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The central role of the prefrontal cortex in directing attention to novel events

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Summary

The physiological basis for the striking decrease of attention to novel events following frontal lobe injury is poorly understood. In this study, event-related potentials (ERPs) were recorded from patients with frontal lobe damage and matched subjects, who controlled the duration of viewing of background, novel and target stimuli. Frontal lobe patients did not differ from normal controls in terms of age, education, estimated IQ or mood. However, they were judged to be more apathetic as measured by self-report and informants' ratings. Patients with frontal lobe damage exhibited markedly reduced amplitude of the novelty P3 response and the duration of viewing of novel stimuli. In contrast, injury to the frontal lobes had a limited impact on P3 amplitude and behavioural responses (viewing duration and reaction time) to target stimuli. A strong correlation was found between measures of apathy and both attenuated P3 amplitude and viewing duration in response to novel but not target stimuli. Differences in amplitude of the novelty P3 response explained a large portion of the variance associated with duration of viewing of novel stimuli. After controlling for the influence of P3 amplitude, there was no association between frontal lobe injury and reduced viewing of novel stimuli. The results of this study suggest that frontal lobe damage leads to diminished visual attention to novel events through its disruption of neural processes underlying the novelty P3 response. These processes appear to regulate the allocation of attentional resources and early exploratory behaviours, and are not limited to immediate orienting responses. Damage to the frontal lobes may prevent the generation of a signal which indicates that a novel event in the environment requires additional attention due to its potential behavioural significance. The disruption of these processes is likely to contribute to the apathy observed in patients after injury to the frontal lobes.

Keywords: frontal lobes; novelty; P3; attention; apathy

Abbreviation: ERP = event-related potential

Introduction

Novelty-seeking is an integral part of normal human behaviour, yet surprisingly little is known about the mechanisms which contribute to the impairment of attention to novel events in patients with frontal lobe damage (Luria, 1973; Hutton *et al*., 1979; Knight, 1984, 1997; Daffner *et al*., 2000*a*). The novelty P3 response is characterized typically as an anteriorly distributed positive event-related potential (ERP) wave associated with the orienting response to novel stimuli (Courchesne *et al*., 1975; Squires *et al*., 1975; Snyder and Hillyard, 1976; Knight, 1984; Hillyard and Picton, 1987; Naatanen, 1992; Baudena *et al*., 1995; Daffner *et al*., 1998, 2000*b*). Both the novelty P3 and the orienting responses are usually considered involuntary and automatic (Courchesne *et al*., 1975; Squires *et al*., 1975; Snyder and Hillyard, 1976; Holdstock and Rugg, 1995; Knight and Scabini, 1998). However, there is evidence to suggest that the novelty P3

response marks the preferential allocation of attentional resources to potentially significant events (Kahneman, 1973; Ohman, 1979; Naatanen, 1992; Daffner *et al*., 1998*a*, 2000*b*; Escera *et al*., 1998).

Frontal lobe injury has been shown to reduce the amplitude of the novelty P3 response (Knight, 1984, 1997; Knight and Scabini, 1998). We investigated whether the reduction of the P3 response was a necessary correlate of diminished allocation of attention to novel stimuli in patients with frontal lobe damage. Previous work has demonstrated that when normal subjects control how long they look at stimuli, the amplitude of the novelty P3 response in frontal regions strongly predicts the duration of viewing of novel stimuli (Daffner *et al*., 1998), suggesting that the P3 might reflect the activity of a neural system that serves to link attentional resources to novel events. A more direct test of this theory was carried out in the current investigation of patients with focal damage to the prefrontal cortex.

We studied patients with chronic infarctions centred in the prefrontal cortex, and normal controls matched for age, education, estimated IQ and mood. ERPs were recorded from scalp electrode sites while subjects viewed a series of line drawings that included a frequent, repetitive background stimulus, an infrequent target stimulus and infrequent novel stimuli (e.g. fragmented or 'impossible' objects). Task instructions emphasized that the study was investigating how people look at different kinds of visual stimuli. Subjects controlled viewing duration by a button press that led to the onset of the next stimulus and served as a measure of visual attention (Berlyne, 1960; Vurpillot, 1968; Loftus and Mackworth, 1978; Daffner *et al*., 1992, 1998, 2000*b*). Subjects also responded to target stimuli by pressing a foot pedal. Based on previous work, we hypothesized that the diminution of attention to novel stimuli following frontal lobe damage would be linked to a disruption of the novelty P3 response.

Methods

Subjects

CT or MRI scans of patients discharged from the Brigham and Women's Hospital (BWH) with a diagnosis of stroke were reviewed. Patients whose infarctions were centred in the frontal lobes (with no extension into parietal cortex) were recruited. Patients with a history of previous strokes, alcohol abuse or dementia were excluded. Eight patients underwent research MRI scans, with three-dimensional reconstruction of images (Shenton *et al*., 1992). In one of these patients, the frontal infarction that had been noted on the initial scans (done 18 months before) was not visible on MRI and thus, experimental data from this patient were not included. Two patients had only CT scans because pacemakers made them ineligible for MRI scans. We therefore report on nine patients with frontal infarctions.

Lesion localization was based on the Damasio template system (Damasio and Damasio, 1989). In patients who were able to have MRI scans, infarct localization was confirmed by reviewing the three-dimensional images that were reconstructed from the MRI data set (Shenton *et al*., 1992) after the boundaries of the lesion had been traced on each slice. Five patients had right frontal infarctions; three had left. One patient had suffered small, bilateral frontal infarctions. All infarctions were centred in the prefrontal cortex. Mean duration post stroke was 1.5 $\pm$ 0.8 years (Table 1).

Normal controls (n = 20) were recruited through advertisements in the Boston community. Subjects were excluded if they had a history of cerebrovascular disease, alcohol abuse, dementia or a focal neurological exam. Informed consent was obtained from all subjects. The study was approved by the Human Research Committee at BWH.

Subjects completed the American version of the National Adult Reading Test (Nelson and O'Connell, 1978; Ryan and Paolo, 1992) and the Ravens Coloured Progressive Matrices Test (Raven *et al*., 1995) to determine an estimated IQ score. Subjects completed the Apathy Scale (Starkstein *et al*., 1993, 1995) (a 14-item survey that evaluates a subject's level of interest, motivation and concern) and the Zung Depression Scale (Zung, 1965) (a 20-item questionnaire about the subject's mood and affective state). Informants who knew the subjects well completed a Personality and Behavioural Inventory (Daffner *et al*., 1999) that included four items evaluating the subject's degree of apathy by assessing his/her level of initiation, participation, interest and motivation.

