Distributed Cortical Network for Visual Attention

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Abstract

The contribution of prefrontal and posterior association cortex to voluntary and involuntary visual attention was assessed using electrophysiological techniques in patients with focal lesions in prefrontal (n = 11), temporal-parietal (n = 10), or lateral parietal cortex (n = 7). Subjects participated in a task requiring detection of designated target stimuli embedded in trains of repetitive stimuli. Infrequent and irrelevant novel visual stimuli were randomly interspersed with the target and background stimuli. Controls generated attention dependent N1 (170 msec) and N2 (243 msec) potentials maximal over extrastriate cortex. Anterior and posterior association cortex lesions reduced the amplitude of both the N1 and N2 potentials recorded over extrastriate cortex of the lesioned hemisphere. The pattern of results obtained reveals that an intrahemispheric network involving prefrontal and posterior association cortex modulates early visual processing in extrastriate regions. Voluntary target detection generated a parietal maximal P300 response (P3b) and irrelevant novel stimuli generated a more fronto-centrally distributed P300 (P3a). Cortical lesions had differential effects on P3a and P3b potentials. The P3b was not significantly reduced in any cortical lesioned group. Conversely, the P3a was reduced by both prefrontal and posterior lesions with decrements most severe throughout the lesioned hemisphere. These data provide evidence that an association cortex network involving prefrontal and posterior regions is activated during orientation to novel events. The lack of a significant effect on the visual target P3b in patients with novelty P3a reductions supports the notion that different neural systems are engaged during voluntary vs involuntary attention to visual stimuli.

INTRODUCTION

Visual attention modulates event-related potentials (ERPs) as early as 75 msec poststimulus presentation. Focused visual attention enhances the amplitude of the extrastriate P1 and N1 potentials to all stimuli in an attended channel (Gonzalez et al., 1994). This enhancement occurs in the initial 200 msec poststimulus delivery and varies as a function of the degree of sustained or phasic attention (Heinzl et al., 1990; Luck et al., 1990). Detection of an infrequent stimulus in an attended visual channel generates an N2 potential followed by a prominent scalp P300 response. The P300 component of the human event-related potential (ERP), first reported in 1965 (Sutton et al., 1965; Desmedt et al., 1965), has been the subject of extensive research in both normal and clinical populations. P3-like potentials have been reported in rats, cats, and monkeys supporting a broad ethological significance (see Swick et al., 1994 for an extensive review).

Theories centered around attention and memory processing have been proposed to account for the cognitive basis of the P300, although no clear consensus has emerged (Verleger, 1988; Donchin & Coles, 1988). Some of this disagreement is due to the fact that the P300 is not a unitary brain potential but measures activation of multiple neocortical and limbic regions. Support for this is provided by scalp topographical studies in normals (Squires et al., 1975; Courchesne et al., 1975; Yamaguchi & Knight, 1991a; Ruchkin et al., 1990a, b; Ruchkin et al., 1992; Bruynant et al., 1993), intracranial recording in epileptic patients (McCarthy et al., 1989; Puce et al., 1991; Paller et al., 1992; Halgren et al., 1995a, 1995b; Baudena et al., 1995) and lesion studies in neurological patients (Knight, 1984; Knight et al., 1989b; Yamaguchi & Knight, 1991b; Yamaguchi & Knight, 1992; Scabini, 1992; Knight, 1996).

Long latency positive scalp potentials differing in scalp topography and latency have been linked to voluntary and involuntary attention and to different aspects of memory processing. Voluntary detection of a task relevant stimulus in either the visual, auditory, or somatosensory modality generates a prominent P300 response maximal over posterior scalp regions (P3b). One proposal is that the P3b is generated during closure of a perceptual task (Verleger, 1988). According to this theory, the P3b is generated during completion of a discrete epoch of stimulus processing and measures inhibition of regional activity involved in processing of expected stimuli (Heit et al., 1990; Schupp et al., 1994). This theory has
the strength of being directly testable in animal P300 models although no such data are available at present. Another prominent theory is that the P3b indexes updating of information in working memory (Donchin & Coles, 1988). Other proposals such as those linking P3b and template matching may be subsumed under the concept of context updating in working memory (Baddeley 1992a, b; Chao et al., 1995). The modality-specific nature of the P3b has also been extensively studied. Topographical EEG studies in normals (Barrett et al., 1987; Johnson, 1989b; but see Naumann et al., 1992), temporal lobectomy patients (Johnson, 1989a) and callosal sectioned patients (Kutas et al., 1990), in addition to magnetoencephalographic studies in normals (Rogers et al., 1991, 1992, 1993a), report that there are modality specificity contributions to the P3b.

Delivery of an irrelevant novel stimulus generates a P300 response (P3a) over widespread anterior and posterior scalp sites. The P3a typically has a more fronto-central scalp distribution and an earlier peak latency than the P3b and has been proposed to be a central marker of the orienting response (Sokolov, 1963; Squires et al., 1975; Courchesne et al., 1975; Knight, 1984; Yamaguchi & Knight, 1991a). A longer latency, posterior scalp positivity generated during recognition memory tasks (~600 msec) predicts subsequent retrieval of memory for the eliciting stimulus and may be distinct from the P3b based on scalp topography and intracranial recording (Neville et al., 1986; Paller et al., 1987; Puce et al., 1991; Rugg, Roberts, Potter, Pickles, & Nagy, 1991; Smith & Guster, 1993).

