Chapter 6

LATERAL AND ORBITAL PREFRONTAL CORTEX CONTRIBUTIONS TO ATTENTION

KAISA M. HARTIKAINEN AND ROBERT T. KNIGHT
Department of Psychology and Helen Wills Neuroscience Institute, University of California, Berkeley, CA, USA

1. PREFRONTAL CORTEX

The prefrontal cortex (PFCx) can be divided into the lateral, orbital and medial PFCx, which all contribute to attentional and novelty processing and flexible behaviors. The cytoarchitecture of lateral prefrontal cortex (LPFCx) is highly organized, differentiated, distinctly layered, granular isocortex while the orbitofrontal cortex (OFCx) is structurally more heterogeneous, less differentiated, agranular limbic cortex (Barbas, 2000). The LPFCx is interconnected with parietal/occipital visual association areas, posterior parietal heteromodal areas, and inferior temporal visual association areas (Kaufer & Lewis, 1999). Other main circuitries of the LPFCx include reciprocal connections with the cingulate and the orbitofrontal cortex. In contrast, the OFCx has extensive direct and indirect connections with limbic areas such as the amygdala complex, hypothalamus, and the hippocampal formation (Cavada et al., 2000), with additional interactions to the inferior temporal visual association areas and LPFCx (Kaufer & Lewis, 1999). The main connections of the LPFCx to association areas and the OFCx to limbic areas determine the primary behavioral functions of these areas, with the LPFCx well-suited for attentional and executive function and the OFCx for affective and reward-related functions.

The PFCx allows for departure from automated actions (Mesulam, 1986). Adjusting behavior depending on the current situation, social context, and foresight requires inhibiting responding to the most salient stimuli as well as inhibiting previously acquired responses. Thus, inhibition is an essential
component of cognitive flexibility and creative behaviors that tend to be compromised in patients with PFCx damage. Response inhibition has been suggested to be a general PFCx function that operates across different cognitive processes and brain regions (Roberts & Wallis, 2000). Both the lateral and the orbital PFCx perform general inhibitory functions, but the distinct cognitive processes that are modulated by these cortical areas differ and reflect the distinct neural circuitries in which they are imbedded. Dias et al. (1996, 1997) have suggested that the lateral prefrontal cortex is responsible for inhibitory control of attentional selection, while the orbitofrontal cortex is responsible for inhibitory control of affective responses. Hence, damage to the lateral prefrontal cortex leads to impairment in shifting attention from one perceptual dimension to another while damage to orbitofrontal cortex leads to an inability to alter behavior when the emotional significance of the stimuli change (Dias et al., 1996, 1997). Deficits in inhibitory mechanisms lead to different clinical symptoms in patients with lateral and orbital PFCx damage. Lack of inhibition is a likely explanation for impulsivity, socially inappropriate or the disinhibited behaviors often observed after orbitofrontal damage (Levine et al., 1999), whereas deficits in attention, inflexible cognition, stimulus bound and perseverative behaviors may be signs of inhibitory deficits in lateral PFCx damage.

2. ELECTROPHYSIOLOGY AND LESION METHODS

Behavioral measurements, recordings of neuronal activity of single cells and neural populations, as well as blood flow changes in response to neural activity have been used to study PFCx function in both intact and lesioned brains. Despite limitations of each method, converging evidence from different techniques provides a more reliable and richer understanding than any single approach to the roles of prefrontal cortices in cognition, emotion, and behavior. The focus of this chapter is on results obtained from electrophysiological studies on neurological patients with focal lateral or orbital prefrontal damage.

Electrophysiological techniques such as electroencephalography (EEG) and event-related brain potentials (ERPs) provide important approaches to study attention and other cognitive processes in humans (Nääätänen, 1992). Lesion studies and functional magnetic resonance imaging (fMRI) help to delineate the brain regions engaged in cognitive processing. However, mental events occur so rapidly that fMRI methods are often not amenable to neuroimaging cognition (McIntosh et al., 1994; 1999). Despite improving
temporal resolution of the fMRI method, the sluggishness of the hemodynamic response underlying the fMRI signal restricts the temporal information into the range of seconds. ERPs have millisecond temporal resolution and are therefore well suited for assessing the kinetics of human cognition in real time. In addition, fMRI is susceptible to artifacts originating from neighboring anatomical structures (e.g., air-filled sinuses), which can compromise reliable imaging of brain regions such as the orbitofrontal cortex. Thus, combining electrophysiology with the lesion method provides both temporal and spatial information and allows insight into the dynamics and neural circuitry of cognitive processes.

