Chapter 34

Prefrontal Cortex: The Present and the Future

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In this chapter the current neuropsychological and physiological evidence linking lateral and orbital prefrontal cortex (PFCx) to human cognition and social

interchange will be reviewed in an attempt to provide a summary of much of the work presented at the Rotman Frontal Lobe meeting and delineated in this book. We will begin with our view of the contributions of lateral prefrontal cortex to executive control. This book provides evidence of a remarkable convergence of lesion, electrophysiological and fMRI data on the role of lateral PFCx in inhibitory control, excitatory modulation, working memory and novelty processing. The electrophysiological data accrued from humans and animals provide important information on the timing of PFCx modulation of cognitive processing. This electrophysiological data is complemented by fMRI findings defining the spatial characteristics of PFCx involvement in a variety of cognitive tasks with evidence mounting for engagement of interleaved inhibitory and excitatory processes during a host of cognitive processes. Finally, the neuropsychological data provides the crucial behavioral confirmation of electrophysiological and functional magnetic resonance imaging (fMRI) findings obtained in normal populations. In our view the most complete picture will emerge from fusion of classic neuropsychological approaches informed by cognitive theory with powerful new techniques to measure human brain physiology. We first review the findings concerning the role of lateral PFCx in executive control of cognition and then discuss the

relevant literature on the contributions of orbital PFCx to social and emotional control. This chapter will not address the role of medial PFCx cortex in various aspects of motor planning nor will we discuss language and PFCx, which is reviewed by Alexander in this volume. A possible separate role for the polar regions may exist, but the evidence currently is inadequate to introduce in this review.

Lateral prefrontal cortex

Introduction

Evidence from neuropsychological, electrophysiological and neuroimaging research supports a critical role of prefrontal cortex in executive control of goal directed behavior. Lateral PFCx, including portions of the inferior, middle and superior frontal gyri, is involved in multiple domains including language, attention and memory (Stuss & Benson, 1984, 1986; Corbetta et al., 1998; D'Esposito et al., 1995, 1999a, b, c; Knight et al., 1998; Chao & Knight, 1998; Dronkers et al., 2000; McDonald et al., 2000; Fuster et al., 2000). Functional MRI and event-related potential (ERP) research has defined the spatial and temporal contributions of lateral PFCx in working memory, attention, response conflict and novelty processing (Jonides et al., 1993,1998; Owen et al., 1998; Knight et al., 1998;

Botvinick et al., 1999; Barch et al., 2000; Prabhakaran et al., 2000). A meta-analysis of neuroimaging studies (Duncan & Owen, 2000) reveals activation of common regions of lateral PFCx in diverse cognitive tasks. PFCx activations in these seemingly diverse cognitive domains center in the posterior portions of the lateral PFCx at the junction of the middle and inferior frontal gyri including portions of dorsal and ventral PFCx (Brodmann areas 9,44,45,46; Rajkowska & Goldman-Rakic, 1995a,b). This suggests that common regions of the human prefrontal cortex are able to control many aspects of human cognition. Further, fMRI research has revealed that extensive areas of dorsal and ventral PFCx are crucial for sustaining neural activations during cognitive performance and more dorsal portions of PFCx appear to be crucial for manipulating neural activity during cognitive performance. Thus, a more complete behavioral and physiological picture of the functions of subregions of human lateral PFCx is emerging.

The extensive reciprocal PFCx connections to virtually all cortical and subcortical structures places PFCx in a unique neuroanatomical position to monitor and manipulate diverse cognitive processes. Lateral prefrontal damage in humans results in behavioral deficits in attention, working memory, planning, response selection, temporal coding,

metamemory, judgment and insight. In advanced bilateral lateral PFCx damage the patient has a flattened affect, manifests perseverative behavior and is unable to properly manage everyday affairs. The patient may be incorrectly diagnosed as being depressed although careful evaluation actually reveals indifference and an amotivational state rather than true feelings of sadness This amotivational state can be differentiated from the amotivation seen in patients with pure superior medial, or orbitofrontal pathology (Stuss, van Reekum, & Murphy, 2000). The amotivational state extends to both the cognitive and emotional domain. For instance, cognitive flexibility and creativity as well as sexual drive are frequently reduced. Frontal release signs (primitive reflexes including snout, rooting, suck, grasp and palmomental) are often observed (Knight & Grabowcky, 2000). The Luria hand-sequencing task where the patient is required to repetitively produce the sequence fist-palm of hand-edge of hand is often abnormal due to perseverative and random errors.

It should be emphasized that the severe lateral prefrontal syndrome is typically observed in bilateral PFCx damage as might be observed in degenerative disease, infiltrating tumors or multiple cortical or subcortical infarctions. This clinical observation emphasizes the inherent redundancy in the capacity of

lateral PFCx function to control cognitive processing. This is not to say that clear behavioral and physiological deficits are not apparent after unilateral damage. Rather, these deficits are not as obvious as one might expect. One intact PFCx is able to control bilateral hemispheric processing to some degree. How this redundancy of function is accomplished is not clear although recent animal work suggests that processing may be accomplished by callosal transfer of information to the intact PFCx (Rossi et al., 1999; Tomita et al, 1999). The use of the intact processes in the undamaged frontal lobe to overcome or compensate for the deficit in the damaged region of the prefrontal lobe has also been hypothesized (Stuss, Delgado & Guzman, 1987).

Neuropsychology

Human behavior is paralleled by a massive evolution of the prefrontal cortex, which occupies up to 35 percent of the neocortical mantle in man. In contrast, prefrontal cortex occupies about 10-12 percent of the cortical mantle in high level non-human primates such as gorillas (Fuster, 1989). Since lateral PFCx cortex is involved in so many aspects of behavior, characterization of a mild prefrontal syndrome can be elusive. Prefrontal damage from strokes, tumors, trauma or degenerative disorders is notoriously

difficult to diagnose since deficits in creativity and mental flexibility may be the only salient findings (Knight, 1991). The patient may complain that he is not able to pay attention as well and that his memory is not quite as sharp. An early lateral PFCx syndrome may become clinically obvious only if the patient has a job requiring some degree of mental flexibility and decision making. However, if the patient has a routinized job or lifestyle, prefrontal damage can be quite advanced before a diagnosis is made. Indeed, many prefrontal tumors are extensive at initial diagnosis. As unilateral prefrontal disease progresses or becomes bilateral pronounced abnormalities invariably become evident. Deficits in attention, planning, response selection, temporal coding, metamemory, judgment and insight predominate. In advanced bilateral lateral PFCx damage perseveration, manifesting behaviorally as being fixed in the present and unable to effectively go forward or backward in time, becomes evident. In association with these deficits, confidence about many aspects of behavior deteriorates. Indeed, prefrontal patients may be uncertain about the appropriateness of their behavior even when it is correct.

The behavioral changes that arise from damage to the prefrontal cortex are notoriously difficult to capture with many standardized neuropsychological

tests. Patients with large prefrontal lesions can perform within the normal range on tests of memory, intelligence and other cognitive functions, one observation that has led to the often-cited "paradox" or "riddle" of the frontal lobes. Even supposedly frontal lobe sensitive tests such as the Wisconsin Card Sorting Test (WCST) sometimes fail to discriminate patients with frontal lesions from normals or those with lesions in other regions (Eslinger & Damasio, 1985; Grafman, Jonas, & Salazar, 1990). In part his is due to a mixing of lesion location. Clinicians and researchers often do not differentiate regions within the frontal lobes. However, when one segregates subregions of PFCx damage a clearer pattern of regional specificity emerges. For instance, tests such as the WCST appear to be more sensitive to dorsolateral than orbitofrontal PFCx (see Stuss et al., this volume). In addition, there is often a lack of specificity as to the precise process that is impaired. For example, the notion that only perseverative errors are made by PFCx lesioned patients in the WCST may contribute to some of the confusion in the literature. Recent findings in patients with lateral PFCx damage indicate that these patients make as many random errors as perseverative errors (Barcelo & Knight, in press). Perseverative errors are traditionally viewed as a failure in inhibition of previous response pattern. A

perseverative error on the WCST is due to failure to shift set to a new sorting criterion. Random errors that are as frequent as perseverative errors reflect a different problem in these patients. A random error occurs when a patient is sorting correctly and switches to a new incorrect sorting category without any prompt from the examiner. Random errors can be viewed as a transient failure in maintaining the goal at hand and may represent a problem with maintenance of neural activity during the sorting task. As will be discussed later, excitation dependent maintenance of distributed neural circuits appears to be a key aspect of PFCx function (for reviews see Knight et al., 1998; D'Esposito et al., 1999a). Other tasks often employed by clinical neuropsychologists to capture lateral PFCx deficits include variations of the Stroop test that is particularly sensitive to failures in inhibitory control and tests of divided attention. However, tests of divided attention are also failed by patients with inferior parietal lobe damage and do not provide a specific assay of PFCx function. It should be emphasized that patients with lesions in different parts of the brain may fail the same task, but for different reasons.