Intracranial recording also supports the view that multiple cortical and limbic regions are activated during the scalp P3b time window (Smith et al., 1990; Halgren et al., 1995a, 1995b; Baudena et al., 1995). Studies reporting intact parietal P3b's in patients with mesial temporal damage due to hypoxia (Polich & Squires, 1993), anterior temporal lobectomy (Johnson, 1988), Herpes simplex encephalitis (Onofrj et al., 1992; O'Donnell et al., 1993), tumor (Rugg, Pickles, Potter, & Roberts, 1991), and hippocampal infarction (Knight, 1996; Knight & Grubowecy, 1994) indicate that although the hippocampus is activated by stimuli that generate scalp P3b potentials, it is unlikely that the brunt of the scalp P3b at midline and posterior scalp sites is due to volume conducted field potentials from hippocampal regions. Intracranial recordings in anterior temporal lobectomy patients reported that P3b responses were intact at midline sites after mesial temporal removal (McCarthy et al., 1989) and noted that hippocampal P3-like activity peaked from 30-50 msec after the scalp P3b further indicating that hippocampal structures were not the prime generator of scalp P3b activity.

Intracranial recording has shown widespread areas of frontal and posterior association cortex in addition to cingulate and mesial temporal regions are activated during tasks that generate scalp P3a potentials (Halgren et al., 1995a, 1995b; Baudena et al., 1995). These intracranial, novelty-related P3a potentials have been proposed to measure neural activity in a distributed multimodal, cortico-limbic orienting system similar to theories proposed for the scalp P3a (Squires et al., 1975; Courchesne et al., 1975; Knight, 1984; Knight, 1996). Animal data suggest the locus coeruleus may contribute to P3a modulation providing further support for the idea that novelty related potentials measure an orienting response (Pineda et al., 1989).

Further support for the existence of multiple P300 generators has been provided by lesion data recorded from neurological patients with focal damage in either dorsolateral prefrontal cortex, temporal-parietal junction, lateral parietal cortex, or hippocampal regions. Discrete damage in the temporal-parietal junction results in reduction of P3a and P3b activity at posterior scalp sites in both the auditory (Knight et al., 1989b) and somatosensory modalities (Yamaguchi & Knight, 1991b, 1992). Verleger and colleagues confirmed that the auditory P3b was reduced by temporal-parietal damage but noted that the visual P3b was not as reduced as the auditory response in their patients (Verleger et al., 1994). Prefrontal lesions reduce earlier latency frontal P3a activity in both the auditory (Knight, 1984; Scabini, 1992) and somatosensory modalities (Yamaguchi & Knight, 1991b). Similarly, lateral parietal damage did not significantly affect auditory or somatosensory P3b responses but reduced novelty P3a potentials in both modalities. Unilateral damage centered in the posterior hippocampal region has no effect on parietal P3b but reduces fronto-central P3a activity in all modalities (Knight, 1996; Knight & Grabowecy, 1994). These lesion results, in conjunction with the data from intracranial and scalp recordings, provide evidence that the P300 is not a unitary phenomenon but instead represents distributed neural activity in cortico-limbic regions engaged during both voluntary and involuntary responses to discrete environmental events. Although this view is more complicated than initial proposals of a unitary nature of P300 activity, it strengthens the potential utility of scalp ERP recording since it provides a means for the measurement of neural activity in distributed brain regions in the millisecond time domain. In the current report the effects of lesions in subregions of anterior and posterior association cortex on early latency extrastriate and longer latency P300 ERPs were assessed to provide further information on the contribution of neocortical regions to visual attention.

**BEHAVIORAL RESULTS**

All subjects were able to perform this simple visual stimulus detection task. Target detection was comparable between controls and neurological patients. False alarm rates also did not vary between groups. Reaction times were not significantly prolonged in the prefrontal or
parietal patients but were slowed in the temporal-parietal group (Table 1).

**ELECTROPHYSIOLOGICAL RESULTS**

**Controls**

*Standard Stimuli*

Standard stimuli elicited a prominent P1-N1 response followed by a broad frontal positivity. The P1 peaked in latency at 132 msec and had a fronto-central scalp distribution. There was an additional small positivity seen as an inflection on the early phase of the P1. This potential was small and unreliable in both controls and patients and will not be considered further. A prominent N1 potential was maximal in amplitude over posterior temporal electrodes. A broad positive potential generated after the N1 onset at about 250 msec, peaked at 370 msec at Fz and was maximal in amplitude over frontal sites.

*Target Stimuli*

Target detection had no significant effect on P1 amplitude or latency but resulted in an increase in N1 amplitude at posterior temporal sites (Fig. 1). The N1 was followed by an N2 potential peaking at 243 msec at T5. This response was maximal over posterior temporal sites (Fig. 3) and was slightly larger over the left hemisphere possibly due to overlapping motor potential activity generated by the righthand button press. The N2 was followed by a prominent parietal maximal P3b. The P3b had an earlier latency at frontal (Fz = 481 msec) vs parietal (Pz = 510 msec) sites F(14, 154) = 3.17, p < 0.05. P3b amplitude was asymmetric at central sites due to overlapping motor potential activity from the button press to detected targets.