Neuroanatomical information from lesion studies (Knight et al., 1998; Knight & Scabini, 1998), intracranial recordings (Baudena et al., 1995; Halgren et al., 1995a, Halgren et al., 1995b; Halgren et al., 1998) and combined neuroimaging and ERP studies (Heinze et al., 1994; Opitz et al., 1999a; Opitz et al., 1999b) have delineated the neural regions responsible for generating several widely studied cognitive ERP components. For instance, attention sensitive visual ERPs, including a positive (P1, 110-160 milliseconds) and a subsequent negative potential (N1, 125-225 milliseconds) have been localized to the extrastriate cortex (Gonzalez et al., 1994; Hillyard & Anllo-Vento, 1998; Martinez et al., 1999), and fMRI studies have confirmed extrastriate attention modulation (Brefczynski & DeYoe, 1999; Chawla et al., 1999; Kastner et al., 1999). Electrophysiological and neurological techniques have also defined a distributed cortical-limbic network activated within 150-400 milliseconds after a novel irrelevant stimulus event (Alain et al., 1998; Halgren et al., 1998, Knight, 1984). Novel stimuli generate the P3a ERP, which is a positive-going component that occurs at about 300-400 milliseconds and is maximal over the anterior scalp. This novelty ERP is proposed to be a central marker of the orienting response (Bahramali et al., 1997; Courchesne et al., 1975; Escera et al., 1998; Knight, 1984; Yamaguchi & Knight, 1991). ERP evidence derived from neurological patients and intracranial ERP recordings in pre-surgical epileptics has revealed that a distributed neural network including the lateral and orbital PFCx, hippocampal formation, anterior cingulate and temporal–parietal cortex is involved in detecting and encoding novel information (Halgren et al., 1998; Knight 1996; Knight 1997; Knight & Scabini, 1998; Verleger et al., 1994; Yamaguchi & Knight, 1991; Yamaguchi & Knight, 1992). Neuroimaging has provided confirmation on the neuroanatomy of this novelty processing system, which engages involuntary attention (Clark et al., 2000; Downar et al., 2000; McCarthy et al., 1997; Menon et al., 1997; Opitz et al., 1999a; Opitz et al., 1999b; Stern et al., 1996; Tulving et al., 1994; Tulving et al., 1996; for a review see Friedman et al., 2001).
Strong convergence of lesion/ERP/fMRI data also has been obtained in voluntary attention paradigms. Voluntary stimulus detection generates a classic P300 or P3b potential that occurs between 300 to 700 milliseconds, has a posterior scalp maxima, and is primarily sensitive to attentional and cognitive factors rather than the physical properties of the stimulus (for reviews, see Picton, 1992 and Polich, 1998). The P300 can be triggered by detection of auditory, visual, somatosensory, and olfactory stimuli as well as by detection of missing stimuli in a train of irrelevant stimuli. The P300 response to missing stimuli highlights the importance of cognitive factors over physical properties in the generation of these late ERP components.

P300 in a voluntary target detection paradigm is referred to as P3b to distinguish it from P3a generated by task-irrelevant novel stimuli. P3a is maximal over fronto-central scalp areas and peaks in amplitude about 50 milliseconds prior to P3b activity, which is maximal over parietal areas. Task-relevant and predictable stimuli lead to small P3a and large P3b responses, while unexpected and novel stimuli result in increased prefrontal P3a amplitude. Several explanations as to the functional significance of P300 have been offered, with most models focusing on attentional and mnemonic mechanisms. P300 amplitude depends on a variety of factors such as probability, context, and relevance of the stimuli, as well as the cognitive processes engaged by the behavioral task (Donchin & Coles, 1988; Katayama & Polich, 1998) The lack of a unitary theory on the functional significance of the P300 reflects the fact that multiple brain regions and cognitive processes generate scalp positivities between 300 to 700 milliseconds after stimulus presentation that contribute to P300. In addition, a variety of evidence indicates that the temporoparietal junction contributes to P300 generation. More important, both P3b and P3a are attenuated by lesions in the temporoparietal junction in all sensory modalities (Figure 1; Knight, 1997; Knight et al., 1989; Yamaguchi & Knight, 1991). Furthermore, event-related fMRI studies have confirmed temporoparietal junction activation during voluntary event detection (Clark et al., 2000; Linden et al., 1999; McCarthy et al., 1997; Menon et al., 1997). Thus, electrophysiological methods in conjunction with lesion studies have proved to be valuable approaches for identifying the neural circuitries involved in cognitive processing.