Experimental procedures

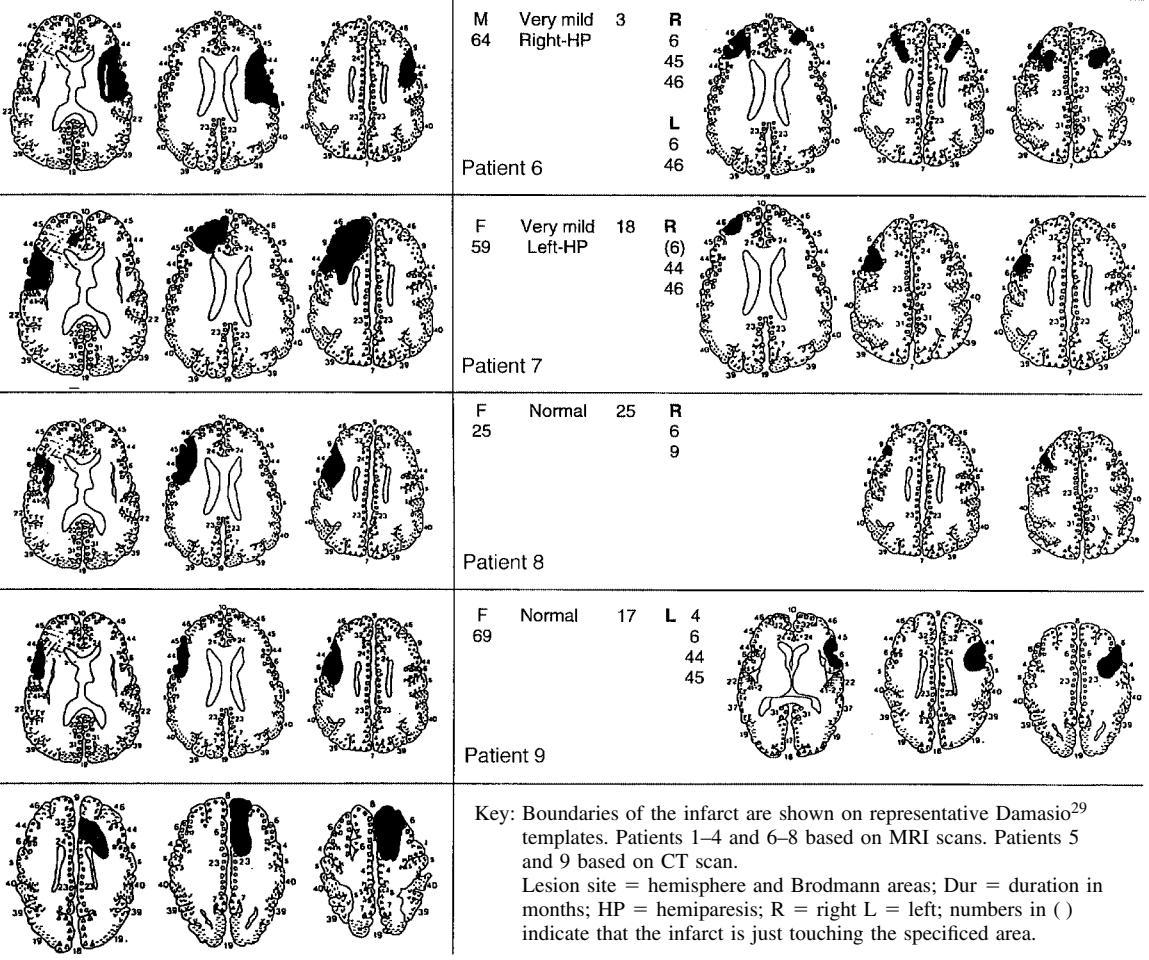
Three hundred line drawings, white on black background, were presented at the centre of a high resolution computer monitor. All stimuli subtended a visual angle of ~2.75° along their longest dimension. There were three categories of visual stimuli: (i) a repetitive background stimulus (a triangle), 70% frequency; (ii) a target stimulus (upside down triangle), 15% frequency; and (iii) novel stimuli, randomly drawn from a set of unusual/unfamiliar line drawings shown only once each, 15% frequency (Fig. 1). Many of the novel stimuli came from the collection of drawings that have been used by Kosslyn and colleagues (Kosslyn *et al*., 1994) and Kroll and Potter (Kroll and Potter, 1984). Stimuli appeared within a fixation box subtending a visual angle of approximately 3.5 $\times$ 3.5°, which remained on the screen at all times. Stimuli were presented in pseudorandom order with the additional constraints that no more than two deviant stimuli were shown consecutively, and that each block of 50 stimuli had the same number of background stimuli and approximately the same number of target and deviant stimuli.

Procedure

Subjects were informed that the experiment involved the study of brain wave responses as they looked at different

Table 1 *Summary of patient information*

Sex Age	Neuro exam	Dur	Lesion site	
F 53	Severe Right-HP	27	L 6 (9) 22 44 45 47	Patient 1
F 72	Moderate Left-HP	13	R 4 6 8 9 10 (44) 46	Patient 2
F 79	Severe Left-HP	33	R 4 6 9 22 44 45 (46) 47	Patient 3
M 62	Normal	16	R (4) (9) 6 44 45	Patient 4
F 72	Mild Right-HP	13	L 4 6 8 24 32	Patient 5
M 64	Very mild Right-HP	3	R 6 45 46 L 6 46	Patient 6
F 59	Very mild Left-HP	18	R (6) 44 46	Patient 7
F 25	Normal	25	R 6 9	Patient 8
F 69	Normal	17	L 4 6 44 45	Patient 9



Key: Boundaries of the infarct are shown on representative Damasio[29] templates. Patients 1–4 and 6–8 based on MRI scans. Patients 5 and 9 based on CT scan.
Lesion site = hemisphere and Brodmann areas; Dur = duration in months; HP = hemiparesis; R = right L = left; numbers in ( ) indicate that the infarct is just touching the specificed area.

kinds of drawings. They were told that they would be viewing a set of drawings and that they could look at each picture for however long they liked. They controlled the viewing duration by a button press that triggered the onset of the next stimulus. Subjects were explicitly told that they would not be asked questions about the pictures at the conclusion of the experiment. Subjects were also told to respond to the designated target stimulus by pressing a foot pedal (ipsilateral to the button press). We called the targets 'Sequence Markers' and indicated to subjects that they were included in the task to help the experimenters keep track of where they were in the sequence of drawings. In the stroke patients, the responding hand/foot used was ipsilateral to the lesion site. In normal controls and the patient with bilateral lesions, the response hand/foot was randomly assigned. Although viewing durations were calculated by subtracting the stimulus onset time from the button press time, all stimuli were displayed for a minimum duration of 600 ms. The interval between the offset of one stimulus and the onset of the next stimulus ranged between 1 and 1.5 s.

ERP recordings

An electrode cap (Electro-Cap International, Eaton, Ohio, USA) was used to hold the 29 active electrodes to the scalp, whose locations were based on the international 10–20 system. They included three midline sites (Pz, Cz, Fz) and 26 lateral sites arranged in four parasagittal rows [(i) CP1/2, FC1/2, FP1/2; (ii) O1/2, P3/4, C3/4, F3/4; (iii) CP5/6, FC5/6, AF7/8; (iv) T5/6, T3/4, F7/8].

All sites were referenced to the left mastoid, and the impedance between each recording site and the reference was reduced to less than 5 kΩ. An electrode was placed beneath the left eye (left mastoid reference) to check for eye blinks and vertical eye movements, and another electrode to the right of the subject's right eye (referenced to an electrode