*Novel Stimuli*

The N1 to the novel stimuli was reduced at widespread scalp sites in comparison to the standard stimuli F(1, 11) = 8.82, p < 0.01 (Fig. 2). Due to interpretation difficulties from a large temporally and spatially overlapping P2 response to the novel stimuli, the novel P1 and N1 will not be considered further. A prominent broadly distributed P2 potential (latency 202 msec at Fz) was maximal over fronto-central sites (Fig. 3). The novel stimuli generated a small N2 response (at Cz: latency 287 msec, amplitude = -2.03 uV). Although the N2 appeared to be largest at Cz (Fig. 3) this effect did not reach significance. A symmetrically distributed P3a potential was generated to the novel stimuli. This response had a comparable latency at all scalp sites (at Cz = 478 msec) that did not differ from the target P3b. The P3a was maximal at midline fronto-central sites and had a more fronto-central distribution than the target P3b.

**Frontals**

*Standard Stimuli*

The P1 had a comparable latency to controls (136 msec) and frontal P1 reductions did not reach significance (Fig. 2). The N1 was reduced in amplitude over the lesioned hemisphere with maximal reductions at posterior temporal electrodes (Fig. 1). N1 latency was unaffected (at T5 = 168 msec). The early phase (250–350 msec) of the broad frontal positivity (P370) generated to the standard stimuli was reduced at fronto-central sites F(14, 294) = 2.94, p < 0.05 (Fig. 2). The reduction in the early phase of the P370 resulted in an apparent latency prolongation at frontal sites F(14, 294) = 4.59, p < 0.025.

*Target Stimuli*

Target P1 did not differ in amplitude or latency from controls. The target N1 was enhanced in amplitude in comparison to standard stimuli (for frontals: F(1, 10) = 5.45, p < 0.05), with maximal effects observed over posterior temporal scalp sites (Fig. 1). The degree of N1 enhancement did not differ from controls. The N2 potential was reduced over the lesioned hemisphere with reductions maximal over posterior temporal sites (at restricted posterior temporal sites: F(1, 21) = 11.70, p < 0.005 (Fig. 3)). N2 latency was not significantly prolonged. Frontal patients generated a P3b that did not differ from controls in latency (Pz = 507 msec), amplitude (at Pz: controls = 11.4 uV; frontals = 12.6 uV) or scalp distribution (Fig. 3).

**Novel Stimuli**

P2 latency (Fz = 193 msec) and amplitude did not differ from controls and there were no lateralized reductions (Fig. 3). N2 latency and amplitude also did not differ from controls. Frontal lesions prolonged the latency of the P3a recorded over all scalp sites (at Cz: controls = 478 msec, frontals = 518 msec; F(1, 21) = 7.49, p < 0.025). The amplitude of the P3a was reduced over scalp.

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**Table 1.** Percent correct targets, false alarm rate, and target reaction times (± S.D.) are shown for controls and all three patient groups.

<table>
<thead>
<tr>
<th>Behavioral Results</th>
<th>% Correct</th>
<th>False Alarm</th>
<th>Reaction Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>98.7 ± 1.2</td>
<td>0.7 ± 0.9</td>
<td>447 ± 52 msec</td>
</tr>
<tr>
<td>Frontal</td>
<td>95.7 ± 6.2</td>
<td>1.6 ± 1.5</td>
<td>463 ± 48 msec</td>
</tr>
<tr>
<td>Parietal</td>
<td>96.9 ± 2.9</td>
<td>1.1 ± 1.9</td>
<td>496 ± 61 msec</td>
</tr>
<tr>
<td>Temporal-Parietal</td>
<td>96.8 ± 2.8</td>
<td>1.7 ± 3.2</td>
<td>494 ± 48 msec*</td>
</tr>
</tbody>
</table>

*p < 0.05
Figure 1. This shows the group averaged data for standard, target, and novel stimuli in controls and frontal (n = 11), temporal-parietal (n = 10), and lateral-parietal (n = 7) patient groups. The data is presented from electrodes over posterior temporal sites in controls (T5 and T6). In the patients, Tpi shows the data from posterior temporal sites (ipsilateral) to the lesioned hemisphere (i.e., T5 data from left and T6 data from right lesioned patients). Tpc shows the data from posterior temporal sites contralateral to the lesion (i.e., T6 data from the left and T5 data from the right lesioned patients).

sites throughout the lesioned hemisphere with maximal reductions over frontal regions (for location: F(14, 294) = 4.47, p < 0.005; Fig. 3).

Temporal-Parietals

Standard Stimuli

The P1 was reduced in amplitude at bilateral fronto-central sites (p < 0.05; Fig. 2). The N1 was reduced over the lesioned hemisphere with maximal reductions observed at posterior temporal sites (p < 0.01; Fig. 1) but latency was not prolonged. The broad positivity following the N1 was reduced at all scalp sites (from 250–500 msec: F(1, 20) = 5.73, p < 0.025; for 250–350 msec: F(1, 20) = 13.51, p < 0.002) and the latency was prolonged (at Cz: controls = 370 msec, temporal-parietal = 457 msec; F(1, 20) = 8.69, p < 0.01).