While conventional neuropsychological tests such as the WAIS may be normal or only show minimal deficits, patients with lateral PFCx cortex damage may

be quite impaired in their daily lives. How can this paradox of relatively good performance on standardized tests be reconciled with impaired functioning in daily life? We will first review the current experimental neuropsychological literature on lateral PFCx dysfunction and then we will present some new concepts drawn from the cognitive psychology literature that may provide additional insight into understanding the human lateral PFCx syndrome. After reviewing the neuropsychological literature we will then discuss the physiological data including ERPs and fMRI which provide delineation of the role of lateral PFCx in human cognition.

a. Temporal processing: Patients with frontal lobe lesions are impaired in tasks involving temporal ordering, such as the sequencing of recent or remote events (McAndrews & Milner, 1991; Milner, Petrides, & Smith, 1985; Moscovitch, 1989; Shimamura, Janowsky & Squire, 1990). These patients are also impaired in making recency judgments (Milner, 1971; Janowsky, Shimamura, & Squire, 1989a; 1989b; Milner, Petrides, & Smith, 1985), a process that also relies on the correct temporal coding of events. Self ordered pointing, a task in which the patient must remember the order in which objects have been indicated, is also impaired in patients with frontal lesions (Petrides & Milner,

1982). Patients with extensive frontal lesions also have little concern for either the past or for the future (Ackerly & Benton, 1947; Goldstein, 1944). These patients are "stuck" in the present world with severe perseveration representing the penultimate example of failure to move across the time dimension. Note that to fluidly move from the present to either the past or the future one must be able to both inhibit the current mental context and find or construct a new mental image which requires excitation dependent activation of neural ensembles as will become apparent when physiological data relevant to PFCx function are reviewed.

b. Explicit memory, source memory and metamemory: While some sources suggest that explicit memory is normal in patients with lateral PFCx damage, a meta-analysis of the published data reveals significant deficits in explicit memory in lateral PFCx patients (Wheeler, Stuss & Tulving, 1995). These deficits are typically not as severe a patients with medial temporal amnesia but this distinction is compromised by the fact that most studies have compared unilateral PFCx lesions to bilateral medial temporal amnestics such as that occurring from CA1 hypoxic damage or Herpes Simplex. In other studies patient with Korsakoff's syndrome or ruptured anterior communicating aneurysms have been

compared to unilateral PFCx patients. Thus, the true degree of explicit memory dysfunction in patients with bilateral PFCx damage has been probably underestimated. If the pathology is in the left PFCx or involves septal/basal-forebrain areas, an encoding deficit is revealed (Stuss et al., 1994). Patients with damage to prefrontal cortex show a disproportionate impairment in the memory for the source of information (Schacter, Harbluk, & McLachlan, 1984; Shimamura & Squire, 1987; Janowsky, Shimamura, & Squire, 1989b). Factual information is correctly recalled but the spatio-temporal context in which the information was acquired is forgotten. These patients also have a diminished ability to make metamemory judgments (Janowsky, Shimamura & Squire, 1989b). Metamemory includes an ability to judge whether or not the answer to a factual question has been or will be correctly retrieved. Patients with frontal lesions are impaired at making these judgments even though their memory for the facts is intact. In contrast, patients with medial temporal amnesia have explicit memory impairments but are quite confident about the limited number of items they recall.

c. Inhibitory control: There is long standing evidence that distraction due to a failure in inhibitory control is a key element of the deficit observed in monkeys on

delayed response tasks (Malmo, 1942; Brutkowski, 1965; Bartus & Levere, 1977). For example, simple maneuvers such as turning off the lights in the laboratory or mildly sedating the animal, which would typically impair performance in intact animals, improved delay performance in animals with PFC lesions. Despite this evidence, remarkably little data has been obtained in humans with PFCx damage. The extant data centers on failures in inhibition of early sensory input as well as problems in inhibition of higher level cognitive processes.

In the sensory domain, it has been shown that inability to suppress irrelevant information is associated with difficulties in sustained attention, target detection and match-to-sample paradigms in both monkeys and humans (Woods & Knight 1986; Richer et al., 1993; Chao & Knight 1995; 1998). Delivery of task irrelevant sensory information disproportionately reduces performance in patients with lateral PFC lesions. For example, presentation of brief high frequency tone pips during a tone matching delay task markedly reduces performance in PFCx patients. In essence, the patient with a lateral PFCx lesion functions in a noisy environment due to a failure in gating out extraneous sensory information.

In the cognitive domain, inhibitory deficits in cognitive tasks requiring suppression of prior learned

material are also observed in patients with lateral PFCx lesions (Shimamura et al., 1995; Mangels et al., 1996). Prior learned information now irrelevant to the task intrudes on performance. For example, words from a prior list of stimuli employed in a memory task may be inappropriately recalled during recall of a subsequent list of words. In essence, the PFC patient is unable to sweep the internal mental slate clean resulting in previously learned material maintaining an active neural representation. Inability to suppress previous incorrect responses may underlie the poor performance of PFCx subjects on a wide range of neuropsychological tasks such as the Wisconsin Card Sorting Task and on Stroop Task (Shimamura et al., 1992). Interestingly, there is some evidence that inhibitory failure extends to some aspects of motoric control. For instance, lateral PFC damage results in a deficit in suppressing reflexive eye movements to task irrelevant spatial locations (Guitton et al., 1985).

d. Working memory/attention: Working memory and attention are core concepts necessary to understand lateral PFCx function. Working memory refers to the ability to maintain information over a delay and to manipulate the contents of this short-term memory storage system. Working memory is ubiquitous to many cognitive tasks. A trivial example of working memory

would be remembering a phone number just obtained from the operator. This task would only require maintenance of the numbers over a few second period and would typically not be impaired in unilateral disease. However, if one were asked to remember the same number over the same few second delay but now also respond at the end of the delay as to whether this number matched a number given a few minutes previously, deficits would emerge in patients with lateral PFCx disease. In the second situation, both maintenance and manipulation of the contents of working memory are required and both of these are dependent on lateral PFCx. Experimental findings provide a critical link between the animal and human working memory literature. Monkeys with bilateral frontal lesions involving the sulcus principalis, proposed to be equivalent to human lateral PFCx (Brodmann areas 9 and 46: Rajkowska & Goldman-Rakic, 1995a,b), are severely impaired at delayed response tasks (Jacobsen, 1935). In delayed response tasks, information critical to perform a certain task is initially presented. The experimenter then interposes a delay period before the animal or human is allowed to perform the task. For successful performance, the information must be reliably held in a short-term working memory buffer during the delay period. Ablation, cryogenic depression or dopamine depletion in the sulcus principalis area results in an inability for

the monkey to retain the critical information at intervals as short as one second (Funahashi et al., 1993).

