ELSEVIER

Acta Psychologica 101 (1999) 159–178

acta psychologica

Prefrontal cortex regulates inhibition and excitation in distributed neural networks

Robert T. Knight [a,b,c,*], W. Richard Staines [a,b,c], Diane Swick [b,c], Linda L. Chao [b,c,d]

[a] *Department of Psychology, University of California, Berkeley, 3210 Tolman Hall, Berkeley, CA 94720-1650, USA*

[b] *Department of Neurology, University of California, Davis, Veterans Medical Center, 150 Muir Road, Martinez, CA 94553, USA*

[c] *Center for Neuroscience, University of California, Davis, Veterans Medical Center, 150 Muir Road, Martinez, CA 94553, USA*

[d] *Laboratory of Brain and Cognition, National Institute of Mental Health, Building 10, Room 4C104, Bethesda, MD 20892, USA*

Abstract

Prefrontal cortex provides both inhibitory and excitatory input to distributed neural circuits required to support performance in diverse tasks. Neurological patients with prefrontal damage are impaired in their ability to inhibit task-irrelevant information during behavioral tasks requiring performance over a delay. The observed enhancements of primary auditory and somatosensory cortical responses to task-irrelevant distractors suggest that prefrontal damage disrupts inhibitory modulation of inputs to primary sensory cortex, perhaps through abnormalities in a prefrontal-thalamic sensory gating system. Failure to suppress irrelevant sensory information results in increased neural noise, contributing to the deficits in decision making routinely observed in these patients. In addition to a critical role in inhibitory control of sensory flow to primary cortical regions, and tertiary prefrontal cortex also exerts excitatory input to activity in multiple sub-regions of secondary association cortex. Unilateral prefrontal damage results in multi-modal decreases in neural activity in posterior association cortex in the hemisphere ipsilateral to damage. This excitatory modulation is necessary to sustain neural activity during working memory. Thus, prefrontal cortex is able to sculpt behavior through parallel inhibitory and excitatory regulation of neural activity in distributed neural networks.

* Corresponding author. Tel.: +1-925-372-2572; fax: +1-925-229-2315; e-mail: rtknight@socrates.berkeley.edu

0001-6918/99/$ – see front matter
PII: S0001-6918(99)00004-9

PsycINFO classifications: 2346; 2520; 2530; 2540; 3213; 3297

Keywords: Prefrontal; Inhibition; Excitation; Attention; Schizophrenia

1. Introduction

In 1935 Jacobsen reported that monkeys with bilateral frontal lesions involving the sulcus principalis, a putative analogue of human dorsolateral prefrontal cortex (Brodmann areas 9 and 46: Rajkowska & Goldman-Rakic, 1995a,b; see Fig. 1), were severely impaired at delayed response tasks (Jacobsen, 1935). In delayed response tasks, subjects are initially presented with information necessary to perform a specific task. The experimenter then interposes a delay period before the animal or human is allowed to perform the task. Thus, for successful performance, the information must be reliably held in a working memory buffer during the delay period. Jacobsen reported that monkeys with prefrontal lesions involving the sulcus principalis were unable to remember the location of a baited well at short retention intervals. The Jacobsen finding provided a landmark observation for insight into the role of prefrontal cortex in organized behavior (Jacobsen, 1935). Subsequent research has shown that prefrontal spatial memory deficits are apparent at delays as short as 1 s (Funahashi, Bruce & Goldman-Rakic, 1993).

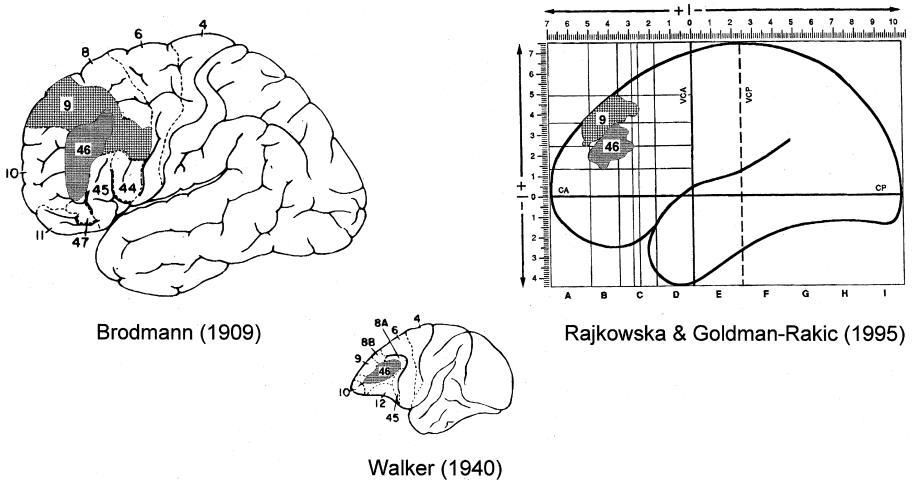

Fig. 1. This figure shows the location of the sulcus principalis area in monkeys considered to be the analogue of areas 9 and 46 in humans. The Bordmann classification and a more recent cytoarchitectonic post-mortem definition of areas 9 and 46 in humans are also shown (see Brodmann, 1909; Goldman-Rakic, 1987; Rajkowska & Goldman-Rakic, 1995a,b). The cytoarchitectonic definitions of Rajkowska and Goldman-Rakic are shown on the Talairach coordinate system. The maps represent the region of cytoarchitectonic overlap of areas 9 and 46 averaged from from five subjects.

The delayed response deficit was initially interpreted to reflect a simple memory problem. However, animal research in the 1940's revealed that a problem with the inhibition of extraneous inputs was a major contributor to the delayed response deficit. These findings led to the formulation of the distractibility hypothesis of prefrontal function (Malmo, 1942; Bartus & Levere, 1977). The distractibility theory postulates that prefrontal patients are unable to suppress responses to irrelevant stimuli in a range of sensory motor and cognitive processes. Impairments in inhibitory control to sensory inputs are found in neurological patients with dorsolateral prefrontal damage and in schizophrenic patients with prefrontal hypometabolism on PET scanning, providing support for the prefrontal-distractibility hypothesis. However, successful performance on the delayed response task requires more than inhibitory control. Subjects must also selectively engage and integrate activity in different brain regions depending on task specific parameters. Single unit data in monkeys (Funahashi et al., 1993), electrophysiological data in normal controls and prefrontal lesioned patients (Chao & Knight, 1998), cerebral blood flow data in normal controls (Jonides, Smith, Koeppe, Mioshima & Mintun, 1993), and neural modelling (Cohen, Braver & O'Reilly, 1996) having shown that combined prefrontal-posterior association cortex activation is required to perform any task requiring a delay. Data from neurological patients has revealed that dorsolateral prefrontal cortex modulates excitatory pathways projecting into subregions of visual and auditory association cortex. Thus, it appears that prefrontal cortex exerts selective and parallel inhibitory and excitatory control to remote brain regions during a variety of behaviors. The net result of parallel and interactive prefrontal modulated neuronal activity results in the higher level functions attributed to prefrontal cortex.

In humans, dorsolateral prefrontal cortex is engaged in diverse cognitive processes including language, motor control, attention, and executive functions. Delayed response paradigms have elements in common with classic working memory tasks (Baddeley, 1992a,b). The main parallel between delayed response and working memory is the necessity to hold information in a temporary buffer. Working memory is well known to be dependent on prefrontal cortex (Petrides, Alivasatos, Meyer & Evans, 1993a,b; Jonides et al., 1993; Knight, 1994). Although the prefrontal cortex is critical for integrative cognitive functions requiring working memory, it is unlikely that this capacity resides in specialized modules in prefrontal regions. More likely, the spectrum of cognitive capacities involving prefrontal cortex is supported by interactions in the extensive bi-directional connections between prefrontal cortex and numerous cortical, limbic, and subcortical regions (Goldman-Rakic, Selemon & Schwartz, 1984; Friedman & Goldman-Rakic, 1994).