Target Stimuli

Target P1 amplitude and latency did not differ significantly from controls. Target N1 latency was prolonged at all scalp sites (at posterior temporal sites = 17 msec; F(1, 20) = 11.47, p < 0.003). The N1 was marginally increased in amplitude in comparison to standards (in temporals: F(1, 9) = 4.96, p < 0.06). The N1 enhancement at posterior temporal sites was reduced in the lesioned hemisphere (for location, controls vs temporals: F(1,
Figure 2. This shows the responses to standard stimuli from midline scalp sites in controls and all three patient groups.

- Fz
- Cz
- Pz

Control
Frontal
Temporo-Parietal
Parietal

4uV

0  400  800 msec

Peak and mean amplitude measures for the P3b over the latency window of 400-700 msec did not significantly differ between controls and temporal-parietal patients (for overall amplitude: \( F(1, 20) = 1.67 \); for scalp distribution: \( F(14, 280) = 1.35 \)). Since the group averaged waveforms showed a possible reduction of the early phase of the P3b, a separate post-hoc analysis of mean amplitude was conducted over latencies of 400-500 msec and 500-600 msec (Fig. 4). There

\[ F(1, 20) = 3.25, p < 0.05; \text{ at posterior temporal sites: } F(1, 20) = 7.77, p < 0.01; \text{ Fig. } 1 \]. The N2 was also reduced in amplitude at posterior sites of the lesioned hemisphere (for location: \( F(14, 280) = 2.76, p < 0.05 \)) with the most pronounced effects at posterior temporal sites \( F(1, 20) = 18.50, p < 0.001; \text{ see Figures } 1 \text{ and } 4 \). N2 latency was on average 20 msec longer than controls but this did not reach significance. Target P3b latency was prolonged by 30 msec relative to controls but this difference also did not reach significance.
Figure 3. The group averaged data for target and novel stimuli are shown for controls and frontal lesions (n = 11). The subtracted waveforms (target minus standard) are shown to isolate task-related ERP differences. The patient data is presented as a function of electrode site ipsilateral or contralateral to lesion (i.e., C3 includes C3 from left and C4 from right lesioned patients). The insert shows the lateral view of the extent of the frontal lesion where maximal lesion overlap across patients occurred.

was no significant reduction of the P3b from 500-600 msec (for overall amplitude: F(1, 20) = 0.45, p = n.s.; for scalp distribution: F(14, 280) = 1.39, p = n.s.). However, the amplitude of the P3b tended to be reduced from 400-500 msec (for overall amplitude: F(1, 20) = 3.61, p < 0.07; Fig. 4).

Novel Stimuli

P2 amplitude was reduced at widespread scalp sites (F(1, 20) = 5.11, p < 0.03; Fig. 4) but latency was not prolonged (at Cz = 184 msec). The N2 was increased in amplitude at widespread scalp sites (at Cz: controls = 2.03 μV temporaless = 4.62 μV, F(1, 20) = 6.86, p < 0.025) and latency was prolonged (at Cz: controls = 287 msec, temporaless-parietal = 340 msec, F(1, 20) = 7.22, p < 0.025). The P3a component was prolonged in latency at all scalp sites (at Cz: controls = 478 msec, temporaless-parietal = 547 msec, F(1, 20) = 14.76, p < 0.001; Fig. 4). P3a amplitude was reduced at widespread scalp sites (F(1, 20) = 7.18, p < 0.025; Fig. 4) with reductions more pronounced over the lesioned hemisphere (for location: F(14, 280) = 3.82, p < 0.01).

Parietals

Standard Stimuli

The P1 was reduced at all electrode sites F(1, 17) = 5.95, p < 0.025; Fig. 2. The N1 was reduced maximally over posterior sites of the lesioned hemisphere (for location: F(14, 238) = 12.76, p < 0.001; at Tpi vs Tpc: F(2, 25) = 4.85, p < 0.02; Fig. 1). N1 latency did not differ from controls. The frontal component of the early phase of the P370 tended to be reduced (for location: F(14, 238) = 2.46, p < 0.08; Fig. 2) and latency was not significantly affected.

Target Stimuli

Target P1 amplitude did not differ from the standards. Similar to temporals, target N1 amplitude was reduced over the lesioned hemisphere (standards vs targets at Tpi vs Tpc in the parietals: F(14, 84) = 6.06, p < 0.01; Fig. 1). N2 latency was comparable to controls (at T5 = 253 msec). N2 amplitude was reduced over bilateral posterior temporal sites with reductions most severe over the lesioned hemisphere (at T5 and T6 for controls vs parietal...
tals: $F(1, 17) = 4.70, p < 0.05$; Figures 1 and 4). Target P3b latency (at Pz = 527 msec) and amplitude (at Pz: controls = 11.4 uV, Parietals = 12.0 uV) did not differ between controls and parietal lesioned patients (Fig. 5).

