The Frontal Cortex and Exogenous Attentional Orienting

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Abstract

■ Normal functioning of the attentional orienting system is critical for effective behavior and is predicated on a balanced interaction between goal-directed (endogenous) processes and stimulus-driven (exogenous) processes. Although both systems have been subject to much investigation, little is known about the neural underpinnings of exogenous orienting. In the present study, we examined the early facilitatory effects and later inhibition of return effects of exogenous cues in patients with frontal and parietal lesions. Three novel findings emerged from this study. First, unilateral frontoparietal damage appears not to affect the early facilitation effects of exogenous cues. Second, dorsolateral prefrontal damage, especially lesions involving the inferior frontal gyrus, produces an exogenous disengage deficit (i.e., the sluggish withdrawal of attention from the ipsilesional to the contralesional field). Third, a subset of patients with dorsolateral prefrontal damage, with lesions involving the middle frontal gyrus, have a reorienting deficit that extends in duration well beyond established boundaries of the normal reflexive orienting system. These results suggest that the dorsolateral prefrontal cortex plays an important role in exogenous orienting and that component processes of this system may be differentially impaired by damage to different parts of the dorsolateral prefrontal cortex. ■

INTRODUCTION

The human visual system is constantly faced with enormous amounts of changing visual stimuli, much of which is irrelevant to behavioral goals. Attentional systems simplify and provide structure to otherwise inchoate sensations by selecting relevant and inhibiting irrelevant stimuli for processing. This selection and inhibition is often influenced by the spatial location of stimuli. When attention is deployed to the location of a potentially interesting stimulus, perceptual processing is initially facilitated (Müller & Rabbitt, 1989; Jonides, 1981). If the information at an attended location is deemed irrelevant for behavioral goals, then perceptual processing at this location is inhibited. This phenomenon is called inhibition of return (IOR; Posner, Rafal, Choate, & Vaughn, 1985). IOR increases the efficiency of search by limiting costly reinspections of the same location (Klein, 2000; Posner & Cohen, 1984; Tipper, Weaver, Jerreat, & Burak, 1984). The goal of this study was to examine the neural underpinnings of attentional facilitation and inhibition in patients with focal brain damage.

Spatial attention is controlled by both endogenous (i.e., top–down, goal-driven, controlled) and exogenous (i.e., bottom–up, stimulus-driven, reflexive) processes (Klein, Kingstone, & Pontefract, 1992; Posner, 1980). Efficient behavior depends on a balanced interaction between the two (Allport, 1989). The endogenous system enables goal-directed behavior such as a driver focusing on a specific route to get to a destination. The exogenous system reacts to external stimuli and can override the endogenous system. For example, a flashing emergency light might reorient the driver's attention away from the road to an ambulance on the side.

The endogenous and exogenous systems also differ in their temporal dynamics. The endogenous system is slow and long acting, whereas the exogenous system is fast and short acting. In a typical endogenous cueing paradigm (Posner, Cohen, & Rafal, 1982), two placeholders are centered on either side of a fixation stimulus. The observer voluntarily orients attention to one of the placeholders when a central cue, such as an arrow, predictively points to the location of the target (e.g., 80% probability). At cue–target onset asynchronies (CTOAs) of 250–300 msec or *more*, normal subjects detect the target faster at validly cued than at invalidly cued locations—the facilitation effect. In a typical exogenous cueing paradigm (Posner & Cohen, 1984), attention is directed reflexively, rather than voluntarily. Here the cue has an abrupt onset, such as a brief increase in luminance in the placeholder, and it is not predictive of target location. At short CTOAs of 150 msec or *less*, normal subjects detect targets faster at locations preceded by a cue at the same location (i.e., a valid cue) than at

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locations preceded by a cue at a different location (i.e., an invalid cue). However, at longer CTOAs of 200 msec or *more*, normal subjects demonstrate IOR. That is, they detect targets slower at validly cued than at invalidly cued locations. More importantly, the IOR effect is observed in exogenous but not in endogenous cueing paradigms. Here we investigate the effects of focal brain damage on the temporal dynamics of this sequence of facilitation and inhibition when the attentional system orients exogenously, as described herein.

Patients with focal brain damage are often used to investigate the neural substrates of attentional orienting. For example, studies of unilateral spatial neglect reveal that spatial attention is mediated by distributed networks involving posterior parietal, dorsolateral prefrontal, and medial frontal cortex along with thalamic and basal ganglia subcortical structures (Chatterjee, 2003). To identify the neural substrate controlling attentional orienting,[1] Posner, Walker, Friedrich, and Rafal (1984) studied patients, many of whom had neglect, and found that patients with parietal but not frontal, temporal, or midbrain damage had difficulty disengaging attention from an ipsilesional cue to a contralesional target. In particular, Posner et al. observed that damage to the superior parietal lobule correlated best with this disengage deficit. This observation was later supported by a positron emission tomography study that found activation in the superior parietal lobule when observers voluntarily shifted attention to the predicted spatial location of an upcoming target (Corbetta, Miezin, Shulman, & Petersen, 1993). More recently, Friedrich, Egly, Rafal, and Beck (1998) found normal endogenous orienting in patients with superior parietal damage, but a disengage deficit in exogenous orienting in patients whose lesions included the temporoparietal junction. Notably, neither report implicated frontal neural networks in the mediation of exogenous orienting.

