

Neural networks underlying endogenous and exogenous visual–spatial orienting

Andrew R. Mayer,^{a,b,*} Jill M. Dorflinger,^{c,d} Stephen M. Rao,^c and Michael Seidenberg^d

^aThe MIND Institute, Albuquerque, NM 87106, United States

^bNeurology Department, University of New Mexico School of Medicine, Albuquerque, NM 87108, United States

^cDivision of Neuropsychology, Medical College of Wisconsin, Milwaukee, WI 53226, USA

^dDepartment of Psychology, Rosalind Franklin University of Medicine and Science, North Chicago, IL 60064-3095 USA

Received 8 December 2003; revised 20 April 2004; accepted 11 June 2004

The orienting of visual–spatial attention is fundamental to most organisms and is controlled through external (exogenous) or internal (endogenous) processes. Exogenous orienting is considered to be reflexive and automatic, whereas endogenous orienting refers to the purposeful allocation of attentional resources to a predetermined location in space. Although behavioral, electrophysiological and lesion research in both primates and humans suggests that separate neural systems control these different modes of orienting, previous human neuroimaging studies have largely reported common neuronal substrates. Therefore, event-related fMRI (ER-fMRI) was used to independently examine different components of the orienting response including endogenous facilitation, exogenous facilitation and inhibition of return (IOR). In contrast to previous studies, endogenous versus exogenous facilitation resulted in widespread cortical activation including bilateral temporoparietal junction, bilateral superior temporal gyrus, right middle temporal gyrus, right frontal eye field and left intraparietal sulcus. Conversely, IOR compared to endogenous facilitation resulted in only a single focus of activation in the left superior temporal gyrus. These findings suggest that endogenous orienting activates a large cortical network to achieve internally generated shifts of attentional resources versus the automatic orienting that occurs with exogenous cues. However, similar networks may mediate endogenous orienting and IOR. The activation of the temporoparietal junction suggests that it is involved in more effortful processes, such as endogenous orienting, as well as in attentional reorienting and locating targets. Current results are discussed in terms of the functional development of the visual–spatial attentional system. © 2004 Elsevier Inc. All rights reserved.

Keywords: fMRI; Visual; Spatial; Attention; Parietal; Orienting

Introduction

The ability to orient attention based on external or internal cues is crucial for performing daily events such as crossing the street. Endogenous (i.e., checking before crossing the street) and exogenous (i.e., reflexively spotting a speeding car) orienting respectively accomplish volitional goals or warn us of sudden visual changes which may signal impending danger. Models of visual orienting (Corbetta and Shulman, 2002) as well as behavioral, electrophysiological and lesion research in humans and primates suggests that separate neural systems control these different modes of orienting (Corbetta and Shulman, 2002; Kastner and Ungerleider, 2000; Kastner et al., 1998; Mangun et al., 1998; Rafal and Henik, 1994). However, neuroimaging studies have largely reported common activations when the two are directly compared (Corbetta et al., 1993; Kim et al., 1999; Nobre et al., 1997; Rosen et al., 1999), suggesting that other factors, such as methodological limitations, may be influencing these neuroimaging results (Pessoa et al., 2003).

Visual orienting is commonly studied through a paradigm in which cues can correctly (valid cue) or incorrectly (invalid cue) predict the location of spatial targets. Cues can result in behavioral facilitation, in which response times are faster for valid compared to invalid trials, or inhibition, in which response times are faster for invalid compared to valid trials (Posner et al., 1985). Cue type and frequency of valid cues determines the mode of orienting (Fig. 1). Centrally presented cues (arrows) that correctly predict (70–80%) target location generate endogenous orienting. Peripheral cues (luminance changes) that predict target location at chance levels generate exogenous orienting. Exogenous cues produce an automatic orienting response with facilitation reaching maximum capacity at stimulus onset asynchronies (SOAs) of 100–200 ms (Mueller and Rabbitt, 1989; Yantis and Jonides, 1990). At SOAs greater than 400 ms, there is a reversal in the facilitatory effect (Fig. 2b), which classically has been called inhibition of return (IOR; Posner et al., 1985). In contrast, facilitatory effects for endogenous

* Corresponding author. The MIND Institute, Suite 200, 801 University Boulevard, Albuquerque, NM 87106. Fax: +1 505 272 7574.

E-mail address: amayer@mind.unm.edu (A.R. Mayer).

Available online on ScienceDirect (www.sciencedirect.com.)