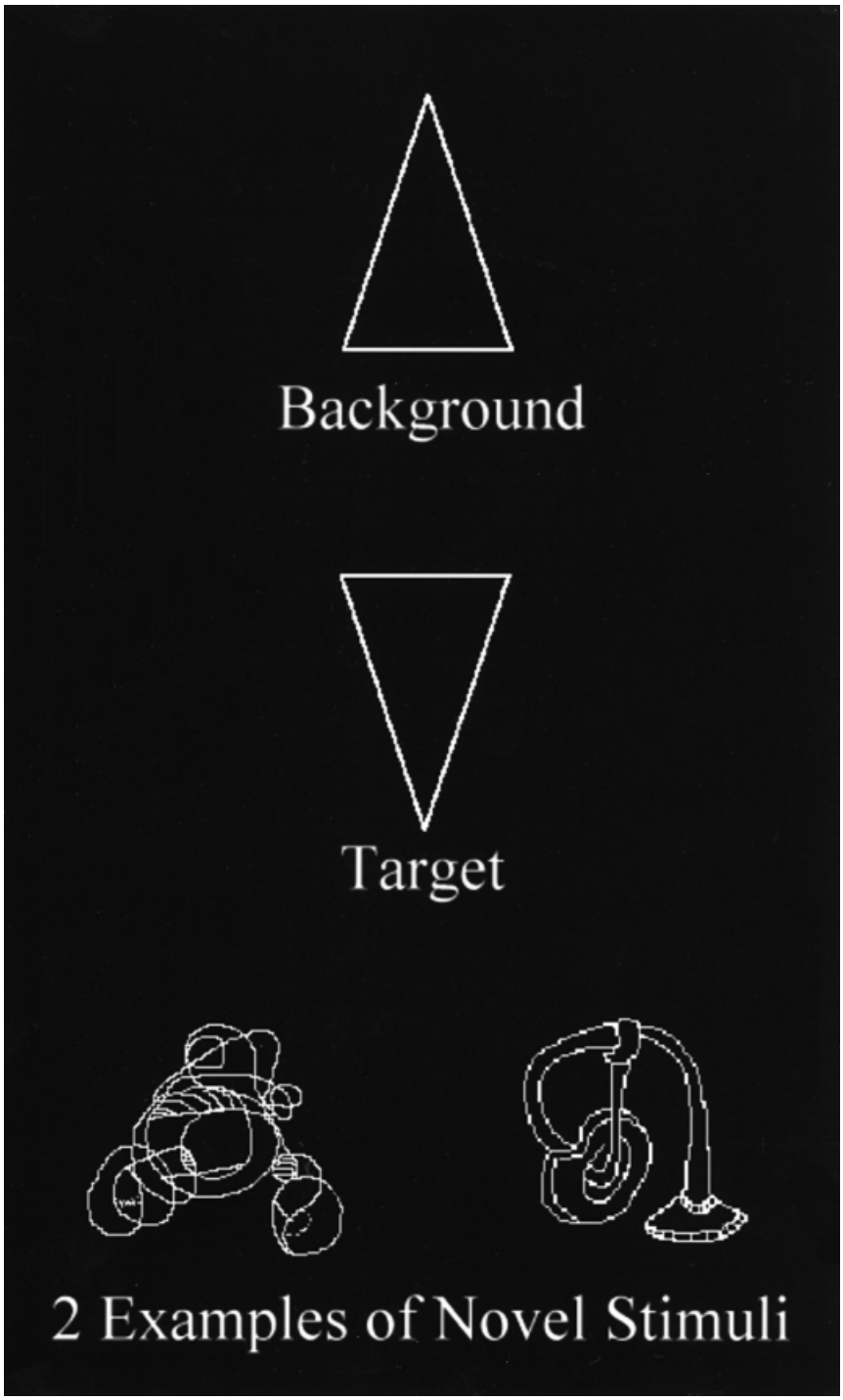


Fig. 1 Repetitive background stimulus (70% frequency), target stimulus (15% frequency) and two examples of the novel stimuli (15% frequency).

to the left of the left eye) to check for lateral eye movements. A final electrode was placed over the right mastoid (referenced to the left) to monitor asymmetrical mastoid activity (none was found).

The EEG was amplified by an SA Instrumentation acquisition system (model H & W 32BA, San Diego, Calif., USA) using a band filter with negative 3 db cut-offs of 0.01 and 40 Hz, and continuously digitized (200 Hz) by a computer yielding 1280 ms of data from each electrode site, beginning 100 ms before stimulus onset.

Data analysis

A continuous record of the raw EEG was stored on hard disk. Off-line, EEG epochs for the three stimulus types (background, target, novel) were averaged separately. Trials

Table 2 *Subject characteristics*

	Normal controls (n = 20)	Frontal lobe patients (n = 9)	P-value
Age (years)	68.3 (7.3)	61.4 (16.4)	n.s.
Education (years)	16.2 (3.1)	14.7 (2.5)	n.s.
Estimated IQ	121.2 (5.8)	116.4 (10.0)	n.s.
Zung score (20-80)	30.4 (4.9)	38.6 (11.9)	n.s.
Apathy scores			
Self-report scale (0-42)	5.7 (3.5)	12.6 (8.6)	<0.05
Informant-based inventory (0-40)	5.7 (4.3)	17.3 (6.5)	<0.001

Values given are mean (standard deviation); n.s. = not significant.

with eye movements or amplifier blocking were excluded from data analysis. In cases with excessive eye blinks, a blink correction programme was employed (Dale, 1994) that computed the impact of the blink on the wave forms in each channel. For the eight patients with unilateral infarctions, data are presented as a function of electrode site ipsilateral or contralateral to the lesion. In the figures, ERPs ipsilateral to the lesion are shown on the right side of the scalp. The P3 response was defined as the peak positive wave between 325 and 600 ms, measured with respect to the average of the 100 ms prestimulus baseline.

Data were analysed using repeated measures ANOVA (analysis of variance). There were two levels of group (normal controls, frontal lobe patients), and for ERP and duration data, three levels of stimulus type (background, target, novel). For ERP measurements, there were three midline electrode sites and 13 lateral electrode sites with two levels, one for each hemisphere. Between-group analyses that yielded significant interactions between group, stimulus type, electrode site or hemisphere resulted in planned contrasts between the levels of the variable. In looking at scalp site interactions with other variables, the data were normalized using a Z-score technique (Kounios and Holcomb, 1994) similar to the method recommended by McCarthy and Wood to avoid problems associated with interpreting site by factor interactions using ANOVA (McCarthy and Wood, 1985). The Geisser–Greenhouse correction (Geisser and Greenhouse, 1959) was applied for all repeated measures with >1 degree of freedom.

Data sets involving the behavioural results (e.g. viewing durations, reaction times) or demographic variables that were not normally distributed were transformed (e.g. inverse function) prior to statistical analyses. If assumptions for parametric analyses were still violated, non-parametric statistics (e.g. Mann–Whitney U tests) were employed. To examine the effects of frontal lobe injury and the novelty P3 response on viewing duration, a path analysis was conducted (Kerlinger and Pedhazur, 1973) based on the causal model in which frontal lobe damage affects viewing duration through its impact on the novelty P3 response. Correlation analysis (Spearman's rho) was used to determine the degree of association between severity of apathy and pertinent electrophysiological and behavioural variables. All P-values reported are two-tailed.