3. LATERAL PREFRONTAL CORTEX

The LPFCx has been implicated in multiple cognitive processes such as executive control, attention, language, and memory (Chao & Knight, 1998; Corbetta, 1998; Dronkers et al., 2000; Fuster et al., 2000; Knight et al., 1998;
McDonald et al., 2000). The crucial role of the LPFCx function in intact human cognition and behavior is indicated by the variety of neurological and psychiatric disorders linked to LPFCx dysfunctions, such as schizophrenia, depression, attention deficit disorder, stroke, Parkinson’s disease and frontal lobe dementia (Akbarian et al., 1995, 1996; Jagust, 1999; Miller et al., 1991; Rosen et al., 2001; Stamm et al., 1993; Weinberger et al., 1986; 1992, Wilkins et al., 1987). Studies using fMRI have also defined the role of the LPFCx in working memory, response conflict, novelty processing, and attention (Barch et al. 2000; Botvinick et al., 1999; D’Esposito et al., 1995, 1999a; D’Esposito et al., 1999b; D’Esposito et al., 1999c; Downar et al., 2000; Jonides et al., 1993, 1998; Owen et al., 1998; Prabhakaran et al., 2000; Rypma & D’Esposito, 2000). In accordance with the imaging results, patients with lesions to the LPFCx have deficits in working memory (Harrington et al., 1998; Müller et al., 2002; Stone et al., 1998), response monitoring (Gehring & Knight, 2000), novelty processing (Knight 1984; Knight & Scabini, 1998), and attention (Barceló et al., 2000; Knight et al., 1998). Evidence combining lesion, electrophysiological and fMRI data has also been essential for delineating the different roles of LPFCx in attentional mechanisms, including early modulation of primary sensory areas, later modulation of association areas as well as involvement in the novelty-driven involuntary attention network.

Single cell recordings in monkeys (Rainer et al., 1998a, Rainer et al., 1998b), lesion studies in humans (Barceló et al., 2000; Knight, 1997; Nilesen-Bohlman & Knight, 1999) and monkeys (Rossi et al., 1999), as well as blood flow data (Büchel & Friston, 1997; Chawla et al., 1999; Corbetta, 1998; Hopfinger et al., 2000; Kastner et al., 1999; Rees et al., 1997) have linked LPFCx to early attentional modulation of extrastriate cortex. Lateral prefrontal cortex attention effects span from early modulation of extrastriate activity beginning 125 milliseconds after stimulus delivery to subsequent visual processing extending throughout the ensuing 500 milliseconds (Barceló et al., 2000).

The LPFCx exerts both facilitatory and inhibitory modulation of posterior sensory and perceptual areas and contributes to both involuntary and voluntary attention networks. Facilitatory modulation of extrastriate activity can be detected as enhancement of visual P1 and N1 potentials in the 100-200 milliseconds range (Mangun, 1995). Facilitatory PFCx modulatory effects on task relevant stimuli are not limited to early sensory processing but also include later processing stages and brain areas (Barceló et al., 2000). Even though in simple detection tasks LPFCx does not appear to have significant contribution to brain potentials (e.g., N2 and P3b) reflecting target detection (Knight & Nakada, 1998; Knight & Scabini, 1998), more demanding cognitive tasks seem to rely on LPFCx modulation of posterior
association areas (Swick, 1998; Swick & Knight, 1999). In addition to facilitatory modulation of relevant stimuli, LPFCx exerts inhibitory modulation of irrelevant stimuli. Consequently, LPFCx damage leads to increased distractibility (Bartus & Levere 1977; Chao & Knight, 1995; 1998; Malmo 1942; Woods & Knight, 1986). Increased distractibility is believed to partially explain the attentional deficits after brain damage (Kaipio et al., 1999). Electrophysiological signs of increased distractibility are enhanced ERP potentials to task-irrelevant stimuli, such as primary auditory cortex evoked response amplitude increase to distractors in LPFCx patients (Chao & Knight, 1998). This inhibitory control of early sensory processing has been linked to a prefrontal-thalamic gating system (Guillery et al., 1998; Knight et al., 1998).