Subsequent animal research revealed that problems with inhibition of extraneous inputs contributed to the delayed response deficit. Simple maneuvers such as turning off the lights in the laboratory or mildly sedating the animal, which would typically impair performance in intact animals, improved delay performance in prefrontal lesioned animals. These observations led to the formulation of the distractibility hypothesis (Malmo, 1942; Bartus & Levere, 1977). This postulates that prefrontal patients are unable to suppress responses to irrelevant stimuli during delay tasks. Impairments in inhibitory control in prefrontal patients and fMRI evidence linking lateral PFCx to inhibitory control provides further support for the prefrontal-distractibility hypothesis. Successful performance on the delayed response task of course requires more than inhibitory control. Subjects must select and activate distributed brain regions depending on task specific parameters. Data from neurological patients has revealed that lateral PFCx modulates excitatory pathways projecting into subregions of visual and auditory association cortices during attention and working memory tasks. In accord with these physiological deficits in

inhibition and excitation, prefrontal patients are distractible and unable to maintain the focus of attention.

Working memory tasks in humans, widely viewed as dependent on lateral PFCx, share a core task structure with the monkey delayed response task. Single unit, lesion, ERP, blood flow and neural modelling (Funahashi et al., 1993, Chao & Knight, 1998, Jonides et al., 1993, Cohen et al., 1996, Rainer et al., 1998a,b) have shown that lateral PFCX is required to perform any task requiring a delay. Thus, delayed response tasks and working memory share some common neural mechanisms in animals and man. Despite the clear link between working memory, delayed response performance and PFCx there have been a limited number of experimental studies on working memory capacity in humans with PFCx lesions. Moreover, working memory tasks are infrequently employed in clinical neuropsychological work. However, all studies examining working memory in patients with lateral PFCx lesions have reported deficits (Chao & Knight, 1995, 1998; Stone et al., 1998; Harrington et al., 1998).

Prefrontal patients are also impaired in their ability to focus attention on task-relevant stimuli (Knight et al., 1981; Damasio, 1985; Woods & Knight, 1986). It should be noted that attention deficits are often more severe after right PFCx damage. Right

prefrontal patients show electrophysiological and behavioral evidence of a dense hemi-inattention to left ear stimuli (Woods & Knight 1986) in accord with the human hemi-neglect syndrome which is more common after right prefrontal or temporal-parietal lesions (Kertesz & Dobrolowski, 1981; Mesulam, 1981, 1998). Increased size of the right frontal lobe in humans may provide the anatomical basis for the hemi-inattention syndrome in humans. In this view the left hemi-neglect syndrome subsequent to right temporal-parietal damage may be due to remote effects of disconnection from asymmetrically organized prefrontal regions.

e. Novelty processing: The capacity to detect novelty in the stream of external sensory events or internal thoughts and the ability to produce novel behaviors is crucial for new learning, creativity and flexible adjustments to perturbations in the environment. Indeed, creative behavior in fields extending from science to the arts is commonly defined in direct relation to the degree of novelty. Prefrontal patients have problems with the solving of novel problems (Godfrey & Rousseaux, 1997; Goldberg et al., 1994) and the generation of novel behaviors (Daffner et al., 2000a,b). In advanced disease indifference, loss of creativity and deficits in orienting to novel stimuli emerge. In accord with these clinical observations,

prefrontal damage results markedly reduces the scalp electrophysiological response to unexpected novel stimuli in the auditory (Knight, 1984; Knight & Scabini, 1998), visual (Knight 1997) and somatosensory modalities (Yamaguchi & Knight, 1991b; Yamaguchi & Knight, 1992). The physiological link between PFCx and novelty processing will be expanded in the physiology section.

f. Behavioral monitoring: Behavioral output is constantly monitored so the incorrect responses can be detected and corrected. One notices this system in operation in everyday behavior such as reaching for the wrong object on a table and attempting to on-line correct the incorrect movement. Another example might be attempting to stop a swing at a baseball pitch that is not in the strike zone. One might extend this notion to the monitoring of complex cognitive and social exchange. For instance, two linked classes of higher level cognitive operations referred to as simulation behavior and reality checking are proposed to be impaired after lateral PFCx damage (Knight & Grabowecky, 2000). Simulation refers to the process of generating internal models of external reality. These models may represent an accurate past or an alternative past, present, or future and include models of the environment, of other people, and of the self. Reality

checking refers to processes that monitor information accrued from interactions with the external world in an effort to accurately represent their spatio-temporal context. These monitoring processes are critical for discriminating between simulations of alternate possibilities and veridical models of the world. Simulation and reality checking are considered "supervisory" (Shallice, 1988), or "executive" (Baddeley & Wilson, 1988; Milner & Petrides, 1984; Stuss & Benson, 1986) and are essential for behavior to be integrated, coherent, and contextually appropriate. Simulation behavior and reality checking are necessary for permitting actions to be dissociated from current environmental constraints. They permit humans to create mental representations of the world that may either draw on prior experience be entirely innovative. A patient who cannot simulate alternatives to a situation becomes "stimulus bound" (Luria, 1966; Lhermitte, 1986; Lhermitte et al., 1986) and is incapable of responding flexibly. Without reality checking, a patient cannot discriminate between internally generated possibilities and the model of the external world as it currently exists. Simulation and reality checking work in concert, allowing humans to simulate manipulations of the external environment, evaluate the consequences of those manipulations, and act on the results of those simulations.

Stimulus bound behavior is typical in PFCx patients (Luria, 1966; Lhermitte, 1986). The patients studied by Lhermitte and colleagues included large lateral PFCx lesions that extended into the orbital and basal ganglia regions in some subjects. Thus, precise behavioral-anatomical conclusions must be tempered. Objects placed in front of prefrontal patients in the Lhermitte studies are picked up and used (utilization behavior) without the patient being asked to do so (Lhermitte, 1986). Behavior of the experimenter may be imitated, even when this behavior is bizarre and socially inappropriate. Thus, patients with frontal lesions appear excessively bound by environmental cues. Patients with prefrontal cortex lesions have also been described as lacking insight and foresight, as incapable of planning either for the near or distant future, and as deficient in creativity (Ackerly & Benton, 1948; Eslinger & Damasio, 1984; Hebb & Penfield, 1940; Damasio, 1985). This set of abnormal behaviors may be a consequence of a deficit in the ability to simulate alternative scenarios of the current situation. Once again precise behavioral-anatomical conclusion cannot be obtained since clear lesion definition is only provided in the Damasio cohort with predominantly orbital damage.

The term "reality checking" refers to those aspects of monitoring the external world that have been

called "reality testing" when they concern the present, and "reality monitoring" when they concern the past. Reality checking includes both an awareness of the difference between an internally generated alternate reality and a current reality, and the maintenance of a true past in the presence of counterfactual alternatives that one might construct. Reality checking is essential for simulation processes to be carried out without compromising the ability to respond to the objective environment. Simulation processes generate an alternate reality that must be evaluated in relation to its divergence from the current reality. Memories are created for both events experienced in the world and events experienced through internally constructed simulations. These two sources of memories must be treated differently in order for them to be used effectively. Given that both internal and external events create memory representations, what cues differentiate our internal models of reality from our internal simulations of reality? Johnson and Raye (1981) studied normal subjects abilities to discriminate between memories of external events and of internally generated events. Rich memory traces with many sensory features were ascribed to external experience. Memories of external events tend to be more detailed and have more spatial and temporal contextual information. Internally generated memories

tend to be abstract and schematic, lacking in detail. These two memory representations form overlapping populations, and similar internal and external events may become confused. Reality checking involves a continual assessment of the relationship between behavior and the environment. As an individual acts on the environment, the consequences of the action must be incorporated into existing plans. If the environment deviates from expectations, one needs to detect this change and plans must be reassessed. It is proposed that these processes of continual reality checking and simulation are impaired in patients with frontal lobe lesions (Knight & Grabowecky, 2000). There is a paucity of neuropsychological literature linking simulation and reality monitoring to PFCx, although some data indicates that monitoring in memory is related to dorsolateral areas, more on the right (Stuss et al., 1994). Reality monitoring has also been proposed as a major mechanism underlying different disturbances of self-awareness (Stuss, 1991; Stuss et al., 2001b).