Disorders of attention are common with frontal damage and include deficits in the ability to sustain attention, divide attention, and, when necessary, switch attention between tasks (Heilman & Valenstein, 1972). However, little is known about the role of prefrontal cortices in the simpler task of orienting attention to exogenous stimuli. Indeed, a prevalent model does not include the frontal lobes in the neural mediation of exogenous orienting (Posner & Petersen, 1990). Rather, this model suggests that the parietal lobe, pulvinar, and superior colliculus of the posterior attention system are the neural substrates of this system. By contrast, more recent models have implicated the frontoparietal networks in exogenous orienting (see Corbetta & Shulman, 2002, for a review; Lepsien & Pollman, 2002, but see Klein, 2004). Specifically, Corbetta and Shulman (2002) suggest that a ventral frontoparietal network is involved in orienting exogenously to unexpected or novel stimuli that fall outside the focus of the task in which an individual is engaged. This model is derived largely from neuroimaging studies and remains to be validated by lesion studies. As such, we conducted this investigation to test the hypothesis that the dorsolateral prefrontal cortex is involved in exogenous orienting. More specifically, we examined both the early facilitation and later inhibition components of exogenous orienting. IOR, the later component of exogenous orienting, is thought to be mediated subcortically (Fectau, Bell, & Munoz, 2004; Bell, Fectau, & Munoz, 2003). However, some have recently speculated that IOR may require cortical involvement (Mayer, Dorflinger, Rao, & Seidenberg, 2004; Mayer, Seidenberg, Dorflinger, & Rao, 2004; Klein, 2000). This speculation with regard to simple exogenous orienting has not been supported by lesion studies (Friedrich et al. 1998; Posner et al., 1985). However, see Stuss et al. (1999) for a study of motoric IOR in the context of increasing task complexity.

To test the hypothesis that the dorsolateral prefrontal cortex is involved in exogenous orienting, we assessed patients with frontal and parietal damage in a target detection paradigm in which exogenous cues were presented at 100 or 750 msec CTOAs. One would expect facilitation at 100 msec and IOR at 750 msec unless exogenous orienting is disrupted by brain damage. In analyzing these patients' data we observed an unusual behavioral pattern in three patients. This behavioral pattern, which we will discuss next, motivated us to further examine the temporal dynamics of exogenous orienting for durations up to 1250 msec CTOA, durations far longer than the usual durations in which facilitation and inhibition are observed.

EXPERIMENT 1: EXOGENOUS ATTENTIONAL ORIENTING

Patients with brain damage were tested in an exogenous cueing paradigm by using a short CTOA that typically produces the facilitation effect and a long CTOA that typically induces the IOR effect. Target detection trials (i.e., no preceding cues) were included to measure orienting times to stimuli in the ipsilesional and contralesional hemifields.

Methods

Participants

Eleven patients (mean age, 59.3 years; range, 45–78 years) with parietal lesions and 13 patients (mean age, 51.9 years; range, 40–74 years) with frontal lesions from chronic (>6 months) stroke were selected from the University of Pennsylvania Center for Cognitive Neuroscience patient database. Patient clinical information is presented in Table 1.

Patients were selected for having a unilateral stroke in either the anterior division or the posterior division of the middle cerebral artery to ensure that the lesions

Table 1. Patient Clinical Information

			Lesion			
Patient	*Sex*	*Age (years)*	*Hemisphere*	*Volume (ml)*	*Location*	*Chronicity*
J.B.$_1$	Female	45	Right	26.0	Parietal	2 years 4 months
S.B.	Female	52	Right	47.9	Parietal	Not applicable
B.G.	Female	53	Left	11.9	Parietal	2 years 9 months
F.H.	Female	66	Right	6.0	Parietal	11 months
C.E.	Female	78	Right	23.7	Parietal	1 year
E.E.	Female	54	Right	34.5	Parietal	7 months
G.P.	Male	77	Left	48.0	Parietal	1 year
D.W.$_1$	Male	51	Left	14.2	Parietal	4 years 1 month
J.J.	Female	56	Left	19.3	Parietal	4 years 8 months
C.B.	Male	48	Right	44.4	Temporoparietal	1 year 4 months
C.W.	Female	72	Right	11.4	Temporoparietal	1 year 2 months
M.P.	Female	59	Right	8.2	Frontal	3 years 3 months
J.D.	Female	73	Right	31.2	Frontal	2 years 10 months
C.H.	Female	52	Right	25.1	Frontal	3 years 1 month
J.B.$_2$	Female	52	Right	34.0	Frontal	9 months
M.M.	Male	74	Right	13.0	Frontal	10 months
M.E.	Female	52	Right	52.2	Frontal	8 years 5 months
J.F.	Male	52	Left	10.6	Frontal	1 year 9 months
H.F.	Male	65	Left	19.4	Frontal	7 months
E.G.	Male	63	Right	139.8	Frontoparietal	2 years 5 months
B.C.	Male	59	Left	26.3	Frontoparietal	3 years 3 months
D.W.$_2$	Male	52	Left	82.5	Frontoparietal	4 years
W.C.	Male	40	Left	87.7	Frontotemporal	3 years 6 months
J.S.	Female	40	Right	88.4	Frontotemporoparietal	1 year 2 months

were primarily in the frontal or temporoparietal regions. This selection was based on the examination of the lesions from magnetic resonance imaging or computed tomography scans and mapping them onto templates by using Montreal Neurological Institute coordinates with MRIcro software. Patients with psychiatric diagnoses or other diseases of the central nervous system are excluded. None of the patients demonstrated neglect or extinction at the time of testing. In the parietal group, there were seven right-hemisphere and four left-hemisphere lesions. In the frontal group, there were eight right-hemisphere and five left-hemisphere lesions. Ten healthy age-matched participants (mean age, 54.3 years; range, 49–65 years) served as a control group and were recruited from the community. This study was approved by the ethics committee of the University of Pennsylvania and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All participants gave written informed consent and were paid for their participation.

