload increases and the area would be overwhelmed by inundating uncensored response options. Under such circumstances, the dorsolateral seems to let these options manifested as exemplified by the behavior of some disinhibited orbital patients. Without the strategic instruction of the dorsal prefrontal cortex, on the other hand, the ventral would mostly follow its hunches in consultation with the limbic system, but execution of these hunches might be poorly coordinated and less goal-directed as a whole. There is in fact some evidence to support this view that hunch-like, moment-to-moment judgment is the contribution of the ventral prefrontal region. In an experiment using the skin conductance response (SCR), patients with ventromedial lesions were impaired when compared with normals during their performance on a gambling task (68). Ventromedial patients are known to play continuously from 'bad' decks, which despite immediate gains lead to larger losses later in the game. Moments before selecting from a bad deck, normals showed high amplitude of SCRs while ventromedial patients did not. These patients responded with increased SCRs only when they had actual loss of money. Without hunch-like ventral input, therefore, one could become insensitive to consequences and would lose foresight. This may also explain why ventral patients exhibit socially inappropriate behavior as if they are oblivious of the consequences.

The question then arises as to what type of cognitive processes would recruit the dorsolateral as opposed to ventral participation. It has been argued that in general more 'demanding' tasks tax the dorsolateral cortex, but it needs to be clarified first whether what people generally feel 'difficult' is indeed what the brain at the cellular level considers demanding. In a recent fMRI study comparing the frontal and cerebellar activation during a word stem completion task, stems with many possible completions (MANY condition) led to increased activity in the left dorsal prefrontal cortex, i.e., the Brodmann areas 9 and 10, while stems with few possible completions (FEW condition) led to activation in the right cerebellar hemisphere (69). From the subjects' point of view, the FEW condition was more 'difficult' as indicated by longer

response time because this condition was more constrained and the subjects could easily get stuck if they did not remember any of the few suitable words. In the MANY condition, by contrast, they quickly and successfully completed the stems. Given that only 2.5 seconds were given for each stem and that stems in the MANY condition were easy, the subjects reported the first word that came to mind rather than trying different words and selecting one. Nonetheless, it is probable that despite this mental process which the subjects were aware of, the MANY condition unconsciously activated a network of numerous internal representations of all the words starting with the stem while the FEW condition activated a few specific items to be retrieved. In the FEW condition, search for a specific word that starts with the stem may be time-consuming but execution of the task itself is simple and clear in that nothing outside the instruction is expected: 'you go find a word starting with the stem and retrieve it'. This does not require any major decision making. To refer to the CEO analogy, it is possible that once the dorsolateral area decides what to do, it hands down the instruction and asks its assistants to carry out the task so that it can look out for more important business that would affect the organism as a whole. It appears that the dorsal prefrontal cortex often divides up workload with other systems which receive its projections, i.e., the cerebellum and the cingulate gyrus (15, 69, 70). This might be one reason why the prefrontal activation was observed in the 'easy' MANY condition rather than the 'difficult' FEW condition.

It is interesting to note that although the dorsolateral prefrontal cortex appears keen on overseeing cognitive activities in general, it does not seem to entertain the idea of overworking itself. In a dual task paradigm, the dorsal prefrontal area is usually activated irrespective of the specific demands of each task in isolation. This is probably because performing more than one task requires some executive regulation, e.g., making decisions on attention and time allocation. Once the demand of the task increases, however, the dorsolateral area disengages itself from the task as indicated by decreased activation and lets the cerebellum or the anterior cingulate cortex take over (69, 70). It is quite counter-intuitive that the dorsolateral cortex breaks down just when the task demand is increased and its maximum function is desired. The precise reason underlying this phenomenon needs further investigation. But, considering the fact that the takeover by the anterior cingulate or the cerebellum is usually associated with less successful performance, one can infer that the dorsolateral participation is primarily for better performance and that the takeover may not signify better suitability of these other structures for the task. In this sense, the dorsolateral cortex can be said

to behave in the same way as the organism as a whole is expected to behave under pressure. If one is asked to do multiple demanding tasks requiring rapid responses, for example, he/she would be able to neither 'think' nor pause for a strategy. A strategy, although it usually increases efficiency, may under pressure even slow down some responses, and it would be better to have a more automatic subsidiary back-up system to be employed. The resulting performance may not be of the same quality it would otherwise be, but the task can be done. Contrary to the dual task paradigm results, levels of cognitive load seem to better correlate with activation levels of the dorsolateral prefrontal cortex in single working memory task paradigms (71-73). In an fMRI study using n-back task, the dorsolateral region showed a linear relationship with working memory load as delay and memory set size were varied (72). Cohen et al. (73) described similar correlation in an fMRI study using n-back task, although they suggested a step function rather than a gradually increasing function. In another fMRI study, activity in the dorsolateral prefrontal cortex was enhanced as the retention intervals increased (74). It is known that simple retention of visual stimuli for short intervals fail to activate the dorsolateral region (17). Longer retention intervals used in Barch et al. (74), on the other hand, would make a greater demand on working memory and would require formulation of a strategy to hold information for longer periods of time. It appears, therefore, that the dorsolateral prefrontal cortex is invariably activated in single working memory task paradigms that require strategic executive control and the level of dorsolateral participation is determined by working memory load of the task in question.

CONCLUDING REMARK

A rough sketch of the functional organization in the brain can be drawn by way of conclusion. Distinct roles are assigned to the motor-related anterior and the sensory-related posterior cortical areas of the brain. The posterior region processes information on the features of perceived objects and their spatial locations, as Ungerleider and Mishkin's two visual streams delineate. Similar processing occurs at a more conceptual level with experienced events and their circumstantial contexts. Posterior region then serves as a site where this type of information is stored for future availability. In the course of consolidating memories, the posterior region consults with both the limbic system and the prefrontal cortex, which can enhance the likelihood that more meaningful objects and significant events will be encoded and consolidated for future reference. Such stored information

can be used for recognition, thereby decreasing the frequency of unnecessary novelty responses which can disrupt ongoing behavior. This information is also used for programming motor activities by the anterior premotor areas, e.g., the supplementary motor area and the frontal eye fields, as well as the motor speech area of Broca. In devising plans for action and performing the actions, the prefrontal cortex is involved in playing an executive role. For optimum plans of action, all sensory input and motivational values need be integrated, compared, and prioritized, and it is sensible for such processes which occur temporally close to motor output to take place physically close to the motor areas in the prefrontal cortex. For optimum performance, the prefrontal cortex, particularly the dorsal area, exerts influence over other performance-related areas to which it projects, e.g., the cerebellum, the basal ganglia, the anterior cingulate, the superior colliculus, and the premotor areas. Working memory and other non-mnemonic executive functions are essential for carrying out such duties. The dorsal and ventral expanses of the prefrontal cortex divide the executive workload in such a manner that while the ventral region is involved in moment-to-moment reactions and inhibition on the basis of affective or knowledge-based associations and categories, the dorsolateral area which in a sense can be seen as a higher-order executive site provides services that facilitate the overall performance on a given task, e.g., strategy, attention management, and the speed of processing. This general pattern of functional specialization in the human brain may be subject to variations depending on individuals' history, with the result that as in hemispheric dominance, some may be more efficient in using the dorsal functions and largely dependent on them but others may show ventral dominance. Notwithstanding the individual variability, it seems indisputable that the prefrontal cortex as a whole serves as an executive site in all human brains.

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