Prefrontal cortex (particularly Brodmann areas 9 and 46) is well known to be involved in both sustained and phasic attention to environmental events (Stuss & Benson, 1986). Sustained attention and phasic orienting capacity have been examined in neurological patients with focal prefrontal lesions using behavioral and event-related potential (ERP) recording techniques. Neurophysiological impairments in these patients include problems with inhibitory control of sensory inputs (Knight, Scabini & Woods, 1989a; Knight, Scabini, Woods & Clayworth, 1989b; Yamaguchi & Knight, 1990, 1991), deficits in selective and sustained attention

(Knight, Hillyard, Woods & Neville, 1981; Woods & Knight, 1986; Knight, 1991), and abnormalities in the detection of novel events (Knight, 1984, 1996, 1997). The inability to inhibit irrelevant inputs and sustain attention, coupled with deficits in novelty detection, impairs the coding and the processing of discrete external events and may underlay the temporal order (Shimamura, Janowsky & Squire, 1990) and decision making impairments observed subsequent to prefrontal damage (Shimamura, 1995a; Shimamura, Jurica, Mangels, Gershberg & Knight, 1995b). Similar to the role prefrontal cortex plays in regulating the interaction with the external world, this region is crucial for attention to and inhibitory control of internal mental representations engaged during working memory, employment of strategies, planning and decision-making (Janowsky, Shimamura, Kritchevsky & Squire, 1989a; Janowsky, Shimamura & Squire, 1989b; Shimamura et al., 1995b; Knight & Grabowecky, 1995; Stuss & Benson, 1984, 1986) The inability to inhibit internal representations of previous responses which are no longer correct contributes to poor performance on the Wisconsin card sorting task (WCST) and the Stroop task (Shimamura, 1995a; Shimamura et al., 1995b; Vendrell et al., 1995). In the WCST task subjects are required to change their criteria for sorting a deck of cards varying in shape or color. Patients with prefrontal damage are impaired at switching to a new sorting criteria and continue to incorrectly sort by the prior rule. This tendency to preseverate is viewed by cognitive theorists as a failure in inhibitory control of prior mental sets. Damage in prefrontal cortex also results in a failure in inhibition of reflexive saccadic eye movements (Guitton, Buchtel & Douglas, 1985; Pierrot-Deseilligny, Rivaud, Gaymard & Agid, 1991). The animal and human data supporting these contentions will be discussed.

2. Inhibition in animals

Inhibition of neural activity under prefrontal control has been reported in a variety of mammalian preparations. Net prefrontal inhibitory control of both subcortical (Edinger, Siegel & Troiano, 1975) and cortical regions has been documented (Alexander, Newman & Symmes, 1976; Skinner & Yingling, 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 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 prefrontal cortex by cooling of cat prefrontal

cortex (crygenic blockade) increased the amplitudes of evoked responses recorded in primary sensory cortex evoked responses (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. 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 intermodality suppression of irrelevant inputs at an early stage of sensory processing. The system is modulated by an excitatory prefrontal projection to the nucleus reticularis thalami. The nucleus reticularis thalami in turn sends inhibitory GABA-ergic projections to sensory relay nuclei, providing a neural substrate for selective sensory suppression (Guillery, Feig & Lozsadi, 1998).

3. Inhibition in humans

The attention deficits and perseveration observed behaviorally in frontal patients have been linked to problems with inhibitory control of posterior sensory and perceptual mechanisms (Lhermitte, 1986; Lhermitte, Pillon & Serdaru, 1986). Early sensory gating deficits (20–50 ms), sustained attention problems (100–500 ms) and abnormalities in the phasic detection of novel events (250–500 ms) are all observed after prefrontal damage. ERPs are brain potentials that are time-locked to the occurrence of sensory, motor, or cognitive events and extracted from the ongoing EEG by signal averaging techniques (Hillyard & Picton, 1987). Because of their excellent temporal resolution, ERPs index the timing of both sensory and cognitive processing in humans that complements both the behavioral measures of cognitive psychology and the spatial resolution advantage of functional neuroimaging techniques.

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 dorsolateral prefrontal cortex, the temporal-parietal junction, or lateral parietal cortex. Evoked responses from primary auditory (Kraus, Ozdamar & Stein, 1982) and somatosensory (Leuders, Leser, Harn, Dinner & Klem, 1983; Sutherling et al., 1988; Wood et al., 1988) cortices were recorded from these patients and age-matched controls (Fig. 2). Damage to primary auditory or somatosensory cortex reduced the early latency (20–40 ms) evoked responses generated in these regions. Posterior association cortex lesions that spared the primary sensory regions had no effect on early sensory potentials and served as a brain-lesioned control group. Prefrontal damage produced disinhibition of both the primary auditory and somatosensory evoked responses (Knight et al., 1989a; Yamaguchi & Knight, 1990). Spinal cord and brainstem potentials were not affected by prefrontal damage, suggesting that the amplitude enhancement was due to abnormalities in either a prefrontal-thalamic or a prefrontal-sensory cortex mechanism.

Chronic disinhibition of sensory inputs likely contributes to some of the behavioral sequelae noted after prefrontal damage. For instance, decision confidence would be decremented in a noisy internal milieu. As discussed, distractibility has

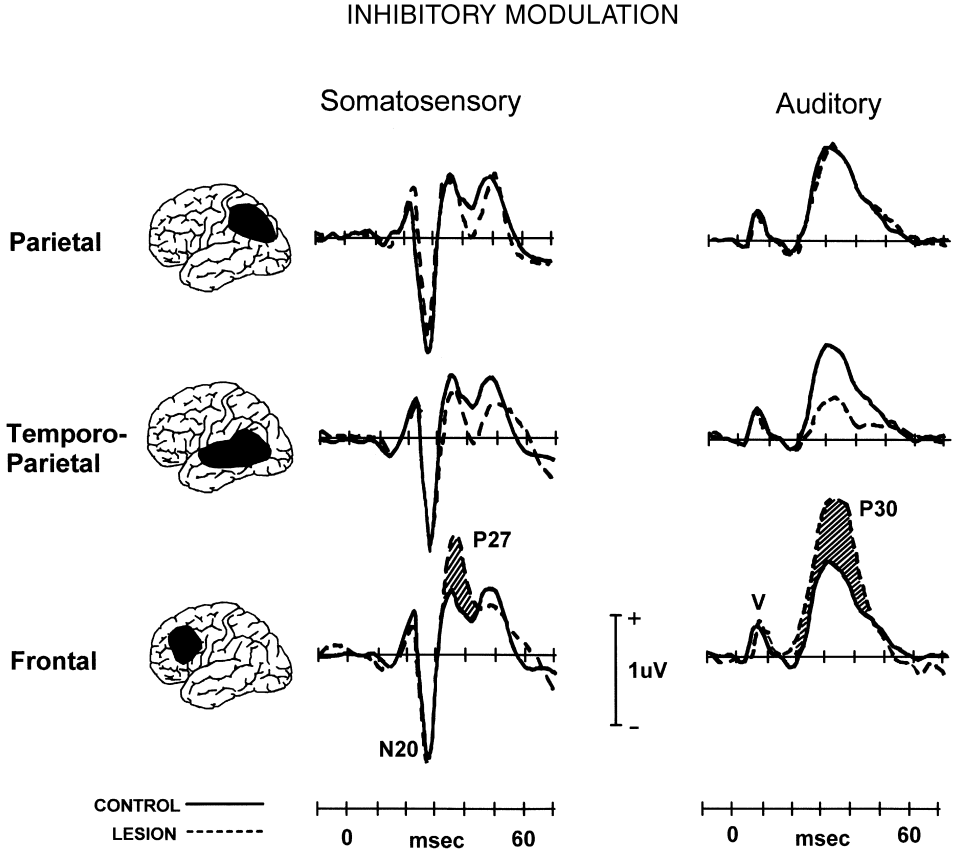

Fig. 2. Primary cortical auditory (AEPs) and somatosensory evoked potentials (SEPs) are shown for controls (solid line) and patients (dashed line) with focal damage in the lateral parietal cortex (top, $n=8$), temporal-parietal junction (middle, $n=13$) or dorsolateral prefrontal cortex (bottom, $n=13$). Reconstructions of the center of damage in each patient group are shown on the left. Somatosensory evoked responses were recorded from area 3b (*N*20; *N* for negative, 20 ms post-stimulation) and areas 1 and 2 on the crown of the post-central gyrus (*P*26; *P* for positive, 26 ms post-stimulation). Stimuli were square-wave pulses of 0.15 ms duration delivered to the median nerve at the wrist. Stimulus intensity was set at 10% above opponents twitch threshold and stimuli were delivered at a rate of 3/s. Damage in posterior cortical regions sparing primary somatosensory cortex had no effect on the *N*20 or earlier spinal cord potentials. Prefrontal damage resulted in a selective increase in the amplitude of the *P*26 response (hatched area). Auditory stimuli were clicks delivered at a rate of 13/s at intensity levels of 50 dB HL. Unilateral damage in the temporal-parietal junction extending into primary auditory cortex reduces *P*30 responses. Lateral parietal damage sparing primary auditory has no effect on *P*30 responses. Dorsolateral prefrontal damage results in normal inferior collicular potentials (wave *V*) but an enhanced *P*30 primary cortical response (hatched area). The shaded area in each modality indicates the area of evoked potential amplitude enhancement (adapted from Knight, 1994).

been proposed to a major component of the delayed response deficit in animals with prefrontal lesions (Malmo, 1942; Brutkowski, 1965; Bartus & Levere, 1977). This inability to suppress irrelevant information is associated with difficulties in target

detection and match-to-sample paradigms. For example, patients with frontal resections are impaired at detecting multiple visual targets embedded among distractors (Richer et al., 1993). Likewise, patients with lesions confined to dorsolateral prefrontal cortex are impaired in a delay task requiring the matching of two environmental sounds only when distractors intervened between cue and target (Chao & Knight, 1995; Chao & Knight, 1998).