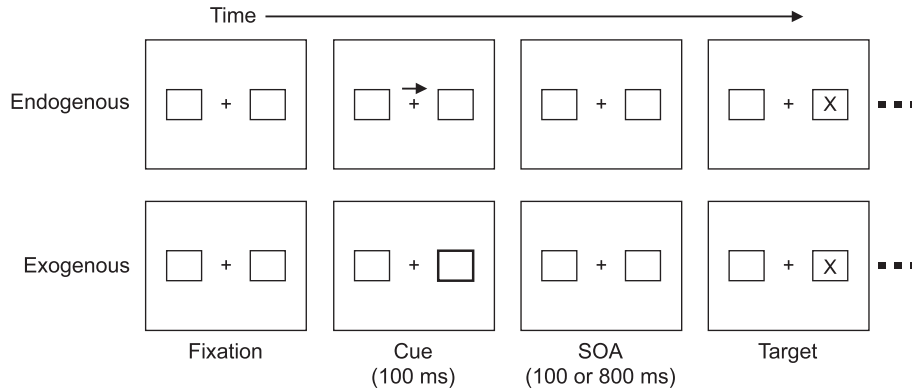


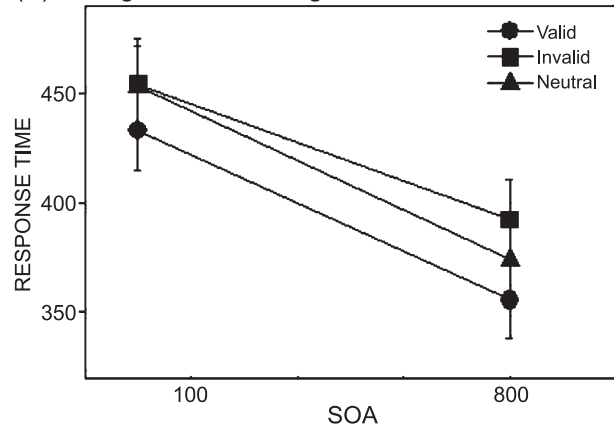
Fig. 1. Diagrammatic representation of the visual display and trial design. Subjects maintained fixation on the central cross throughout the duration of the experiment. Cues in the exogenous (luminosity change in one or both of the boxes) and endogenous (unidirectional or bidirectional arrow) indicated the appearance of an upcoming target. The target (letter X) appeared in one of the boxes following a pseudorandom SOA of either 100 or 800 ms. Cues correctly indicated the location of the upcoming target (valid trial) in 50% of the exogenous and 70% of the endogenous trials.

orienting reach maximum capacity at SOAs greater than 250–300 ms and remain relatively stable (Jonides and Irwin, 1981; Jonides and Mack, 1984; Mueller and Findlay, 1988; Mueller and Rabbitt, 1989; Rafal and Henik, 1994).

As evidenced in the preceding paragraph, orienting consists of several independent components including facilitation, inhibition and attentional reorienting following invalid cues. Previous studies comparing endogenous and exogenous orienting utilized behavioral paradigms that produced IOR rather than exogenous facilitation (Rosen et al., 1999) or employed block designs (Corbetta et al., 1993; Kim et al., 1999; Nobre et al., 1997), which combined different components of the exogenous response including facilitation, IOR and attentional reorienting following invalid cues. Recent research suggests that IOR and exogenous facilitation may be mediated by separate (Klein, 2000) rather than common (Sapir et al., 1999) networks with cortical areas acting in conjunction with retinotectal pathways to produce IOR (Danziger et al., 1997; Klein, 2000; Lepsien and Pollmann, 2002; Mayer et al., in press; Taylor and Klein, 1998). Specifically, recent event-related fMRI (ER-fMRI) studies have reported increased activation of frontal oculomotor areas (Lepsien and Pollmann, 2002; Mayer et al., in press), temporal–occipital and parietal areas (Mayer et al., in press) for IOR compared to exogenous facilitation. Finally, previous studies comparing endogenous and exogenous orienting also blocked valid with invalid trials, which have subsequently shown activation in distinct cortical networks secondary to attentional reorienting (Arrington et al., 2000; Corbetta et al., 2000; Thiel et al., 2004).

Therefore, reports of “common networks” subserving exogenous and endogenous orienting may reflect the combination of different components of the orienting response. We used event-related fMRI (ER-fMRI) to investigate the neuronal substrates involved in endogenous facilitation, exogenous facilitation and IOR independent of the effects of reorienting. ER-fMRI is superior to blocked designs for cognitive studies because it allows for the generation of separate hemodynamic impulse response functions on a trial-by-trial basis. We predicted that endogenous facilitation would result in widespread cortical activation when directly compared to exogenous facilitation secondary to the more effortful allocation of attentional resources in endogenous facilitation. In contrast, we hypothesized that there would be extensive overlap

(A) Endogenous Orienting



(B) Exogenous Orienting

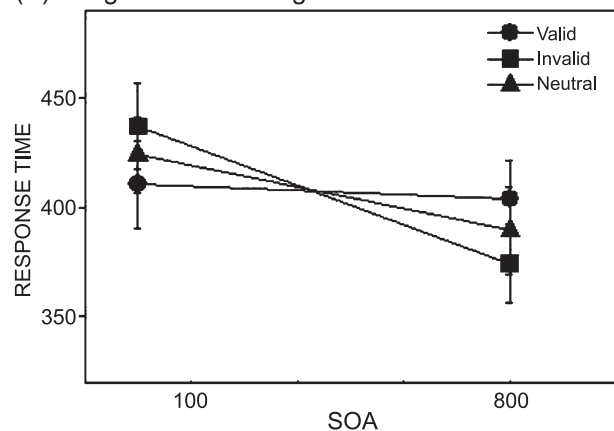


Fig. 2. Behavioral data for valid (●), neutral (▲), and invalid trials (■) for the endogenous (A) and exogenous (B) conditions. In the endogenous condition, facilitation (faster response for valid compared to invalid) is present at 100 and 800 ms SOAs, but the maximum capacity of cueing (facilitation, costs, and benefits) is not reached until the 800 ms SOA. In contrast, in the exogenous condition maximum cueing is present at the 100 ms SOA, and a full reversal in cueing effects are observed at the 800 ms SOA (inhibition). This is the classical biphasic response pattern indicative of IOR.

between neural systems mediating endogenous facilitation and IOR secondary to the more cortical nature of the IOR network (Lepsien and Pollmann, 2002; Mayer et al., in press).

Methods

Subjects

Twelve (four male, eight female) right-handed (mean Edinburgh Handedness Inventory score = 87.8 ± 10.5) adult volunteers (mean age = 26.6 ± 6.4) participated in the study. Subjects with a history of neurological disease, major psychiatric disturbance, substance abuse or psychoactive prescriptive medications were excluded. Informed consent was obtained from subjects according to institutional guidelines at the Medical College of Wisconsin.

Procedure

Subjects performed both an exogenous and endogenous cueing task while in the scanner environment (Fig. 1). Stimuli were projected onto an opaque screen mounted near the subject's feet (viewing distance = 200 cm). In both conditions, the basic visual display consisted of a black background with two white 2.5×2.5 cm boxes (visual angle = 0.72°) located 9 cm from a central fixation cross measuring 1.5×1.5 cm (visual angle = 0.43°). Subjects were instructed to maintain central fixation throughout the course of the experiment. Each trial began with a 100 ms cue followed by the appearance of an X in one of the two boxes at a pseudorandom SOA of either 100 or 800 ms. Target locations were 2.6° visual eccentricity from fixation. Subjects were instructed to make a keypress with their right index finger as soon as the target appeared. Following target presentation, subjects were instructed to continue to maintain central fixation (i.e., baseline state).