Results

Subject characteristics

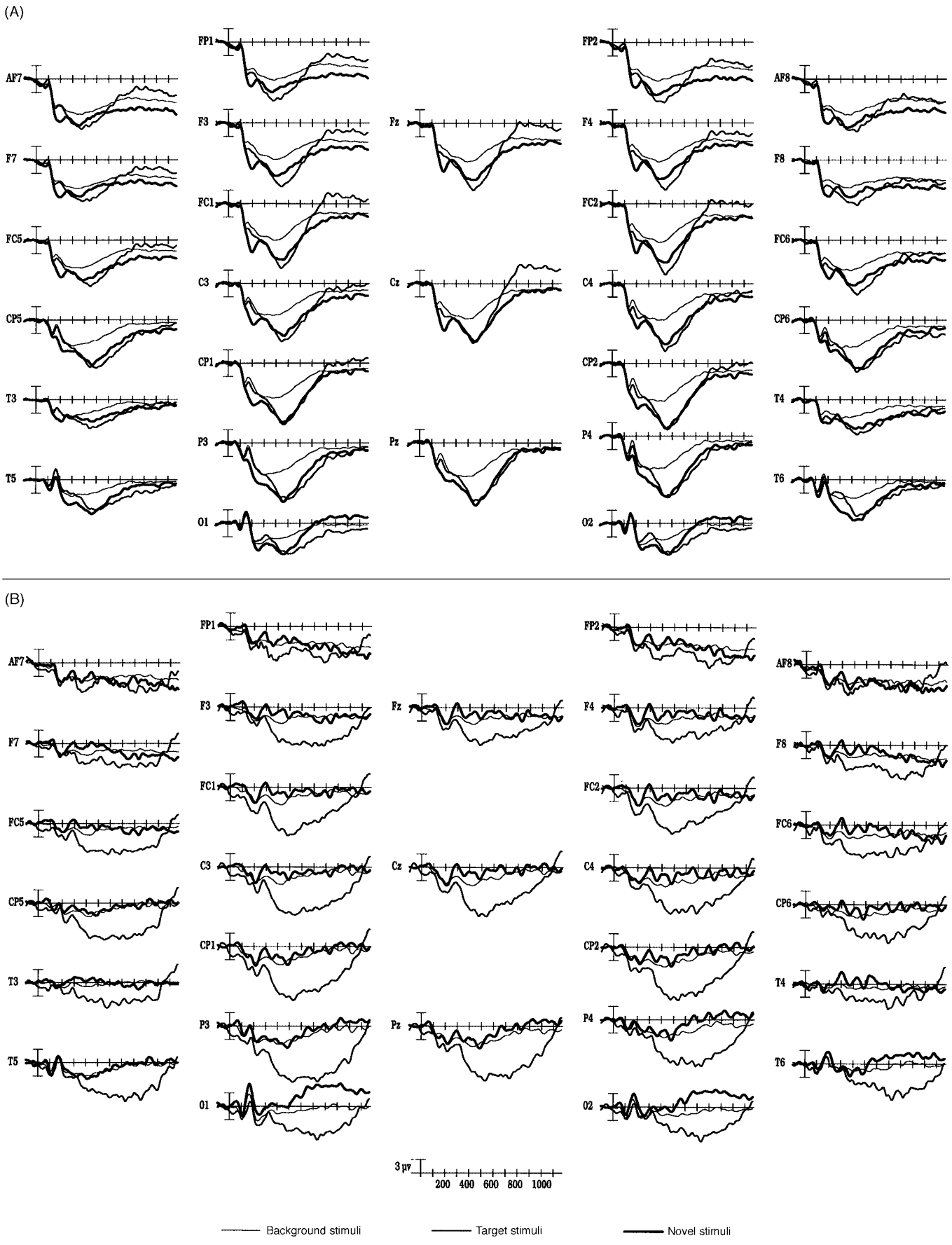
Patients with frontal lobe strokes and normal controls did not differ significantly in terms of age, education, estimated IQ (Nelson and O'Connell, 1978; Ryan and Paolo, 1992; Raven *et al*., 1995) or Zung Depression Scale scores (Zung, 1965). Frontal lobe patients exhibited increased apathy as measured by self-report on the Apathy Scale (Starkstein *et al*., 1993, 1995) ($P < 0.05$) and informant-based judgements on the Personality and Behavioural Inventory (Daffner *et al*., 1999) ($P < 0.001$) (Table 2). According to these measures, the frontal lobe patients were mildly apathetic.

P3 data

Figure 2 presents the grand average ERP plots for the group of normal control subjects and frontal lobe patients. P3 mean amplitude and latency data at midline sites are summarized in Table 3.

The grand average plots revealed a similar pattern of response to that observed in individual subjects, as shown by an example of midline ERP plots from a normal control subject and a frontal lobe patient (Fig. 3).

P3 amplitude was significantly smaller for frontal lobe patients than normal controls [main effect of group, midline: $F(1,27) = 14.26$, $P < 0.001$; lateral: $F(1,27) = 18.3$, $P < 0.001$]. Moreover, P3 latency was longer for frontal lobe patients than normal controls across all stimulus types and midline electrode sites [$F(1,27) = 7.91$, $P < 0.01$]. P3 amplitude in response to different stimulus types varied across groups [stimulus type by group interaction, midline: $F(2,54) = 7.77$, $P < 0.01$; lateral: $F(2,54) = 6.81$, $P < 0.01$]. For normal controls, the amplitude of the P3 response to novel stimuli was equal to that of target stimuli (midline: $P > 0.9$; lateral: $P > 0.4$), both of which were larger than to background stimuli (midline and lateral: Ps < 0.001) (Fig. 2). In contrast, for frontal lobe patients, the P3 response to novel stimuli was no larger than to background stimuli


(A)
AF7
F7
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F3
FC1
C3
CP1
P3
O1
Fz
Cz
Pz
FP2
F4
FC2
C4
CP2
P4
O2
AF8
F8
FC6
CP6
T4
T6
(B)
3 μv
200 400 600 800 1000
Background stimuli
Target stimuli
Novel stimuli

(midline: $P > 0.3$; lateral: $P > 0.2$), both of which were smaller than to target stimuli (midline: Ps < 0.01; lateral: Ps < 0.05). Figure 4A illustrates the voltage difference maps of the P3 response to target or novel stimuli minus the P3 response to background stimuli in normal controls and frontal lobe patients.

P3 amplitude to novel stimuli was smaller for frontal lobe patients than for normal controls [midline: $F(1,27) = 23.14$, $P < 0.001$; lateral: $F(1,27) = 26.35$, $P < 0.001$] across all scalp locations (i.e. no group by electrode site interaction). In contrast, only at anterior sites was P3 amplitude to target stimuli smaller for frontal lobe patients than normal controls [group by electrode site interaction, midline: $F(2,54) = 7.11$, $P < 0.01$; lateral: $F(12,324) = 3.14$, $P < 0.05$]. Figure 4B illustrates the voltage difference maps of the P3 amplitude of normal controls minus frontal lobe patients for each stimulus type, demonstrating the marked group difference in response to novel stimuli.

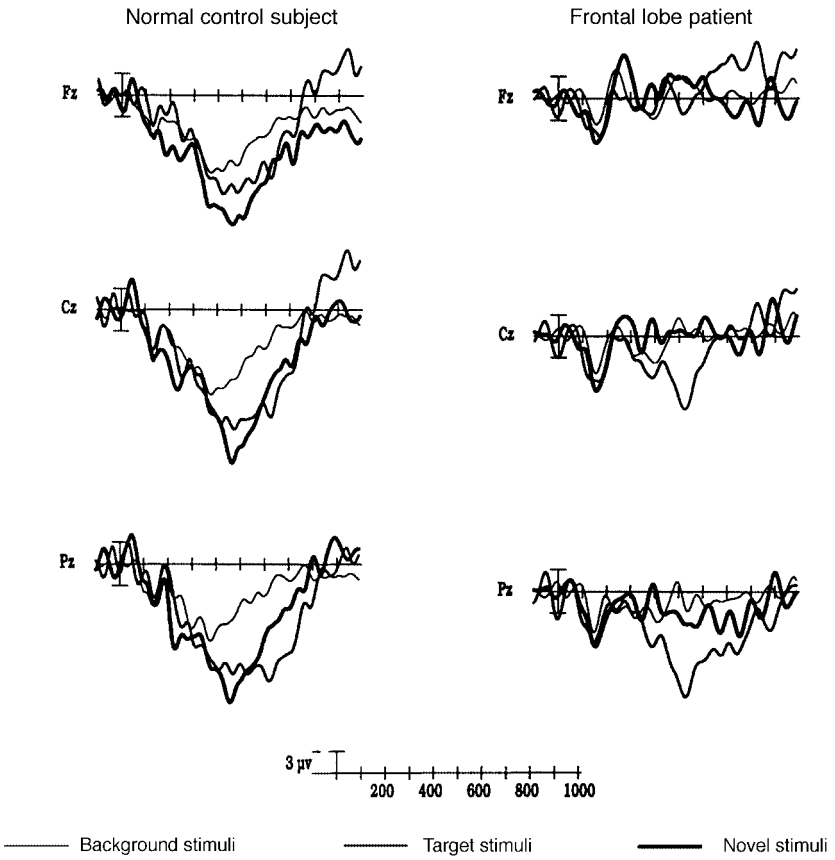

Fig. 3 Example of midline ERP plots for a normal control subject (10) and a frontal lobe patient (6).