There is extensive literature supporting an abnormality in prefrontal function in schizophrenics. Findings of altered dorsolateral prefrontal function include evidence from both cerebral blood flow (Weinberg, Berman & Zec, 1986; Weinberg, Berman, Suddath & Torrey, 1992) and post-mortem studies (Akbarian et al., 1995, 1996). Thus, schizophrenia may represent a "non-lesion" model of prefrontal dysfunction in humans. Schizophrenics are also reported to have a deficit in inhibitory control of auditory processing. Freedman and colleagues developed and ERP auditory gating paradigm to study inhibitory control in schizophrenics. In normals, presentation of a pair of clicks results in a decrease in amplitude of the evoked response to the second stimulus in the pair. This response suppression occurs in a latency range of 30–65 msec and has been referred to as the P50 gating paradigm in the schizophrenia literature. This finding has been disputed by some authors (Kathman & Engel, 1990), but this may be due in part to differences in recording parameters and state of alertness (Boutros, Zouridakis & Overall, 1991a; Boutros, Overall & Zouridakis, 1991b; Smith, Boutros & Schwarzkopf, 1994; Griffith, Hoffer, Adler & Zerbe, 1995). Freedman, Adler, Waldo, Pachtman and Franks (1983) reported that the second stimulus in a pair of auditory pulses did not habituate in schizophrenics. This electrophysiological findings supported the longstanding proposal that schizophrenics fail to properly filter extraneous inputs (McGhie & Chapman, 1961; Venables, 1964).

This auditory gating deficit is reliably seen in a significant percentage of non-psychotic relatives of schizophrenics and has been proposed to be a neurophysiologicl trait for schizophrenia. Phenotypic segregation of schizophrenics and first order relatives using the auditory gating paradigm has been employed in recent genetic studies. This research has isolated a putative schizophrenia gene localized to a region of chromosome 15q 13–14 which controls alpha 7 nicotinic receptor expression (Freedman et al., 1997). Thus, the neural network controlling the P50 gating deficit is of both theoretical and clinical relevance. We examined auditory gating in patients with dorsolateral prefrontal damage and in age-matched controls (see Fig. 3). An initial study has shown that controls have normal suppression of the second stimulus in an auditory pulse pair. Prefrontal patients showed evidence of an inhibitory failure in the auditory gating paradigm in both ears. As can be seen in Fig. 3, prefrontal patients showed problems with suppression of the second stimulus in both ears with the defect more apparent in the ear contralateral to prefrontal damage (Knight, Finkbeiner & Lawler, in preparation). This failure to suppress is observed for both an early latency component generated in auditory cortex (P35) and a later component (P50) thought to arise in the thalamus. The data suggests that prefrontal cortex dysfunction may underlie or contribute to the auditory gating deficit in schizophrenics.

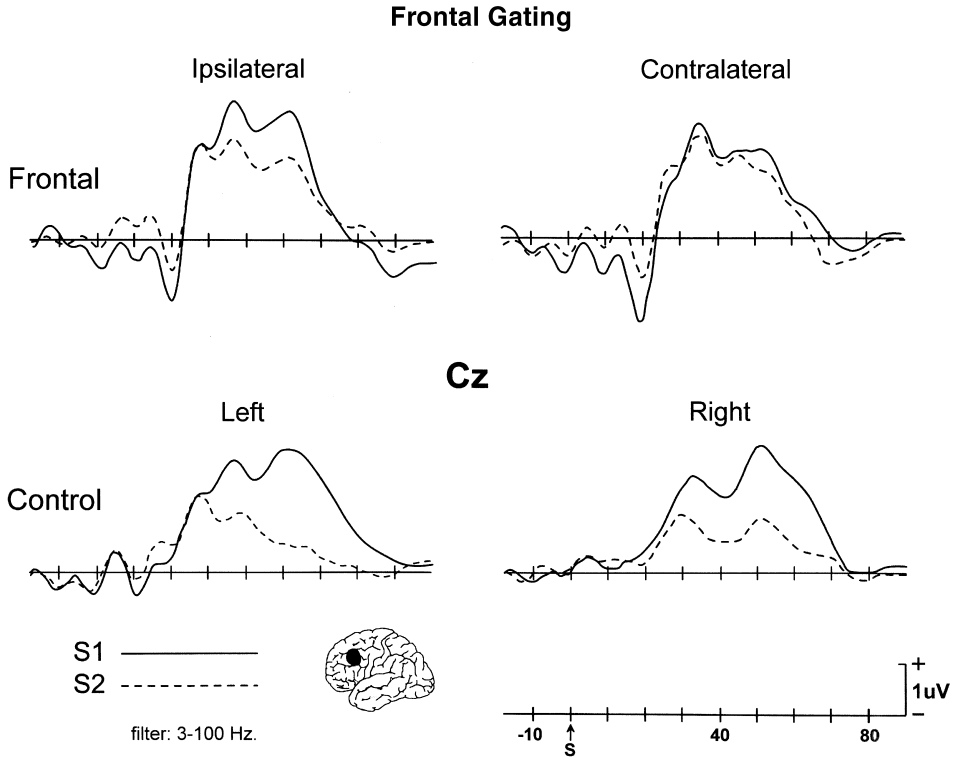

Fig. 3. ERPs from control and prefrontal patients in an auditory gating paradigm. The probe-target interstimulus intervals was 500 ms, with an intertrial interval of 10 s. Click trains were presented randomly between the two ears to subjects watching silent movies. EEG (3–100 Hz; 2048 Hz digitization rate) was recorded from Fz, Cz, Pz Additional electro-oculography (EOG) electrodes were placed vertical and horizontal to the eye. All electrodes were referred to a balanced mastoid reference. There were seven left and two right stroke patients with unilateral damage in the dorsolateral prefrontal cortex (61.7 years, three females). Controls were matched for mean age (59.2, four females). Controls and patients were free of psychiatric disease and had no family history of schizophrenia or major affective disease. The center of lesion overlap for the frontal patients is shown. The data for the left or right ear of controls and the ear ipsilateral or contrateral to prefrontal damage are shown. There is no evidence of gating of either the *P*35 or *P*50 component of the ERP.

4. Motor control and inhibition

Inhibitory modulation of sensory input is also important in motor control. Transmission through somatosensory afferents in under constant modulation. The predominant effect is inhibition of the ascending sensory paths. Gating of sensory inputs is reported at all levels of the neuraxis, from the segmental reflex to the primary cortical receptive zones (Mackay & Crammond, 1989; Shin & Chapin, 1990a, b). There are two mechanisms for the control of this sensory input during movement. Firstly, projections from specific supraspinal structures can centrifugally

through ascending paths can be altered by afferent volleys arising from peripheral receptor discharge, termed centripetal modulation.

In primates, the prefrontal cortex has direct reciprocal connections with the parietal cortex, including the primary sensory region (Mountcastle, 1984; Pandya & Barnes, 1987). A net inhibitory influence of the prefrontal cortex onto both cortical and subcortical structures has been shown to act at the dorsal column nuclei (Coulter, 1974; Ghez & Pisa, 1972), the thalamus (Tsumoto, Nakamura & Iwama, 1975), and at the primary somatosensory cortex (Yamamoto, Samejima & Oka, 1988; Chapin & Woodward, 1981). In the somatosensory system. Yamaguchi and Knight (1990, 1991) demonstrated that patients with damage to the prefrontal cortex centered in areas 9 and 46 exhibited enhanced somatosensory evoked potentials (SEPs) to median nerve stimulation. Selective enhancement of the P26 component of the SEP which is known to arise in the crown of the post-central gyrus (Sutherling et al., 1988) was proposed to arise from loss of inhibition of activity in the primary sensory cortex.