Two exogenous and three endogenous imaging series were collected. The exogenous imaging series were always collected first to avoid the establishment of a validity bias (Carter et al., 1995; Whitehead et al., 1997). Each imaging series consisted of 130 pseudorandomly presented active trials (valid, invalid or neutral) and 60 fixation trials. In both exogenous imaging series (Fig. 1), a total of 60 trials (23%) consisted of neutral trials in which an abrupt change in luminance occurred around the edge of both boxes. Spatial cues consisted of a luminance change in one box that correctly indicated the location of the target in 50% of the remainder of the trials (100 valid trials, 100 invalid trials). In the endogenous series (Fig. 1), a total of 90 trials (23%) consisted of neutral cues in which a bidirectional arrow was presented foveally, slightly above the fixation stimulus. Spatial cues were unidirectional arrows that correctly indicated the location of the target in 70% of the remainder of the trials (210 valid trials, 90 invalid trials).

In both the exogenous and endogenous conditions, the intertrial interval was randomly jittered to allow for the best sampling of the hemodynamic response (Burock et al., 1998). This was accomplished by applying a random seed to the 2.5-s epochs (equivalent to repetition time) that contained cueing trials or only the basic visual display and then sorting all epochs by the random seed. No further restraints were applied to the sorting procedure, and trial length ranged from 2.5–15 s. This procedure also allowed for the statistical establishment of the baseline resting state in the

regression model, which corresponded to the neuronal activation associated with maintaining fixation on the central cross.

Functional MR imaging

At the beginning of the scanning session, high resolution, spoiled gradient-recalled at steady state anatomic images were collected [TE (echo time) = 5 ms, TR (repetition time) = 24 ms, 40° flip angle, number of excitations (NEX) = 1, slice thickness = 1.2 or 1.3 mm, FOV (field of view) = 24 cm, resolution = 265×192]. Whole-brain fMRI was conducted on a commercial 1.5 T scanner (Signa, General Electric Medical Systems, Milwaukee) equipped with a prototype 30.5 cm i.d. three-axis local gradient head coil and an elliptical endcapped quadrature radio frequency coil. Echo-planar images were collected using a single-shot, gradient-echo echoplanar pulse sequence [TE = 40 ms; FOV = 24 cm; matrix size = 64×64]. Twenty-two contiguous sagittal 6-mm-thick slices were selected to provide coverage of the entire brain (voxel size: $3.75 \times 3.75 \times 6$ mm). For each of the imaging series, 190 sequential echo-planar images were collected per run with a TR of 2.5 s.

Image processing and statistical analyses

Functional images were generated using Analysis of Functional NeuroImages (AFNI) software package (Cox, 1996). Time series images were spatially registered in both two- and three-dimensional space to minimize effects of head motion. A deconvolution analysis was used to generate one impulse response function (IRF) for each condition on a voxel-wise basis. Each IRF was relative to the baseline state (fixation) and based on the first five TRs poststimulus onset. Anatomical and functional images were then interpolated to volumes with 1 mm^3 voxels, coregistered, converted to a standard stereotaxic coordinate space (Talairach and Tournoux, 1988) and blurred using a 3-mm Gaussian full-width half-maximum (FWHM) filter. A voxel-wise repeated measures ANOVA and planned comparison *t* tests were performed for the image occurring 5.0–7.5 s poststimulus onset from the cue, corresponding to the peak of hemodynamic response function (Cohen, 1997). To investigate the neural substrates of endogenous facilitation, exogenous facilitation and IOR independent of the effects of reorienting, only valid trials were entered into the ANOVA. The significance threshold for activation peaks corresponded to $P < 0.001$ for all comparisons. To minimize false positives, a minimum cluster size of 0.25 ml was also required (Forman et al., 1995). These two thresholds were determined based on 10,000 Monte Carlo simulations demonstrating that the chance probability of obtaining a significant activation cluster for an entire volume (Type I error) was less than 1×10^{-5} .

A conjunction analysis was also performed to identify regions that were commonly activated in endogenous facilitation and IOR compared to exogenous facilitation (Price and Friston, 1997). Due to the increased sensitivity of this analysis, a significance threshold corresponding to $P < 0.005$ and minimum cluster size of 0.25 ml was applied to the results.

Behavioral results

Two 3×2 [Cue Type (Valid, Invalid, Neutral) \times SOA (100, 800 ms)] ANOVAs were performed to verify that the documented effects of endogenous and exogenous orienting were present in the

