Prefrontal modulation of visual processing in humans

Francisco Barceló[1,2], Shugo Suwazono[2,3] and Robert T. Knight[2]

[1] *Department of Psychobiology, Faculty of Psychology, Complutense University, Somosaguas 28223, Madrid, Spain*

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

[3] *Department of Integrated Neuroscience, Brain Research Institute, Niigata University, Japan*

Correspondence should be addressed to R.T.K. (rtknight@socrates.berkeley.edu)

Single neuron, evoked potential and metabolic techniques show that attention influences visual processing in extrastriate cortex. We provide anatomical, electrophysiological and behavioral evidence that prefrontal cortex regulates neuronal activity in extrastriate cortex during visual discrimination. Event-related potentials (ERPs) were recorded during a visual detection task in patients with damage in dorsolateral prefrontal cortex. Prefrontal damage reduced neuronal activity in extrastriate cortex of the lesioned hemisphere. These electrophysiological abnormalities, beginning 125 ms after stimulation and lasting for another 500 ms, were accompanied by behavioral deficits in detection ability in the contralesional hemifield. The results provide evidence for intrahemispheric prefrontal modulation of visual processing.

Attention allows us to deal efficiently with the myriad of closely spaced and timed environmental events. Visual attention involves modulation of the excitability of extrastriate neurons through descending projections from hierarchically ordered brain structures[1–11]. Single-cell recordings[12–14], lesion studies[15,16] (Rossi *et al.*, *Soc. Neurosci. Abstr.*, **25**, 6.1, 1999) and blood-flow data[17–24] indicate that prefrontal cortex modulates extrastriate processing. Neuroimaging studies provide spatial information regarding brain regions engaged during visual processing, but the temporal dynamics of prefrontal–extrastriate interactions are not well defined in humans[17–20].

Noninvasive scalp recordings of event-related potentials are extensively used to investigate modulation of activity of visual pathways in humans[1–6]. Attended visual stimuli evoke distinct ERP signatures. Attention enhances amplitudes of early positive P1 (110–160 ms) and negative N1 (125–225 ms) brain potentials, which originate from ventral and dorsal extrastriate pathways[6,25–28]. Homologs of these early human ERP components are linked to increased firing of V4 neurons in monkeys[6,25–28]. In contrast, a negative N2 (250–450 ms) potential, which is maximal over posterior inferior temporal scalp, is evoked only by detected targets in a stream of attended visual stimuli and is related to post-discrimination processes[3,5,30]. Dipole source analyses propose N2 generators in the inferior temporal cortex[5,30].

Here we assessed ERPs and behavioral performance in patients with prefrontal damage engaged in a difficult bi-field visual-discrimination task. ERPs were recorded from ten patients with unilateral focal lesions in the dorsolateral prefrontal cortex and ten age-matched controls. Subjects detected inverted triangles (targets) embedded in rapid trains of upright triangles (standards) randomly presented to the ipsilesional and contralesional visual fields. Prefrontal damage decreased neural responses recorded from ipsilesional extrastriate cortex for both visual standards and targets. Electrophysiological deficits consisted of diminished early extrastriate responses to all stimuli (125 ms) together with prominent reductions of post-selection target-related neuronal activity (200–650 ms) in inferior temporal areas of the lesioned hemisphere. These electrophysiological deficits in extrastriate processing were accompanied by deficits in detection in the contralesional visual field.

Results

Behavior

Controls correctly reported 93.9% of targets as compared with an overall 82.3% correct rate in patients ($F_{1,18} = 7.5$, $p < 0.02$). There was an interaction between group and field of presentation, with prefrontal patients showing a target detection deficit in the contralesional field (for miss rate, $F_{1,18} = 7.6$, $p < 0.01$; **Fig. 1a**). Overall mean response times were not slower in patients versus controls, although a trend was observed (579 ± 61 ms and 531 ± 49 ms, respectively; $F_{1,18} = 3.65$, $p < 0.07$). An interaction between group and visual field revealed that the patients' reaction times were prolonged to contralesional as compared with ipsilesional targets ($F_{1,18} = 42.1$, $p < 0.0001$; **Fig. 1a**).