Physiology

Physiology research strongly supports, and extends, the results demonstrated in the neuropsychological literature. The physiological literature demonstrates the temporal unfolding of frontal lobe processes. In

this section, we will emphasize that basic concepts such as inhibitory and excitatory control, a bias to novelty and response monitoring can provide useful physiological constructs to begin to understand PFCx function.

a. Inhibitory control: PFCx inhibitory control of subcortical (Edinger et al., 1975) and cortical regions has been documented in a variety of mammalian preparations (Alexander et al., 1976; Skinner & Yingling, 1977; Yingling & Skinner, 1977). Galambos (1956) provided the first physiological evidence of an inhibitory auditory pathway in mammals with the description of the brainstem olivo-cochlear bundle. The olivo-cochlear bundle projects from the olivary nucleus in the brainstem to the cochleus in the inner ear. Stimulation of this bundle results in inhibition of transmission from the cochlea to the brainstem cochlear nucleus as measured by reductions in evoked responses in the auditory nerve. This pathway provides a system for early sensory suppression in the auditory system. The evidence for sensory filtering at the cochlear or brainstem level in humans is controversial, with most laboratories finding no evidence of attention-related manipulation of the brainstem auditory evoked response (Woods & Hillyard, 1978; Woldorff & Hillyard, 1991).

Subsequent research in the 1970's reported evidence of a multi-modal prefrontal-thalamic inhibitory system in cats that regulates sensory flow to primary cortical regions. Reversible suppression of the cat PFC by cooling (cryogenic blockade) increased the amplitudes of evoked responses recorded in primary cortex in all sensory modalities (Skinner & Yingling, 1977; Yingling & Skinner, 1977). Conversely, stimulation of the thalamic region (nucleus reticularis thalami) surrounding the sensory relay nuclei resulted in modality specific suppression of activity in primary sensory cortex. This effect is also observed in all sensory modalities. These data provided the first physiological evidence of a prefrontal inhibitory pathway regulating sensory transmission through thalamic relay nuclei. This prefrontal-thalamic inhibitory system provides a mechanism for modality specific suppression of irrelevant inputs at an early stage of sensory processing. As noted, this system is modulated by an excitatory lateral PFCx projection to the nucleus reticularis thalami, although the precise course of anatomical projections between these structures is not well understood. The nucleus reticularis thalami in turn sends inhibitory GABA-ergic projections to sensory relay nuclei, providing a neural substrate for selective sensory suppression (Guillery et al., 1998).

There is also evidence in humans that the PFCx exhibits control on other cortical and subcortical regions. For example, ERP studies in patients with focal PFCx damage has shown that primary auditory and somatosensory evoked responses are enhanced (Knight et al., 1989a; Yamaguchi & Knight, 1990; Chao & Knight, 1998) suggesting disinhibition of sensory flow to primary cortical regions. In a series of experiments, task irrelevant auditory and somatosensory stimuli (monaural clicks or brief electric shocks to the median nerve) were presented to patients with comparably sized lesions in lateral PFCx, the temporal-parietal junction, or lateral parietal cortex. Evoked responses from primary auditory (Kraus et al., 1982) and somatosensory (Leuders et al., 1983; Sutherling et al., 1988; Wood et al., 1988) cortices were recorded from these patients and age-matched controls. Damage to primary auditory or somatosensory cortex in the temporal-parietal lesion group reduced the early latency (20-40 msec) evoked responses generated in these primary cortical regions. Posterior association cortex lesions in the lateral parietal lobe sparing primary sensory regions had no effect on early sensory potentials and served as a brain-lesioned control group. Lateral PFC damage resulted in enhanced amplitudes of both the primary auditory and somatosensory evoked responses (Knight et al., 1989a;

Yamaguchi & Knight, 1990; Chao & Knight, 1998). Spinal cord and brainstem potentials were not affected by lateral PFC damage, suggesting that the amplitude enhancements were due to abnormalities in either a prefrontal-thalamic or a prefrontal-sensory cortex mechanism. These results are in accord with the findings reported in the 70's by Yingling and Skinner in their cat model of PFC dependent sensory gating.

Behavioral and imaging evidence of the involvement of lateral PFC in inhibitory control does not provide direct support for the hypothesis that there are inhibitory signals from PFC directed either toward early sensory cortices or excitatory PFC inputs to the Gabaergic nucleus reticularis thalami resulting in a net inhibitory control of sensory flow. In contrast, the combined ERP/patient studies as described are able to measure the temporal dynamics of inhibitory control and provides powerful evidence in humans that the PFC provides a net inhibitory regulation of early sensory transmission.

b. Excitatory control: Attention allows us select from the myriad of closely spaced and timed environmental events. Attention is crucial for virtually all cognitive abilities. Indeed, recent cognitive theorists have begun to refer to attention/working memory highlighting that these two constructs are inextricably

linked. In addition to suppressing response to irrelevant stimuli, subjects must excite and sustain neural activity in distributed brain regions in order to perform attention/working memory tasks. Neural modelling employing prefrontal excitatory modulation of distributed brain regions has successfully modeled prefrontally mediated behaviors in normals and prefrontal dysfunction in schizophrenia (Cohen & Servan-Schrieber, 1992; Cohen et al., 1996). These authors postulate that dorsal PFCx controls task context by regulating posterior association cortex through excitatory connections. Desimone (1998) has proposed a competition based model of visual attention wherein visual neurons involved in processing of different aspects of the visual world are mutually inhibitory. In this view an excitatory signal to selective visual neurons would result in inhibition of nearby non-task relevant visual neurons resulting in a sharpening of the attentional focus. Patients with focal prefrontal damage fail to maintain excitatory control of posterior association cortex resulting in failures in attention/working memory.

Selective attention to an ear, a region of the visual field or a digit increases the amplitude of sensory evoked potentials to all stimuli delivered to that sensory channel (Hillyard et al., 1973). There is evidence that attention reliably modulates neural

activity at early sensory cortices including secondary and perhaps primary sensory cortex (Woldorff et al., 1993; Grady et al., 1997; Somers et al., 1999; Steinmetz et al., 2000). Visual attention involves modulation in the excitability of extrastriate neurons through descending projections from hierarchically ordered brain structures (Hillyard & Anllo-Vento, 1998). Single cell recordings in monkeys (Fuster et al., 2000; Funahashi et al., 1993; Rainer et al., 1998a,b), lesion studies in humans (Knight, 1997; Nielsen-Bohlman & Knight, 1999; Knight et al., 1998; Barcelo et al., 2000) and monkeys (Rossi et al., 1999) and blood flow data (McIntosh et al., 1994; Buchel & Friston, 1997; Chawla et al., 1999; Rees et al., 1997; Kastner et al., 1999; Corbetta et al., 1998; Hopfinger et al., 2000) have linked PFCx to control of extrastriate cortex during visual attention.

Modulation of visual pathway activity has been extensively investigated in humans using event-related potentials (ERPs). Attended visual stimuli evoke distinct ERP signatures. Attention enhances extrastriate ERP amplitudes for all stimuli in an attended channel with changes apparent in the initial 100-200 milliseconds after delivery of a to be attended visual stimulus (Heinze et al., 1994; Mangun, 1995; Martinez et al., 1999; Woldorff et al., 1997). These early human ERP components have been linked to

increased firing of extrastriate neurons in monkeys (Luck et al., 1997) providing a powerful parallel between the human and animal literature.