Figure 1. Grand averaged ERPs from lesion patient and control groups in a simple detection paradigm across stimulus modalities illustrate the effects of frontal, temporo-parietal junction, parietal, and hippocampal lesions on target and novelty processing. Brain images at the left illustrate the average lesion location. Prefrontal lesions reduced novelty P3a across modalities, but had no effect on the target P3b. Temporo-parietal junction lesions affect both novelty P3a and target P3b leading to marked reductions in amplitudes to auditory and somatosensory stimuli and partial reduction to visual stimuli. Lateral parietal lesion had no significant effect on either P3a or P3b amplitudes or latencies. Hippocampal damage leads to significant reductions in P3a over the frontal sites, but P3b remained intact.

In addition to its critical role in voluntary attention, the LPFCx is a key component of the novelty network that engages involuntary attentional mechanisms. Mismatch negativity (MMN) studies indicate that lateral
prefrontal cortex initiates the novelty detection cascade prior to activation of other brain regions. If the novel event is sufficiently engaging, posterior cortical and medial temporal regions are recruited for further processing (Alain et al., 1998; Alho et al., 1994; Knight, 1996). PFC\textsubscript{x} novelty activation recorded with ERPs or neuroimaging habituates to repeated exposures to novel events and is modality independent (Knight, 1984; Knight & Scabini, 1998; Peterson et al., 1999; Raichle et al., 1994; Yamaguchi & Knight, 1991). Furthermore there is a marked reduction of novelty P3a in patients with LPFC\textsubscript{x} damage, whereas the P3b in a simple detection paradigm remains largely unaffected (Knight & Scabini, 1998, Figure 1; Daffner et al., 2000). These findings highlight the significant contributions of the PFC\textsubscript{x} to involuntary attention networks.

Involuntary and voluntary attentional mechanisms rely on distributed neural networks comprised of multiple brain areas. Figure 1 illustrates the value of the lesion method in determining contributions of specific brain areas to attentional and novelty processing. Similar to LPFC\textsubscript{x}, lesions of the hippocampal formation lead to clear P3a amplitude reduction, but have no significant effect on P3b (Knight, 1996). This finding provides evidence for the role of the hippocampal formation in novelty detection. Contrary to its involvement in novelty P3a generation, the hippocampal formation does not seem to contribute significantly to most scalp recorded target P3bs. In contrast, lesions of the temporo-parietal area lead to reduction in both P3a and P3b in all modalities (Knight, 1997; Knight et al., 1989; Verleger et al. 1994; Yamaguchi & Knight, 1991). Hence, the temporo-parietal junction is critical in multimodal processes involving both irrelevant novel and relevant recurring events engaging both involuntary and voluntary attentional mechanisms. Lateral parietal lesions can affect either P3a or P3b. Lateral parietal lesions serve as a brain-damage control comparison, since the ERP amplitude reductions from focal brain damage to the LPFC\textsubscript{x}, temporo-parietal junction, and hippocampal formation are not the result of general brain lesion effects, but rather are specific to lesion location and disrupting the circuits involved in novelty and target processing.

4. ORBITAL PREFRONTAL CORTEX

The extensive neuroanatomical connections of the orbital prefrontal cortex with the limbic system (Barbas, 2000; Cavada, 2000; Price, 1999), as well as its connections to lateral prefrontal cortex make it a region well suited for integrating emotion and motivation with cognition and behavior. The orbitofrontal cortex is believed to play a variety of roles in guiding adaptive, motivated, and emotion regulated behaviors. Clinical evidence
since the landmark case of Phineas Gage in 1848 has highlighted the significance of the orbitofrontal cortex in emotional and social behavior (Dimitrov et al., 1999; Eslinger, 1999; Harlow, 1993; Macmillan, 2000; Nies, 1999). Lesions of the orbitofrontal cortex result in impaired social skills, emotional lability, and decreased impulse control.

