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Peelen, M.V.; Heslenfeld, D.J.; Theeuwes, J.

published in

NeuroImage
2004

DOI (link to publisher)

[10.1016/j.neuroimage.2004.01.044](https://doi.org/10.1016/j.neuroimage.2004.01.044)

document version

Publisher's PDF, also known as Version of record

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citation for published version (APA)

Peelen, M. V., Heslenfeld, D. J., & Theeuwes, J. (2004). Endogenous and Exogenous Attention Shifts are Mediated by the Same Large-Scale Neural Network. *NeuroImage*, 22(2), 822-830.
<https://doi.org/10.1016/j.neuroimage.2004.01.044>

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Endogenous and exogenous attention shifts are mediated by the same large-scale neural network

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Received 16 October 2003; revised 24 December 2003; accepted 24 January 2004

Available online 14 April 2004

Event-related fMRI was used to examine the neural basis of endogenous (top-down) and exogenous (bottom-up) spatial orienting. Shifts of attention were induced by central (endogenous) or peripheral (exogenous) cues. Reaction times on subsequently presented targets showed the expected pattern of facilitation and inhibition in both conditions. No difference in brain activity was observed when the two orienting conditions were contrasted with a liberal threshold, showing that both forms of orienting were mediated by the same neural network. Compared to within-block control trials, both endogenous and exogenous orienting activated a fronto-parietal network consisting of premotor cortex, posterior parietal cortex, medial frontal cortex and right inferior frontal cortex. Within these regions, equally strong activation was observed for both orienting conditions. It is concluded that endogenous and exogenous orienting are mediated by the same large-scale network of frontal and parietal brain areas.

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Keywords: Visual Attention; Spatial orienting; Functional MRI; Event-related fMRI; Endogenous; Exogenous; Human

Introduction

An important question in attention research is how attention is allocated in visual space. Generally, a distinction is made between two types of attentional orienting: endogenous and exogenous orienting (Jonides, 1981). Endogenous or top-down orienting refers to the controlled, voluntary allocation of attention. Exogenous or bottom-up orienting refers to the automatic, involuntary allocation of attention. A frequently used paradigm to study endogenous and exogenous orienting is Posner's cueing paradigm (Posner, 1980; Posner and Cohen, 1984). Subjects have to respond as fast as possible to a peripheral target, which is preceded by a central or peripheral cue. In the endogenous orienting condition, a central cue (typically an arrow) points to the most likely location of the subsequent target. Typically, the time to respond to targets

presented at the cued location is shorter than the time to respond to targets presented at the uncued location, suggesting that attention was endogenously shifted to the cued location. In an exogenous orienting condition, typically a brief peripheral onset cue is presented at one of the target locations. The cue is not predictive about the location of the subsequent target and it is assumed that the cue attracts attention automatically. Similar to central cueing, subjects are faster in responding to targets presented at the cued location than at the uncued location. However, unlike in central cueing, when the stimulus onset asynchrony (SOA) between cue and target exceeds approximately 250 ms, subjects respond slower to targets presented at the cued location (Klein, 2000; Posner and Cohen, 1984). This phenomenon, called inhibition of return (IOR), occurs only in typical exogenous orienting conditions. Note that although peripheral cueing does not preclude endogenous attention shifts, and central cueing may not preclude exogenous attention shifts, their relative contribution may be expected to be small given the types of cues and their predictive values.

Research on monkeys and neurological patients has revealed that the two forms of orienting may be mediated, at least in part, by different neural structures. Patients with lesions in the superior colliculus (SC), as in progressive supranuclear palsy, have difficulty with exogenous but not endogenous orienting (Rafal and Henik, 1994; Rafal et al., 1988). Research on macaque monkeys also showed that the SC is involved in exogenous orienting (Milner et al., 1978; Robinson and Kertzman, 1995) but not in endogenous orienting (Robinson and Kertzman, 1995). In contrast, patients with lesions in the temporo-parietal junction (TPJ), including superior temporal gyrus, have difficulty interpreting endogenous cues, but their attention can be attracted by peripheral onsets (Rafal and Henik, 1994). Contrary to this finding, recent studies on left unilateral neglect patients, often resulting from lesions to or near to the TPJ, show a specific deficit in exogenous orienting (Bartolomeo and Chokron, 2002; Bartolomeo et al., 2001). Further support for a role of the TPJ in exogenous orienting comes from an fMRI study by Corbetta et al. (2000). They showed that the TPJ is strongly activated when a peripheral target is detected, in particular when it is presented at an unattended location.