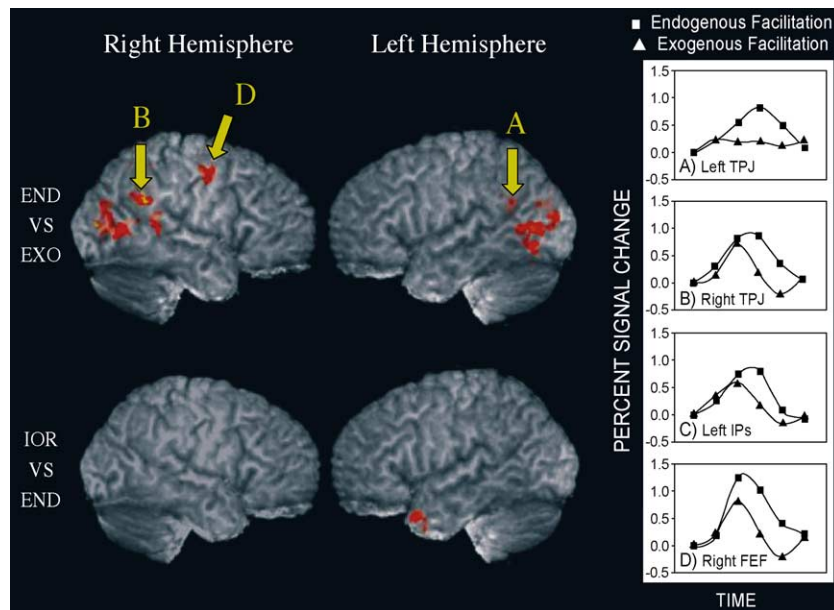


Fig. 3. Differential patterns of activations ($P < 0.001$) for endogenous (END) compared to exogenous (EXO) facilitation (top row) and IOR compared to endogenous (END) facilitation (bottom row). In the first comparison, endogenous facilitation resulted in widespread cortical activation (areas of increased activation in red) including the (A) left TPJ, (B) right TPJ, (C) left IPs (not displayed in pages), and (D) right FEF. Hemodynamic response functions for the right and left TPJ, left IPs, and right FEF activations are displayed for endogenous (square) and exogenous facilitation (triangle). In contrast, the comparison IOR versus endogenous facilitation resulted only in a single focus of increased activation (area of increased activation in red) for IOR in the left superior temporal gyrus.

scanner environment. Reaction times shorter than 100 ms or longer than 2500 ms were considered anticipatory or missed responses, respectively, and were discarded from future analyses.

In the endogenous condition (Fig. 2a), the validity \times SOA interaction term was significant ($F_{2,22} = 6.51$, $P < 0.05$). Follow-up tests indicated that a validity effect (valid $<$ invalid) and benefits (valid $<$ neutral) from cueing were established at both SOAs, but that costs (neutral $<$ invalid) were only present at the

800 ms SOA ($t > 2.2$, $P < 0.05$ in all cases). The lack of costs at the early SOA supports previous suggestions that the maximal effects of endogenous orienting occur at SOAs of 300 ms or longer (Jonides and Irwin, 1981; Mueller and Findlay, 1988; Rafal and Henik, 1994).

In the exogenous condition (Fig. 2b), the validity \times SOA interaction term was also significant ($F_{2,22} = 23.26$, $P < 0.05$). Follow-up tests indicated that exogenous facilitation reached its

Table 1

Areas of activation for endogenous versus exogenous facilitation and IOR versus endogenous facilitation comparisons based on the Talairach atlas

Region	Laterality	CM (Endogenous Facilitation > Exogenous Facilitation)					CM (IOR > Endogenous Facilitation)				
		BA	X	Y	Z	Vol (ml)	BA	X	Y	Z	Vol (ml)
<i>Parietal and temporal lobes</i>											
Intraparietal sulcus	L	19	-23	-80	19	1.679					
Inferior parietal lobule (IPL)	R	40	28	-51	39	1.479					
Inferior parietal lobule (IPL)/ superior temporal gyrus (STG)	R	39/40	54	-51	28	0.284					
Inferior parietal lobule (IPL)/ superior temporal gyrus (GTs)	L	39/40	-38	-56	26	0.693					
Superior temporal gyrus (GTs)	R	22	50	-43	15	0.510					
Superior temporal gyrus (GTs)	L						38	-38	8	-28	0.288
Middle temporal gyrus (GTm)	R	37/39	46	-63	9	0.526					
<i>Frontal lobe</i>											
Frontal eye fields (FEF)	R	6	40	-8	45	0.617					
<i>Occipital lobe</i>											
Middle occipital gyrus	R	19	35	-76	16	1.095					
	L	19	-46	-69	7	0.524					
	L	19	-42	-71	-5	0.257					
Cuneus	R	7	2	-76	36	0.294					

Center of mass (CM) and volume (Vol) are listed for each cluster.

maximum at the 100 ms SOA, as evidenced by significant benefits, costs and validity effect from cueing ($t > 2.2$, $P < 0.05$ in all cases). A full reversal in the benefits, costs, and validity effect was present at the 800 ms SOA, ($t > 2.2$, $P < 0.05$ in all cases), indicative of IOR. The behavioral results observed in the scanner replicate previous behavioral studies of both endogenous and exogenous orienting.

FMRI results

In contrast to previous studies (Kim et al., 1999; Nobre et al., 1997), a comparison of endogenous facilitation at the 800 ms SOA versus exogenous facilitation at the 100 ms SOA resulted in several unilateral and bilateral foci of activation (Fig. 3 and Table 1), although both of these conditions were associated with similar behavioral effects. Endogenous facilitation resulted in bilateral activation of the temporoparietal junction (TPJ; BA 39/40) and middle occipital gyrus (BA 19). Unilateral activation of the right inferior parietal lobule (IPL; BA 40), left intraparietal sulcus (IPs; BA 19), right superior (BA 22) and middle (BA 37/39) temporal gyri, right frontal eye field (FEF; BA 6) and right cuneus (BA 7) were found for endogenous facilitation. Similar to previous results (Kim et al., 1999), there were no areas of increased activation associated with exogenous compared to endogenous facilitation.

A single focus of preferential activation in the inferior aspects of the left superior temporal gyrus (BA 38) was identified for IOR compared to endogenous facilitation at the 800 ms SOA (Fig. 3 and Table 1). Finally, no differences were observed between endogenous facilitation at the 800 compared to 100 ms SOA. The results of exogenous facilitation versus IOR are presented elsewhere (Mayer et al., in press).

In addition, we performed a conjunction analyses (Price and Friston, 1997) to identify the neuronal structures that were commonly activated in endogenous facilitation and IOR in comparison to exogenous orienting (Table 2). The results of this analysis included bilateral activation of the middle occipital gyrus (BA 19) and precentral gyrus (BA 4/6) including the FEFs, right superior (BA 22) and middle (BA 37/39) temporal gyri, right inferior parietal lobe (BA 40), right TPJ (BA 39/40) and left

superior occipital gyrus (BA 19). The results of this analysis support previous suggestions that endogenous facilitation and IOR may rely on common neural networks (Rosen et al., 1999).