Experimental Procedure

Stimuli were displayed on a computer monitor placed 57 cm in front of the subject. The visual display consisted of a black background with two dark gray outline boxes (placeholders) measuring 1.5 × 1.5 cm and located 7 cm to the left and the right of a light gray central fixation cross subtending 0.5 cm. Cues were administered by superimposing a light gray placeholder over a dark gray placeholder. The target was a 0.5-cm light gray asterisk. Participants responded to the target with a speeded keypress. Age-matched control subjects responded with their dominant hand and patients responded with their

ipsilesional hand. Response time (RT) was recorded by the computer and measured in milliseconds from the time the target appeared on the screen.

Participants sat in a dimly lit room, with their chin on a chin rest. All types of trials were illustrated for them. They were instructed to maintain their gaze on the fixation stimulus, told that the cue was not predictive of target location, and asked to respond to the target by pressing the space bar as quickly and as accurately as possible.

Each trial began with a 100-msec warning tone (880 Hz). Following a 400-msec delay, either a target occurred (i.e., a target-only trial) or a 100-msec cue occurred. If a cue occurred, either a target followed at 100 or 750 msec CTOA, or a catch (i.e., no target) trial occurred. Subjects were given a practice block of 25 trials, followed by 16 blocks of experimental trials. All subjects took a break between blocks of trials. In each block there were 54 trials consisting of 5 validly cued and 5 invalidly cued trials for each CTOA and hemifield, 2 target-only trials for each hemifield, and 10 catch trials. The different trial types were presented in a random order. Trials were terminated and the target was removed when the subject pressed the key or 1500 msec after the onset of the target, whichever came first. Intertrial interval was 1000 msec. Data collection took approximately 1 hr.

Response time. Separate analyses were conducted for each of the three groups of participants on RT between 150 and 1500 msec. No behavioral differences by hemisphere of lesion were found. A three-factor repeated measures analysis of variance (ANOVA) was conducted on median correct RT with target status (valid or invalid cue), hemifield (right, left for controls; ipsilesional, contralesional for patients), and CTOA (100, 750 msec) as factors. In addition, a one-factor repeated measures ANOVA was conducted on median correct RT for the target-only trials with hemifield as a factor. Mean RTs and ANOVAs are presented in Table 2. Facilitation and IOR effects were calculated (i.e., invalidly cued RT minus validly cued RT) for the short and long CTOAs, respectively, as presented in Figure 1.

Response accuracy. Error types are as follows: A response executed before the target onset is considered a false alarm; a failure to respond to the target within 1500 msec of target is considered a miss; and a response within 150 msec of target onset is considered an anticipation.

Results

Behavioral Results

Age-matched control subjects. These subjects showed facilitation effects at 100 msec and IOR at 750 msec as evidenced by the ANOVA on their RT data. This analysis revealed a significant Target Status × CTOA interaction, $F(1,9) = 38.69$, $p < .001$, with faster RT at a validly cued than invalidly cued location (395 vs. 432 msec) at 100 msec CTOA and with slower RT at validly cued than invalidly cued location (439 vs. 411 msec) at 750 msec CTOA. Planned comparisons confirmed these observations (both Fs > 14.03, both ps $< .01$). No other main effects or interactions were significant (all Fs < 3.50, all ps $> .09$). There were no differences in their ability to detect targets in the right and left hemifields (413 vs.

Table 2. Mean Correct Response Time (RT) as a Function of Hemifield, Cue–Target Onset Asynchrony (CTOA), and Target Status for Age-matched Controls and Parietal and Frontal Patients

			RT (msec)			
Hemifield	*CTOA*	*Target Status*	*Age-matched Controls*	*Parietals*	*Frontals (n = 13)*	*Frontals (n = 10)*
Ipsilesional/RVF[a]	100	Validly cued	398	547	450	474
		Invalidly cued	432	604	479	494
	750	Validly cued	438	582	488	497
		Invalidly cued	407	551	481	487
	N/A	Target only	413	578	481	502
Contralesional/LVF[a]	100	Validly cued	392	567	470	489
		Invalidly cued	432	635	520	537
	750	Validly cued	439	614	504	521
		Invalidly cued	415	595	511	503
		Target only	4101	597	500	517

[a]Ipsi- and contralesional field for patients, right (RVF) and left visual field (LVF) for age-matched controls.

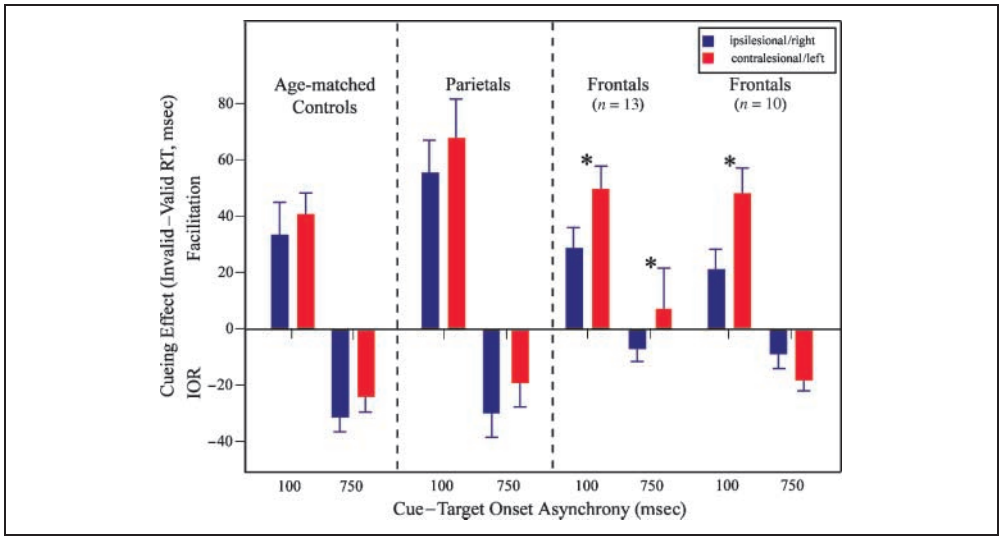

Figure 1. Experiment 1. Mean facilitation and IOR effects for age-matched controls, parietal patients, and frontal patients (n = 13 includes all frontal patients; n = 10 excludes patients J.B.$_2$, M.M., and D.W.$_2$) and as a function of cue–target onset asynchrony (CTOA). The asterisks represent statistically significant differences in effects between ipsilesional and contralesional hemifields for patients and right and left hemifields for age-matched controls.