Electrophysiology

Prefrontal patients (**Fig. 1b**) and controls showed the normal pattern of larger early ERPs over temporo-occipital regions contralateral to the visual field of stimulation (across groups, $F_{1,18} = 8.9$, $p < 0.01$ for the P1 responses at contralateral versus ipsilateral temporo-occipital sites; $F_{1,18} = 45.7$, $p < 0.0001$ for the N1 response). However, P1 responses to standard stimuli were reduced in patients as compared with controls, but only in the hemisphere ipsilateral to prefrontal damage ($p < 0.05$ for contralesional standards at Pi; $p < 0.01$ for both contra- and ipsilesional standards at TOi; **Fig. 2a** and **3a**). Contralesional targets also evoked reduced P1 responses at the ipsilesional temporo-occipital areas of patients ($p < 0.01$; data not shown). P1 latencies were shortened at the temporo-occipital electrode ipsilateral to prefrontal damage ($p < 0.005$; 125 ms for patients; 145 ms for

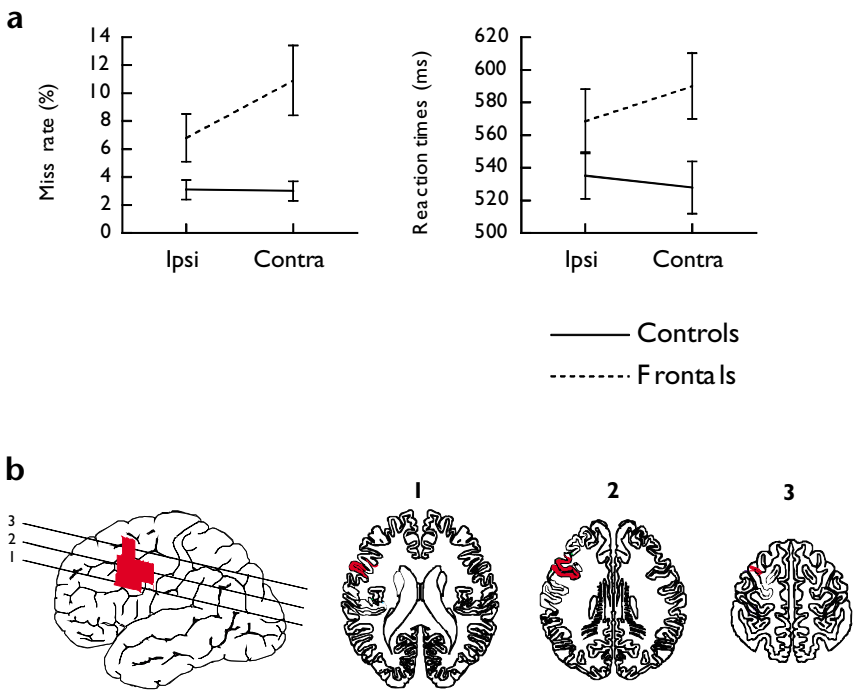

Fig. 1. Visual attention deficits and prefrontal lesions. (**a**) Behavioral indices of attention. Miss rate (left) and reaction times (right) for patients and controls as a function of the visual field of target presentation (Contra, contralesional field for patients, right field for controls; Ipsi, ipsilesional field for patients, left field for controls). A 'miss' was defined as a failure to respond 300–800 ms following a target. The interaction between group and visual field was significant for both measures. Vertical bars indicate s.e. (**b**) Group-averaged reconstruction of the extent of prefrontal damage. Both left and right prefrontal lesions are reflected onto the left side for averaging. Maximal lesion overlap (>67%) was observed in Brodmann areas 6, 8, 9 and 46 and encompassed portions of the middle and superior frontal gyri. The average tissue loss was 41.4 cm^3 per patient. Software permitted reconstruction of the lateral perspective of lesions, determination of lesion volumes and putative cytoarchitectonic areas damaged.

controls). N1 amplitude and latency did not differ between groups at TOi (205 ms for patients; 203 ms for controls). Prefrontal lesions abolished the N2 component and reduced the P3b response to target stimuli generated in the ipsilesional extrastriate cortex ($F_{1,18} = 15.1$, $p < 0.001$ for N2 at TOi; $F_{1,18} = 7.5$, $p < 0.02$ for P3b at TOi; **Figs. 2b** and **3d** and **e**).