Discussion

Contrary to several previous neuroimaging studies of visual orienting (Corbetta et al., 1993; Kim et al., 1999; Nobre et al., 1997; Rosen et al., 1999), current results indicate that there are significant differences between exogenous and endogenous orienting when the effects of facilitation, IOR and attentional reorienting are independently examined. The current study demonstrated that endogenous facilitation utilized a large cortical network for mediating shifts of attention and identifying targets compared to exogenous facilitation. These results suggest that there are separate neural networks for the control of effortful versus automatic shifts of attention, two cognitive operations that are fundamental to most organisms. In contrast, endogenous facilitation and IOR appear to use similar neural networks to mediate these two processes. Previous studies may have minimized the contributions of different cortical sites in endogenous versus exogenous orienting by combining the different components of the orienting response (Pessoa et al., 2003).

A blocked design study (Kim et al., 1999) directly comparing endogenous versus exogenous orienting reported only left posterior parietal and bilateral temporal occipital activation. The comparison of endogenous versus exogenous facilitation in the current study resulted in bilateral activation of the TPJ, right FEF, right IPL, right middle and superior temporal gyrus, bilateral middle occipital gyrus, and left IPs. Several structures activated by endogenous facilitation, including the TPJ and FEF, are also activated by attentional reorienting following invalid trials (Arrington et al., 2000; Corbetta et al., 2000). The blocking of invalid and valid trials in the previous experiment may have resulted in activation of these structures for both the exogenous and endogenous conditions, ultimately resulting in cancellation. Previous studies may have compounded this cancellation effect by combining exogenous facilitation with IOR, and then comparing it to endogenous orienting. This is supported by recent FMRI studies

Table 2

Results of the conjunction analysis examining common areas of activation for endogenous versus exogenous facilitation and IOR versus exogenous facilitation

Region	Laterality	CM (Common Areas for Endogenous Facilitation and IOR > Exogenous Facilitation)				
		BA	X	Y	Z	Vol (ml)
<i>Parietal and temporal lobes</i>						
Inferior parietal lobule (IPL)	R	40	42	-43	30	0.294
Inferior parietal lobule (IPL)/ superior temporal gyrus (STG)	R	39/40	55	-53	27	0.272
Superior temporal gyrus (GTs)	R	22	52	-45	15	0.954
Middle temporal gyrus (GTm)	R	37/39	47	-63	8	0.900
<i>Frontal lobe</i>						
Precentral gyrus (FEF)	R	4/6	39	-7	44	0.459
Precentral gyrus and FEF	L	4/6	-43	-6	38	0.754
<i>Occipital lobe</i>						
Middle occipital gyrus (GOM)	R	19	39	-77	7	0.441
	L	19	-47	-74	8	0.339
Superior occipital gyrus (GOs)	L	19	-23	-77	25	0.418

Coordinates are based on the Talairach atlas and center of mass (CM) and volume (Vol) are listed for each cluster.

which suggest that IOR may be partially regulated by anterior oculomotor, temporal–occipital and parietal areas (Lepsien and Pollmann, 2002; Mayer et al., *in press*).

Endogenous versus exogenous facilitation also resulted in activation of several parietal areas including the left IPs, the right IPL and bilateral TPJ. The activation of left posterior parietal areas is not surprising given that posterior parietal areas have been associated with shifting and maintaining attention at cued locations (Corbetta et al., 2000; Friedrich et al., 1998; Hopfinger et al., 2000; Mesulam, 1994; Posner and Peterson, 1990; Rushworth et al., 2001; Yantis et al., 2002). This result suggests that endogenous facilitation may be associated with more effortful shifts of attentional resources compared to the automatic shifting of attention following exogenous cues. The lateralization of findings to the left posterior parietal cortex may be reflective of increased verbal mediation in endogenous facilitation or secondary to the symbolic nature of the endogenous cues (Nobre et al., 1997; Posner, 1994). Increased activation in the parietal lobes could also be indicative of greater demands on working memory during the endogenous condition, as several imaging studies have suggested that the posterior parietal lobes may act in conjunction with the prefrontal cortex to coordinate working memory functions (Jonides et al., 1998; Veltman et al., 2003). However, unlike previous studies of orienting (Rosen et al., 1999), prefrontal areas associated with working memory were not activated during the endogenous condition in the current experiment.

Other researchers (Gitelman et al., 1999; Hopf and Mangun, 2000; Hopfinger et al., 2000) have proposed that the posterior parietal cortex (i.e., dorsal stream) may hierarchically control the superior and middle temporal gyrus (i.e., ventral stream) and temporal–occipital areas as part of the top-down attentional (i.e., endogenous) system. Current and previous results (Kim et al., 1999) also support this hypothesis, as endogenous versus exogenous facilitation resulted in increased temporal–occipital activation in area hMT+, right superior temporal gyrus activation and activation of the left IPs. Other imaging experiments have reported activity in the superior and middle temporal gyri for cued, covert shifts of visual attention (Corbetta et al., 2000; Gitelman et al., 1999; Hopfinger et al., 2000; Yantis et al., 2002) and for target detection (Corbetta et al., 2000). Area hMT+ has been posited to play a role in the spatial and featural aspects of visual attention (Beauchamp et al., 1997) and has extended connectivity to the attentional network and to the superior temporal gyrus (Gitelman et al., 1999; Selemon and Goldman-Rakic, 1988).