Table 3 *P3 amplitude and latency at midline sites*

	Normal controls			Frontal lobe patients		
	Background	Target	Novel	Background	Target	Novel
P3 amplitude in μV (mean ± SEM)						
Fz	9.49 (0.66)	15.88 (1.13)	14.95 (1.01)	5.45 (0.98)	9.39 (1.69)	6.83 (1.50)
Cz	9.01 (0.54)	14.64 (1.19)	15.28 (1.07)	6.27 (0.81)	12.70 (1.77)	6.90 (1.59)
Pz	8.96 (0.54)	15.06 (1.06)	15.64 (0.94)	6.56 (0.80)	13.85 (1.58)	7.70 (1.40)
P3 latency in ms (mean ± SEM)						
Fz	394.75 (15.00)	456.50 (15.32)	427.50 (16.79)	455.56 (22.37)	491.67 (22.84)	477.22 (25.02)
Cz	385.50 (14.74)	455.00 (11.58)	449.50 (17.41)	455.00 (21.98)	509.44 (17.26)	457.22 (25.95)
Pz	392.75 (16.10)	475.00 (14.49)	455.75 (14.63)	462.22 (24.00)	512.78 (21.60)	488.89 (21.81)

Fig. 2 Grand average ERP plots for midline and lateral sites in response to background stimuli (thin lines), target stimuli (thick lines) and novel stimuli (bold lines) for (**A**) normal control subjects and (**B**) frontal lobe patients. For stroke patients, ERPs ipsilateral to the lesion are shown on the right side of the figure.

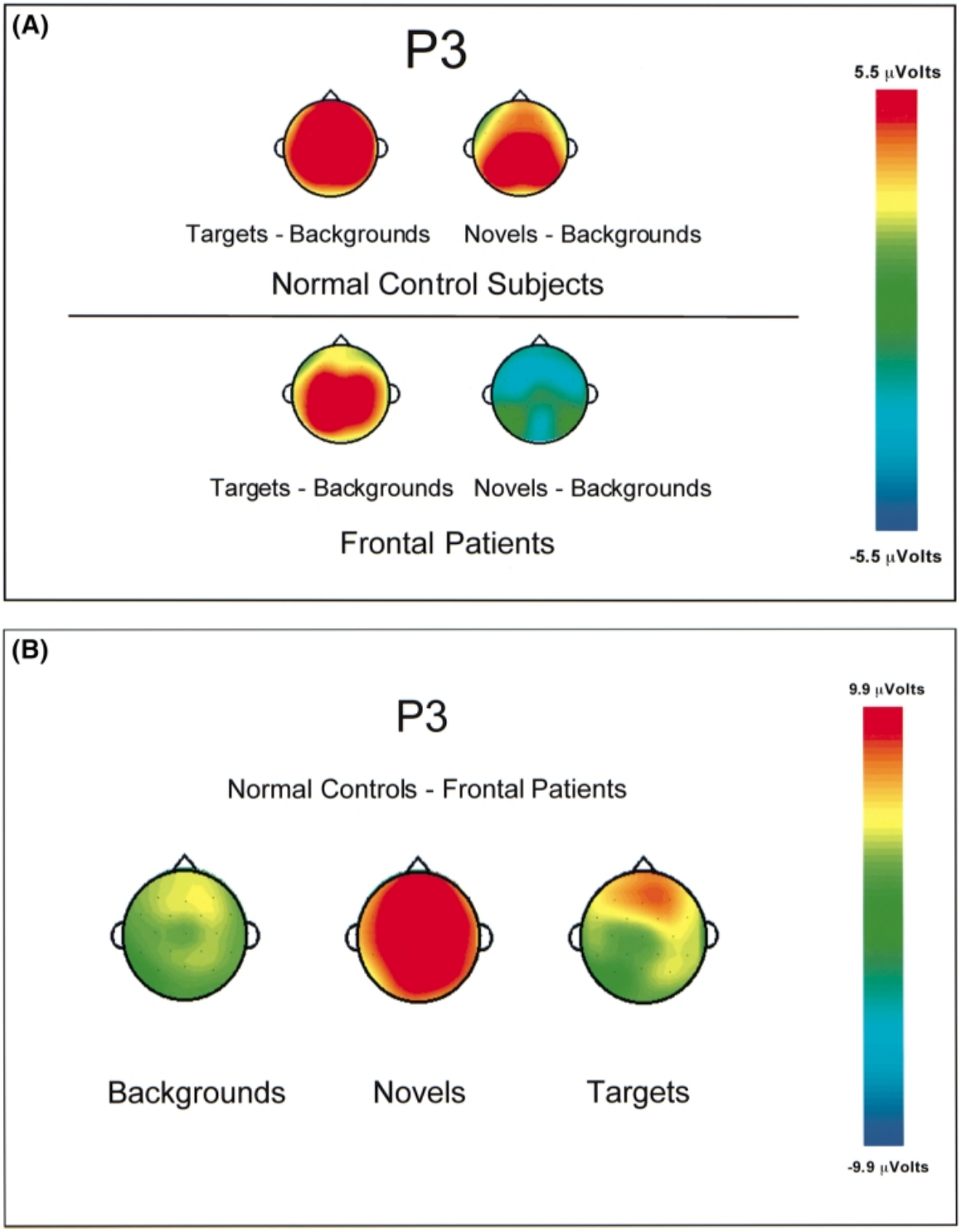

Fig. 4 Voltage difference maps. (**A**) P3 response to target or novel stimuli minus P3 response to background stimuli in normal control subjects and frontal lobe patients. Unlike normal controls, frontal lobe patients do not respond differently to novel stimuli compared with background stimuli. (**B**) P3 amplitude of normal control subjects minus P3 amplitude of frontal lobe patients for each stimulus type, illustrating the striking group difference in response to novel stimuli. Responses ipsilateral to the lesion in stroke patients are shown on the right side of the scalp.

For normal controls, the P3 response to all stimulus types was asymmetric (larger at right hemisphere sites) [main effect of hemisphere, $F(1,19) = 11.66$, $P < 0.01$]. In contrast, frontal lobe patients did not exhibit any difference in P3 amplitude between ipsi- and contralesional hemisphere sites ($P > 0.2$).

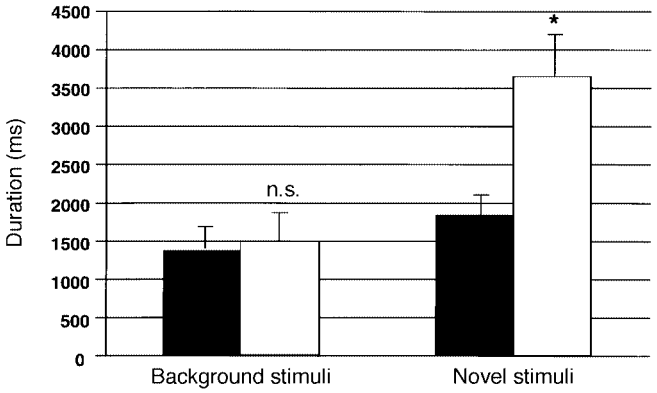

Fig. 5 Viewing duration of novel and background stimuli (mean ± standard error of the mean) for frontal lobe patients (black columns) and normal controls (white columns). There was a significant stimulus type by group interaction ($P < 0.01$). *$P < 0.05$.

Note that as a further check of the reliability of our P3 peak amplitude measures, the data were also analysed using mean amplitude measurements between 325 and 600 ms. These analyses (not shown) yielded almost identical statistical results to those seen for the P3 peak amplitude data.