Difference waveforms associated with target-discrimination processes were computed by subtracting ERPs for the standard from the target ERPs[5,30–32]. This differential activation encompassed an early negativity (peak latency, 203 ms at T5; **Fig. 2b**) and the N2 (peak latency, 365 ms at T5) as well as subsequent target-related P3b activity (peak latency, 580 ms at Pz). The scalp topography of the early negativity was similar to that of the N1 response, with a maximum at temporo-occipital sites contralateral to stimulation (compare scalp topography of N1 versus early target-related negativity; **Fig. 3b** and **c**). To assess prefrontal contributions to this post-discrimination activation, we measured difference-ERP amplitudes in consecutive 50-ms windows from 0 to 700 ms post-stimulus. Grand means from three representative time windows are shown (**Fig. 3c–e**). Significant interactions were observed among group, hemisphere and field of stimulation starting 200 ms post-stimulus, with the topography of these effects changing rapidly over time. Frontal patients showed reduced difference-wave amplitudes 200–250 ms after stimulation at the ipsilesional temporo-occipital area ($p < 0.05$; **Fig. 3c**). This ipsilesional reduction in amplitude was significant only when stimuli were presented to the contralesional visual field ($F_{1,18} = 5.96$, $p < 0.03$; **Fig. 3c**). Patients had a prominent N2 (365 ms) amplitude reduction over central, temporo-occipital, parietal and occipital areas of the lesioned hemisphere ($p < 0.001$; **Figs. 2b** and **3d**). N2-amplitude effects were independent of the visual field of display, occurring for stimuli presented either ipsilateral or contralateral to prefrontal damage. This effect was supported by a significant main interaction between group and hemisphere, but not field of stimulation from 350–450 ms after stimulus delivery ($F_{1,18} = 9.96$, $p < 0.006$; **Fig. 3d**).

Topographical analyses of normalized ERP amplitudes confirmed that different scalp voltage distributions accompanied the early and late difference-wave effects[33]. In both groups, voltage distribution of difference waves for the earliest target selection effects (200–250 ms post-stimulus) were strongly lateralized, with maximal intensity occurring at the temporo-occipital electrode contralateral to stimulation ($F_{1,18} = 28.9$; $p < 0.001$ for the linear trend; **Fig. 3c**). A change in topography of the scalp voltage distribution occurred from 350 to 450 ms after stimulation, resulting a U-shaped distribution with maximal amplitudes over temporo-occipital sites contralateral to stimulation ($F_{1,18} = 47.2$, $p < 0.001$ for the quadratic trend; **Fig. 2b**). The initially contralateral N2 became progressively bilaterally distributed (**Fig. 3d**). Frontal patients also showed reduced P3b responses over ipsilesional temporo-occipital areas ($F_{1,18} = 4.8$, $p < 0.05$; **Figs. 2b** and **3e**), but not over midparietal regions. This effect could not be attributed to group differences in P3b peak latency at Pz (controls, 580 ms; prefrontal-lesioned, 570 ms; $p = 0.8$).

Discussion

Unilateral prefrontal lesions impaired the ability to detect visual targets presented rapidly in the visual field contralateral to damage. This behavioral deficit was accompanied by reduced early (125 ms) and longer-latency (200–650 ms) neuronal activity generated in extrastriate regions of the lesioned hemisphere. The results provide information about the nature and timing of disrupted extrastriate processing after prefrontal damage.

Three distinct neural mechanisms seem compromised by prefrontal damage in this difficult bi-field discrimination task. First, prefrontal damage reduced stimulus-evoked P1 activity to standards and targets alike over ipsilesional parietal and temporo-occipital areas. The P1 peak measures neural activity in the dorsal and ventral divisions of extrastriate cortex[6,25–28,34]. These early P1 differences suggest a deficit in tonic prefrontal modulation of attention to the contralateral visual field. Our protocol required simultaneous attention to both fields. Thus, we cannot distinguish whether the P1 reduction subsequent to prefrontal damage may be further frac-