From ERP studies in patients with lateral PFC damage, evidence has accumulated that human lateral PFC regulates attention dependent extrastriate neural activity through three distinct mechanisms. These mechanisms include: (1) an attention dependent enhancement of extrastriate cortex, (2) a tonic excitatory influence on ipsilateral posterior areas for all sensory information including attended and non-attended sensory inputs and (3) a phasic excitatory influence of ipsilateral posterior areas to correctly perceived task relevant stimuli. In these ERP studies, patients with unilateral PFC lesions (centered in Brodmann's areas 9 and 46) performed a series of visual attention experiments. In the task, non-target stimuli consisted of upright triangles, which were presented rapidly to both visual fields (4 degrees from the fovea). Targets were rarely presented (10% of all stimuli) and consisted of inverted triangles presented randomly in each visual field. In one experiment, patients and age-matched controls were asked to press a button whenever a target appeared in either visual field (Barcelo et al., 2000). In another experiment, subjects were required to allocate attention to only one visual field (Yago & Knight, 2000).

An interesting pattern of results emerged from these two experiments. First, both experiments revealed that lateral PFC provides a tonic excitatory influence to ipsilateral extrastriate cortex. Specifically, the P1 component of the visual ERP is markedly reduced in amplitude for all stimuli presented to the contralesional field. Importantly, this tonic influence is attention independent since a reduced P1 potential in extrastraite cortex was found ipsilateral to PFC damage for all visual stimuli (attended and non-attended targets and non-targets) presented to the contralesional field This tonic component may be viewed as a modulatory influence on extrastriate activity.

As noted previously, it is well known that attention increases the amplitude of extrastriate ERPs in normals with effects onsetting by about 50-100 milliseconds post stimulus delivery. The second experiment (allocating attention to only one visual field) provided evidence of the temporal kinetics of prefrontal-extrastriate interactions. In essence, attention effects on extrastriate cortex were normal in the first 200 milliseconds of processing in PFCx patients and severely disrupted after 200 milliseconds (Yago & Knight, 2000). This finding suggests that other cortical areas are responsible for attention dependent regulation of extrastriate cortex in the first 200 milliseconds. A candidate structure for this influence

based on the neuroimaging and clinical literature would be inferior parietal cortex. It is conceivable that inferior parietal cortex is responsible for the early reflexive component of attention whereas PFC is responsible for more controlled and sustained aspects of visual attention onsetting after the parietal signal to extrastriate cortices.

The third observation from these experiments is the finding that lateral PFC has been shown to send a top-down signal to extrastriate cortex when a task relevant event is detected during an attention task. There are two types of stimuli typically presented in an attended channel, one task irrelevant and one requiring detection and a behavioral response. The amplitude of both the irrelevant and relevant stimuli is enhanced in an attended channel. As discussed previously, PFCx is responsible for regulating this channel specific attention enhancement. When a relevant target event is detected in an attended channel another distinct electrophysiological event is generated in addition to the channel specific enhancement. This top-down signal onsets at about 200 milliseconds after a correct detection, extends throughout the ensuing 500 milliseconds and is superimposed on the channel specific ERP attention enhancement (Suwazono et al., 2000). Damage to lateral PFCx results in marked decrements in the top-down signal accompanied by

behavioral evidence of impaired detection ability (Barcleo et al., 2000).

The temporal parameters of this human PFCx-extrastriate attention modulation are in accord with single unit recordings in monkeys that reveal enhanced prefrontal stimulus detection-related activity 140 ms post-stimulus onset (Rainer et al., 1998a,b) and other studies revealing top-down activation of inferior temporal neurons 180-300 ms post-target detection (Tomita et al., 1999). Finally, there is a vigorous debate in the single unit and fMRI research domains on the whether lateral PFCx is organized by modality (Wilson & Goldman-Rakic, 1993; Courtney et al., 1998; Romanski et al., 1999) or whether lateral PFCx, and more particularly dorsolateral PFCx, functions in a modality independent executive manner during working memory and object and spatial integration (Rao et al., 1997; Assad et al., 1998; D'Esposito et al., 1999b; Miller, 1999; Fuster et al., 2000). Evidence from PFCx lesioned patients (Mulleret al,, in press) supports the notion that the lateral portion of PFCx may function in a task independent manner to control and integrate distributed neural activity in some cognitive tasks.

Projections from prefrontal areas 45 and 8 to inferior temporal (IT) areas TE and TEO have been demonstrated in monkeys (Webster et al., 1994) providing a possible glutamatergic pathway by which

lateral prefrontal cortex could facilitate visual processing. A similar failure of prefrontal excitatory modulation is observed in the auditory modality. Prefrontal lesions markedly reduce the attention sensitive N100 component throughout the hemisphere ipsilateral to damage (Chao & Knight, 1998). There are well-described prefrontal projections to the superior temporal plane, which may subserve this excitatory PFCx-auditory cortex input (Alexander et al., 1976). The auditory and visual data provide clear evidence that lateral PFCx cortex is crucial for maintaining distributed intrahemispheric neural activity during auditory and visual attention/working memory tasks.

c. Novelty processing: The neural mechanisms of novelty detection and the production of novel behavior are receiving increasing attention. Multiple experimental approaches have focussed on the biological mechanisms of novelty processing. Behavioral and electrophysiological data have shown that novel events are better remembered (Von Restorff, 1933; Karis et al., 1984). On a molecular basis, genetic studies of novelty seeking behavior in humans have provided a link to the short arm of chromosome 11 and the dopamine D4 receptor gene (Benjamin et al., 1996; Ebstein et al., 1996). Integrative neuroscience approaches including neuropsychological, electrophysiological and cerebral

blood flow techniques have revealed that a distributed neural network including lateral PFCx, temporal-parietal junction, hippocampus and cingulate cortex is engaged both by novelty detection and during the production of novel behaviors.

Studies in normals have shown that novel items generate a late-positive ERP peaking in amplitude at about 300-500 milliseconds that is maximal over the anterior scalp. This novelty ERP is proposed to be a central marker of the orienting response (Sokolov, 1963; Courchesne et al., 1975; Knight, 1984; Yamaguchi & Knight, 1991; Bahramali et al., 1997; Escera et al., 1998). ERP evidence derived from neurological patients with lateral PFCx damage (Yamaguchi & Knight, 1991,1992; Verleger et al., 1994; Knight, 1996; Knight, 1997; Knight et al., 1989b) and intracranial ERP recordings in pre-surgical epileptics (Halgren et al., 1998) has revealed that a distributed neural network including lateral and orbital PFCx, hippocampal formation, anterior cingulate and temporal-perietal cortex is involved in detecting and encoding novel information (Halgren et al., 1998). Neuroimaging results have confirmed the lesion and intracranial evidence on the neuroanatomy of the novelty processing system (Tulving et al., 1994; 1996; Stern et al., 1996; McCarthy et al., 1997; Menon et al., 1997; Opitz et al., 1999a,b; Yoshiura et al., 1999; Linden et al.,

1999; Downar et al., 2000; Clark et al., 2000; Kiehl et al., in press). The lateral PFCx contribution is a key component of this novelty network. For instance, unlike posterior cortical and hippocampal activity, PFCx novelty activation recorded with ERPs or neuroimaging habituates to repeated exposures to novel events and is modality independent (Knight, 1984; Yamaguchi & Knight, 1991; Knight & Scabini, 1998; Raichle et al., 1994; Petersson et al., 1999). Importantly, lateral PFCx also appears to initiate the novelty detection cascade prior to activation of other brain regions as revealed by lesion-ERP studies. If the novel event is sufficiently engaging, posterior cortical and medial temporal regions are recruited for further processing (Ahlo et al., 1994; Knight, 1996; Alain et al., 1998).

Novelty, of course, is an elusive concept dependent on both the sensory parameters of an event and the context in which it occurs. As an example, the unexpected occurrence of a visual fractal would typically engage the novelty system. Conversely, if one would were presented with a stream of visual fractals and suddenly a picture of an apple occurred this would also drive the novelty system. In the first case the visual complexity of the fractal drives the novelty response. In the second situation the local context of repeated fractals would be violated by the insertion of

a picture of an apple and this would also engage the novelty network. Sensory parameters and local context have powerful effects on electrophysiological and behavioral response to novelty (Comerchero & Polich, 1998, 1999; Katayama & Polich, 1998) and this effect is also dependent on lateral PFCx (Suwazono et al., 2000; Barcelo & Knight, 2000).