The aim of the present study was to compare in detail the neural architecture of endogenous and exogenous orienting in healthy humans by using event-related fMRI. Previous imaging studies reported both large overlap and differences in brain activity

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

between the two types of orienting (Corbetta et al., 1993; Kim et al., 1999; Nobre et al., 1997; Rosen et al., 1999). The amount of overlap depended on the baseline against which the orienting conditions were compared (which differed between studies), but overlap was found in at least two studies in right posterior parietal cortex (PPC) (Corbetta et al., 1993; Kim et al., 1999; Nobre et al., 1997; Rosen et al., 1999), left PPC (Corbetta et al., 1993; Kim et al., 1999; Rosen et al., 1999), bilateral premotor cortex (Kim et al., 1999; Nobre et al., 1997; Rosen et al., 1999), and supplementary motor area (SMA) and anterior cingulate cortex (ACC) (Kim et al., 1999; Nobre et al., 1997). These areas are commonly found in attention studies and are thought of as constituting a large-scale attentional network (Corbetta et al., 2002; Gitelman et al., 1999; Hopfinger et al., 2000; Mesulam, 1981). In contrast, differential activation (endogenous > exogenous) was found in a rather diverse range of areas: bilateral superior frontal cortex (Corbetta et al., 1993), left posterior parietal cortex (Kim et al., 1999; Nobre et al., 1997), bilateral temporo-occipital cortex (Kim et al., 1999), and right dorsolateral prefrontal cortex (Rosen et al., 1999). Apparently, the differences between endogenous and exogenous orienting were hard to replicate. As a consequence, the question about the neural difference between the two types of orienting processes remains unanswered.

Several issues may account for the poor replicability of the differences between orienting conditions: (1) Comparing endogenous and exogenous tasks versus shifts. All previous studies used blocked designs such that the endogenous condition, the exogenous condition, and the control condition were presented in separate runs. The disadvantage of this approach is that differences in brain activity between runs may be due to irrelevant differences between tasks, rather than differences between the two types of shifts. Among those differences between tasks may be expectation, arousal, effort, and mnemonic, behavioral and other demands (e.g., Fletcher and Henson, 2001; Rosen et al., 1998). (2) Demonstration of exogenous orienting. Whereas endogenous orienting was well established in all four studies, three of the studies were not able to demonstrate exogenous orienting (i.e., IOR at longer cue-target intervals). Corbetta et al. (1993) did not require manual responses in the exogenous condition, Nobre et al. (1997) found facilitation rather than inhibition at long SOAs, and Kim et al. (1999) did not use SOAs longer than 200 ms in their exogenous blocks. Differences between orienting conditions are difficult to interpret in the absence of evidence for exogenous orienting. (3) Adequate eye-movement control. Controlling for eye movements is important in attention studies, in particular as eye movements and endogenous attention shifts activate similar brain areas (e.g., Corbetta and Shulman, 1998; Perry and Zeki, 2000). Nobre et al. (1997) reported eye movements larger than 1° on 11% of the trials in their six subjects, while Rosen et al. (1999) found eye movements larger than 3° on 5% of the trials, and up to 3° on the remaining trials, in four subjects (the other nine were not tested). Corbetta et al. (1993) did not report on the recorded eye movements, but mentioned it as a possible cause for the difference in superior frontal activation between the two orienting conditions. (4) Generalization of results. None of the studies used a proper random-effects analysis (i.e., between-subjects variability as source of error) to generalize the results to the population, which may have contributed to the poor replicability of the reported findings (see, e.g., Friston et al., 1999).

The present study was designed to take care of these issues in the following way: (1) Instead of presenting control trials in a

separate block, they were embedded within each experimental block to control for differences between blocks in terms of expectation, stimulation, arousal, and task demands. Control trials consisted of a neutral cue that did not provide information regarding the location of the subsequent target. The amount of brain activation obtained in control trials was subtracted from the amount of brain activation obtained in cued trials, yielding a pure estimate of the attentional shift induced by endogenous and exogenous cues, respectively. (2) We analyzed MRI data only from those subjects who demonstrated the expected reaction time pattern in both the endogenous ($RT_{\text{valid}} < RT_{\text{invalid}}$) and exogenous ($RT_{\text{valid}} > RT_{\text{invalid}}$) orienting condition. This was done to ensure that the imaged processes differed as much as possible in terms of the relative contribution of endogenous and exogenous orienting. (3) Only subjects who were able to keep their eyes on a central fixation cross during critical periods of a trial were admitted to the MRI experiment. This was done by screening all subjects in a prior eye-movement experiment that was identical to the MRI experiment. (4) All statistical analyses were done with subject-variability as source of error (i.e., random-effects), to generalize the results and increase their reliability.

In sum, we compared typical endogenous and exogenous attention shifts, as verified for each subject by the RT pattern, while controlling for eye movements and irrelevant differences between tasks. Based on the findings of previous imaging studies (Corbetta et al., 1993; Kim et al., 1999; Nobre et al., 1997; Rosen et al., 1999), we expected that both forms of orienting would activate a large-scale neural network including bilateral premotor cortex, bilateral posterior parietal cortex and medial frontal cortex. The critical question was whether endogenous and exogenous orienting would lead to reliable differences in activation when task factors are controlled.