Endogenous compared to exogenous facilitation also resulted in activation of the right FEF, as well as in bilateral activation of visual centers. The FEFs have previously been linked to the generation of endogenous saccades to the contralateral visual field (Henik et al., 1994; Paus, 1996), to the covert reorienting of endogenous attention (Arrington et al., 2000; Corbetta and Shulman, 2002; Corbetta et al., 2000; Henik et al., 1994; Paus, 1996) and with IOR (Lepsien and Pollmann, 2002; Mayer et al., *in press*). Lesions of the FEF result in increased response latencies for endogenously triggered saccades and decreased response latencies for exogenously triggered saccades to the contralateral hemifield (Rafal et al., 1994). This finding is consistent with current results indicating that the right FEF may be more important for endogenous versus exogenous facilitation.

Endogenous facilitation also resulted in bilateral activation of the TPJ and the right IPL. These results are consistent with lesion data demonstrating that patients with TPJ lesions show greater

deficits for endogenous compared to exogenous orienting for validly cued trials (Rafal and Henik, 1994) and deficits in generating the endogenous P300 potential (Knight et al., 1989). The activation of the TPJ for endogenous facilitation raises questions about a strict localization view of the TPJ for disengaging and reorienting attentional focus following invalid trials (Corbetta et al., 2000; Friedrich et al., 1998) and supports broader models specifying multiple roles for the neuronal substrates of the attentional network (Corbetta and Shulman, 2002; Gitelman et al., 1999; Mesulam, 1994). Current analyses included only valid trials, rendering it unlikely that TPJ activation was the result of attentional reorienting.

A recent review (Corbetta and Shulman, 2002) proposed that endogenous attention is mediated by a frontoparietal network in which the IPs acts in conjunction with the FEFs to maintain top-down control. Current results are consistent with this proposal as both of these structures were activated in the endogenous facilitation condition. This review also proposed that the TPJ should demonstrate increased activation for exogenous processes, as it is generally modulated by the detection of unattended or low frequency events. However, current results indicate increased activation in the TPJ for endogenous, or top-down orienting. A reformulation of this hypothesis is that the TPJ is preferentially activated by cognitive tasks requiring more effortful or volitional shifts of attentional focus, such as those with invalid trials, top-down orienting or low frequency events.

Exogenous compared to endogenous facilitation did not result in any unique areas of activation, suggesting a degree of redundancy in the development of the visual–spatial attention network (Mesulam, 1994). Previous studies have also reported a lack of unique activation for exogenous versus endogenous orienting (Kim et al., 1999) and exogenous facilitation versus IOR (Lepsien and Pollmann, 2002; Mayer et al., *in press*). Recent studies have shown that both exogenous facilitation and IOR commonly activate retinotectal structures, such as the superior colliculi (Lepsien and Pollmann, 2002; Mayer et al., *in press*; Sapir et al., 1999), suggesting that IOR and endogenous orienting may also utilize similar structures as the more primitive exogenous orienting reflex.

Previous results (Rosen et al., 1999) have suggested that common neural networks may regulate endogenous orienting and IOR. Current results support this hypothesis, as a direct comparison of IOR versus endogenous facilitation resulted in only a single focus of activation in the inferior aspects of the superior temporal gyrus in spite of the significant differences in behavioral effects for these conditions. A conjunction analyses (Price and Friston, 1997) revealed that several areas, including the FEFs, right parietal areas, right medial and superior temporal gyri and bilateral temporal–occipital areas, were commonly activated in both endogenous facilitation and IOR compared to exogenous facilitation. IOR may have developed to prevent organisms from responding to visual stimuli that occur in rapid succession in the same spatial location (Jonides and Irwin, 1981; Posner and Cohen, 1984; Posner et al., 1985) or may inhibit subsequent saccades to similar locations (Klein, 2000; Taylor and Klein, 1998). The activation of these structures in IOR and endogenous facilitation suggests that similar neuronal resources may be employed to prevent exogenous facilitation from dominating visual attention.

The current experiment was limited by several factors. First, it is difficult to determine whether the reported differences between endogenous and exogenous facilitation are the result of endoge-

nous shifting, endogenous target processing or an interaction between both of these functions. Previous work (Corbetta et al., 2000) utilized extremely long SOAs to demonstrate that distinct anatomical areas within the parietal lobe were responsible for shifting and maintaining attention (IPs) versus detecting the appearance of a target (TPJ). To produce exogenous facilitation, targets must occur within 100–300 ms of cues, precluding the possibility of utilizing an extended SOA in the current experiment. This experimental limitation, coupled with the relative temporal insensitivity of the BOLD response, makes it difficult to determine the precise cause of the increased activation observed during endogenous facilitation. However, the bilateral activation of the TPJ and unilateral (left) activation of the IPs suggests that current results may reflect a combination of both increased shifting of attentional resources and increased target processing during endogenous facilitation.

Second, eye movements were not monitored in the current experiment, raising the possibility that subjects had more difficulty maintaining fixation in one of the conditions. It is possible that areas of oculomotor activation observed during endogenous facilitation may be the result of more frequent eye movements in this condition. However, previous studies have demonstrated that healthy subjects are very capable of maintaining fixation in the MR environment during endogenous and exogenous tasks and execute eye movements on only 3–6% of total trials (Arrington et al., 2000; Rosen et al., 1999; Thiel et al., 2004), which suggests that current results are not secondary to increased eye movements. Finally, it is possible that the lack of counterbalancing in the current experiment to avoid a validity bias in the exogenous condition may have produced ordering effects in our results.

Nonetheless, to our knowledge, this is the first experiment to demonstrate distinct differences between endogenous and exogenous facilitation when the two are directly compared and suggest that processes are not completely mediated by the same neuronal system (Kim et al., 1999; Rosen et al., 1999). Moreover, these results can not be solely attributed to the nonspecific effects of SOA, such as increased response preparedness, as the comparison of endogenous facilitation at the 100 and 800 ms SOAs did not reveal any significant areas of activation. Current and recent (Lepsien and Pollmann, 2002; Mayer et al., in press) fMRI studies suggest a model of visual orienting in which IOR may have first developed to inhibit bottom-up orienting, followed by the development of a more sophisticated top-down system to volitionally control the orienting of attention to particular locations in visual space. IOR may represent the first functional step resulting in more efficient monitoring of the visual space by preventing the visual system from being overwhelmed by innocuous sensory events. Top-down control of attentional orienting may have developed to volitionally allocate attention to different spatial locations and to further modulate bottom-up orienting.