**Novel Stimuli**

P2 latency and amplitude did not differ from controls. The novel N2 was enhanced in amplitude over all scalp sites $F(1, 17) = 8.36, p < 0.01$ but latency was not significantly different from controls. The P3a was marginally prolonged in latency in the parietal patients (at Cz = 517 msec, $F(1, 20) = 3.91, p < 0.06$). The amplitude of the P3a was decreased with reductions most pronounced over frontal sites of the lesioned hemisphere (for location, controls vs. frontals: $F(14, 238) = 3.09, p < 0.05$; Fig. 5).

**DISCUSSION**

Association cortex lesions had prominent effects on both early and long latency attention related visual ERPs. Prefrontal and posterior cortical lesions altered stimulus processing in extrastriate regions as early as 150 msec poststimulus presentation. An N1 potential peaking at about 170 msec was recorded to all stimulus types. This potential was maximal over posterior temporal sites in accord with detailed scalp dipole localization studies suggesting a source in extrastriate cortex (Towle et al., 1993; Gonzalez et al., 1994). In controls, N1 was increased in amplitude for target stimuli with effects most pronounced at extrastriate sites. Prefrontal and posterior cortical lesions had differential effects on the N1. Dorsolateral prefrontal lesions decreased N1 amplitude over the lesioned hemisphere for all visual stimuli with maximal reductions seen at posterior temporal sites. However, the degree of target related N1 enhancement was comparable to controls over extrastriate cortex of both the lesioned and intact hemisphere in frontal patients. Posterior association cortex lesions resulted in prominent reductions of the N1 recorded over extrastriate regions of the lesioned hemisphere. Unlike frontal patients, patients with posterior lesions were unable to modulate the amplitude of the N1 as a function of stimulus relevancy.

These results suggest that prefrontal cortex provides a facilitatory input to stimulus processing in extrastriate cortex for all stimulus types during sustained visual attention with effects onsetting as early as 100 msec poststimulus delivery. This suggests there is a net excitatory
prefrontal pathway to extrastriate regions active during sustained attention. Network analysis from PET data in humans (McIntosh et al., 1994), blood flow data in humans (Roland, 1982), and data from single unit and lesion studies in monkeys (Mikami et al., 1982; Fuster et al., 1985; Watanabe, 1986a, b; Funahashi et al., 1993) also supports a prominent role of prefrontal cortex in control of visual processing in extrastriate areas during sustained attention and spatial memory tasks. Dorsolateral prefrontal damage due to structural lesions (Knight et al., 1981; Wilkins et al., 1987) or dopamine loss (Stam et al., 1993) reduces both behavioral and ERP measures of sustained attention in the auditory modality suggesting that dorsolateral prefrontal cortex is involved in multimodal control of sustained attention. Additional deficits in inhibitory control of distracting inputs (Bartus & Levcic, 1977; Woods & Knight, 1986; Knight et al., 1989a; Yamaguchi & Knight, 1990; Chao & Knight, 1995) also contributes to the problems in sustained attention observed in prefrontal patients.

The ability to produce selective target enhancement in patients with unilateral frontal lesions could be due to input to extrastriate cortex from the intact contralateral prefrontal region or from posterior association cortex. A prefrontal explanation is unlikely since a crossed prefrontal-extrastriate pathway might also be expected to counter loss of facilitatory effects on the N1. A more likely explanation is that target N1 enhancement is due to a phasic shift of attention to task relevant stimuli under control of posterior association cortex (Luck et al., 1990). Studies emphasizing spatial aspects of the task are necessary to further address this issue. The severe ipsilateral reduction and inability to generate stimulus specific N1 enhancement in the posterior lesioned patients can be explained by at least two hypotheses. Posterior lesions may have directly destroyed N1 generators in parietal-occipital and temporal-occipital cortex since these regions were lesioned to some extent in all patients. Alternatively, it is conceivable that the posterior lesions resulted in loss of both sustained and phasic attention modulation of the N1. This possibility is supported by ERP data in the auditory modality reporting ERP and behavioral decreases in measures of sustained attention in posterior lesioned patients (Woods et al., 1993). This issue could be addressed by utilizing lateralized presentations in more difficult signal detection tasks in conjunction with three-dimensional lesion reconstruction techniques (Damasio & Frank, 1992) and dipole modeling (O'Donnell et al., 1993).

Caution is needed in comparing the current results to...
those reported in prior visual attention studies employing ERPs (Mangun, 1995). Most of these studies have employed lateralized stimulus arrays and divided or cued attention paradigms (Mangun & Hillyard, 1987, 1988, 1990). These designs permit comparison of attended and unattended stimuli, which was not possible in the current study. The current experiment was focused principally on the cortical contributions to the P300 and employed easily discriminable full field stimuli. This relatively simple experimental design was reflected in the absence of a significant difference in error or false alarm rate in all patient groups in comparison to controls. It is likely that lateralized stimulation would result in signal detection deficits in the visual field contralateral to the lesioned hemisphere.

The late positivity (P370) generated to standard stimuli had a fronto-central distribution in controls suggesting this potential may have measured early latency No/Go P300 activity. No/Go potentials are reported to be more fronto-central in humans (Schupp et al., 1994; Roberts et al., 1994) and Go/No-Go tasks reliably influence single unit activity in monkey prefrontal cortex (Watanabe, 1986a, b; Pragay et al., 1987). However, the current task was not a classic Go/No-Go design (Pfefferbaum et al., 1985) and standard stimuli in auditory and somatosensory experiments with identical task structure to this visual study do not generate long latency No/Go potentials (Knight et al., 1989; Yamaguchi & Knight, 1991a, 1991b). Thus, the P370 may be an exogenous visual potential unrelated to withholding of a motor response.