In addition to prefrontal cortex, other areas such as the somatosensory cortex, cerebellum, and basal ganglia, may be involved in the modulation of sensory input during movement. Corticothalamic influences from the primary and secondary somatosensory areas modulate the transmission of tactile inputs through the thalamus in the cat (Gosh, Murray, Turman & Rowe, 1994). These effects could be facilitory via direct connections to thalamic relay nuclei or inhibitory through local inhibitory interneurons and the nucleus reticularis thalami, thus complementing the prefrontal-thalamic sensory control mechanism discussed above. The cerebellum receives convergent cutaneous and proprioceptive inputs and has also been implicated in the gating of these inputs (Apps, Atkins & Garwicz, 1997). In addition, the basal ganglia appears to be involved in the gating of noxious somatosensory stimuli (Chudler & Dong, 1995). Thus, through its intricate connections with higher motor areas via the thalamus, the basal ganglia may also contribute the gating of somatosensory inputs. The functional implications of these sensory gating mechanisms remains to be established for normal motor control.

5. Selective attention and prefrontal cortex

In a seminal report, Hillyard, Hink, Schwent and Picton (1973) found that focussed attention to tones in one ear resulted in a systematic negative enhancement of evoked potentials to all stimuli in that ear. This enhancement onsets at about 50 ms post-stimulation and was shown to be sustained for at least 200 and 500 ms (Hansen & Hillyard, 1980). These electrophysiological results were critical to attention theorists. First, stimulus discriminability was shown to be dependent on the degree of attention related evoked potential enhancement, providing a link between physiology and attention in humans. Second, the early onset of the attention modulation provided clear evidence of an early sensory filtering mechanism in humans, addressing the long-standing early vs. late selection controversy (Broadbent, 1958; Treisman, 1960; Kahneman & Treisman, 1984). Subsequent work has shown that the

effects of attention can onset as early as 25 ms after stimulation, indicating that humans are able to exert attention effects on inputs to the primary auditory cortex (McCallum, Curry, Cooper, Pocock & Papakostopoulos, 1983; Woldorff & Hillyard, 1991; Woldorff et al., 1993). Early onset selective attention effects have also been reported in the visual and somatosensory modalities (Desmedt, Hut & Bourguet, 1983; Woods, 1990). In the visual modality attention may not modulate primary sensory activity in calcarine cortex but instead acts on subsequent stages of processing in visual association cortices (Gomez-Gonzalez, Clark, Fan, Luck & Hillyard, 1994; Mangun, 1995).

Normal subjects generate comparable selective attention effects for left or right ear stimulation. Left prefrontal patients have an intact pattern but reduced in amplitude attention effect in both ears. A different pattern is observed after right prefrontal damage. Right prefrontal patients show electrophysiological and behavioral evidence of a dense hemi-inattention to left ear stimuli (Knight et al., 1981). This parallels the human hemi-neglect syndrome which is more common after right hemisphere lesions in prefrontal or temporal-parietal cortex. Hemi-neglect is a dramatic syndrome consisting of a failure to attend or orient to stimuli in the hemispace contralateral to right hemisphere damage (Mesulam, 1981; Kertesz & Dobrolowski, 1981; Hier, Mondlock & Caplan, 1983; Stein & Volpe, 1983). Patients are often unaware of their deficit and deny there is anything wrong despite obvious weakness on the left side of the body. One popular theory states that the contralateral neglect after temporal-parietal or prefrontal right hemisphere damage is due to innate hemispheric attention asymmetries. The left frontal lobe is proposed to be capable of allocating attention only to the contralateral right hemispace, whereas the right frontal lobe can allocate attention to both the contralateral and ipsilateral hemispace. Thus, neglect is mild or not apparent after left hemisphere lesions since the intact right hemisphere is capable of allocating attention to both hemi-spaces. Dense contralateral neglect is seen after right hemisphere damage since the left hemisphere is incapable of allocating attention to the left hemi-space.

The right frontal lobe is larger than the left in humans, and this asymmetry may provide the underlying anatomical substrate or the hemi-inattention syndrome in humans (Wada, Clarke & Hamm, 1975; Weinberger, Luchins, Morisha & Wyatt, 1982). Posterior association cortex lesions in the temporal-parietal junction have comparable attention deficits for left and right sided lesions indicating that these areas are not asymmetrically organized for auditory selective attention (Woods, Knight & Scabini, 1993). This suggests that some aspects of the hemi-neglect syndrome subsequent to temporal-parietal damage may be due to remote effects of disconnection from asymmetrically organized prefrontal regions.

Attention allocation is better at short versus long interstimulus intervals in prefrontal lesioned patients. This could be due to either a problem with temporal bridging or to a distractibility deficit. Prefrontal cortex is necessary for bridging temporal discontinuities (Fuster, 1989), and attention deficits at longer interstimulus intervals might be due to temporal bridging problems. However, at longer interstimulus intervals prefrontal subjects are also more likely to encounter intervening irrelevant stimuli. ERP-behavioral experiments provide evidence supporting the

distractibility hypothesis. In normal subjects, delivery of an irrelevant stimulus in the non-attended ear during a dichotic experiment has no effect on attention effects to a subsequent stimulus in the attended ear unless the stimulus is highly deviant (Woods & Knight, 1996; Woods et al., 1993). However, presentation of an irrelevant stimulus reduces attention to a subsequent stimulus in prefrontal patients. This effect is particularly pronounced in the ear contralateral to a prefrontal lesion at long interstimulus intervals. Since attention performance is improved in prefrontal patients if no irrelevant stimuli are present, the results favor distractibility due to a failure in inhibition as a major contributor to prefrontal attention deficits (Woods & Knight, 1986).

Behavioral and electrophysiological experiments have also documented as important role for prefrontal cortex in inhibiting response to irrelevant sensory information in delay tasks (Chao & Knight, 1995, 1998). Prefrontal patients were tested on an auditory delayed-match-to-sample task. Subjects reported whether a cue (S1) and a subsequent target (S2) sound were identical. On some trials, S1 and S2 were separated by a silent period of 5 s. On other trials, the 5 s delay between S1 and S2 was filled with irrelevant tone pips. Frontal patients were impaired behaviorally when distractor stimuli were presented in the interstimulus interval. Electrophysiologically, prefrontal patients generated enhanced primary auditory cortex evoked responses to the distractor tone pips presented in the delay window. The early latency Na component generated in primary auditory cortex was enhanced and the degree of enhancement of the subsequent Pa component correlated with the number of delay errors in the prefrontal patients. This supports a failure in inhibitory control of irrelevant sensory inputs during the delay window (Chao & Knight, 1998).

6. Prefrontal cortex and excitatory control

In addition to suppressing response to irrelevant stimuli, subjects must sustain neural activity in distributed brain regions in order to perform delay and working memory tasks. There is evidence of failure in excitatory control in patients with prefrontal damage. Prefrontal lesioned patients were tested on an auditory delayed-match-to-sample task. As noted above, prefrontal patients were behaviorally impaired by distractors and generated enhanced primary auditory cortex evoked responses to these tones. In addition to this inhibitory failure, prefrontal patients had problems in excitatory modulation of activity in posterior association cortex.

Visual stimuli elicit a prominent, attention-sensitive N170 (N1) scalp potential that is maximal over temporal-occipital sites (Mangun & Hillyard, 1988; Luck, Heinze, Mangun & Hillyard, 1990; Mangun, 1995). Topographic and dipole modeling studies have suggested an N170 source in extrastraite cortex (Gomez-Gonzalez et al., 1994). The influence of prefrontal cortex on the visual N170 has been examined in both non-linguistic and linguistic tasks. In one non-linguistic experiment, controls and frontal patients performed a visual detection task requiring detection of a infrequent target imbedded in a series of irrelevant background and novel stimuli

(Knight, 1997). Dorsolateral prefrontal damage decreased visual N170 amplitude for all stimuli in the lesioned hemisphere. N170 was normal in the non-lesioned hemisphere. Maximal reductions were seen at posterior temporal sites over extrastriate cortex (Fig. 4a,b). Performance was slow but accurate. This may be due to the fact that the subjects could make the discrimination (inverted from upright triangles) with visual information from only one hemi-field.