Behavioural data

There were significant differences in the length of time in which frontal lobe patients and normal controls viewed novel and background stimuli [stimulus type by group interaction: $F(1,27) = 8.82$, $P < 0.01$] (Fig. 5). Although there were no group differences in how long subjects looked at background stimuli ($P > 0.3$), frontal lobe patients spent significantly less time looking at novel stimuli than normal controls ($P < 0.05$). Both groups spent more time viewing novel than background stimuli, although the effect was much more robust in the normal control group ($P < 0.001$) than the frontal lobe group ($P < 0.05$).

Subjects varied in terms of the rate at which they tended to move through the stimulus set. Response times in stroke subjects may have been affected by non-specific alterations in speed of motor or cognitive processing. To help control for these factors, we constructed a measure of proportionality (ratio of viewing duration of novels to viewing duration of backgrounds). This ratio is particularly informative since the novel stimuli are defined in terms of their deviance from background stimuli. Frontal lobe patients exhibited a significantly smaller ratio of viewing of duration novels to viewing of duration backgrounds than normal controls [frontal lobe patients: 1.40 (0.12) versus normal controls: 2.84 (0.41), $F(1,28) = 12.00$, $P < 0.01$].

In terms of responses to target stimuli, there were no significant group differences in reaction time, percentage of correct hits, number of false alarms, viewing duration of targets, or ratio of viewing duration of targets to viewing duration of backgrounds (Table 4).

Table 4 *Responses to target stimuli*

	Normal controls	Frontal lobe patients	*P*-value
Reaction time (ms)	1361 (161)	1453 (197)	n.s.
Percentage of hits	96% (1)	93% (5)	n.s.
Number of false alarms	0.4 (0.1)	2.3 (2.0)	n.s.
Viewing durations (ms)	2664 (244)	3111 (442)	n.s.
Ratio of viewing durations of targets : viewing durations of backgrounds	2.2 (0.2)	2.3 (0.3)	n.s.

Values given are mean (standard error of the mean); n.s. = not significant.

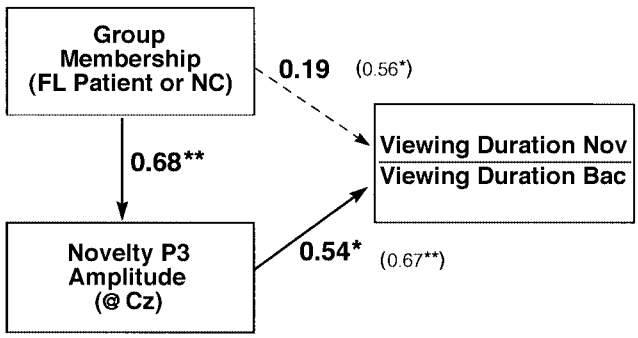

Fig. 6 Path analysis of the relationship between group membership [frontal lobe (FL) patients versus normal controls (NC)], novelty P3 response, and ratio of viewing duration of novel stimuli : viewing duration of background stimuli. Path coefficients are shown in bold. Zero-order correlations are in parentheses. (The P3 response to background stimuli did not explain any more of the variance and thus was not included in the model.)
*$P < 0.01$; **$P < 0.001$.

Path analysis

To further investigate the major hypothesis of this study, a path analysis was conducted of the relationship among the variables of group membership (frontal lobe patients versus normal controls), novelty P3 response and ratio of viewing duration of novels to viewing duration of backgrounds (Fig. 6). It revealed a strong association between group membership and novelty P3 amplitude, with a correlation coefficient of 0.68 ($P < 0.001$). There was also a strong correlation between the amplitude of the novelty P3 response and ratio of viewing duration of novels to viewing duration of backgrounds, that remained significant after controlling for the impact of group membership (path coefficient = 0.54, $P < 0.01$). In contrast, after controlling for the impact of the novelty P3 response, there was no association between frontal lobe injury and reduced viewing duration of novel relative to background stimuli (correlation coefficient = 0.19, $P > 0.4$), suggesting that the neural processes indexed by the novelty P3 response mediate viewing duration of novel stimuli.

Table 5 *Correlations between experimental variables and apathy scales*

	Apathy	
	Informant-based score	Self-reported score
Ratio of duration of novels : duration of backgrounds	-0.60**	-0.44**
Ratio of P3 novels at Cz : P3 backgrounds at Cz	-0.63**	-0.52*
Ratio of duration of targets : duration of backgrounds	n.s.	n.s.
Ratio of P3 targets at Cz : P3 backgrounds at Cz	n.s.	n.s.
Reaction time to targets	n.s.	n.s.
Percentage of hits	n.s.	n.s.

*$P < 0.05$; $P < 0.01$; n.s. = not significant.

Correlations between experimental variables and apathy scores

There was a strong inverse relationship between apathy scores and the ratio of viewing duration of novel stimuli to viewing duration of background stimuli, and between apathy scores and the ratio of the amplitude of the P3 response to novel stimuli to the amplitude of the P3 response to background stimuli (Table 5). In contrast, there were no significant correlations between electrophysiological or behavioural responses to target stimuli and apathy measures (Table 5).

Regional or lateralized differences within the prefrontal cortex

Given the small sample size, only limited analysis was conducted on the impact of different lesion sites within the prefrontal cortex on attention to novel stimuli. The three patients with the most circumscribed lesions within the dorsolateral prefrontal cortex (patients 7, 8 and 9) did not differ significantly from the three patients with the largest frontal lesions (patients 1, 2 and 3) in terms of the novelty P3 amplitude or viewing duration of novel relative to background stimuli. Similarly, there were no significant differences in these variables between the three patients with lesions in the left hemisphere (patients 1, 5 and 9) and the three patients with comparable lesions in the right hemisphere (patients 2, 3 and 4).

Discussion

The process of orienting and attending to novel stimuli is essential for adapting to a rapidly changing environment (Berlyne, 1960; Sokolov, 1963; Daffner *et al*., 1994, 1998). The frontal lobes appear to play an important role in this process. For example, monkeys with injury to frontal cortex exhibit autonomic or locomotive responses that do not differ between novel and repetitive stimuli, and fail to demonstrate a range of exploratory behaviours (Jacobsen, 1936; French and Harlow, 1955; Welker, 1961; Butter, 1964; Kimble *et al*., 1965; Mesulam, 1986, 1998). Novelty-seeking behaviour in humans appears to have a similar dependency on the frontal lobes. Thus, it is commonly observed that patients with injury to the frontal cortex are apathetic and uninterested in novel aspects of their environment. However, there has been very limited investigation of the physiology underlying these changes.

ERPs have helped to elucidate the neurophysiological underpinnings of novelty processing in humans. Unexpected novel stimuli evoke characteristic patterns of ERPs including the novelty P3 wave, an important index of the orienting response (Courchesne *et al*., 1975; Squires *et al*., 1975; Snyder and Hillyard, 1976; Knight, 1984; Hillyard and Picton, 1987; Naatanen, 1992; Baudena *et al*., 1995; Daffner *et al*., 1998, 2000*b*). Lesion studies in humans point to a major disruption of the novelty P3 response following focal injury, especially to frontolimbic circuits. For example, cerebrovascular infarctions in the prefrontal cortex and posterior hippocampus result in a markedly reduced surface novelty P3 amplitude in all three sensory modalities (Knight, 1984, 1996, 1997; Knight and Scabini, 1998). Furthermore, deviant visual or auditory stimuli evoke a novelty P3 wave with large local gradients or polarity inversions in dorsolateral prefrontal cortex, anterior cingulate gyrus and posterior parahippocampus in patients undergoing depth electrode studies for possible surgical treatment of epilepsy (Alain *et al*., 1989; Baudena *et al*., 1995; Halgren *et al*., 1995).