Task relevant target and irrelevant novel stimuli generated N2-P3b and N2-P3a potentials in controls that differed in scalp distribution. The target N2 was recorded over central and temporal sites with maximal amplitude over posterior temporal electrodes. This foci scalp localization suggests that the target N2 measures modality specific neural activity in visual association cortex (Simon et al., 1977). N2 potentials are generated by attention to rare events and often occur as an N2-P2 complex, although they may also occur independently. The N2 was followed by a large amplitude P3b maximal over parietal sites. Novel stimuli generated a different response pattern. A P2 potential (202 mscc) not seen in the target response was maximal over the fronto-central scalp. The P2 was followed by a small N2, which tended to be maximal at central sites. This P2 may be similar to the P165 often generated prior to N2-P3a responses (Naatanen, 1986). The N2 was followed by a large P3a potential, which had a more fronto-central distribution than the P3b generated to targets.

Cortical lesion had differential effects on target and novelty responses. The target N2 was reduced over posterior temporal sites of the lesioned hemisphere by prefrontal, parietal, and temporal-parietal lesions. This pattern was similar to that observed for the N1 and provides additional support for the proposition that a distributed prefrontal-posterior association cortex network modulates attention related neural activity in extrastriate regions (Mesulam, 1981). Prefrontal and lateral parietal lesions had no significant effect on the latency or amplitude of the target P3b generated in this simple detection task. A similar result was obtained in the auditory (Knight et al., 1989b) and somatosensory modalities (Yamaguchi & Knight, 1991b, 1992) implying that substantial regions of dorsolateral prefrontal and lateral parietal association cortex are not necessary for performance in relatively simple detection tasks that generate parietal maximal P3b potentials. Lesion studies in patients with orbito-frontal and medial prefrontal damage due to trauma (Wirsen et al., 1992) or tumor resection (Nasman & Dori, 1993) and intracranial recordings in epileptics (Baudena et al., 1995) indicate that ventro-medial and orbitofrontal cortex may contribute to frontal scalp positivities generated in simple detection tasks. More difficult categorization tasks generate late frontal positivities that are reduced by posterior dorso-lateral prefrontal lesions (Swick & Knight, 1993), suggesting that both task difficulty and stimulus novelty influences the amount of prefrontal activation.

Temporal-parietal lesions resulted in a more complex picture. There was no significant reduction of the target P3b, although inspection of the grand averaged waveforms followed by a post hoc analysis over selected latency windows revealed a trend for reduction of the early phase of the P3b at posterior scalp sites. This contrasts with the marked P3b reduction observed in the auditory (Knight et al., 1989b; Scabini, 1992; Verleger et al., 1994) and somatosensory modalities (Yamaguchi & Knight, 1991b, 1992) in patients with comparable temporal-parietal lesions due to stroke. The results of the current study are in accord with those of Verleger and colleagues (1994) who found less visual than auditory P3b reduction in temporal-parietal lesioned stroke patients. The ERP findings in lesioned patients indicate that multiple brain regions contribute to the parietal scalp P3b. Some of these are modality specific and may reside in primary or secondary association cortex. This could account for the auditory and somatosensory P3b reductions subsequent to temporal-parietal damage since AI and SII would be damaged by these lesions. Conversely, VI and VII are not significantly damaged by these lesions and may explain the partially preserved P3b in these patients. MEG studies have provided additional evidence that multiple posterior brain regions including modality specific cortex contribute to visual and auditory P3b potentials recorded at the scalp (Rogers et al., 1991, 1992, 1993a).

The superior temporal sulcus (STS) receives multimodal input in monkeys and humans (Desimone & Ungerleider, 1986; Hikosaka et al., 1988; Seltzer & Pandya, 1989b; Rogers et al., 1993b). Cortex in the STS is invariably damaged by temporal-parietal infarcts, and intracranial recordings in epileptics have reported P3b activity.
in this region (Halgren et al., 1995a). However, there was no significant reduction of the visual P3b in these patients with STS damage. Combined STS and primary or secondary association cortex damage may be needed to reduce the P3b.

Electrodes inserted into the hippocampal region in humans record large endogenous potentials during tasks that generate scalp P3b potentials (Halgren et al., 1980). These mesial temporal potentials are delayed in latency and onset by 30-50 msec in comparison to scalp P3b activity (McCarthy et al., 1989). The STS has direct connections to the entorhinal cortex (Amaral et al., 1983), providing access to the hippocampus proper. One possible interpretation is that cortical P3b activity measures readout of information from temporal-parietal cortex to hippocampal regions during updating of distributed cortico-hippocampal working memory circuits (Donchin & Coles, 1988; Colombo et al., 1990; Eichenbaum et al., 1994).