N170 reductions in frontal patients were also observed in tasks using verbal stimuli (Swick & Knight, 1996, in press; Swick, in press). In two different experiments, subjects read centrally presented words and pronounceable nonwords and performed lexical decision or recognition memory tasks. In controls, both stimulus types elicited an N170 that was maximal at posterior temporal and occipital electrodes. In controls, N170 was significantly larger over the left hemisphere in both tasks, similar to previous studies with words (Neville, Kutas, Chesney & Schmidt, 1986; Curran, Tucker, Kutas & Posner, 1993). N170 amplitude over extrastriate recording sites was markedly reduced in frontal patients ipsilateral to damage, but peak latency was unaffected (see Fig. 5). These visual experiments indicate that dorsolateral prefrontal cortex provides an ipsilateral facilitory input to neural processing in extrastriate cortex, enhancing neural activity within 120 ms post-stimulus (Raines, Azaad & Miller, 1998). Further support for prefrontal modulation of visual processing in extrastriate areas during sustained attention and spatial memory performance comes from blood flow data in humans (Roland, 1982), networks analyses of PET and fMRI results (McIntosh, Grady, Ungerleider, Haxby, Rapoport & Horwitz, 1994; Buchtel & Friston, 1997), and single unit and lesion data in monkeys (Fuster, 1985; Funahashi et al., 1993). Projections from prefrontal areas 45 and 8 to higher order visual association areas TE and TEO in the inferior temporal cortex have been demonstrated in monkeys (Webster, Bachevalier & Ungerleider, 1994). This anatomical connection provides a pathway by which prefrontal cortex could exert a facilitory influence on activity in posterior visual association cortex.

Similar effects of an ipsilateral reduction of neural activity in auditory association cortex have been observed after prefrontal damage (Knight, 1997; Swick & Knight, 1996; Swick, in press). Both the S1 and S2 stimuli generate a prominent N100 ERP response which measures neural activity in auditory association cortex (Woods, 1990). Prefrontal lesions markedly reduced the N100 component generated to both the S1 and S2 stimuli throughout the hemisphere ipsilateral to damage (Fig. 4c,d; Chao & Knight, 1998; Knight, 1997). Additional intrahemispheric reductions of longer latency attention-related prefrontal activity were also observed. There are well described prefrontal projections to auditory cortex in the superior temporal plane which may subserve this excitatory input (Alexander et al., 1976). Together, these findings provide evidence that dorsolateral prefrontal cortex is crucial for inhibiting distracting information as well as maintaining distributed intrahemispheric neural activity during auditory working memory. This result is also in accord with findings that patients with prefrontal lesions are impaired in their ability to focus attention on task-relevant stimuli (Fuster, 1989; Knight et al., 1981; Damasio, 1985; Woods & Knight, 1986).

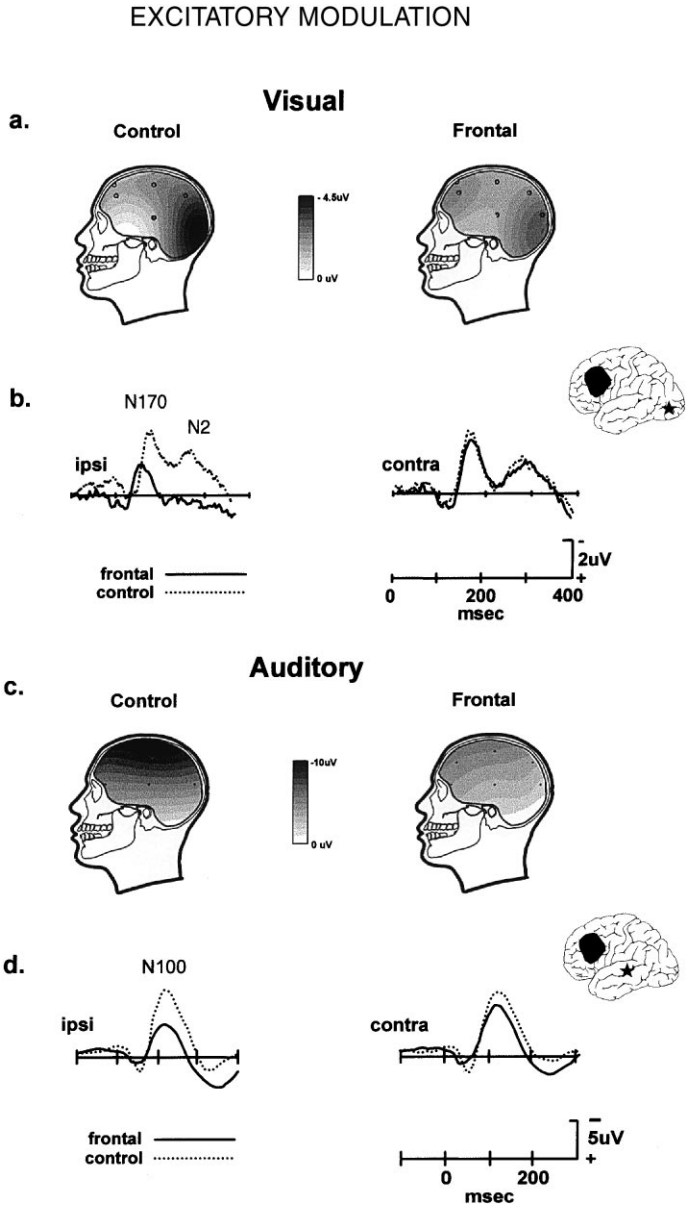

Fig. 4. Topographic maps display the scalp voltage distribution of the *N*170 generated to targets in a visual detection task for controls and prefrontal patients. The extrastriate focus of the *N*170 is reduced ipsilateral to prefrontal damage. The shaded area on the brain shows the area of lesion overlap, while the star indicates a putative generator location of the *N*170 is extrastriate corex (a). On the bottom are group averaged ERPs for target stimuli in controls and prefrontal patients ($n = 11$; (b)). Waveforms are from posterior temporal electrodes (*T*5/*T*6 in controls), and ipsilateral (ipsi) or contralateral (contra) to lesion. Fig. 4c,d. Similar format to Fig. 4a,b. Topographic maps and wavefroms are shown from an auditory delayed match to sample paradigm in controls and frontals ($n = 10$). There is a prominent intrahemispheric decrease in the *N*100 auditory evoked potential.

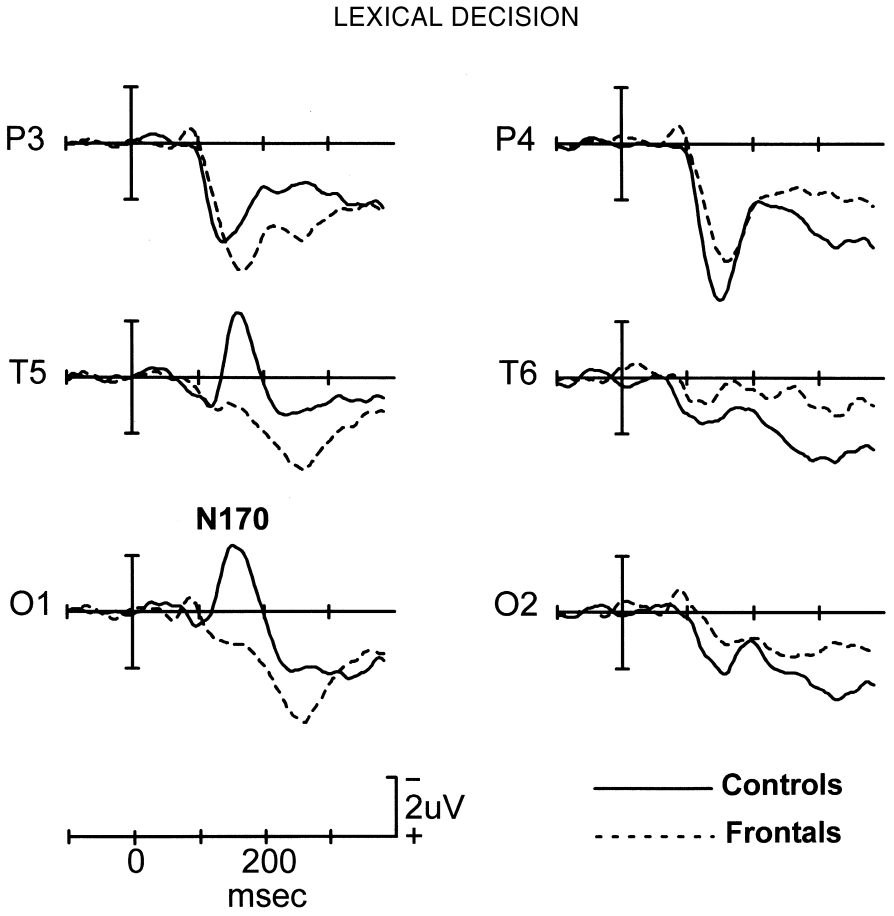

Fig. 5. ERPs recorded from left and right parietal, Posterior temporal, and occipital electrodes in controls and patients with damage to dorsolateral prefrontal cortex. These ERPs were elicited by visually presented words in a lexical decision task. The left lateralized *N*170 component was reduced by left prefrontal lesions (adapted from Swick, in press).