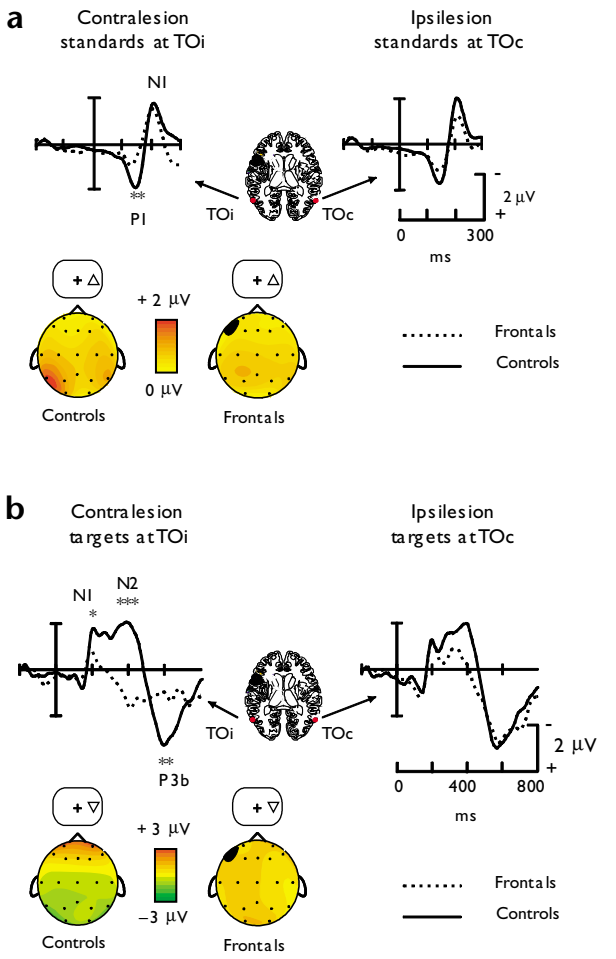

Fig. 2. Early and late ERPs and voltage maps. (**a**) Group-averaged ERPs to contralesion standards as recorded from the ipsilesional temporo-occipital electrode (TOi for patients, T5 for controls), and ERPs to ipsilesion standards as recorded from the contralesional electrode (TOc for patients, T6 for controls). Voltage maps show the distribution of the P1 peak to contralesional standards (that is, right standards for controls). The P1 peak reached a maximum over the T5 electrode in the control group, but was significantly reduced in the patients. (**b**) Group averages of the difference waveforms (targets minus standards) evoked by contralesional stimulation at the ipsilesional temporo-occipital electrode (TOi for patients, T5 for controls), and evoked by ipsilesional stimuli at the contralesional temporo-occipital electrode (TOc for patients, T6 for controls). Voltage maps show the difference wave averaged over 350–450 ms poststimulation (N2). The N2 response to contralateral targets observed in controls was absent over the ipsilesional extrastriate area of frontal patients. The subsequent P3b was reduced at TOi. Asterisks indicate significant group differences in amplitude: $*p < 0.05$; $**p < 0.01$; $***p < 0.001$.

tionated into pre-stimulus (tonic) versus stimulus-locked (phasic) attention-specific components[6,18–20,26,34]. In contrast with the deficit in P1 modulation for all contralesional stimuli, target-specific activity recorded from extrastriate cortex within the first 200 ms did not differ between patients and controls (**Fig. 2b**). These results are compatible with the notion that the post-selection analysis of target features may not have initiated at this early processing stage.

Second, with further analysis of target features, we observed a deficit in ERP responses to contralesional targets over ipsilesional temporo-occipital areas that lasted from 200 to 300 ms after the stimulus. This time window encompassed an early negativity starting at the N1 peak and lasting to N2 onset (**Figs. 2b** and **3c**). Early target-specific activity (200–250 ms) had a scalp distribution similar to that for the N1 response, and may reflect a normal enhancement of the N1 generator that is reduced in prefrontal patients. The findings indicate that prefrontal lesions disrupted the activation of neural populations in ipsilesional inferior temporal cortex that are specialized in the early analysis of object features[6,7,9,27]. The temporal parameters of this target-specific modulation are in accord with single-neuron recordings in monkeys revealing enhanced prefrontal target-related activity 140 ms after stimulus onset[13] and top-down activation of inferior temporal neurons 178–300 ms after target detection[11], providing some convergence between the monkey single-neuron and human ERP data.

Third, unilateral prefrontal lesions abolished N2 (350–450 ms) and P3 (450–650 ms)activity at ipsilesional inferior temporal areas in response to targets presented both contra- and ipsilesionally. In controls, the N2 was initially contralateral, with maximal amplitude occurring in inferior temporo-occipital areas[5,30]. The N2 response became progressively evident at temporo-occipital sites in both hemispheres, regardless of the visual field of stimulation[15,19,30]. Because N2 is triggered after target selection, it is proposed to measure post-selection target-feature analysis within inferior temporo-occipital cortex that requires bilateral hemispheric interaction[5,6,24,30]. Impairments in this longer-latency interhemispheric interaction may contribute to some of the more global processing deficits frequently observed following prefrontal damage.

In monkeys, prefrontal cortex projects to inferior temporal cortex[7,10,11]. Single-cell studies show that prefrontal neurons discharge tonically even in the absence of stimulation, possibly reflecting active maintenance of an attention template in working memory[7,12,13,35]. A deficit in this tonic maintenance capacity may be reflected initially by lowered ipsilesional extrastriate P1 responses to all stimuli. It is possible that target matching to a tonically maintained extrastriate template could trigger later ERP components. However, given evidence obtained in monkeys performing detection tasks[11], a phasic facilitory input from prefrontal cortex is probably involved in triggering post-selection activity in the ensuing 200–650 ms after target detection. Prefrontal lesions may disrupt this later phasic intrahemispheric re-entrant feedback mechanism between prefrontal and extrastriate cortex. This signal would provide the neural enhancement required for a full post-selection analysis of object features in extrastriate cortex[35]. Our evidence for task-specific intrahemispheric control of visual processing is in accord with other lesion data supporting intrahemispheric prefrontal control of auditory[36] and motor processing[37].