This model predicts complete overlap between exogenous facilitation and endogenous facilitation/IOR, as well as predicting that IOR and endogenous processes would be more likely to utilize similar cortical networks in addition to retinotectal pathways. This model is also consistent with Mesulam's (1994) work, in which he proposed that the different components of the attentional network contain the cognitive program for several complex attentional functions that may be both specialized and redundant. This redundancy in function explains why several core components of

the visual attention network, including parietal areas and FEFs, are activated by different aspects of orienting such as endogenous facilitation, IOR and attentional reorienting following invalid cues (Arrington et al., 2000; Corbetta et al., 2000; Lepsien and Pollmann, 2002; Mayer et al., in press).

In conclusion, current results are consistent with electrophysiological and lesion data suggesting that endogenous compared to exogenous facilitation is mediated by a large cortical network including frontal, parietal and temporal areas. Moreover, results indicate that neural networks subserving endogenous facilitation and IOR are comparable and that both may have developed as a means of regulating bottom-up attentional processes.

Acknowledgments

This research was supported by grants from the National Institutes of Health (P01 MH51358, R01 MH57836; SMR), Medical College of Wisconsin General Clinical Research Center (M01 RR00058) and the W.M. Keck Foundation. Special thanks to Doug Ward for helpful comments.

References

- Arrington, C.M., Carr, T.H., Mayer, A.R., Rao, S.M., 2000. Neural mechanisms of visual attention: object-based selection of a region in space. *J. Cognit. Neurosci.* 12, 106–117.
- Beauchamp, M.S., Cox, R.W., DeYoe, E.A., 1997. Graded effects of spatial and featural attention on human area MT and associated motion processing areas. *J. Neurophysiol.* 78, 516–520.
- Burock, M.A., Buckner, R.L., Woldorff, M.G., Rosen, B.R., Dale, A.M., 1998. Randomized event-related experimental designs allow for extremely rapid presentation rates using functional MRI. *NeuroReport* 9, 3735–3739.
- Carter, C.S., Krenner, P., Chaderjian, M., Northcutt, C., Wolfe, V., 1995. Asymmetrical visual-spatial attentional performance in ADHD: evidence for a right hemispheric deficit. *Biol. Psychiatry* 37, 789–797.
- Cohen, M., 1997. Parametric analysis of fMRI data using linear systems methods. *NeuroImage* 6, 93–103.
- Corbetta, M., Shulman, G.L., 2002. Control of goal-directed and stimulus-driven attention in the brain. *Nat. Rev., Neurosci.* 3, 201–215.
- Corbetta, M., Miezin, F.M., Shulman, G.L., Petersen, S.E., 1993. A PET study of visuospatial attention. *J. Neurosci.* 13, 1202–1226.
- Corbetta, M., Kincade, J.M., Ollinger, J.M., McAvoy, M.P., Shulman, G.L., 2000. Voluntary orienting is dissociated from target detection in human posterior parietal cortex. *Nat. Neurosci.* 3, 292–297.
- Cox, R.W., 1996. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput. Biomed. Res.* 29, 162–173.
- Danziger, S., Fendrich, R., Rafal, R.D., 1997. Inhibitory tagging of locations in the blind field of hemianopic patients. *Conscious Cogn.* 6, 291–307.
- Forman, S.D., Cohen, J.D., Fitzgerald, M., Eddy, W.F., Mintun, M.A., Noll, D.C., 1995. Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. *Magn. Reson. Med.* 33, 636–647.
- Friedrich, F.J., Egly, R., Rafal, R.D., Beck, D., 1998. Spatial attention deficits in humans: a comparison of superior parietal and temporal-parietal junction lesions. *Neuropsychology* 12, 193–207.
- Gitelman, D.R., Nobre, A.C., Parrish, T.B., LaBar, K.S., Kim, Y.H., Meyer, J.R., Mesulam, M.M., 1999. A large-scale distributed network for covert spatial attention: further anatomical delineation based on stringent behavioural and cognitive controls. *Brain* 122, 1093–1106.