7. Conclusions

The accumulated evidence from behavioral, electrophysiological and blood flow techniques supports the long held clinical view that prefrontal cortex is crucial for integrative behavior. The data has revealed the existence of both inhibitory and excitatory prefrontal control of distributed neural activity in posterior brain regions. The unique capacity of prefrontal cortex to simulataneouly modulate activity in multiple brain regions is paralleled by the enormous evolution of prefrontal cortex in humans. This neuroanatomical and regulatory capacity makes prefrontal cortex ideally suited to subserve human cognition.

Acknowledgements

This work was supported by the National Institute of Neurological Disorders and Stroke grants NS21135 and PO17778 to RTK, the Veterans Administration Medical Research Service and Medical Research Council of Canada (to WRS). Special thanks to Clay Clayworth for technical assistance in all phases of work.

References

Alexander, G. E., Newman, J. D., & Symmes, D. (1976). Convergence of prefrontal and acoustic inputs upon neurons in the superior temporal gyrus of the awake squirrel monkey. *Brain Research*, *116*, 334–338.

Akbarian, S., Huntsman, M. M., Kim, J. J., Tafazolli, A., Potkin, S. G., Bunney, W. E., & Jones, E. G. (1995). GABAa receptor subunit gene expression in human prefrontal cortex: comparison of controls and schizophrenics. *Cerebral Cortex*, *5*, 550–560.

Akbarian, S., Kim, J. J., Potkin, S. G., Hetrick, W. P., Bunney, W. E., & Jones, E. G. (1996). Maldistribution of interstitial neurons in prefrontal white matter of the brains of schizophrenic patients. *Archives of General Psychiatry*, *53*, 425–436.

Apps, R., Atkins, M. J., & Garwicz, M. (1997). Gating of cutaneous input to cerebellar climbing fibres during a reaching task in the cat. *Journal of Physiology*, *502*, 203–214.

Baddeley, A. (1992a). *Working memory. Science*, *255*, 556–560.

Baddeley, A. (1992b). Working memory; the interface between memory and cognition. *Journal of Cognitive Neuroscience*, *4*, 281–288.

Bartus, R. T., & Levere, T. E. (1977). Frontal decortication in Rhesus monkeys. A test of the interference hypothesis. *Brain Research*, *119*, 233–248.

Broadbent, D. E. (1958). *Perception and communication.* London: Pergamon Press.

Brodmann, K. (1909). *Vergleichende lokalisationlehre der grosshirnrinde in ihren prinzipoen dargestellt auf grund des zellenbaues* (p. 324). Leipzig: JA Barth.

Brutkowski, S. (1965). Functions of prefrontal cortex in animals. *Physiological Reviews*, *45*, 721–746.

Boutros, N. N., Zouridakis, G., & Overall, J. (1991a). Replication and extension of P50 findings in schizoprenia. *Clinical Electroencephalography*, *22* (1), 40–45.

Boutros, N. N., Overall, J., & Zouridakis, G. (1991b). Test-retest reliability of the mid-latency auditiry evoked response. *Psychiatry Research*, *39*, 181–192.

Buchtel, C., & Friston, K. J. (1997). Modulation of connectivity in visual pathways by attention: cortical interations evaluated with structures equation modelling and fMRI. *Cerebral Cortex*, *7*, 768–778.

Chao, L. L., & Knight, R. T. (1995). Human prefrontal lesions increase distractibility to irrelevant sensory inputs. *Neuroreport, 6*, 1605–1610.

Chao, L. L., & Knight, R. T. (1998). Contribution of human prefrontal cortex to delay performance. *J. Cognitive Neuroscience*, *10* (2), 167–177.

Chapin, J. K., & Woodward, D. J. (1981). Modulation of sensory responsiveness of single somatosensory cortical cells during movement and arousal behaviors. *Experimental Neurology*, *72*, 164–178.

Cheng, J., Brooke, J. D., Misiaszek, J. E., & Staines, W. R. (1995). The relationship between the kinematics of passive movement, the stretch of extensor muscles of the leg and the change induced in the gain of the soleus H reflex in humans. *Brain Research*, *672*, 89–96.

Chudler, E. H., & Dong, W. K. (1995). The role of the basal ganglia in nociception and pain. *Pain*, *60*, 3–38.

Cohen, J. D., Braver, S. B., & O'Reilly, R. C. (1996). A computational approach to prefrontal cortex, cognitive control and schizophrenia: recent developments and current challenges. *Philosophical Transactions of the Royal Society of London*, *351*, 1515–1527.

Curran, T., Tucker, D. M., Kutas, M., & Posner, M. I. (1993). Topography of the N400: brain electrical activity reflecting semantic expectancy. *Electroencephalography and clinical Neurophysiology*, *88*, 188–209.

Damasio, A. S. (1985). The frontal lobes. In K. M. Heilman, E. Valenstein, *Clinical neuropsychology* (2nd ed., pp. 339–374). New York: Oxford University Press.

Desmedt, J. E., Hut, N. T., & Bourguet, M. (1983). The cognitive P40, N60 and P100 components of somatosensory evoked potentials and the earliest signs of sensory processing in man. *Electroencephalography and clinical Neurophysiology*, *56*, 272–282.

Edinger, H. M., Siegel, A., & Troiano, R. (1975). Effect of stimulation of prefrontal cortex and amygdala diencephalic neurons. *Brain Research*, *97*, 17–31.

Freedman, R., Adler, L. E., Waldo, M. C., Pachtman, E., & Franks, R. D. (1983). Neurophysiological evidence for a defect in inhibitory pathways in schizophrenia: comparison of medicated and drug-free patients. *Biological Psychiatry*, *18*, 537–551.

Freedman, R., Coon, H., Myles-Worsley, M., Orr-Urtreger, A., Olincy, A., Davis, A., Polymeropoulos, M., Holik, J., Hopkins, J., Rosenthal, J., Waldo, M. C., Reimherr, F., Wender, P., Yaw, J., Young, D. A., Breese, C. R., Adams, C., Parrerson, D., Adler, L. E., Kruglyak, L., Leonard, S., & Byerly, W. (1997). Linkage of a neurophysiological deficit in schizophrenia to a chromosome 15 locus. *Proceedings of the National Academy of Sciences*, *94*, 587–592.

Friedman, H. R., & Goldman-Rakic, P. S. (1994). Coactivation of prefrontal and inferior parietal cortex in working memory tasks revealed by 2DG functional mapping in the Rhesus monkey. *Neuroscience*, *14*, 2775–2788.

Funahashi, S., Burce, C. J., & Goldman-Rakic, P. S. (1993). Dorsolateral prefrontal lesions and oculomotor delayed-response performance: Evidence for mnemonic scotomas. *Journal of Neuroscience*, *13*, 1479–1497.

Fuster, J. M. (1985). The prefrontal cortex, mediator of cross-temporal contingencies. *Human Neurobiology*, *4*, 169–179.

Fuster, J. M. (1989). *The prefrontal cortex: anatomy, physiology, and neuropsychology of the frontal lobe* (2nd ed.). New York: Raven Press.

Galambos, R. (1956). Suppression of auditory nerve activity by stimulation of efferent fibers to the cochlea. *Journal of Neurophysiology*, *19*, 424–437.

Goldman-Rakic, P. S., Selemon, L. D., & Schwartz, M. L. (1984). Dual pathways connecting the dorsolateral prefrontal cortex with the hippocampal formation and parahippocampal cortex in the Rhesus monkey. *Neuroscience*, *12*, 719–743.

Goldman-Rakic, P. S. (1987). Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In F. Plum, *Handbook of physiology: the nervous system* (pp. 373–417). Baltimore: *American Physiology Society Baltimore*.