Neuroimaging findings in normal also support a critical role in PFCx in responding to novel events and solving new problems (See Duncan & Owen, 2000 for a review). These neuropsychological, ERP and neuroimaging findings support a central role of lateral prefrontal cortex in the processing of novelty (Godfrey & Rousseaux, 1997; Kimble et al., 1965). Single unit data from monkeys has also supports a prefrontal bias towards novelty (Rainer & Miller, 2000)

d. Response monitoring: Major advances have developed in our understanding of the neural basis of implementing neural control of behavioral output. First, the discovery of an ERP response referred to as the error-related negativity (ERN) has provided an online measure of a subject's performance monitoring (Gehring et al., 1993). Second, neuroimaging data has implicated a prefrontal-cingulate network in error response monitoring and correction (McDonald et al., 2000; Kiehl et al., 2000). Finally, lesion-ERP

evidence obtained from patients with lateral PFCx damage supports the notion that PFCx controls cingulate related error activity (Gehring & Knight, 2000). Cohen and colleagues have suggested that the role of PFCx in response monitoring is to provide a stable representation of the task at hand (Carter et al., 1999; Cohen et al., 2000). This permits better suppression of distracting information lessening the chance of an error. These authors suggest that the cingulate ERN and fMRI blood flow response to errors is a manifestation of conflict detection by the anterior cingulate (areas 24 and 32). Thus, if the representation of the task is weakened by PFCx damage, conflict increases on all trials and an ERN is generated to all stimuli. This view places the PFCx in an executive position regarding anterior cingulate function. An alternative model consistent with the accrued data posits that the activity reflected in the ERN represents an affective or motivational signal. In this view, the cingulate signal as measured by the ERN would serve an alerting function that mobilizes affective systems, rather than immediate corrective action, perhaps via cingulate connections with the amygdala and brainstem autonomic nuclei. This conception of the ERN would be consistent with dissociations between ERN activity and compensatory behavior and with reports of medial frontal ERN-like

activity in response to stimuli with negative hedonic significance (Vidal et al., 2000; Falkenstein et al., 2000; Luu et al., in press).

Case Report, the Lateral Prefrontal Syndrome: Patient W.R.

A case study exemplifies the effects of lateral prefrontal lesions. W.R., a 31-year-old lawyer, presented to the Neurology clinic with family concern over his lack of interest in important life events. When queried as to why he was in the clinic, the patient stated that he had "lost his ego". His difficulties began four years previously in 1978 when he had a tonic-clonic seizure after staying up all night and drinking large amounts of coffee while studying for midterm exams in his final year of law school. An extensive neurological evaluation conducted at that time at the NIH including EEG, CT scan, and PET scan were all unremarkable. The diagnosis of generalized seizure disorder exacerbated by sleep deprivation was given and he was placed on dilantin. W.R. graduated from law school but did not enter a practice because he couldn't decide where to take the bar exam. Over the next year he worked as a tennis instructor in Florida. He then broke off a 2-year relationship with a woman and moved to California to live near his brother who was also a lawyer. His brother reported that he was indecisive, procrastinated

in carrying out planned activities and that he was becoming progressively isolated from family and friends. The family attributed these problems to a "mid-life crisis". Four months prior to neurological consultation W.R.'s mother died. At the funeral and during the time surrounding his mother's death the family noted that he expressed no grief regarding his mother's death. The family decided to have the patient re-evaluated. W.R. was pleasant but somewhat indifferent to the situation. General neurological exam was unremarkable. A mild snout reflex was present. W.R. made both perseverative and random errors on the Luria hand-sequencing task and was easily distracted during the examination. His free recall was two out of three words at a five-minute delay. He was able to recall the third word with a semantic cue. On questioning about his mother's death W.R. confirmed that he did not feel any strong emotions, either about his mother's death or about his current problem. The patient's brother mentioned that W.R. "had never lost it" emotionally during the week after his mother's death, at which point W.R. immediately interjected "and I'm not trying not to lose it." Regarding his mother's death, he stated "I don't feel grief, I don't know if that's bad or good." These statements were emphatic, but expressed in a somewhat jocular fashion (witzelsucht). W.R. was asked about changes in his

personality. He struggled for some minutes to describe changes he had noticed, but did not manage to identify any. He stated "Being inside, I can't see it as clear." He was distractible and perseverative, frequently reverting to a prior discussion of tennis, and repeating phrases such as "yellow comes to mind" in response to queries of his memory. When asked about either the past or the future, his responses were schematic and stereotyped. He lacked any plans for the future, initiated no future oriented actions and stated "It didn't matter that much, it never bothered me" that he never began to practice law. A CT scan revealed a left lateral prefrontal glioblastoma, which had grown through the corpus callosum into the lateral right frontal lobe. After discussion of the serious nature of the diagnosis, W.R. remained indifferent. The family were distressed by the gravity of the situation and showed appropriate anxiety and sadness. Interestingly, they noted that their sadness was alleviated when in the presence of W.R.

Discussion of Patient W.R.**:** W.R. remained a pleasant and articulate individual despite of his advanced frontal tumor. However, he was unable to carry out the activities to make him a fully functioning member of society. His behavior was completely constrained by his current circumstances. His jocularity was a

reaction to the social situation of the moment, and was not influenced by the larger context of his recent diagnosis. He appeared to have difficulty with explicit memory and source monitoring, with little confidence in his answers to memory queries, complicated by frequent intrusions from internal mental representations. Thus, metamemory was impaired and he was unable to sustain working memory processes. He was distractible and was unable to sustain normal working memory. Perseverative errors were common in both the motor and cognitive domain. A prominent aspect of his behavior was a complete absence of counterfactual expressions. In particular, WR expressed no counterfactual emotions, being completely unable to construe any explanation for his current behavioral state. He seemed unable to feel grief or regret, nor was he bothered by their absence even though he was aware of his brother's concern over his absence of emotion. These observations suggest that damage in lateral PFCx leads to deficits in reality monitoring, a process that is essential for the normal planning and decision-making functions necessary for normal human behavior. Behavioral analysis of this case highlights the role of lateral PFCx in virtually all aspects of human cognition.

Orbitofrontal Cortex

Introduction

In the simplest formulation, lateral prefrontal cortex may be viewed as the central executive for cognitive control with orbitofrontal cortex serving as the central executive for emotional and social control. In contrast to lateral prefrontal damage, orbitofrontal damage spares many cognitive skills but dramatically affects all spheres of social behavior (Stone et al., 1998; Bechera et al., 1998). The orbitofrontal patient is frequently impulsive, hyperactive and lacking in proper social skills despite showing intact cognitive processing on a range of tasks typically impaired in the lateral PFCx lesioned patient. In some cases the behavioral syndrome is so severe that the term acquired sociopathy has been used to describe the resultant personality profile of the orbitofrontal patient. However, unlike true sociopaths, orbitofrontal patients typically feel remorse for their inappropriate behavior. Primitive reflexes such as snout, suck, rooting and grasp are not often observed. Severe social and emotional dysfunction is typically observed only in bilateral orbital disease as might be observed after head trauma, orbital meningioma or certain degenerative disorders such as frontal-temporal dementia. Thus, there appears to be redundancy in both lateral and orbital human PFCx with one intact PFCx

being able to sustain many aspects of either cognitive and social function. Similar to recent advances in segregating function of lateral PFCx into dorsal and ventral divisions, progress has been made in parcellation of orbital PFCx function. The ventromedial portion of the orbital PFCx has associated with the use of internal autonomic states in the guidance of goal directed behavior. The ventromedial portion of human orbital PFCx has also been proposed to be involved in inhibitory processing of emotional stimuli. The lateral portions of orbital PFCx have been implicated in the rapid establishment of reward-punishment associations (Shimamura, 2000; See Rolls this volume). Tests of social and cognitive skills reveal a double dissociation between lateral and orbital PFCx damage. Lateral PFCx damage impairs working memory and attention capacity but spares theory of mind. Conversely, orbital PFCx damage leaves working memory intact but impairs theory of mind. There is some suggestion of an important role of the polar region, but this has not yet been conclusively determined.