410 msec) based on the one-factor ANOVA on the target-only trials ($F < 1$).

Mean accuracy was 98.4%. Errors consisted of false alarms (1.5%), misses (< 0.1%), and anticipations (< 0.1%). Given the low error rates, no further analyses were conducted.

Parietal patients. These patients showed facilitation effects at 100 msec and IOR at 750 msec as evidenced by the ANOVA on their RT data. This analysis revealed a significant Target Status × CTOA interaction, $F(1,10) = 92.13$, $p < .0001$, with faster RT at validly cued than invalidly cued locations (577 vs. 596 msec) at 100 msec CTOA and with slower RT at validly cued than invalidly cued locations (598 vs. 573 msec) at 750 msec CTOA. Planned comparisons confirmed these observations (both Fs > 14.72, both ps < .01). No other effects or interactions were significant (all Fs < 3.91, all ps > .07). There were no differences in their ability to detect targets in the ipsilesional and contralesional hemifields (578 vs. 597 msec) based on the one-factor ANOVA on the target-only trials ($F < 1$).

Mean accuracy was 95.5%. Errors consisted of false alarms (2.4%), misses (1.8%), and anticipations (0.3%).

Frontal patients. The frontal patients showed facilitation at 100 msec CTOA but did not show IOR at 750 msec CTOA. The three-factor ANOVA revealed a significant effect of target status, $F(1,12) = 9.52$, $p < .01$, reflecting faster RT at validly cued than invalidly cued locations (478 vs. 498 msec). A significant Target Status × CTOA interaction was also observed, $F(1,12) = 24.20$, $p < .001$. The planned comparison revealed a significant facilitation effect at 100 msec, $F(1,12) = 48.88$, $p < .0001$, with faster RT at validly cued than invalidly cued locations (460 vs. 500 msec). However, no difference in RT was observed ($F < 1$) between validly

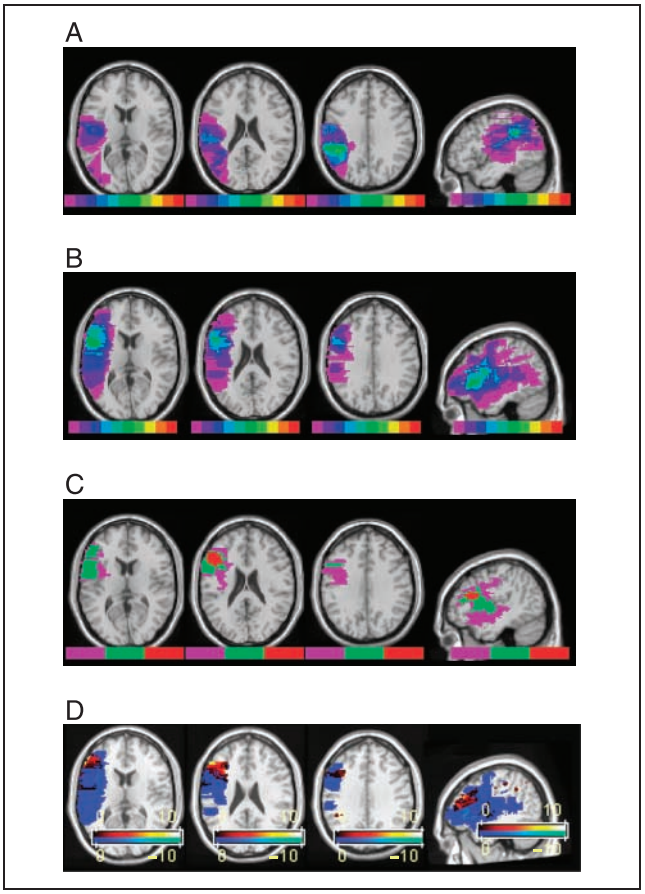

Figure 2. The templates of patients' lesions are overlaid within the same hemisphere. (A) Lesion overlap of patients with parietal damage. (B) Lesion overlap of the patients with frontal damage and the exogenous disengage deficit at short CTOAs. (C) Lesion overlap of the patients with frontal damage that had an asymmetrical facilitation at long CTOAs. The color bar in A, B, and C represent the number of patients with lesions at a specific location. The color purple represents one patient, and each color to the right of the bar indicates an additional patient. (D) Represents a subtraction image, in which the lesions represented in B are subtracted from those in C. The color bar represents chi-square values, ranging from −10 to +10, for comparisons at specific voxels.

cued and invalidly cued locations (both 496 msec) at 750 CTOA. In addition, RT was faster in the ipsilesional than the contralesional hemifield (475 vs. 501 msec), $F(1,12) = 34.49$, $p < .0001$. And finally, a significant Target Status × Hemifield interaction was also found, $F(1,12) = 9.92$, $p < .01$, revealing a greater facilitation effect in the contralesional than the ipsilesional field (29 vs. 11 msec). No other significant effect or interactions were observed (all Fs < 2.58, $p > .1$). The one-factor ANOVA on the target-only trials was not significant, $F(1,12) = 4.12$, $p > .06$, demonstrating no significant RT differences in the ipsilesional and contralesional hemifields (481 vs. 500 msec).