Gomez-Gonzalez, C. M. G., Clark, V. P., Fan, S., Luck, S. J., & Hillyard, S. A. (1994). Sources of attention-sensitive visual event-related potentials. *Brain Topography*, *7*, 41–51.

Gosh, S., Murray, G. M., Turman, A. B., & Rowe, M. J. (1994). Corticothalamic influences on transmission of tactile information in the ventroposterolateral thalamus of the cat: effect of reversible inactivation of somatosensory cortical areas I and II. *Experimental Brain Research*, *100*, 276–286.

Griffith, J., Hoffer, L. E., Adler, L. E., & Zerbe, G. O. (1995). Effects of sound intensity on a midlatency evoked response to repeated auditory stimuli in schizophrenics and normal controls. *Psychophysiology*, 32, 460–466.

Guillery, R. W., Feig, S. L., & Lozsade, D. A. (1998). Paying attention to the thalamic reticular nucleus. *Trends in Neuroscience*, *21*, 28–32.

Guitton, D., Buchtel, H. A., & Douglas, R.M. (1985). Frontal lobe lesions in man cause difficulties in suppressing reflexive glances and in generating goal-directed saccades. *Experimental Brain Research*, *58*, 455–472.

Hansen, J.C., & Hillyard, S. A. (1980). Endogenous brain potentials associated with selective auditory attention. *Electroencephalogr Clinical Neurophysiology*, *49*, 277–290.

Hier, D. B., Mondlock, J., & Caplan, L. R. (1983). Recovery of behavioral abnormalities after right hemisphere stroke. *Neurology*, *33*, 345–350.

Hillyard, S. A., Hink, R. F., Schwent, U. L., & Picton, T. W. (1973). Electrical signs of selective attention in the human brain. *Science*, *182*, 177–180.

Hillyard, S. A., & Picton, T. W. (1987). Electrophysiology of cognition. In F. Plum, *Handbook of physiology: the nervous system* (pp. 519–584). Baltimore: *American Physiology Society*.

Jacobsen, C. F. (1935). Functions of frontal association areas in primates. *XXX Archives of Neurology and Psychiatry*, *33*, 58–569.

Janowsky, J. S., Shimamura, A. P., Kritchevsky, M., & Squire, L. R. (1989a). Cognitive impairment following frontal lobe damage and its relevance to human amnesia. *Behavioral Neuroscience*, *103*, 548–560.

Janowsky, J. S., Shimamura, A. P., & Squire, L. R. (1989b). Source memory impairment in patients with frontal lobe lesions. *Neuropsychologia*, *27*, 1043–1056.

Jonides, J., Smith, E. E., Koeppe, R. A., Mioshima, S., & Mintun, M. A. (1993). Spatial working memory in humans as revealed by PET. *Nature*, *363*, 623–625.

Kahneman, D., & Treisman, A. (1984). Changing views of attention of automaticity. In R. Parasuraman & R. Davies, *Varieties of attention* (pp. 29–61). San Diego: Academic Press.

Kathman, N., & Engel, R. R. (1990). Sensory gating in normals and schizophrenics: a failure to find strong P50 suppression in normals. *Biological Psychiatry*, *27*, 1216–1226.

Kertesz, A., & Dobrolowski, S. (1981). Right-hemisphere deficits, lesion size and location. *Journal of Clinical Neurophysiology*, *3*, 283–299.

Knight, R. T., Hillyard, S. A., Woods, D. L., & Neville, H. J. (1981). The effects of frontal cortex lesions on event-related potentials during auditory selective attention. *Electroencephalography and Clinical Neurophysiology*, *52*, 571–582.

Knight, R. T. (1984). Decreased response to novel stimuli after prefrontal lesions in man. *Electroencephalography and clinical Neurophysiology*, *59*, 9–20.

Knight, R. T., Scabini, D., & Woods, D. L. (1989a). Prefrontal Cortex gating of auditory transmission in humans. *Brain Research*, *504*, 338–342.

Knight, R. T., Scabini, D., Woods, D. L., & Clayworth, C. C., (1989b). Contribution of the temporal-parietal junction to the auditory P3. *Brain Research*, *502*, 109–116.

Knight, R. T. (1991). Evoked potential studies of attention capacity in human frontal lobe lesions. In H. Levin, H. Eisenberg & F. Benton, *Frontal lobe function and dysfunction* (pp. 139–153). New York: Oxford University Press.

Knight, R. T., (1994). Attention regulation and human prefrontal cortex. In A. M. Thierry, J. Glowinski, P. Goldman-Rakic & Y. Christen (pp. 160–173). *Motor and cognitive functions of the prefrontal cortex.* Research and Perspectives in Neurosciences.

Knight, R. T., & Grabowecky, M. (1995). Escape from linear time: prefrontal cortex and conscious experience. In M. Gazzaniga, *The cognitive neurosciences* (pp. 1357–1371). Cambridge, MA: MIT Press.

Knight, R. T. (1996). Contribution of human hippocampal region to novelty detection. *Nature*, *383*, 256–259.

Knight, R. T. (1997). Distributed cortical network for visual stimulus detection. *Journal of Cognitive Neuroscience*, *9*, 75–91.

Knight, R. T., Finkbeiner, A., & Lawler, R. (in preparation). Prefrontal cortex dysfunction contributes to the schizophrenic P50 gating deficit.

Kraus, N., Ozdamar, O., & Stein, L. (1982). Auditory middle latency responses (MLRs) in patients with cortical lesions. *Electroencephalography and Clinical Neurophysiology*, *54*, 275–287.

Leuders, H., Leser, R. P., Hard, J., Dinner, D. S., & Klem, G. (1983). Cortical somatosensory evoked potentials in response to hand stimulation. *Journal of Neurosurgery*, *58*, 885–894.

Lhermitte, F., Pillon, B., & Serdaru, M. (1986). Human anatomy and the frontal lobes. Part I: Imitation and utilization behavior: A neuropsychological study of 75 patients. *Annals of Neurology*, *19*, 326–334.

Lhermitte, F. (1986). Human autonomy and the frontal lobes. Part II: patient behavior in complex and social situations: the "environmental dependency syndrome". *Annals of Neurology*, *19*, 335–343.

Luck, S. J., Heinze, H. J., Mangun, G. R., & Hillyard, S. A. (1990). Visual event-related potentials index focussed attention within bilateral stimulus arrays. II. Functional dissociation of P1 and N1 components. *Electroencephalography and Clinical Neurophysiology*, *75*, 528–542.

MacKay, W. A., & Crammond, D. J. (1989). Cortical modification of sensorimotor linkages in relation to intended action. In W. A. Hershberger *Volitional action* (pp. 169–193). Elsevier: New York.

Malmo, R. R. (1942). Interference factors in delayed response in monkeys after removal of frontal lobes. *J. Neurophysiology*, *5*, 295–308.

Mangun, G. R., & Hillyard, S. A. (1988). Spatial gradients of visual attention: behavioral and electrophysiological evidence. *Electroencephalography and clinical Neurophysiology*, *70*, 417–428.

Mangun, G. R. (1995). Neural mechanisms of visual selective attention. *Psychophysiology*, *32*, 4–18.

McCallum, W. C. Curry, S. H., Cooper, R., Pocock, P. V., & Papakostopoulos, D. (1983). Brain event-related potentials as indicators of early selective processes in auditory target localization. *Psychophysiology*, *20*, 1–17.

McGhie, A., & Chapman, J. (1961). Disorders of attention and perception in early schizophrenia. *British Journal of Medicine Psychology*, *34*, 103–116.

McIntosh. A. R., Grady, C. L., Ungerleider, L. G., Haxby, J. V., Rapoport, S. I., & Horwitz, B. (1994). Network analysis of cortical visual pathways mapped with PET. *J. Neuroscience*, *14*, 655–666.

Mesulam, M. M. (1981). A cortical network for directed attention and unilateral neglect. *Annals of Neurology*, *10*, 309–325.

Neville, H., Kutas, M., Chesney, G., & Schmidt, A. (1986). Event-related brain potentials during initial encoding and recognition memory of congruous and incongruous words. *Journal of Memory and Language*, *25*, 75–92.

Pandya, D. N., & Barnes, C. L. (1987). Architecture and connections of the frontal lobe. In E. Perecman *The frontal lobes revisited* (pp. 41–72). New York: IRBN.