The novelty P3a was reduced by both frontal and posterior association cortex lesions. Reductions were more severe for temporal-parietal patients but this group also had significantly larger lesions. The findings of P3a reductions by all association cortex lesions suggest that widespread interconnected areas of the cortex are activated by stimulus novelty. The results in lesioned patients are in accord with intracranial recording in epileptic patients demonstrating that multiple cortical and limbic sites respond to novel stimuli (Halgren et al., 1995a, 1995b; Baudena et al., 1995; Scabini & McCarthy, 1993).

Extensive connections between frontal and posterior cortex may provide the anatomical substrate for this distributed novelty related cortical activation (Schwartz & Goldman-Rakic, 1984; Petrides & Pandya, 1988; Seltzer & Pandya, 1989a; Cavada & Goldman-Rakic, 1989; Friedman & Goldman-Rakic, 1994). The Galvanic Skin Response (GSR), a peripheral autonomic measure of orientation, is also reduced by frontal, posterior, and hippocampal lesions (Tranel & Damasio, 1994; Knight, 1996) providing additional evidence that widespread cortical and limbic regions are involved in orientation to novel events.

Stimulus novelty is an important contributor to normal memory function (von Restorff, 1933; Karis et al., 1984; Metcalfe, 1993). The hippocampal region may be a critical component of the novelty response measured by the scalp P3a. Posterior hippocampal infarcts do not reduce the parietal P3b but result in widespread multimodal decrements of the scalp recorded P3a (Knight, 1996; Knight & Grabowecky, 1994). Novelty induced P3a activity has been reported in the hippocampal region from intracranial recordings in epileptics (Halgren et al., 1995b; Scabini & McCarthy, 1993), and PET and fMRI findings have reported novelty related increases in blood flow in hippocampal and cortical areas (Tulving et al., 1994; Stern et al., 1996). These results suggest that the hippocampal region maintains a template for recent sensory events. Sufficient deviations from this neural representation may activate distributed brain regions to enhance processing of novel and potentially biologically significant events. Well characterized hippocampal-prefrontal connections could subserve this distributed activation (Goldman-Rakic et al., 1984). This hippocampal-cortical novelty network may contribute to the classic von Restorff effect wherein out of context or novel stimuli are better remembered (von Restorff, 1933).

METHODS

Subjects

Controls and 3 patient groups were tested. The control group consisted of 12 right-handed subjects matched in age, sex, socioeconomic status, and education to the patient population (62 ± 11 yrs.; 11 male, 1 female). Controls were recruited from hospital personnel and relatives of the patients. Controls had no history of neurological or psychiatric disease but were not selected for unusually good health for age. Patients were selected on the basis of a unilateral focal lesion in either anterior or posterior association cortex as determined by CT or MRI scanning. Patients were recruited from the outpatient clinics of the Martinez Veterans Administration Medical Center and affiliated hospitals. The research was approved by the Human Subjects Review Committees of the Martinez VA and the University of California, Davis.

All lesions in the current report were due to a single stroke in branches of the middle cerebral artery (Damasio, 1983) and were at least one year post onset. All patients were right-handed. Craniotomy patients with cortical resections for tumor, AVM epilepsy were excluded from the current study to avoid possible effects of current shunting through skull defects. In addition, neuropsychological deficits may differ in patients with comparable sized lesions due to stroke or tumor (Anderson et al., 1990). Patients with medical complications, psychiatric disturbance, substance abuse, psychoactive drug treatment, or other neurological diseases were excluded. All patients had normal or corrected visual acuity and no patient had any significant weakness. Lesions were transcribed onto a template system developed in our laboratory (Frey et al., 1987; see Knight et al., 1988 for details). Software permitted reconstruction of the lateral perspective of the lesion, determination of lesion volume, putative cytoarchitectonic area damaged and construction of group averaged lesions. Details of neuropsychological deficits in these patients are available in other publications (Yamaguchi & Knight, 1991b).

Frontal Patients

This group consisted of 11 patients with focal infarctions centered in the dorsolateral prefrontal cortex. All cases were due to occlusion of precentral and/or prefrontal
branches of the middle cerebral artery. The average age of the patients was 63 ± 8 yrs. All subjects were right-handed and male (8 left and 3 right). Lesions centered in Broadman's areas 9, 44, and 46 with variable amounts of damage in areas 6, 8, and 45. The mean lesion volume was 42.7 cc. Visual fields were intact in all frontal lesioned patients. Multiple axial sections through the lesion and a reconstructed lateral view of the center of lesion overlap are shown for each patient (see Figures 3 and 6).

**Temporo-Parietal Patients**

This group consisted of 10 patients with infarctions in the temporo-parietal junction (see Figures 4 and 7). All cases were due to infarction in the posterior division of the middle cerebral artery (61 ± 6 yrs; 9 males, 1 female; 7 left, 3 right). These patients had occlusion of the posterior temporal branch perfusing the temporoparietal junction, with some subjects having additional damage extending into more rostral areas of the parietal lobe.
that were lesioned in the pure lateral parietal group. The lesions centered in the posterior temporal plane (area 22) and adjacent superior temporal sulcus (STS), middle temporal gyrus and inferior portions of areas 39 and 40. There were additional variable amounts of damage in areas 37 and 7. Four temporal-parietal patients (3L; 1R) had partial inferior quadrinopias. The mean lesion volume was 76.9 cc in this group. This group had significantly larger lesions than the frontal $F(1, 19) = 6.49, p < 0.019$, and parietal group $F(1, 15) = 6.20, p < 0.024$.