Mean accuracy was 95.6%. Errors consisted of false alarms (3.4%), misses (0.9%), and anticipations (0.1%).

Post Hoc Analyses

Frontal patient subgroups. Although at first glance the frontal patients demonstrated greater contralesional than ipsilesional facilitation at 100 msec CTOA and no IOR at 750 CTOA, three of these patients (J.B.$_2$, M.M., and D.W.$_2$) performed qualitatively differently than the other frontal patients. Remarkably, these patients continued to demonstrate contralesional facilitation at 750 msec CTOA (119, 102, and 51 msec for J.B.$_2$, M.M., and D.W.$_2$, respectively) with no comparable ipsilesional facilitation (8, −25, and 4 msec for J.B.$_2$, M.M., and D.W.$_2$, respectively). To ensure that our finding of the lack of inhibition effects at 750 msec in the group analysis was not a Type 2 error, brought about by the abnormal facilitation observed in these three patients, we reanalyzed the data from the remaining 10 patients with frontal lesions.

The reanalysis in the 10 patients revealed both facilitation at 100 msec CTOA and IOR at 750 msec CTOA as evidenced by a statistically significant Target Status × CTOA interaction, $F(1,9) = 36.29$, $p < .001$. Planned comparisons confirmed facilitation effects at the 100 msec CTOA, $F(1,9) = 36.83$, $p < .001$, with faster RT at an validly cued than at invalidly cued location (481 vs. 516 msec) and significant IOR effects at 750 msec CTOA, $F(1,9) = 6.01$, $p < .04$, with slower RT at a validly cued than at invalidly cued locations (509 vs. 495 msec). A significant Target Status × CTOA × Hemifield interaction, $F(1,9) = 35.75$, $p < .001$, suggested an asymmetrical distribution of effects between hemifields. With direct contrasts, the asymmetric effects were observed for facilitation at 100 msec (48 vs. 21 msec), $F(1,9) = 43.04$, $p < .0001$, but not for IOR at 750 msec (18 vs. 10 msec), $F(1,9) = 3.59$, $p > .09$. This facilitation asymmetry may reflect deficit in disengaging from an ipsilesional cue to respond to a contralesional target.[2,3]

Mean accuracy was 98.0% with errors consisting of false alarms (0.9%), misses (< 0.1%), and anticipations (1.1%).

Further group differences. Although only the frontal patients showed hemifield differences in facilitation, it is possible that the frontal, parietal, and the age-matched control groups differ in the magnitude of their facilitation and IOR effects. The data as shown in Figure 1 raise the possibility that the parietal group may have a larger facilitation effect than the other groups, and the frontal patients may have a smaller IOR effect than the other groups. We conducted unpaired t tests to test these hypotheses and found a larger facilitation effect in the parietal than frontal patients (62 vs. 35 msec), $t(19) = 2.42$, $p < .05$. However, no statistically significant differences were observed in facilitation effect between the parietal patients and the age-matched controls (62 vs. 37 msec), $t(19) = 2.07$, $p > .05$, or between the frontal patients and the age-matched controls, $t(18) < 1$. A significantly smaller IOR effect was observed in the frontal patients than in the age-matched controls (14 vs. 28 msec), $t(18) = -2.19$, $p < .05$, but no significant differences were observed between the frontal and parietal patients (14 vs. 24 msec), $t(19) = -1.01$, $p > .3$, or between the parietal patients and the age-matched controls (24 vs. 28 msec), $t(19) < 1$.

Anatomical Results

Lesions of patients from magnetic resonance imaging or computed tomography scans were mapped onto templates using Montreal Neurological Institute coordinates with MRIcro software. The patients' lesions were overlaid as though they all occurred within the same hemisphere because we did not observe hemispheric behavioral differences. The lesion overlap maps are presented in Figure 2 as follows: Figure 2A illustrates the parietal lesions; B illustrates the frontal lesions associated with the disengage deficit; C illustrates the frontal lesions associated with contralesional facilitation at the long CTOA; and D shows the subtraction of the three patients with the facilitation at long CTOAs from the 10 lesions of the other patients with frontal lesions depicted as a voxelwise chi-square map. The frontal patients who exhibited a disengage deficit at 100 msec CTOA were most likely to have lesions centered on the inferior frontal gyrus (Brodmann's areas [BA] 44, 45, and ventral 6) and frontal patients who exhibited contralesional facilitation at the long CTOA had lesions involving the middle frontal gyrus (BA ventral 9, 46). Parietal patients had lesions that overlapped maximally in the inferior parietal lobule (BA 40, 39).

Discussion

Three main findings emerged from this experiment. First, all patients showed a facilitation effect. Thus, unilateral cortical frontoparietal damage is not sufficient to disrupt the facilitation effect of an exogenous cue.

The facilitation effects differed between the frontal and parietal patients, but because neither group differed from normal control subjects it is difficult to ascribe impairment to one or the other group. Second, the patients with frontal lesions demonstrated a disengage deficit (i.e., greater facilitation in the contralesional hemifield at the short CTOA). The lesions associated with this disengage deficit centered on the inferior frontal gyrus. Third, three of the patients with frontal lesions continued to show a facilitation effect in the contralesional field at the long CTOA. The behavior of these three patients, whose lesions centered on the middle frontal gyrus, differed qualitatively from the other frontal patients and the age-matched controls. We designed the next experiment to replicate these initial observations and further explore the temporal dynamics of the attentional orienting system at longer CTOAs.