In contrast to well-preserved cognitive skills and only subtle difficulties in formal neuropsychological tests, the effect of orbitofrontal damage on a patient’s social behavior is considerable and may cause significant adverse consequences in their personal lives. Several reasons underlie impaired social skills in orbitofrontal patients: impaired insight (Leduc et al., 1999), difficulty in inferring mental states of others (Stone et al., 1998), failure to use emotions in guiding decisions (Bechara et al., 2000; Damasio, 1996), deficits in emotion recognition (Hornak et al., 1996), and impaired knowledge of moral rules or an inability to apply them (Anderson et al., 1999). Further functions assigned to the orbitofrontal cortex that may be crucial for successful social behavior include labeling reward values to outcomes of voluntary action and updating the reward contingencies in a rapidly changing environment (Rolls, 2000), inhibiting previously but no longer rewarded behaviors (Dias et al., 1996, 1997), and modulating orientation to irrelevant environmental stimuli (Rule et al., in press).

Although patients with orbitofrontal lesions often present with emotional lability and impulsive behavior, advanced dorsolateral prefrontal cortex lesions typically result in blunted affect and apathy. The blunted emotional state seen in dorsolateral patients is accompanied by attenuation of electrophysiological responses to novel stimuli (Paradiso et al., 1999), reflecting impairment in involuntary attentional mechanisms (Knight, 1984, Figure 1). In contrast, orbitofrontal patients show electrophysiological enhancement to novel environmental sounds (Rule et al., in press) as well as context dependent enhancement of responses to recurring events (Hartikainen et al., 2001, Figure 2). These enhanced electrophysiological responses suggest a failure in inhibitory mechanisms that may also underlie the impulsive behavior observed in OFCx patients.

In contrast to diminished late ERP amplitudes seen in association with brain damage to LPFCx, temporo-parietal junction, and hippocampal formation, significantly enhanced ERPs are observed subsequent to OFCx damage. These enhanced ERP responses provide electrophysiological evidence for the inhibitory role of OFCx in humans (Hartikainen et al., 2001; Rule, 2000). Unlike in LPFCx damage, where the impairment of inhibitory control can be observed using traditional neuropsychological testing such as the Wisconsin card sorting test, in OFCx damage many neuropsychological “frontal lobe” measures remain intact (Stuss et al., 2000). Thus, neuropsychological testing often fails to detect deficits in the inhibitory
control in OFCx patients, despite sometimes significant adverse effects on everyday life due to disinhibition, whereas enhanced ERPs show promise for laboratory detection of neural disinhibition in OFCx patient’s responses (Hartikainen et al., 2001; Rule et al., in press).

Figure 2. Enhanced ERPs to visual targets subsequent to bilateral orbitofrontal damage. Lesion reconstruction of 6 bilateral orbitofrontal patients is shown in the upper part of the figure. Average lesion location is indicated with shades of gray in the orbitofrontal area. The gray scale corresponds to lesion overlap across patients. The orbitofrontal lesions included bilateral damage in areas 10, 11, 12, and 13 with maximal damage in ventromedial orbitofrontal cortex. Orbitofrontal patients and age-matched controls discriminated between upright and inverted triangles (target). Targets were randomly presented in the left (LVF) or right visual (RVF) hemifield (150 milliseconds). A brief task-irrelevant novel (150 milliseconds) stimulus selected from international affective picture system (Center for the Study of Emotion and Attention, 1999) was presented centrally 350 milliseconds prior to the target. Difference wave reflecting LVF and RVF target processing, with the target ERP from the preceding novel stimuli subtracted (i.e., ERP to novel stimuli not followed by a target is subtracted from ERP to targets preceded by novel stimuli). The target stimuli waveforms with maximal amplitudes are shown for the LVF target from F3 and for the RVF from P3. Significantly enhanced target ERPs were observed in patients with OFCx lesions, with frontal P3 enhancement to LFV targets and posterior N2 enhancement to RVF targets (after Hartikainen et al., 2001).
OFCx seems to exert inhibitory modulatory control over anterior and posterior brain regions. Furthermore this modulation appears to be hemispheric specific. Figure 2 illustrates this hemispheric asymmetry with ERP enhancement subsequent to bilateral orbitofrontal lesion observed, which suggests distinct modulatory effects on the left and the right hemispheres. ERPs to left visual field (LVF) targets showed frontocentral P3 enhancement, while right visual field (RVF) targets were associated with significant parieto-temporal N2 enhancement in orbitofrontal patients. Posterior N2 enhancement may reflect release of posterior association areas from orbitofrontal inhibitory control. Likewise the frontal P3 enhancement may reflect loss of orbitofrontal inhibitory modulation of lateral prefrontal circuitries involved in attentional processes. There are some well-known hemispheric asymmetries in attentional processes such as more frequently observed hemispatial neglect following right hemisphere damage (Mesulam, 1981). Attentional asymmetries in performance due to novel emotional stimuli have been reported in healthy subjects and in patients with OFCx damage (Hartikainen et al., 2000a; Hartikainen et al., 2000b; Hartikainen et al., 2001). Asymmetries in attentional processes and in OFCx-hemisphere interactions may therefore be reflected in these asymmetrically enhanced ERP patterns observed after bilateral orbitofrontal damage.