Although the parietal and temporo-parietal group overlapped in damage, they were anatomically differentiated by the degree of involvement in the posterior lateral temporal gyrus, superior temporal sulcus, middle temporal gyrus and inferior areas 39 and 40 (see Figures 7 and 8; axial cut 3). The mean lesion volume in the temporo-parietal group that did not overlap with the parietal group averaged 48.6 cc, which did not differ in volume from the frontal or parietal groups.

**Parietal Patients**

This group consisted of 7 patients with infarctions in the lateral parietal lobe sparing the posterior temporal plane (see Figures 5 and 8). All cases were due to infarction in the angular and posterior parietal branches of the middle
cerebral artery (60 ± 11 yrs; 8 males, 1 female). Lesions centered in areas 39 and 40 (angular and supramarginal gyri; 4 left, 3 right) with variable amounts of damage in areas 37 and 7. One patient had a partial right inferior quadrantanopsia. The mean lesion volume was 36.9 cc.

**Experimental Design**

Subjects sat in a reclining chair in a sound attenuated (43 dB) recording chamber 1.6 meters from a video monitor. They fixated a central red spot and were instructed to press a button with their right hand upon detection of a designated target stimulus embedded in trains of repetitive stimuli (standards). The subjects were instructed to press as accurately and quickly as possible and to respond only to the designated target stimulus. The standard stimuli consisted of repetitive triangles delivered at a rate of 1 per second. Target stimuli were infrequent, random (9.6%) triangle inversions with the constraint that two targets could not occur sequentially. In addition to the target stimuli, irrelevant novel stimuli were randomly presented on 9.6% of the trials. There were two types of novel stimuli. The first consisted of jumbled pieces of the triangle stimuli used for the standards and target. The second type of novel stimulus consisted of line drawings of familiar objects such as a bell or a banana. There were a total of 6 jumbled triangles (4.8%) and 6 line drawings of visual objects (4.8%), which repeated in random order throughout the experiment with the constraint that two novels did not occur sequentially (see Figure 9 for an example of the stimuli employed). The stimuli were presented as white line drawings on a black background. All stimuli subtended 5 degrees of visual angle and were matched in luminance. The background luminance was 0.4 foot lamberts and the stimuli were 5.2 foot lamberts. The visual stimuli did not encroach on the partial inferior quadrantanopsias present in five of the posterior lesioned patients. The experimental session consisted of two recording blocks each about 8–10 minutes long and containing 500 stimuli designed to produce replications of the waveforms. Five minute rest periods were given between each block. The data were collapsed across blocks for statistical analysis.

**Electrophysiological Techniques**

Brain electrical activity was recorded from Ag/AgCl electrodes placed at 15 scalp sites (Fpz, F3, Fz, F4, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, Oz) based on the 10–20 system and beneath the outer edge of the left eye. All sites were
Figure 9. This shows examples of the individual stimuli employed in the experiment. Figures 9a and 9b show the standard and target stimuli. Figures 9c and 9d show examples of the two types of irrelevant novel stimuli.

Data Analysis

Peak amplitude of individual components was measured relative to the 200 msec prestimulus baseline. Latency was measured relative to stimulus onset. Measurement windows were determined from inspection of individual subjects’ averages and grand averages. The major exogenous components were measured in windows of 110–160 msec for the P1, 125–210 msec for the N1 and 250–500 msec for the aftergoing positivity. Endogenous components were measured in a window of 150–250 msec for the novelty P2, and 200–400 msec for the N2 and 400–700 msec for the P3 for both target and novel stimuli. Since the standard stimuli generated prominent responses up to 600 msec poststimulation, measurements were made on both raw and subtracted waveforms (target-standard) to isolate task related ERP activity. These measurements yielded comparable findings and the statistics from the unsubtracted waveforms are reported in the results. Mean amplitude measurements over defined windows were employed for some components as noted in the results section. No significant differences for standard, target, or novel components between right and left lesioned patients in any group were observed, perhaps due to the small sample sizes in each subgroup. For this reason, the data are presented as a function of electrode site contralateral (c) or ipsilateral (i) to the lesion. For instance, in the figures, P1 includes data from P3 for left lesions and P4 for right lesions and P2 would include data from the unlesioned left or right hemisphere. Planned comparisons were performed between controls and each patient group. Scalp voltages were subjected to repeated measures analysis of variance with appropriate Geisser-Greenhouse corrections for inappropriate degrees of freedom due to violation of the sphericity assumption. Only those scalp distributions found to be significant are reported in the results section. Variables showing significance after this correction were further analyzed by appropriate ANOVA. In the results section the original degrees of freedom and F values are reported when appropriate. Epsilon values ranged from 0.16–0.32 for all comparisons. Scalp topography distributions between conditions (i.e., target vs novel) and patient groups were compared after normalization of amplitudes (McCarthy & Wood, 1985). Percent correct, false alarms, and reaction times were tabulated in windows of 200–1000 msec poststimulus delivery.

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REFERENCES