Visual attention involves the tonic activation of a template or representation of the sought-after stimulus that can be used to guide top-down selection of object features and spatial locations[7]. Single-cell recordings in animals[11–14,35] and neuroimaging studies in humans[17–21,23] provide evidence that dorsolateral prefrontal cortex is important for holding these temporary representations in working memory. Within this framework, we propose that damage in a prefrontal–extrastriate intrahemispheric network disrupts early activation and subsequent post-perceptual matching of templates held in working memory with incoming sensory information. Evidence from lesions, although clearly implicating dorsolateral prefrontal cortex in extrastriate processing, does not permit a more fine-grained neuroanatomical analysis of the prefrontal subregions involved in tonic versus pha-

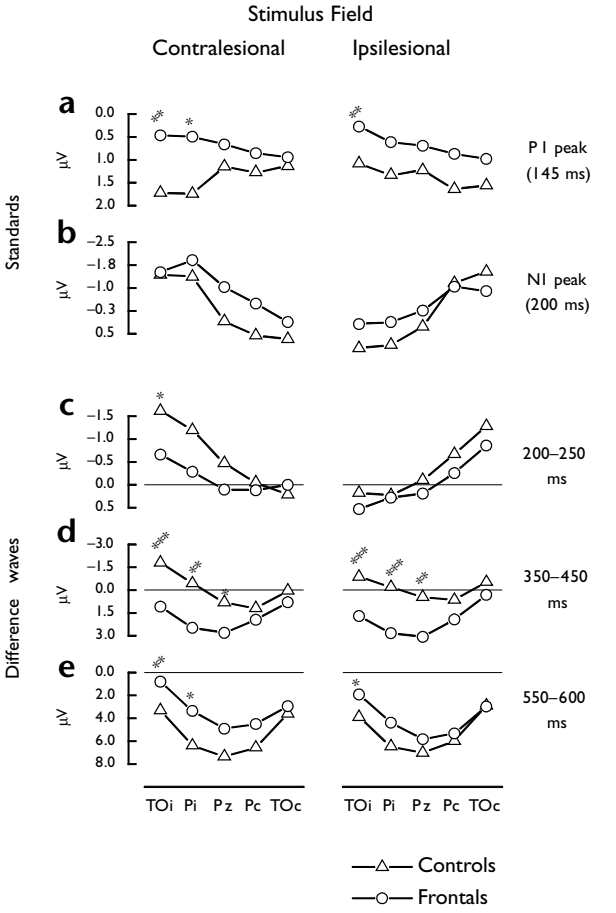

Fig. 3. Scalp topography of early and late extrastriate responses. Scalp distribution of grand mean ERP amplitudes for prefrontal patients and controls at ipsilesional and contralesional temporo-occipital (TOi/TOc), parietal (Pi/Pc) and midparietal (Pz) areas, plotted as a function of the field of stimulus presentation. (**a**, **b**) Mean amplitudes of early P1 and N1 responses to standards. (**c**–**e**) Mean difference waves (target minus standard) from three time-windows after stimulation. Changes from 0 μV reflect differential ERP responses to targets as compared with standards. Note the different voltage scales for different ERP measures. Asterisks indicate significant group differences: *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

sic extrastriate processing. Damage was maximal in areas 6, 8, 9 and 46 of the middle and superior prefrontal gyrus and extended into other prefrontal fields in individual patients.

In summary, neuroimaging studies implicate prefrontal cortex in the modulation of extrastriate responses to attended sensory events[17–21,23]. We used the temporal resolution of event-related potentials coupled with lesion analysis to demonstrate that prefrontal cortex regulated visual processing in extrastriate cortex as early as 125 milliseconds after stimulus delivery, and that subsequent visual processing depended on prefrontal cortex throughout the ensuing 500 milliseconds.

Methods

Patient selection. Ten patients were selected on the basis of a unilateral focal lesions to their dorsolateral prefrontal cortex as determined by computed tomography (CT) or magnetic resonance imaging (MRI) scanning. Lesions were due to single stroke (nine patients) or craniotomy (one patient) and were restricted to lateral prefrontal cortex. Maximal lesion overlap (>67% across patients) comprised Brodmann's areas 6, 8, 9 and 46 (**Fig. 1b**; refs. 38, 39). Variable amounts of damage in Brodmann's areas 6, 8, 9, 10, 44, 45 and 47 occurred in individual patients. There were three right- and seven left-lesioned patients. Testing took place at least one year after injury. Medical complications, psychiatric disturbance, substance abuse, psychoactive drug treatment or other neurological diseases were criteria for exclusion. All patients had normal or corrected-to-normal visual acuity. Three patients had upper-motor-neuron weakness in the limbs contralateral to their lesions and responded with their ipsilesional limbs. The average age of patients was 65.4 ± 13.5 years (3 female; 7 male). Patients were matched by 10 controls free of neurological or psychiatric disease for age (66.3 ± 6.5 years), sex and education. The research was approved by the Human Subjects Review Committees of the Martinez Veterans Administration Research Service and the University of California.