5. CONCLUDING REMARKS

ERP lesion studies have provided converging evidence with animal research and brain imaging methods and have helped to clarify the roles of prefrontal cortex in attentional mechanisms. Damage to LPFCx impairs early facilitatory modulation of extrastriate processing of relevant stimuli as well as disrupts inhibitory modulation of distracting irrelevant events. These findings demonstrate the integral role of the LPFCx in voluntary attentional selection and in contributing to reliable neural signal-to-noise ratio in posterior sensory and perceptual brain areas. In addition to early modulation of sensory areas, the LPFCx is involved in voluntary attention, modulating posterior association areas and contributing to P3b when demanding cognitive operations are required. More automated tasks do not seem to rely on LPFCx modulation as evidenced by preserved P3b in a simple detection task after LPFCx damage. In addition to deficits in voluntary attentional mechanisms, involuntary attentional mechanisms that are engaged by novel stimuli are disrupted in lateral prefrontal cortex damage. ERP evidence for significant disruption of novelty processing in lateral prefrontal damage is clear.
In comparison to significant reduction of novelty P3a in lateral prefrontal damage (Knight & Scabini, 1998, Figure 1), the enhanced, rather than diminished, responses to auditory and somatosensory novel stimuli suggest no significant disruption in general novelty processing after orbitofrontal damage (Rule et al., in press). The orbitofrontal cortex seems to modulate, rather than generate, novelty responses. Habituation depends on this modulatory effect, and failure in habituation to auditory and somatosensory novel stimuli is observed in orbitofrontal patients (Rule et al., in press).

The orbitofrontal cortex seems to play a complex and context dependent inhibitory modulatory role that is evident from enhanced late ERP responses to both task-relevant and irrelevant stimuli (Figure 2; Hartikainen et al., 2001; Rule et al., in press). Amplitudes of the late N2 and P3 ERP components to targets that were preceded by novel stimuli were significantly enhanced. Despite bilateral orbitofrontal damage, the pattern of ERP enhancement depended on the field of target presentation. This suggests distinct and lateralized OFCx-hemisphere interactions during attention modulation. Left visual field targets produced enhanced frontal positivity that may reflect release of lateral prefrontal processes, possibly similar to those involved in generating P3a. Right visual field targets produced left posterior N2 enhancement, possibly reflecting resource allocation to target discrimination in the posterior parieto-temporal association areas in the absence of orbital inhibitory modulation of posterior areas. The functional significance of these ERP findings remains to be established. However, it is apparent from these results that there is a clear modulatory effect of orbitofrontal cortex on both anterior and posterior brain structures in attentional processes.

Future fMRI studies on patients with focal brain damage to orbitofrontal cortex may provide a more detailed picture of the specific brain areas involved in these asymmetrically disinhibited ERP responses. Converging results from ERP studies in focal brain damage and fMRI studies on intact brain have consolidated many of the theories related to the role of the prefrontal cortex in attention. To further elucidate the contribution of the lateral and orbital prefrontal cortices in attentional modulation of other brain areas, fMRI studies on patients with frontal damage using similar paradigms to those used in ERP studies may prove useful.

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