EXPERIMENT 2: ATTENTIONAL ORIENTING AT LONGER CTOAs

In this experiment we examined the exogenous attention system over a longer duration because of the abnormal temporal dynamics observed in three patients who showed facilitation at 750 msec CTOA. We wished to learn whether the temporal dynamics of these patients' exogenous orienting system was simply slowed such that IOR might appear at longer CTOAs.

In the previous experiment, two of the three patients, J.B.$_2$ and D.W.$_2$, had substantially greater error rates than the other patients (19.9% and 15.5% for J.B.$_2$ and D.W.$_2$, respectively, vs. 2.0%), resulting primarily from false alarms to ipsilesional cues. To limit these errors, we also incorporated an error tone (220 Hz) that indicated a false alarm or a miss.

Methods

Participants

Patients J.B.$_2$, M.M., and D.W.$_2$, from the previous experiment were further tested in this procedure.

Experimental Procedure

The same procedure was used as in Experiment 1 with the following exceptions. A cue occurred before every target at CTOAs of 750, 1000, or 1250 msec. In addition, when an error occurred (i.e., false alarm or miss) a 200-msec tone (220 Hz) that was easily distinguished from the warning tone (880 Hz) sounded. Patient J.B.$_2$ participated in 9 blocks and patients M.M. and D.W.$_2$ participated in 10 blocks of experimental trials. The experimental trials followed a block of 25 practice trials. In each block there were 70 trials consisting of 5 validly cued and 5 invalidly cued trials for each CTOA and each hemifield and 10 catch trials.

Response time. Separate three-factor repeated measures ANOVAs were conducted for each patient on mean correct RT greater than 150 msec and less than 3 *SD* from the mean with target status (validly cued, invalidly cued), hemifield (ipsilesional, contralesional), and CTOA (750, 1000, 1250 msec) as factors.

Results

Patient means are presented in Table 3 and the ANOVAs are presented in Table 4. All three patients showed contralesional facilitation for validly cued targets at all three CTOAs. In the ipsilesional hemifield, J.B.$_2$ did not show facilitation effects (both Fs < 2.98, both ps $> .08$) at the 750 or 1000 msec CTOA, but did show IOR at 1250 msec CTOA, $F(1,72) = 4.45$, $p < .05$. M.M. showed a facilitation effect at 750 msec CTOA, $F(1,96) = 64.94$, $p < .0001$, but not at the 1000 msec CTOA, $F(1,96) = 1.52$, $p > .2$. M.M. also showed IOR at 1250 msec CTOA, $F(1,96) = 7.77$, $p < .01$. D.W.$_2$ showed facilitation at all three CTOAs. The facilitation effects were equivalent across both hemifields at 750 msec CTOA, but diminished in the ipsilesional field for the 1000 and 1250 msec CTOAs.

All three patients were reasonably accurate. J.B.$_2$'s mean accuracy was 89.7%. Errors consisted of false alarms (7.8%), misses (2.4%), and anticipations (0.1%). A further 1.6% of the data fell outside the 3 *SD* range. M.M.'s mean accuracy was 99.9%. Errors consisted of misses (0.1%). A further 0.6% of the data fell outside the 3 *SD* range. D.W.$_2$'s mean accuracy was 96.9%. Errors consisted of false alarms (2.7%) and misses (0.4%). A further 1.0% of the data fell outside the 3 *SD* range.

Discussion

This experiment replicated the observation that facilitation for validly cued contralesional targets occurred in these patients at 750 msec CTOA and extended up to 1250 msec CTOA. We term this abnormal pattern of contralesional facilitation at long CTOAs a ''reorienting deficit'' for reasons elaborated in the general discussion. Patient J.B.$_2$ and M.M. only showed IOR in the ipsilesional hemifield at the longest CTOA. Patient D.W.$_2$ did not show IOR at any location or CTOA, but the facilitation effect was greater in the contralesional than ipsilesional hemifield.

GENERAL DISCUSSION

The frontal lobes are an integral part of attentional networks, especially when attention is engaged in selection of stimuli over time. Classically, patients with

Table 3. Mean Correct Response Time (RT) Greater than 150 msec and Less than 3 *SD* Above the Mean as a Function of Hemifield, Cue–Target Onset Asynchrony (CTOA), and Target Status for Patients J.B.$_2$, M.M., and D.W.$_2$

			RT (msec)/Effect Size (msec)					
Hemifield	*CTOA*	*Target Status*	*J.B.$_2$*		*M.M.*		*D.W.$_2$*	
Ipsilesional	750	Validly cued	488		485		467	
		Invalidly cued	507	19	517	32*	489	22
	1000	Validly cued	508		496		447	
		Invalidly cued	505	−3	501	5	476	29*
	1250	Validly cued	515		509		440	
		Invalidly cued	492	−23*	498	−11*	456	16*
Contralesional	750	Validly cued	489		539		543	
		Invalidly cued	605	116*	553	14*	561	24*
	1000	Validly cued	482		538		485	
		Invalidly cued	582	100*	558	20*	556	71*
	1250	Validly cued	478		543		487	
		Invalidly cued	532	54*	551	8*	553	66*

*$p < .05$.

dorsolateral prefrontal lesions have difficulties remaining vigilant over extended periods. Whether these patients also have deficits in attentional dynamics over a shorter time scale is not known. To our knowledge, the role of dorsolateral prefrontal damage in simple exogenous orienting has not been previously investigated.

Our study revealed three findings. First, exogenous cues facilitated target detection despite frontoparietal damage. Second, lesions of the dorsolateral prefrontal cortex, especially inferior frontal gyrus, produced a difficulty with disengaging from an ipsilesional location to which attention has been directed exogenously. Third, some patients with dorsolateral prefrontal damage, likely within the posterior middle frontal gyrus, had a reorienting deficit that was remarkably prolonged in duration. We discuss each of the findings and their implications for the organization of attentional systems.