The current study confirms that damage to prefrontal cortex in humans profoundly disrupts the novelty P3 response. The decrease in the amplitude of the novelty P3 response was more widespread than that reported by Knight (Knight, 1984, 1997). This result may indicate that the decision-making task we employed placed greater demands on a more extensive part of the prefrontal cortex. The novelty P3 response is typically characterized in young and middle-aged adults as having an earlier latency and a more anterior scalp distribution than the target P3 response (Courchesne *et al*., 1975; Knight and Scabini, 1998), a pattern that was not found in our control subjects. The most likely explanation for the different pattern we observed is the age of our normal control subjects (mean of 68 years). Studies that have examined the impact of aging on the P3 wave have demonstrated a marked change in scalp distribution as subjects get older (Knight, 1987; Friedman *et al*., 1993, 1997; Fabiani and Friedman, 1995; Anderer *et al*., 1996), with a significant shift in P3 amplitude towards anterior sites in response to novel and target stimuli. Often, as in our study, no significant difference in the scalp distribution of novel versus target P3 waves has been found (Friedman *et al*., 1993; Fabiani and Friedman, 1995). Moreover, in older subjects, the novelty P3 latency is

frequently not significantly shorter than the target P3 latency (Snyder and Hillyard, 1979; Friedman *et al*., 1993).

Frontal lobe damage significantly reduced attention to novel stimuli as measured by viewing duration. The amplitude of the novelty P3 response accounted for much of the variance associated with the preferential viewing of novel stimuli. The novelty P3 response thus appears to reflect cerebral activity that determines the enhanced allocation of attentional resources to potentially significant events. The absence of a significant association between frontal lobe injury and reduced viewing of novel stimuli after controlling for the impact of the novelty P3 response strongly suggests that frontal damage leads to diminished attention to novelty through a disruption of neural processes underlying the novelty P3 response. In keeping with other reports in the literature (Knight, 1984; Yamaguchi and Knight, 1991), frontal lobe injury had a limited effect on the P3 amplitude and behavioural responses to target stimuli.

Depth electrode studies (Alain *et al*., 1989; Baudena *et al*., 1995) have suggested that the P3 activity of frontal regions precedes that of posterior regions. Thus, damage to the frontal lobes may prevent the generation of a 'signal' indicating that a novel event requires additional attention (Baudena *et al*., 1995; Daffner *et al*., 1998). Such impairment in orienting and allocating attention to novelty could be a critical early step in undermining more complex aspects of exploratory behaviour. Apathy (defined in terms of reduced motivation, initiative and exploration) (Marin, 1990, 1991) is a common feature of frontal lobe injury. Marin and colleagues have used experimental measures of interest in novelty to quantify apathy (Marin *et al*., 1991). In the current study, a strong negative correlation was found between measures of apathy and P3 amplitude as well as viewing of novel stimuli. The link between apathy and diminished responsiveness to novel stimuli appears to be selective, as no correlation was noted between apathy and electrophysiological or behavioural responses to target stimuli.

We found that patients with relatively circumscribed lesions within the dorsolateral prefrontal cortex exhibited a similar reduction of novelty P3 amplitude and viewing duration of novel relative to background stimuli as patients with the large lesions that involved much more of the frontal lobes. This suggests that the dorsolateral prefrontal cortex may make a particularly important contribution to responding to novelty, as has been shown in primate studies (Mesulam, 1986). However, the small size of the sample in this study limits conclusions about the function of specific prefrontal regions in the processing of novel events. It will be interesting to determine whether the right hemisphere plays a greater role than the left in distributing attention to novel stimuli, which would be consistent with other studies indicating a right hemisphere specialization for the orienting of attention (Mesulam, 1981, 1998; Heilman *et al*., 1993; Gitelman *et al*., 1999). In support of this possibility, normal controls exhibited larger P3 responses at right hemisphere sites, a finding in keeping with other results in the ERP literature (Alexander *et al*., 1995; Daffner *et al*., 1998). However, the three patients with left frontal damage did not differ significantly from the three patients with right-sided infarctions of similar size and distribution, in terms of P3 amplitude or proportional viewing of novel stimuli.

In summary, three conclusions can be drawn. First, the novelty P3 response reflects neural processes that actively allocate attentional resources to potentially significant events in the environment. Secondly, the prefrontal cortex serves as a critical component of this novelty processing system. Finally, damage to this system appears to contribute to the reduced attention to novel events and the emergence of apathy commonly observed in patients with frontal lobe injury.

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References

Alain C, Richer F, Achim A, Saint Hilaire JM. Human intracerebral potentials associated with target, novel, and omitted auditory stimuli. Brain Topogr 1989; 1: 237–45.

Alexander JE, Porjesz B, Bauer LO, Kupermann S, Morzorati S, O'Connor SJ, et al. P300 hemispheric amplitude asymmetries from a visual oddball task. Psychophysiology 1995; 32: 467–75.

Anderer P, Semlitsch H, Saletu B. Multichannel auditory event-related brain potentials: effects of normal aging on the scalp distribution of N1, P2, N2 and P300 latencies and amplitudes. Electroencephalogr Clin Neurophysiol 1996; 99: 458–72.

Baudena P, Halgren E, Heit G, Clarke JM. Intracerebral potentials to rare target and distractor auditory and visual stimuli. III. Frontal cortex. Electroencephalogr Clin Neurophysiol 1995; 94: 251–64.

Berlyne DE. Conflict, arousal, and curiosity. New York: McGraw-Hill; 1960.

Butter CM. Habituation of responses to novel stimuli in monkeys with selective frontal lesions. Science 1964; 144: 313–5.

Courchesne E, Hillyard SA, Galambos R. Stimulus novelty, task relevance and the visual evoked potential in man. Electroencephalogr Clin Neurophysiol 1975; 39: 131–43.

Daffner KR, Scinto LF, Weintraub S, Guinessey JE, Mesulam MM. Diminished curiosity in patients with probable Alzheimer's disease as measured by exploratory eye movements. Neurology 1992; 42: 320–8.

Daffner KR, Scinto LF, Weintraub S, Guinessey J, Mesulam MM. The impact of aging on curiosity as measured by exploratory eye movements. Arch Neurol 1994; 51: 368–76.

Daffner KR, Mesulam MM, Scinto LF, Cohen LG, Kennedy BP, West WC, et al. Regulation of attention to novel stimuli by frontal lobes: an event-related potential study. Neuroreport 1998; 9: 787–91.

Daffner KR, Mesulam MM, Cohen LG, Scinto LFM. Mechanisms underlying diminished novelty-seeking behavior in patients with probable Alzheimer's disease. Neuropsychiatry Neuropsychol Behav Neurol 1999; 12: 58–66.

Daffner KR, Mesulam MM, Holcomb P, Calvo V, Acar D, Chabrerie A, et al. Disruption of attention to novel events after frontal lobe injury in humans. J Neurol Neurosurg Psychiatry 2000a; 68: 18–24.

Daffner KR, Mesulam MM, Scinto LFM, Calvo V, Faust R, West WC, et al. The influence of stimulus deviance on electrophysiologic and behavioral responses to novel events. J Cogn Neurosci. In press 2000b.

Dale AM. Source localization and spatial discriminant analysis of event-related potentials: linear approaches (brain cortical surface). Dissertation Abstracts International 1994; 55-07B: 2559.

Damasio H, Damasio AR. Lesion analysis in neuropsychology. New York: Oxford University Press; 1989.

Escera C, Alho K, Winkler I, Naatanen R. Neural mechanisms of involuntary attention to acoustic novelty and change. J Cogn Neurosci 1998; 10: 590–604.

Fabiani M, Friedman D. Changes in brain activity patterns in aging: the novelty oddball. Psychophysiology 1995; 32: 579–94.

French GM, Harlow HF. Locomotor reaction decrement in normal and brain-damaged rhesus monkeys. J Comp Physiol Psychol 1955; 48: 496–501.