Stimuli and procedure. Subjects sat in a comfortable chair 1.6 m from a video monitor in a sound-attenuated recording chamber. They were instructed to fixate a central yellow crosshair and to press a button upon detection of randomly occurring targets embedded in streams of task-irrelevant stimuli delivered to both visual hemifields. Thus, subjects were required to continuously allocate attention across the entire visual field. We chose this bi-field attention task to reduce the possibility of differential effort or arousal that could arise from a blocked design. We reasoned that if patients had problems in detecting contralesional targets, blocked hemifield design might result in reduced effort, compounding any behavioral deficit. Targets were inverted triangles interspersed within trains of repetitive, upright triangles (standards) and task-irrelevant unique, novel, color images such as pictures of fish or flowers. The probability associated with each stimulus type was 20%, 70% and 10% for targets, standards and novels, respectively. Stimuli were presented for 107 ms either 5° to the left or 5° to the right of the central crosshair. Interstimulus intervals were either 200 ms or 900 ms (Bernoulli distribution with $p = 0.5$), and 2 targets were never presented sequentially. All stimuli subtended 5° of visual angle and were matched in luminance. The background luminance was 0.4 foot-lamberts and the stimuli were 5.2 foot-lamberts. To avoid fatigue, data were gathered in 2 separate 1-h sessions run several days apart; each session consisted of 12 blocks of ~150 stimuli. Subjects were instructed to respond as quickly as possible to targets in any location. To respond, the right hand was used by all subjects but three patients with motor weakness, who responded with the hand ipsilateral to the lesioned hemisphere. Behavioral performance was comparable between these three patients and the other seven prefrontal patients. A 'hit' was defined as a correct detection 300–800 ms following target presentation. Failure to respond in that window was recorded as a 'miss'. We examined responses to visual standards and targets not preceded by novel stimuli, as prefrontal lesions modify novelty-related neuronal processing in all modalities. Here we also observed altered novelty processing; these effects are discussed elsewhere[40,41].

ERP recording and analysis. Brain electrical activity was recorded from tin electrodes placed at 19 scalp sites (Fp1, Fpz, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1 and O2) according to the 10–20 system. The electro-oculogram (EOG) was measured with four electrodes attached to the left and right canthi of both eyes, as well as beneath and above the outer edge of the left eye. Electrode impedances were kept below 5 kΩ. All sites were referenced to linked mastoids. The EEG was amplified (band pass, 0.1–100 Hz), digitized (256 Hz per channel) and digitally stored in a PC for off-line analysis. The averaging epoch was 1024 ms, including a 200-ms baseline. Trials were automatically rejected from further analysis on the basis of blinks, EMG artifacts in the scalp channels (peak-to-peak amplitude, 80 μV) or lateral eye movements as monitored in the horizontal EOG. The mean rejection rate was 14.8% for left hemifield-target trials and 14.6% for right hemifield-target trials, with no significant differences noted between patients and controls.

As behavioral and electrophysiological performance were comparable for left- and right-lesioned prefrontal patients, performance and electrophysiological data are presented for stimuli delivered in the visual field ipsilateral or contralateral to the lesion. For example, TOi refers to the averaged ERP data from the T5 electrode for left prefrontal lesions com-

bined with data from the T6 electrode from right prefrontal lesions. Similarly, Pi equals P3 for left lesions averaged with P4 electrode data from right lesions. Ipsilesional ERP data were compared to left hemisphere ERP data from controls, and *vice versa*. Although no significant differences were noted between left- and right-lesioned patients, power considerations due to the size of the groups precluded definitive conclusions about hemispheric laterality.