Petrides, M., Alivasatos, B., Meyer, E., & Evans, A. C. (1993a). Dissociation of human mid-dorsolateral from posterior dorsolateral frontal cortex in memory processing. *Proceedings of the National Academy of Science*, *90*, 873–877.

Petrides, M., Alivisatos, B., Meyer, E., & Evans, A. C. (1993b). Functional activation of the human prefrontal cortex during the performance of verbal working memory tasks. *Proceedings of the National Academy of Science*, *90*, 878–882.

Pierrot-Deseillingny, C. H., Rivaud, S., Gaymard, B., & Agid, Y. (1991). Cortical control of reflexive visually-guided saccades. *Brain*, *114*, 1473–1485.

Raines, G., Azaad, W. F., & Miller, E. K. (1998). Selective representation of relevant information in the primate prefrontal cortex. *Natwe*, *393*, 577–579.

Rajkowska, G., & Goldman-Rakic, P. S. (1995a). Cytoarchitechtonic definition of prefrontal areas in the normal human cortex: I. Remapping of areas 9 and 46 using quantitative criteria. *Cerebral Cortex*, *5*, 307–322.

Rajkowska, G., & Goldman-Rakic, P. S., (1995b). Cytoarchitechtonic definition of prefrontal areas in the normal human cortex: II. Variability in locations of areas 9 and 46 and relationship to the Talairach coordinate system. *Cerebral Cortex*, *5*, 323–337.

Richer, F., Decary, A., Lapierre, M. F., Rouleau, I., Bouvier, G., & Saint-Hilaire, J. M. (1993), Target detection deficits in frontal lobectomy. *Brain and Cognition*, *21*, 203–211.

Roland, P.E. (1982). Cortical regulation of selective attention in man. A regional cerebral blood flow study. *Journal of Neurophysiology*, *48*, 1059–1078.

Shimamura, A. P., Janowsky, J. S., & Squire, L. R. (1990). Memory for the temporal order of events in patients with frontal lobe lesions and amnesic patients. *Neuropsychologia*, *28*, 803–814.

Shimamura, A. P. (1995a). Memory and the frontal lobe. In M. Gazzaniga, *The cognitive neurosciences* (pp. 803–813). Boston: MIT Press.

Shimamura, A. P., Jurica, P. J., Mangels, J. A., Gershberg, F. B., & Knight, R. T. (1995b). Susceptibility to memory interference effects following frontal lobe damage: findings from tests of paired-associated learning. *Journal of Cognitive Neuroscience*, *7*, 144–152.

Shin, H. -C., & Chapin, J. K. (1990a). Modulation of afferent transmission to single neurons in the ventroposterior thalamus during movement in rats. *Neuroscience Letters*, *108*, 116–120.

Shin, H. -C., & Chapin, J. K. (1990b). Movement induced modulation of afferent transmission to single neurons in the ventroposterior thalamus and somatosensory cortex in rat. *Experimental Brain Research*, *81*, 515–522.

Skinner, J. E., & Yingling, C. D. (1977). Central gating mechanisms that regulate event-related potentials and behavior. *Progress in Clinical Neurophysiology*, *1*, 30–69.

Smith, D. A., Boutros, N. A., & Schwarzkopf, S. B. (1994). Reliability of P50 auditory event-related potential indices of sensory gating. *Psychophysiology*, *31*, 495–502.

Stein, S., & Volpe, B. T. (1983). Classic parietal neglect syndrome after subcortical right frontal lobe infarction. *Neurology*, *33*, 797–799.

Stuss, D. T., & Benson, F. (1984). Neuropsychological studies of the frontal lobes. *Psychological Bulletin*, *95*, 3–28.

Stuss, D. T., Benson, D. F. (1986). *The frontal lobes.* New York: Raven Press.

Sutherling, W. W., Crandall, P. H., Darcey, T. M., Becker, D. P., Levesque, M. F., & Barth, D. S. (1988). The magnetic and electric fields agree with intracranial localizations of somatosensory cortex. *Neurology*, *38*, 1705–1714.

Swick, D., & Knight, R. T. (1996). Dorsolateral prefrontal cortex modulates visual processing in extrastriate cortex. *Society for Neuroscience*, *Abstracts*, *22*, 1107.

Swick, D., & Knight, R. T., Lesion (in press). studies of prefrontal cortex modulates visual processing in extrastriate cortex. In R. Parasuraman, *The attentive brain* .

Swick, D., (in press). Effects of prefrontal lesions on lexical processing and repetition priming: and ERP study. *Cognitive Brain Research*.

Treisman, A. M. (1960). Contextual cues in selective listening. Quarterly *Journal of Experimental Psychology*, *12*, 242–248.

Tsumoto, T., Nakamura, S., & Iwama, K. (1975). Pyramidal tract control over cutaneous and kinesthetic sensory transmission in the cat thalamus. *Experimental Brain Research*, *22*, 281–294.

Venables, P. (1964). Input dysfunction in schizophrenia. In B. A. *Maher, Progess in experimental personality research* (pp. 1–47). Orlando: Academic Press.

Vendrell, P., Junque C., Pujol, J., Jurado, M. A., Molet, J., & Grafman, J. (1995). The role of prefrontal regions in the Stroop task. *Neuropsychologia*, *33*, 341–352.

Wada, J.A., Clarke, R., & Hamm, A. (1975). Cerebral hemispheric asymmetry in humans. *Archives of Neurology*, *32*, 239–246.

Webster, M. J., Bachevalier, J., & Ungerleider, L. G. (1994). Connections of inferior temporal areas TEO and TE with parietal and frontal cortex in macaque monkeys. *Cerebral Cortex*, *5*, 470–483.

Weinberger, D.R., Luchins, D.J., Morisha, J., & Wyatt, R. J. (1982). Asymmetric volumes of the right and the left frontal and occipital regions of the human brain. *Annals of Neurology*, *11*, 97–100.

Weinberger, D. R., Berman, K. F., & Zec, R. F. (1986). Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia, I: regional cerebral blood flow evidence. *Archives of General Psychiatry*, *43*, 114–124.

Weinberger, D. R., Berman, K. F., Suddath, R., & Torrey, E. F. (1992). Evidence of dysfunction of a prefrontal-limbic network in schizophrenia: a magnetic resonance imaging and regional blood flow study of discordant monozygotic twins. *American Journal of Psychiatry*, *149*, 890–897.

Woldorff, M. G., & Hillyard, S.A. (1991). Modulation of early auditory processing during selective listening to rapidly presented tones. *Electroencephalograph of Clinical Neurophysiology*, *79*, 170–191.

Wood, C. C., Spencer, D. D., Allison, T., McCarthy, G., Williamson, P. D., & Goff, W. B. (1988). Localization of human sensorimotor cortex during surgery by cortical surface recording of somatosensory evoked potentials. *Journal of Neurosurgery*, *68*, 99–111.

Woods, D. L., & Hillyard, S. A. (1978). Attention at the cocktail party: Brainstem evoked responses reveal no peripheral gating. In D. A. Otto, *Multidisciplinary perspectives in event-related brain potential research* (pp. 230–233). Washington, DC, US Government Printing Office.

Woods, D. L. (1990). The physiological basis of selective attention: implications of event-related potential studies. In J. Rohrbaugh, J. R. Johnson & R. Parasurman, *Event-related brain potentials* (pp. 178–210). New York: Oxford University Press.

Woods, D. L., & Knight, R. T. (1986). Electrophysiological evidence of increased distractibility after dorsolateral prefrontal lesions. *Neurology*, *36*, 212–216.

Woods, D. L, Knight, R. T., & Scabini, D. (1993). Anatomical substrates of auditory selective attention: behavioral and electrophysiological effects of temporal and parietal lesions. *Cognitive Brain Research*, *1*, 227–240.

Yamaguchi, S., & Knight, R. T. (1990). Gating of somatosensory input by human prefrontal cortex. *Brain Research*, *521*, 281–288.

Yamaguchi, S., & Knight, R. T. (1991). Anterior and posterior association cortex contributions to the somatosensory P300. *Journal of Neuroscience*, *11*, 2039–2054.

Yamamoto, T., Samejima, A., & Oka, H. (1988). Short latency activation of local circuit neurons in the cat somatosensory cortex. *Brain Research*, *461*, 199–203.

Yingling, C. D, & Skinner, J. E. (1977). Gating of thalamic input to cerebral cortex by nucleus reticularis thalami. *Progress Clinical Neurophysiology*, *1*, 70–96.