- Henik, A., Rafal, R., Rhodes, D., 1994. Endogenously generated and visually guided saccades after lesions of the human frontal eye fields. *J. Cogn. Neurosci.* 6, 400–411.
- Hopf, J.M., Mangun, G.R., 2000. Shifting visual attention in space: an electrophysiological analysis using high spatial resolution mapping. *Clin. Neurophysiol.* 111, 1241–1257.
- Hopfinger, J.B., Buonocore, M.H., Mangun, G.R., 2000. The neural mechanisms of top-down attentional control. *Nat. Neurosci.* 3, 284–291.
- Jonides, J., Irwin, D.E., 1981. Capturing attention. *Cognition* 10, 145–150.
- Jonides, J., Mack, R., 1984. On the cost and benefit of cost and benefit. *Psychol. Bull.* 96, 29–44.
- Jonides, J., Schumacher, E.H., Smith, E.E., Koeppel, R.A., Awh, E., Reuter-Lorenz, P.A., Marshuetz, C., Willis, C.R., 1998. The role of parietal cortex in verbal working memory. *J. Neurosci.* 18, 5026–5034.
- Kastner, S., Ungerleider, L.G., 2000. Mechanisms of visual attention in the human cortex. *Annu. Rev. Neurosci.* 23, 315–341.
- Kastner, S., De Weerd, P., Desimone, R., Ungerleider, L.G., 1998. Mechanisms of directed attention in the human extrastriate cortex as revealed by functional MRI. *Science* 282, 108–111.
- Kim, Y.H., Gitelman, D.R., Nobre, A.C., Parrish, T.B., LaBar, K.S., Mesulam, M.M., 1999. The large-scale neural network for spatial attention displays multifunctional overlap but differential asymmetry. *NeuroImage* 9, 269–277.
- Klein, R.M., 2000. Inhibition of return. *Trends Cogn. Sci.* 4, 138–147.
- Knight, R.T., Scabini, D., Woods, D.L., 1989. Prefrontal cortex gating of auditory transmissions in humans. *Brain Res.* 502, 109–116.
- Lepsien, J., Pollmann, S., 2002. Covert reorienting and inhibition of return: an event-related fMRI study. *J. Cogn. Neurosci.* 14, 127–144.
- Mayer, A.R., Seidenberg, M., Dorflinger, J., Rao, S.M., in press. An event-related fMRI study of exogenous orienting: supporting evidence for the cortical basis of inhibition of return? *J. Cogn. Neurosci.*
- Mangun, G.R., Buonocore, M.H., Girelli, M., Jha, A.P., 1998. ERP and fMRI measures of visual spatial selective attention. *Hum. Brain Mapp.* 6, 383–389.
- Mesulam, M.M., 1994. Neurocognitive networks and selectively distributed processing. *Rev. Neurol.* 150, 564–569.
- Mueller, H.J., Findlay, J.M., 1988. The effect of visual attention on peripheral discrimination thresholds in single and multiple element displays. *Acta Psychol.* 69, 129–155.
- Mueller, H.J., Rabbitt, P.M., 1989. Reflexive and voluntary orienting of visual attention: time course of activation and resistance to interruption. *J. Exp. Psychol. Hum. Percept. Perform.* 15, 315–330.
- Nobre, A.C., Sebestyen, G.N., Gitelman, D.R., Mesulam, M.M., 1997. Functional localization of the system for visuospatial attention using positron emission tomography. *Brain* 120, 15–533.
- Paus, T., 1996. Location and function of the human frontal eye-field: a selective review. *Neuropsychologia* 34, 475–483.
- Pessoa, L., Kastner, S., Ungerleider, L.G., 2003. Neuroimaging studies of attention: from modulation of sensory processing to top-down control. *J. Neurosci.* 23, 3990–3998.
- Posner, M.I., 1994. Attention: the mechanisms of consciousness. *Proc. Natl. Acad. Sci. U. S. A.* 91, 7398–7403.
- Posner, M.I., Cohen, Y., 1984. Components of visual orienting. In: Bouma, H., Bowhuis, D. (Eds.), *Attention and Performance*. Lawrence Erlbaum, London, pp. 531–556.
- Posner, M.I., Peterson, S.E., 1990. The attentional system of the human brain. *Annu. Rev. Neurosci.* 13, 25–42.
- Posner, M.I., Rafal, R., Choate, L., Vaughn, L., 1985. Inhibition of return: neural basis and function. *Cogn. Neuropsychol.* 2, 211–228.
- Price, C.J., Friston, K.J., 1997. Cognitive conjunction: a new approach to brain activation experiments. *Neuroimage* 5, 261–270.
- Rafal, R., Henik, A., 1994. The neurology of inhibition: integrating controlled and automatic processes. In: Dagenbach, D.E., Carr, T.H. (Eds.), *Inhibitory Processes in Attention, Memory, and Language*. pp. 1–51. Academic Press, San Diego, CA, USA.
- Rafal, R., Egly, R., Rhodes, D., 1994. Effects of inhibition of return on voluntary and visually guided saccades. *Can. J. Exp. Psychol.* 48, 284–300.
- Rosen, A.C., Rao, S.M., Caffarra, P., Scaglioni, A., Bobholz, J.A., Woodley, S.J., Hammeke, T.A., Cunningham, J.M., Prieto, T.E., Binder, J.R., 1999. Neural basis of endogenous and exogenous spatial orienting. A functional MRI study. *J. Cogn. Neurosci.* 11, 135–152.
- Rushworth, M.F., Paus, T., Sipila, P.K., 2001. Attention systems and the organization of the human parietal cortex. *J. Neurosci.* 21, 5262–5271.
- Sapir, A., Soroker, N., Berger, A., Henik, A., 1999. Inhibition of return in spatial attention: direct evidence for collicular generation. *Nat. Neurosci.* 2, 1053–1054.
- Selemon, L.D., Goldman-Rakic, P.S., 1988. Common cortical and subcortical targets of the dorsolateral prefrontal and posterior parietal cortices in the rhesus monkey: evidence for a distributed neural network subserving spatially guided behavior. *J. Neurosci.* 8, 4049–4068.
- Talairach, J., Tournoux, P., 1988. *Co-Planar Stereotaxic Atlas of the Human Brain*. Thieme, New York.
- Taylor, T.L., Klein, R.M., 1998. On the causes and effects of inhibition of return. *Psychon. Bull. Rev.* 5, 625–643.
- Thiel, C.M., Zilles, K., Fink, G.R., 2004. Cerebral correlates of alerting, orienting and reorienting of visuospatial attention: an event-related fMRI study. *NeuroImage* 21, 318–328.
- Veltman, D.J., Rombouts, S.A., Dolan, R.J., 2003. Maintenance versus manipulation in verbal working memory revisited: an fMRI study. *NeuroImage* 18, 247–256.
- Whitehead, R., MacKenzie, T., Schliebner, S., Bachorowski, J.A., 1997. Effects of cue validity upon performance in the attentional cueing paradigm. *Percept. Mot. Skills* 84, 787–798.
- Yantis, S., Jonides, J., 1990. Abrupt visual onsets and selective attention: voluntary versus automatic allocation. *J. Exp. Psychol. Hum. Percept. Perform.* 16, 121–134.
- Yantis, S., Schwarzbach, J., Serences, J.T., Carlson, R.L., Steinmetz, M.A., Pekar, J.J., Courtney, S.M., 2002. Transient neural activity in human parietal cortex during spatial attention shifts. *Nat. Neurosci.* 5, 995–1002.