Target-related mean and peak amplitudes of ERP components were measured relative to a 200-ms prestimulus baseline. Early extrastriate ERPs for standards were measured in windows of 110–155 ms for the P1 and 190–210 ms for the N1. Target-related components were measured in similar windows for the P1 and N1 and in windows of 350–370 ms for the N2 and 560–600 for the target P3b. Peak latencies for these components were measured relative to target onset. For statistical tests of scalp topography, mean ERP amplitudes were subjected to a series of ANOVAs with group (patients, controls) as the between-subject factor and visual hemifield (ipsilesional, contralesional), hemisphere (lesioned, intact) and electrode (central, temporo-occipital, parietal and occipital) as the repeated measures factors. Separate ANOVAs carried out on ERP activity from electrodes F7, F3, F4 and F8 did not reveal significant group differences at frontal areas. A finer temporal analysis of the attention effects was performed on the difference waveforms obtained by subtracting the standard ERPs from the target ERPs[31,32]. Mean difference-wave amplitudes were measured in consecutive 50-ms windows from 0 to 700 ms post-stimulus. Amplitudes were then normalized to assess the scalp distribution of voltages independent of source strength. Vector length was defined as the square root of the sum of squared difference-wave amplitudes over all locations, calculated separately for each group and visual hemifield[33]. Percentages of hits and misses, as well as hit response times were analyzed by ANOVA with group and visual hemifield as independent factors. Significance levels are reported using the uncorrected degrees of freedom. When appropriate, we used Greenhouse-Geisser corrections to yield corrected probability values.

Acknowledgements

Supported by Fundación Complutense del Amo, Comunidad de Madrid grant 08.5/0012/98 and NINDS grant NS21135. We thank Clay C. Clayworth for technical support. An earlier version of this work was presented at the 39th Meeting of the Society for Psychophysiological Research (Granada 1999).