Disorders of emotional control and social regulation are frequent accompaniments of acquired neurological disease and are receiving increasing attention in the clinical and research arena (Stuss & Alexander, 2000). In the 1930's, Kluver & Bucy

described prominent affective and visual processing changes in monkeys with bilateral anterior temporal ablations. During this same period, Papez described the classic “Circle of Papez” or limbic brain in humans encompassing the anterior cingulate, hippocampus, septum and hypothalamus. However, the two most critical components of the human emotional control network, orbitofrontal cortex and amygdala, were not included in the original concept proposed by Papez. A seminal observation linking brain damage and personality alteration can be traced to 1848 in Cavendish, Vermont. A well-respected train company employee, Phineas Gage, was working clearing rocks necessary for the laying down of a new rail line. An unfortunate accident propelled an iron tamping rod through his skull. Remarkably, given that the rod weighed 13 pounds, was over 3 feet long and antibiotics were not yet discovered, Gage survived. However, marked changes in his previous calm and organized personality ensued. Gage became more labile and disinhibited in his behavior and was noted to use profanity and make irreverent statements. His acquaintances noted that “Gage was no longer Gage”. His problems continued unabated until he died of uncontrolled seizures 12 years later in San Francisco. Inspection of his skull indicates that the tract of the bar injured bilateral orbitofrontal cortex and the anterior portion of the

left temporal lobe. However, the role of orbitofrontal cortex in social behavior was largely neglected until the 1960's.

The most common cause of orbitofrontal and amygdala damage is closed head injury with about 100,000 people per year in the US alone experiencing a closed head injury severe enough to damage these critical brain injuries. Orbitofrontal and amygdala damage in not limited to head trauma and can also be observed in dementing disorders such as Pick's disease or fronto-temporal dementia which has been linked to abnormalities in chromosome 17 in some cases. In addition, tumors including meningiomas and gliomas can affect these areas and infections such as herpes simplex have a particular predilection for the limbic brain. Patients with an acquired non-progressive lesion such as that due to head trauma may return to a high level of pre-injury cognitive function. However, as predicted by the Gage case, patients with orbitofrontal or amygdala damage are impaired to varying degrees in emotional control, social interaction and decision making involving interpersonal choices and behaviors. Many patients are initially diagnosed incorrectly with a personality disorder when in fact they have damaged their emotional brain. Neurological examination, other than for frequent anosmia, is invariably normal if damage is restricted

to orbital PFCx and there was no significant axonal shear at the initial time of injury. Frontal release signs including snout, suck, grasp and rooting are absent. Remarkably little is known about the neural underpinnings of this severely compromised "social self".

Neuropsychology

Several investigators have provided neuropsychological data implicating orbital/ ventral-medial PFCx in emotional and social regulation (Tranel & Damasio, 1994; Bechera et al., 1994; 1997; 2000; Rolls et al., 1994; Grafman et al., 1993; Shammi & Stuss, 1999; Stone et al., 1998; Hartikainen et al., 2000). Disorders of emotional control and social regulation due to orbital PFCx dysfunction are frequent accompaniments of psychiatric disease such as obsessive compulsive disorder and drug abuse (London et al., 2000; Volkow & Fowler, 2000) as well as acquired neurological disease including head trauma, dementia and tumors. Thus, the societal costs of orbital PFCx dysfunction are immense. Developmental aspects of acquired orbital PFCx damage in children and adolescents are even less well understood than adult dysfunction (Price et al., 1990). Patients with adult acquired orbital PFCx are aware of their problems and know the actual rules of proper social behavior despite failures to properly implement

them. Childhood acquired orbital PFCx damage may result in a failure to both implement and learn the rules of proper social discourse (Anderson et al., 1999). Changes in emotional disposition are routinely observed in patients who have suffered damage to the orbitofrontal cortex. Damage to this brain region has been associated with a variety of social-emotional dysfunctions, including personality change, risk taking, impulsivity, emotional outbursts and social inappropriateness. Three theories have been proposed to explain the disordered behavior subsequent to orbital damage in humans. These include the somatic marker hypothesis put forth by Damasio and colleagues (Bechera et al., 1994; see Tranel this volume), impaired linking or reward and punishment proposed by Rolls (Rolls et al., 1994; Rolls this volume) and emotional disinhibition accompanied by enhanced central nervous system responsivity recently proposed by Rule, Shimamura and Knight (Rule et al., 1999; Shimamura, 2000).

For example, Damasio and colleagues have shown that patients with orbital PFCx lesions elicit inappropriate emotional responses and abnormal galvanic skin responses in a gambling task in which subjects must inhibit high-risk gambles (Bechera et al., 1997). These authors propose that damage in the ventromedial PFCX impairs generation of a somatic state that can be

used as a guide to control behavior. This proposal is supported by reduced anticipatory GSRs in patients with ventromedial damage. In another study a group of lateral PFCx and a group orbital PFCx patients were studied in working memory and theory of mind (TOM) tasks. TOM refers to a person's ability to infer another person's or group of person's internal mental state. TOM is viewed as one of the highest forms of social abilities. A double dissociation was observed. Lateral PFCx patients had difficulties with working memory but were not impaired on TOM tasks. Orbital PFCx patients were normal on working memory tasks but failed TOM tasks (Stone et al., 1998). This finding has been replicated and extended to indicate some potential importance of the right frontal region in another cohort of lateral and orbital lesioned patients (Stuss et al., 2001). Taken together, these findings are consistent with the notion that this brain region is intricately involved in the analysis, monitoring and control of emotionally laden stimuli and social interchange.

Physiology

Functional neuroimaging currently has had difficulty with imaging orbital PFCx due to susceptibility artifacts from nearby sinuses and a limited number of studies have been published (i.e. Schoenbaum et al., 1998; Nobre et al., 1999; Elliott et al., 2000).

Recent studies indicate success with neuroimaging of orbital regions (Doherty et al., 2001; Rolls this volume). As noted in the Neuropsychology section, three theories have been proposed to explain the disordered behavior subsequent to orbital PFCx damage in humans and all are supported by physiological data. The somatic marker hypothesis (Bechera et al., 2000) proposes that ventromedial orbital PFCx or the right sensory cortical damage impairs generation of an appropriate somatic feeling needed to guide behavior (Tranel, 1994; Bechera et al., 1997; see Tranel this volume). The somatic marker hypothesis is supported by a decreased galvanic skin response (GSR), a peripheral autonomic measure of orienting, in orbital PFCx patients. Another view proposes impairments in linking of reward and punishment (Rolls et al., 1994) and finds support from single unit, PET and some fMRI research (Elliott et al., 2000; see Rolls this volume). A third theory, the dynamic filtering hypothesis, has also been proposed to explain some components of the orbital PFCx behavioral syndrome (Rule et al., 1999; Shimamura, 2000). This theory posits that orbital PFCx patients are unable to inhibit response to certain emotional and social stimuli and is supported by enhanced ERP measures of orienting to novel emotionally laden stimuli in these patients. The enhanced central nervous system response to emotional auditory and somatosensory

stimuli in orbital PFCx patients is in accord with the disinhibited, impulsive behavior observed after orbital PFCx damage in humans and monkeys (Butter et al., 1969,1970; Roberts et al., 2000). Interestingly, Macaque monkeys with orbitofrontal lesions fail to habituate to novel auditory and visual stimuli (Butter et al., 1970). Importantly, these findings suggest regional specificity within the prefrontal cortex. ERPs to novel emotional stimuli are disinhibited patients with orbital PFCx lesions, whereas patients with lateral PFCx lesions show decreased novelty responses to these same stimuli (Knight & Scabini 1998). These results indicate that orbital patients may have an excessive central nervous response to irrelevant stimuli. Direct connections from orbitofrontal cortex to posterior parietal cortex (area 7A) have been identified (Cavada et al., 2000). Orbitofrontal cortex could be exerting inhibitory control over novelty related activity in the temporal-parietal region via these fibers. Loss of this control might contribute to the disinhibited behavior so frequently observed in these patients. Elements of all three notions of orbital function are likely correct and a more complete concept of orbital contributions to social and emotional behavior is likely to emerge in the ensuing years.