Friedman D, Simpson G, Hamberger M. Age-related changes in scalp topography to novel and target stimuli. Psychophysiology 1993; 30: 383–96.

Friedman D, Kazmerski V, Fabiani M. An overview of age-related changes in the scalp distribution of P3b. [Review]. Electroencephalogr Clin Neurophysiol 1997; 104: 498–513.

Geisser S, Greenhouse SW. On methods in the analysis of profile data. Psychometrika 1959; 24: 95–112.

Gitelman DR, Nobre AC, Parrish TB, LaBar KS, Kim YH, Meyer JR, et al. A large-scale distributed network for covert spatial attention: further anatomical delineation based on stringent behavioural and cognitive controls. Brain 1999; 122: 1093–106.

Halgren E, Baudena P, Clarke JM, Heit G, Marinkovic K, Devaux B, et al. Intracerebral potentials to rare target and distractor auditory and visual stimuli. II. Medial, lateral and posterior temporal lobe. Electroencephalogr Clin Neurophysiol 1995; 94: 229–50.

Heilman KM, Watson RT, Valenstein E. Neglect and related disorders. In: Heilman KM, Valenstein E, editors. Clinical neuropsychology. 3rd ed. New York: Oxford University Press; 1993. p. 279–336.

Hillyard SA, Picton TW. Electrophysiology of cognition. In: Mountcastle VB, Plum F, Geiger ST, editors. Handbook of physiology, Sect. 1, Vol. 5, Pt. 2. Bethesda (MD): American Physiological Society; 1987. p. 519–84.

Holdstock JS, Rugg MD. The effect of attention on the P300 deflection elicited by novel sounds. J Psychophysiol 1995; 9: 18–31.

Hutton JT, Johnston CW, Shapiro I, Pirozzolo FJ. Oculomotor programming disturbances in the dementia syndrome. Percept Mot Skills 1979; 49: 312–4.

Jacobsen CF. Studies of cerebral function in primates I: the function of the frontal association areas in monkeys. Comp Psychol Monogr 1936; 13: 3–50.

Kahneman D. Attention and effort. Englewood Cliffs (NJ): Prentice-Hall; 1973.

Kerlinger FN, Pedhazur EJ. Multiple regression in behavioral research. New York: Holt, Rinehart & Winston; 1973.

Kimble DP, Bagshaw MH, Pribram KH. The GSR of monkeys during orienting and habituation after selective partial ablations of the cingulate and frontal cortex. Neuropsychologia 1965; 3: 121–8.

Knight RT. Decreased response to novel stimuli after prefrontal lesions in man. Electroencephalogr Clin Neurophysiol 1984; 59: 9–20.

Knight RT. Aging decreases auditory event-related potentials to unexpected stimuli in humans. Neurobiol Aging 1987; 8: 109–13.

Knight R. Contribution of human hippocampal region to novelty detection. Nature 1996; 383: 256–9.

Knight RT. Distributed cortical network for visual attention. J Cogn Neurosci 1997; 9: 75–91.

Knight RT, Scabini D. Anatomic bases of event-related potentials and their relationship to novelty detection in humans. [Review]. J Clin Neurophysiol 1998; 15: 3–13.

Kosslyn SM, Alpert NM, Thompson WL, Chabris CF, Rauch SL, Anderson AK. Identifying objects seen from different viewpoints: a PET investigation. Brain 1994; 117: 1055–71.

Kounios J, Holcomb PJ. Concreteness effects in semantic processing: ERP evidence supporting dual-coding theory. J Exp Psychol Learn Mem Cogn 1994; 20: 804–23.

Kroll JF, Potter MC. Recognizing words, pictures, and concepts: a comparison of lexical, object, and reality decisions. J Verb Learn Verb Behav 1984; 23: 39–66.

Loftus GR, Mackworth NH. Cognitive determinants of fixation location during picture viewing. J Exp Psychol Hum Percept Perform 1978; 4: 565–72.

Luria AR. The frontal lobes and the regulation of behavior. In: Pribram KH, Luria AR, editors. Psychophysiology of the frontal lobes. New York: Academic Press; 1973. p. 3–26.

Marin RS. Differential diagnosis and classification of apathy. [Review]. Am J Psychiatry 1990; 147: 22–30.

Marin RS. Apathy: a neuropsychiatric syndrome. [Review]. J Neuropsychiatry Clin Neurosci 1991; 3: 243–54.

Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. Psychiatry Res 1991; 38: 143–62.

McCarthy G, Wood CC. Scalp distributions of event-related potentials: ambiguity associated with analysis of variance models. Electroencephalogr Clin Neurophysiol 1985; 62: 203–8.

Mesulam MM. A cortical network for directed attention and unilateral neglect. [Review]. Ann Neurol 1981; 10: 309–25.

Mesulam MM. Frontal cortex and behavior. Ann Neurol 1986; 19: 320–5.

Mesulam MM. From sensation to cognition. [Review]. Brain 1998; 121: 1013–52.

Naatanen R. Attention and brain function. Hillsdale (NJ): Lawrence Erlbaum; 1992.

Nelson HE, O'Connell A. Dementia: the estimation of premorbid intelligence levels using the New Adult Reading Test. Cortex 1978; 14: 234–44.

Ohman A. The orienting response, attention, and learning: an information-processing perspective. In: Kimmel HD, Van Olst EH, Orlebeke JF, editors. The orienting reflex in humans. Hillsdale (NJ): Lawrence Erlbaum; 1979. p. 443–71.

Raven JC, Court JH, Raven J. Coloured progressive matrices, section 2. In: Raven JC, Court JH, Raven J, editors. Manual for Raven's progressive matrices and vocabulary scales. Oxford (UK): Oxford Psychologists Press; 1995. p. 1–73.

Ryan J, Paolo A. A screening procedure for estimating premorbid intelligence in the elderly. Clin Neuropsychol 1992; 6: 53–62.

Shenton ME, Kikinis R, Jolesz FA, Pollak SD, LeMay M, Wible CG, et al. Abnormalities of the left temporal lobe and thought disorder in schizophrenia: a quantitative magnetic resonance imaging study. N Engl J Med 1992; 327: 604–12.

Snyder E, Hillyard SA. Long-latency evoked potentials to irrelevant, deviant stimuli. Behav Biol 1976; 16: 319–31.

Snyder E, Hillyard SA. Changes in visual event-related potentials in older persons. In: Hoffmeister F, Muller C, editors. Brain function in old age: evaluation of changes and disorders. Berlin: Springer-Verlag; 1979. p. 112–25.

Sokolov EN. Higher nervous functions: the orienting reflex. Annu Rev Physiol 1963; 25: 545–80.

Squires NK, Squires KC, Hillyard SA. Two varieties of long-latency positive waves evoked by unpredictable auditory stimuli in man. Electroencephalogr Clin Neurophysiol 1975; 38: 387–401.

Starkstein SE, Fedoroff JP, Price TR, Leiguarda R, Robinson RG. Apathy following cerebrovascular lesions. Stroke 1993; 24: 1625–30.

Starkstein SE, Migliorelli R, Manes F, Teson A, Petracca G, Chemerinski E, et al. The prevalence and clinical correlates of apathy and irritability in Alzheimer's disease. Eur J Neurol 1995; 2: 540–6.

Vurpillot E. The development of scanning strategies and their relation to visual differentiation. J Exp Child Psychol 1968; 6: 632–50.

Welker WI. An analysis of exploratory and play behavior in animals. In: Fiske DW, Maddi SR, editors. Functions of varied experience. Homewood (IL): Dorsey Press; 1961. p. 175–226.

Yamaguchi S, Knight RT. Anterior and posterior association cortex contributions to the somatosensory P300. J Neurosci 1991; 11: 2039–54.

Zung WWK. A self-rating depression scale. Arch Gen Psychiatry 1965; 12: 63–70.

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