All our patients benefited from exogenous cues in detecting targets, despite the fact that the cue was not predictive of where the target would appear. That is, their attention was captured reflexively by the exogenous cue. This finding suggests that the initial exogenous orienting process may be mediated subcortically, as suggested by recent neurophysiological evidence

Table 4. Three-factor Analyses of Variance (ANOVA) for Patients J.B.$_2$, M.M., and D.W.$_2$ with Target Status (Validly Cued, Invalidly Cued), Cue–Target Onset Asynchrony (CTOA; 750, 1000, 1250 msec), and Hemifield (Ipsilesional, Contralesional) as Factors

	Patients								
	J.B.$_2$			*M.M.*			*D.W.$_2$*		
	df	*F Statistic*	*p*	*df*	*F Statistic*	*p*	*df*	*F Statistic*	*p*
Target status	1,36	98.86	<.0001	1,48	34.29	<.0001	1,41	332.51	<.0001
CTOA	2,72	4.12	<.05	2,96	<1		2,82	72.56	<.0001
Hemifield	1,36	14.30	<.001	1,48	163.08	<.0001	1,41	212.311	<.0001
Target Status × CTOA	2,72	10.29	<.0001	2,96	15.92	<.0001	2,82	19.18	<.0001
Target Status × Hemifield	1,36	126.43	<.0001	1,48	1.94	>.1	1,41	50.65	<.0001
CTOA × Hemifield	2,72	4.55	<.05	2,96	1.00	>.3	2,82	3.69	<.05
Target Status × CTOA × Hemifield	2,72	<1		2,96	13.08	<.0001	2,82	10.81	<.0001

demonstrating that the superior colliculus mediates an early orienting response to an exogenous cue (Fectau et al., 2004; Bell et al., 2003). By contrast, Corbetta and Shulman (2000) suggested that a ventral frontoparietal network primarily involving the temporoparietal junction and inferior frontal gyrus mediates exogenous orienting. Our patients suggest that unilateral damage to the ventral dorsolateral frontal or the posterior parietal cortex does not impair the initial stages of reflexive orienting to an exogenous cue.

After the initial facilitation effects of a valid cue, the frontal patients' behavior diverged from that of normal subjects and patients with parietal damage. These frontal patients segregated into two qualitatively different groups. In one group, exogenous orienting was disrupted such that attention was less easily disengaged from an ipsilesional cue to a contralesional target at short CTOAs. This group had damage most often to the inferior frontal gyrus. The finding is consistent with the view that the inferior frontal gyrus mediates exogenous orienting (Corbetta & Shulman, 2002), but indicates that the frontal involvement occurs after the initial reflexive phase.

A second group of patients with frontal damage continued to show facilitation for validly cued contralesional targets at long CTOAs. This group had damage centered within the posterior middle frontal gyrus. How might we explain this prolonged contralesional facilitation? One possibility is that the subjects had a prolonged inability to disengage from an ipsilesional cue. On this account, the contralesional facilitation would be the result of the cost of attention remaining engaged ipsilesionally in the invalidly cued condition when the target appeared contralesionally. However, such a prolonged disengage mechanism is unlikely to account for the prolonged contralesional facilitation. If attention remained engaged at the precise location of the ipsilesional cue, then targets in the ipsilesional hemifield at long CTOAs should be detected faster when validly cued than when not. This pattern of behavior was not observed. Rather, two patients exhibited the opposite pattern demonstrating ipsilesional IOR at the longest CTOA.

We propose an alternate explanation, which we term the reorienting deficit, which expands on an idea proposed by Corbetta and Shulman (2002). On this view, the ventral frontoparietal network acts as a circuit breaker for the orienting system. In an exogenous cueing experiment, subjects are prepared to detect a target. This task introduces a reflexive exogenous reaction to a cue, but still retains an endogenous component insofar as a specific target is being sought. The cue, which is nonpredictive and is thus irrelevant to the task, becomes a circuit-breaking event for the task to find the target as the attention system reflexively reacts to the location of the cue. After reflexively reacting to the cue, subjects normally reorient to the task of detecting the target. If this reorienting process were impaired, then subjects would be slower to reorient to contralesional targets and produce an asymmetric facilitation effect. On this account, the middle frontal gyrus is a critical component of the frontoparietal attentional network mediating interactions of the exogenous and endogenous orienting systems. This notion is supported by an imaging study demonstrating middle frontal gyrus involvement in reorienting processes in spatial cueing (Lepsien & Pollman, 2002). Consistent with this explanation, Corbetta and Shulman (2002) proposed that frontoparietal networks mediate this interaction. However, they postulated that this system is lateralized to the right hemisphere. With our patients with chronic brain damage, we did not confirm this lateralization claim.

This idea of a reorientation deficit receives some support from the pediatric literature. Young children often do not show IOR (Brodeur & Enns, 1997). A recent study by MacPherson, Klein, and Moore (2003) demonstrated that children do demonstrate IOR, but under specific conditions. Using a single cue procedure, such as the one we used, children did not have IOR at long CTOAs. However, when a double-cue procedure was used, where attention was reoriented via an abrupt onset at center, the typical adult pattern of early facilitation and later IOR was observed at the peripherally cued location. This finding suggested that in young children, if attention is not reoriented from the peripherally cued location (i.e., via an abrupt onset at center), IOR does not develop. MacPherson et al. suggested that a reorienting process is necessary for the development of IOR. As we have already discussed, a similar reorienting deficit may be present in our patients with damage to the posterior middle frontal gyrus.