Case Report, the Orbital Prefrontal Syndrome: Patient JL

A case study exemplifies the effects of orbital PFCx lesions. Patient JL was seen in neurological consultation on the inpatient psychiatric service in 1988. He was admitted to the Psychiatric service after an altercation at an intersection where he got into a cursing and shoving match with a driver who cut him of as he was crossing a street. JL was a 42-year-old accountant with a Masters degree at the time of evaluation. He had been in excellent health until an accident at a party 13 years prior where he fell off a third floor balcony and sustained a severe coup injury to his frontal lobe. CT scanning revealed extensive bilateral damage to his orbital PFCx. Both the ventromedial and lateral portions of the orbital PFCx were destroyed. JL developed grand mal seizures after the accident, which were well controlled with dilantin. Clinical and experimental neuropsychological evaluation revealed a double dissociation between cognitive and social function. Lateral PFCx was spared and all test of cognitive function related to lateral PFCx were intact. For instance, J.L.'s IQ remained at a pre-morbid level of 128. Clinical and experimental tests of memory including measures of source and metamemory were intact. Attention capacity and working memory were excellent. In contrast to his excellent cognitive

performance, since the incident J.L. has had prominent problems in emotional and social control. He has gotten into numerous street altercations and has been arrested several times. He is socially inappropriate and notes) that he "comes on too strong" to women. Woman laboratory personnel where patient J.L. has been tested report that he is constantly coming on to them. When queried further, he reports that he might ask a woman to marry him after 1-2 days of knowing her. When asked if he thought this behavior was appropriate, patient J.L. responded no. Importantly patient J.L. knows his behavior is inappropriate but is unable to control it. J.L. is also unable to handle the financial resources that accrued as a settlement for his accident and required a conservator to manage his affairs. During the interview patient J.L. often laughed inappropriately. His neurological examination was normal including testing of language, attention, memory and perception. He admitted to obsessive compulsive behaviors such as counting the numbers on car license plates. Testing of working memory was normal but J.L. failed Theory of Mind tests, which require the ability of a person to infer another person's mental or emotional state.

Discussion of Patient J.L.: Patient J.L. manifests the typical orbital PFCx syndrome of intact executive

control of cognitive processes and severely impaired executive control of social and emotional behavior (See Rolls' and Tranel's contributions this volume). His IQ was superior and he scored well in all conventional tests of attention, memory and language. Yet, he was severely impaired in his everyday social behavior and in making appropriate life decisions as in managing his financial affairs. Remarkably, when queried about what was the appropriate social or emotional response or the proper decision regarding personal affairs, patient J.L. was able to respond correctly. His problems became evident when he had to implement on-line behavior. Explication of this apparent paradox of knowledge versus failure to implement such knowledge is a great challenge for the future.

Where are we going

What will the future bring to our understanding of prefrontal function? Given the vast expansion of prefrontal cortex in humans, explication of the function of this brain region appears to a fundamental for a complete understanding human cognition in both health and disease. Advances have been made in multiple domains. Cognitive psychology has provided a welcome

addition to the classic neuropsychological approach and new areas of behavioral theory and analysis have enriched our understanding of PFC function. We believe that the next decade will witness an even greater implementation of sophisticated cognitive theory to prefrontal research. Approaches drawn from the discipline of social cognition and from the study of behaviors such as decision making and reality monitoring, are certain to provide a broader and ecologically valid approach to understanding PFC function. This fusion of theory and experiment will provide important new insights into the role of orbital frontal cortex in social behavior. This book has provided different views on the nature of orbital frontal function in humans. We expect that Frontal Lobe 2010 will provide a more integrated view of how this vast expanse of prefrontal cortex enables the social being.

One area likely to receive increasing attention is the contribution of PFC to the evaluation and implementation of context in behavior. The notion of context is broadly has been applied to seemingly diverse areas including probability learning, social regulation and novelty detection. For instance, in the social domain, a behavior in one situation might be very appropriate while the same behavior could be quite counter productive in another situation. Humans are

able to fluidly draw on prior experience to set and implement the appropriate context for the current situation. Similarly, in the area of novelty processing the effects of local context are extremely powerful. For instance, the occurrence of a visual fractal in a stream of common visual objects would elicit a powerful novelty response to the fractal. However, the occurrence of a common object in a stream of fractals would also elicit a powerful novelty response. Research on the role of PFC in application of context dependent parameters to behavior may prove critical for understanding the role of PFC in mental flexibility.

Single unit studies in monkeys has been crucial in developing new models of PFC function. The classic ideas of segregation of function have been challenged by findings that PFC neurons are more plastic than traditional views might suggest. The concept of rapid learning and plasticity of PFC neurons is in accord with the neurological literature revealing profound alterations in mental flexibility in patients with PFC damage. This single unit research dovetails nicely with the explosion of insights drawn from fMRI research. Novel insights into segregation versus integration of function in subregions of prefrontal has fueled the debate. We now enjoy a powerful interplay between human and monkey research that heralds major advances on the understanding of cognitive processes.

We certainly believe that Frontal Lobe 2010 will provide a clearer answer to the question of segregation versus overlapping of function in prefrontal cortex. We predict that as in many scientific controversies, the final answer will blend data drawn from both camps.

How these executive processes are implemented at a neural level is perhaps the greatest challenge for a true understanding of PFC function. We certainly hope that Frontal Lobe 2010 will fill in the crucial gaps in our understanding this central aspect of human cognition. The notion that engagement of parallel inhibition and excitation can be a useful construct for understanding PFC function is receiving support from single unit, lesion, ERP and functional neuroimaging research. Advances in the fusion of these experimental approaches may provide new insights into both the temporal and spatial aspects of PFC dependent executive control. Consideration of the neuropharmacology of PFC function will be necessary for a complete understanding of prefrontal function and we hope this volume has focussed attention on this needed part of the frontal lobe riddle.

The nature of the neural code both at the local single unit level and the systems interaction level is, of course, central to a complete picture of PFC function. How do single units in a subregion of PFC interact to produce the needed output signal to other

brain regions? Are neurons concerned with inhibition intertwined with those involved in excitation? What is the nature of the output signal from PFC to other neural regions? Is it a coherent burst of neural activity such as a gamma oscillation? These questions are only beginning to be addressed but promise great insights into how PFC implements executive control.

What else might be discussed at Frontal Lobe 2010? Certainly we are in the middle of an explosion of new methods to image the human brain and this exponential progress is likely to continue. Fusion of electrophysiological and functional magnetic resonance methods promises new insights into the temporal-spatial dynamics of human cognition. Optical imaging techniques have developed which may improve temporal and spatial resolution. Perhaps as important, optical techniques can be used to image infants extending the field of imaging to the gamut of human development. We wouldn't be surprised if Frontal Lobe 2010 yields novel information on the development of the frontal lobe from infancy to adulthood.

Finally, why bother with all this fuss about the prefrontal cortex? Is it because scientists deserve to study what fascinates them? Certainly that brings and keeps many researchers to the frontal lobe table. However, that is not the true reason we spend our time studying prefrontal cortex. Rather, we know that this

brain region holds the key to understanding normal and disordered cognition with profound implications for both the individual and society.

"The frontal lobes have provided the tools to now study how tools are actually devised in the human mind."

Stuss and Knight 2001

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