RECEIVED 2 NOVEMBER 1999; ACCEPTED 10 FEBRUARY 2000

1. Hillyard, S. A., Mangun, G. R., Woldorff, M. G. & Luck, S. J. in *The Cognitive Neurosciences* (ed. Gazzaniga, M. S.) 665–681 (MIT Press, Cambridge, Massachusetts, 1995).
2. Hillyard, S. A. & Anllo-Vento, L. Event-related brain potentials in the study of visual selective attention. *Proc. Natl. Acad. Sci. USA* **95**, 781–787 (1998).
3. Luck, S. J. Multiple mechanisms of visual-spatial attention: recent evidence from human electrophysiology. *Behav. Brain Res.* **71**, 113–123 (1995).
4. Müller, M. M., Teder-Salejarvi, W. & Hillyard, S. A. The time course of cortical facilitation during cued shifts of spatial attention. *Nat. Neurosci.* **1**, 631–634 (1998).
5. Wijers, A. A., Lange, J. J., Mulder, G. & Mulder, L. J. M. An ERP study of visual spatial attention and letter target detection for isoluminant and nonisoluminant stimuli. *Psychophysiology* **34**, 553–565 (1997).
6. Mangun, G. R. Neural mechanisms of visual selective attention. *Psychophysiology* **32**, 4–18 (1995).
7. Desimone, R. & Duncan, J. Neural mechanisms of selective visual attention. *Annu. Rev. Neurosci.* **18**, 193–222 (1995).
8. Posner, M. I. & Dehaene, S. Attentional networks. *Trends Neurosci.* **17**, 75–79 (1994).
9. Webster, M. J. & Ungerleider, L. G. in *The Attentive Brain* (ed. Parasuraman, R.) 19–34 (MIT Press, Cambridge, Massachusetts 1999).
10. Webster, M. J., Bachevalier, J. & Ungerleider, L. G. Connections of inferior temporal areas TEO and TE with parietal and frontal cortex in macaque monkeys. *Cereb. Cortex* **5**, 470–483 (1994).
11. Tomita, H., Ohbayashi, M., Nakahara, K., Hasegawa, I. & Miyashita, Y. Top-down signal from prefrontal cortex in executive control of memory retrieval. *Nature* **401**, 699–703 (1999).
12. Wilson, F. A. W., Scalaidhe, P. O. & Goldman-Rakic, P. S. Dissociation of object and spatial processing domains in primate prefrontal cortex. *Science* **260**, 1955–1958 (1993).
13. Rainer, G., Asaad, W. F. & Miller, E. K. Selective representation of relevant information by neurons in the primate prefrontal cortex. *Nature* **393**, 577–579 (1998).
14. Rao, S. C., Rainer, G. & Miller, E. K. Integration of what and where in the primate prefrontal cortex. *Science* **276**, 821–824 (1997).
15. Knight, R. T. A distributed cortical network for visual attention. *J. Cogn. Neurosci.* **9**, 75–91 (1997).
16. Nielsen-Bohlman, L. C. & Knight, R. T. Prefrontal cortex involvement in visual working memory. *Cogn. Brain Res.* **8**, 299–310, 1999.
17. Büchel, C. & Friston, K. J. Modulation of connectivity in visual pathways by attention: Cortical interactions evaluated with structural equation modeling and fMRI. *Cereb. Cortex* **7**, 768–778 (1997).
18. Chawla, D., Rees, G. & Friston, K. J. The physiological basis of attentional modulation in extrastriate visual areas. *Nat. Neurosci.* **2**, 671–676 (1999).
19. Rees, G., Frackowiak, R. & Frith, C. Two modulatory effects of attention that mediate object categorization in human cortex. *Science* **275**, 835–838 (1997).
20. Kastner, S., Pinsk, M. A., De Weerd, P., Desimone, R. & Ungerleider, L. G. Increased activity in human visual cortex during directed attention in the absence of visual stimulation. *Neuron* **22**, 751–761 (1999).
21. McIntosh, A. R. *et al.* Network analysis of cortical visual pathways mapped with PET. *J. Neurosci.* **14**, 655–666 (1994).
22. Corbetta, M., Miezin, F. M., Shulman, G. L. & Petersen, S. E. A PET study of visuospatial attention. *J. Neurosci.* **13**, 1202–1226 (1993).
23. Corbetta, M. Frontoparietal cortical networks for directing attention and the eye to visual locations: Identical, independent, or overlapping neural systems? *Proc. Natl. Acad. Sci. USA* **95**, 831–838 (1998).
24. Tootell, R. B. H. *et al.* The retinotopy of visual spatial attention. *Neuron* **21**, 1409–1422 (1998).
25. Heinze, H. J. *et al.* Combined spatial and temporal imaging of brain activity during visual selective attention in humans. *Nature* **372**, 543–546 (1994).
26. Martinez, A. *et al.* Involvement of striate and extrastriate visual cortices areas in spatial attention. *Nat. Neurosci.* **2**, 364–369 (1999).
27. Clark, V. P., Fan, S. & Hillyard, S. A. Identification of early visual evoked potential generators by retinotopic and topographic analyses. *Hum. Brain Mapp.* **2**, 170–187 (1995).
28. Woldorff, M. G. *et al.* Retinotopic organization of early visual spatial attention: effects as revealed by PET and ERP data. *Hum. Brain Mapp.* **5** 280–286 (1997).
29. Luck, S. J., Chelazzi, L., Hillyard, S. A. & Desimone, R. Neural mechanisms of spatial selective attention in areas V1, V2, and V4 of macaque visual cortex. *J. Neurophysiol.* **77**, 24–42 (1997).
30. Smid, H. G. O. M., Jakob, A. & Heinze, H.-J. An event-related brain potential study of visual selective attention to conjunctions of color and shape. *Psychophysiology* **36**, 264–279 (1999).
31. Hansen, J. C. & Hillyard, S. A. Endogenous brain potentials associated with selective auditory attention. *Electroencephalogr. Clin. Neurophysiol.* **49**, 277–290 (1980).
32. Karayanidis, F. & Michie, P. T. Evidence of visual processing negativity with attention to orientation and color in central space. *Electroencephalogr. Clin. Neurophysiol.* **103**, 282–297 (1997).
33. McCarthy, G. & Wood, C. C. Scalp distributions of event-related potentials: an ambiguity associated with analysis of variance models. *Electroencephalogr. Clin. Neurophysiol.* **62**, 203–208 (1985).
34. Valdes-Sosa, M., Bobes, M. A., Rodríguez, V. & Pinilla, T. Switching attention without shifting the spotlight: object-based attentional modulation of brain potentials. *J. Cogn. Neurosci.* **10**, 137–151 (1998).
35. Miller, E. K. The prefrontal cortex: Complex neural properties for complex behavior. *Neuron* **22**, 15–17 (1999).
36. Chao, L. L. & Knight, R. T. Contribution of human prefrontal cortex to delay performance. *J. Cogn. Neurosci.* **10**, 167–177 (1998).
37. Rosahl, S. K. & Knight, R. T. Role of prefrontal cortex in generation of the contingent negative variation. *Cereb. Cortex* **2**, 123–134 (1995).
38. Rajkowska, G. & Goldman-Rakic, P. S. Cytoarchitechtonic definition of prefrontal areas in the normal human cortex: I. Remapping of areas 9 and 46 using quantitative criteria. *Cereb. Cortex* **5**, 307–322 (1995).
39. Rajkowska, G. & Goldman-Rakic, P. S. 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. *Cereb. Cortex* **5**, 323–337 (1995).
40. Knight, R. T. & Scabini, D. Anatomic bases of event-related potentials and their relationship to novelty detection in humans. *J. Clin. Neurophysiol.* **15**, 3–13 (1998).
41. Knight, R. T. Decreased response to novel stimuli after prefrontal lesions in man. *Electroencephalogr. Clin. Neurophysiol.* **59**, 9–20 (1984).