The interpretation of a contralesional disengage deficit with inferior frontal gyrus damage and a reorienting deficit with middle frontal damage is based largely on the Posner et al. (1984) ''disengage, move, engage'' model of attention. However, one of the issues raised by Klein (2000) is whether IOR begins, as posited by Posner and Cohen (1984), when attention leaves the cued location or when cue onset occurs with the IOR effect initially masked by early facilitation. If the latter is true, an alternate interpretation is that the early facilitation asymmetry could—at least partly—reflect a deficit in IOR to invalidly cued contralesional targets. Thus, it is possible that the inferior and middle frontal gyrus patients do not have qualitatively different deficits. Rather, both groups might demonstrate varying degrees or time courses of disengagement or inhibition of ipsilesional cues, and reorienting or facilitation to contralesional targets.

We did not find evidence that parietal damage affected exogenous attentional orienting. Indeed, the pattern of performance of our patients was similar to that of the age-matched controls. This finding would seem to run contrary to the received wisdom about the role of the parietal cortex in spatial attention. This inconsistency might be accounted for by some critical differences

between our study and others. The classic disengage deficit Posner et al. (1984) reported in patients with parietal lesions was in the context of a paradigm that did not use purely exogenous cues. In their study, the cues were predictive of the location of the target. Also, many of their patients had overt neglect, which was not true of our cohort of subjects. Finally, on average, their patients responded considerably slower than ours. In another study, Friedrich et al. (1998) did observe a disengage deficit in patients with temporoparietal junction lesions. However, they found this deficit at 50 msec but not at 150 msec CTOA. Thus, the posterior attentional networks may be involved in an orienting response at a shorter time scale than anterior networks.

Another goal of the study was to examine the cortical mediation of IOR. Although previous studies suggest that the retinotectal pathway is important for IOR (Sapir, Soroker, Berger, & Henik, 1999; Danziger, Fendrich, & Rafal, 1997; Posner et al., 1985), the posterior parietal cortex in conjunction with the superior colliculus has been implicated in the generation of IOR (Klein, 2000, 2004). This hypothesis follows from studies showing that IOR occurs when the eyes have moved to a different location (Maylor & Hockey, 1985) and when a cued object moves (Tipper et al., 1994), coupled with the rationale that the superior colliculus, which codes in retinal and not environmental spatial coordinates, is by itself unlikely to inhibit coordinates that are independent of eyes or body movement. This hypothesis is further supported by recent single-cell recordings in rhesus monkeys demonstrating that the superior colliculus is necessary, but not sufficient for IOR (Dorris, Klein, Everling, & Munoz, 2002). Finally, a recent activation study demonstrated that involvement of the right posterior parietal area, and middle frontal gyrus in generating IOR (Mayer, Dorflinger, et al., 2004; Mayer, Seidenberg, et al., 2004).

Frontal lesions did appear to have an effect on IOR. First, the typical time course of IOR was not observed in patients with the reorienting deficit. In addition, in frontal patients without a reorienting deficit we found a trend toward less ipsilesional IOR. By contrast, parietal damage did not diminish IOR. This observation is consistent with previous reports of normal IOR in parietal patients (Friedrich et al. 1998; Posner et al., 1985). The posterior parietal cortex may, however, mediate IOR under more complex conditions. Sapir, Hayes, Henik, Danziger, and Rafal (2004) reported that damage to the intraparietal sulcus preserves IOR in retinal but not environmental coordinates. Thus, the parietal cortex might only be necessary for IOR when retinal coordinates are remapped into more complex coordinates (Liu et al., 2005).

In conclusion, our findings suggest that parts of the dorsolateral prefrontal cortex play specific roles in the organization of spatial attention as it unfolds over time. Specifically, damage to the inferior frontal gyrus impairs the ability to rapidly disengage attentional resources from ipsilesional spatial locations at short CTOAs and may hinder the development of ipsilesional IOR. Damage to the posterior middle frontal gyrus is more likely to impair a reorienting process after attention reacts reflexively to an exogenous ipsilesional cue. An attentional system that is impaired in reorienting to the task at hand after a peripheral cue may underlie the clinical observation that many patients with dorsolateral prefrontal lobe damage are distractible and that irrelevant environmental stimuli interfere with their voluntary control of attention.

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Notes

1. In their paradigm, peripheral valid cues were predictive (80%) of target location, making the paradigm not purely an exogenous one. In our experiments the cues occurred equally in either location and are not predictive of the target location.
2. On target-only (i.e., no cue) trials, detection of a target in the ipsilesional hemifield was 15 msec faster than detection of a target in the contralesional hemifield (502 vs. 517 msec). When a cue occurred prior to target onset, this difference was again observed with mean RT to ipsilesionally validly cued locations 15 msec faster than mean RT to contralesionally validly cued locations (474 vs. 489 msec). This difference reflects an ipsilesional detection bias. However, this difference was much larger on invalidly cued trials, with mean RT to ipsilesionally invalidly cued locations 43 msec faster than mean RT to contralesionally invalidly cued locations (494 vs. 537 msec), reflecting an asymmetric cost to detecting targets when the cues occur in the opposite hemifield, which reflects an impairment in disengaging from an ipsilesional cue. In their paradigm, peripheral valid cues were predictive (80%) of target location, making the paradigm not purely an exogenous one. In our experiments the cues occurred equally in either location and are not predictive of the target location.
3. We further looked at patients with lesions confined to the frontal lobes without extension into the anterior parietal lobe ($n = 6$). These patients continued to show greater facilitation in the contralesional than ipsilesional hemifield (43 vs. 17 msec), $F(1,5) = 18.83$, $p < .01$. In addition, IOR was present in the contralesional hemifield, $F(1,5) = 8.27$, $p < .05$, and was absent ($F < 1$) in the ipsilesional hemifield (14 vs. 3 msec).

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