Methods

Subjects

Nineteen subjects (11 females) participated in the MRI experiment. Their mean age was 22.9 years (range 18–32 years). Subjects were selected by their performance in a prior behavioral and eye-movement experiment (see EOG procedures) that took place about 2 weeks before the MRI experiment. All subjects were right-handed by self-report. No subject reported a history of neurological or psychiatric illness and all had normal or corrected-to-normal vision. Subjects gave informed consent and were paid for participation. The protocol was approved by the Ethical Committee of the Free University Medical Center, Amsterdam, The Netherlands.

Stimuli and tasks

To elicit endogenous and exogenous shifts of attention, we used a modified version of Posner's cueing paradigm (Posner, 1980). In the endogenous task, centrally presented arrows were used to induce voluntary shifts of attention. In the exogenous task, peripheral luminance onsets were used to draw attention automatically (see Fig. 1). The background display consisted of three empty white boxes, with a white fixation cross in the center box, which were presented continuously during the entire run. The boxes were $1^\circ \times 1^\circ$ wide, with a center-to-center distance of 5° . Four different

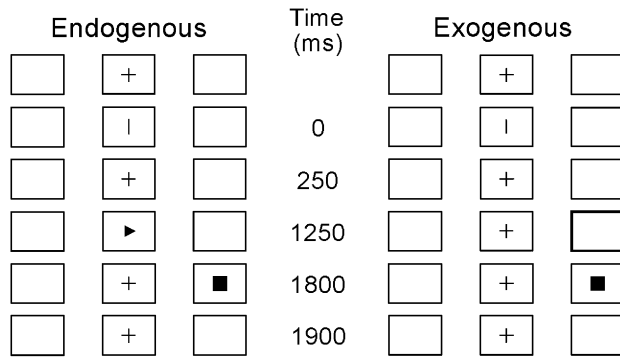


Fig. 1. Endogenous and exogenous cueing tasks. The disappearance of the horizontal part of the fixation cross indicated the start of a trial. The cue was presented for 250 ms (endogenous) or 50 ms (exogenous); the target was presented for 100 ms. After presentation of the target, the fixation cross was present for 3000, 4000 or 5000 ms before the start of a new trial. The shown trials are valid target trials. See text for probabilities of occurrence of the different trial types. Not drawn on scale.

blocks were presented: an endogenous block (central arrows) with targets, an endogenous block without targets, an exogenous block (peripheral onsets) with targets and an exogenous block without targets. Data obtained in blocks without targets are not discussed in this paper.

The start of a trial was indicated by the disappearance of the horizontal line of the fixation cross for 250 ms. One thousand milliseconds later, the cue appeared. In the endogenous task, the cue consisted of a small arrow that pointed either to the left or to the right or to both sides (with equal probability). The double arrow served as neutral cue. The cue was presented for 250 ms. Five hundred fifty milliseconds after the onset of the cue a target was presented. The target consisted of a brief (100 ms), small (0.3°) square in the center of one of the peripheral boxes. The cue indicated the location of the target correctly in 75% of the trials. Subjects responded to this target by pressing a button with their right index finger. To prevent premature responses, in one out of three trials, no target appeared (catch trials), and subjects had to withhold their response. After the presentation of the target, the background display was present for 3000, 4000 or 5000 ms before a new trial began.

In the exogenous task, the cue consisted of a brief brightening (50 ms) of one of the three boxes (with equal probability). The brightening of one of the peripheral boxes was assumed to elicit an exogenous shift of attention, while the brightening of the center box served as neutral cue. Again, 550 ms after the onset of the cue, a target was presented in one of the peripheral boxes in two out of three trials. The cues were noninformative with respect to the location of the target; that is, the target location was independent of the cue location. Apart from the cues, cue durations and contingencies, the exogenous task was identical to the endogenous task.

In both tasks, subjects were informed about the probabilities of cues and targets. Subjects were instructed to respond as accurately and fast as possible. Trials were presented in blocks of 27. In endogenous blocks, cue validity varied between 67% and 83% per side (mean 75%). Each block started and ended with the presentation of the background display for 6000 ms. At the end of each block, subjects were given visual feedback about their performance. Subjects started a new block themselves by pressing the response button. Each block lasted 2.9 min.

EOG procedures

Before subjects performed the tasks in the scanner, they were tested in a screening experiment, identical to the MRI experiment. The purpose of this experiment was to select subjects by their behavioral performance and their ability to keep their eyes fixated during critical periods of a trial, as eye movements could not be recorded in the scanner.

Subjects were seated in a comfortable chair 130 cm away from a 15-in. VGA monitor on which the stimuli were presented. The room was dimly illuminated. A personal computer controlled the presentation of the stimuli and the acquisition of reaction times using ERTS software (Berlinger, 1992). Subjects responded with their right index finger by pressing a button that was fixed to the right armrest of the chair. After one block of practice, subjects performed six blocks of each orienting condition with targets and two blocks of each condition without targets. The order of conditions was counterbalanced across subjects; blocks without targets will not be discussed. At the end of the EOG experiment, subjects performed two additional endogenous blocks in which they were instructed to make eye movements to the cued box.

Horizontal and vertical electro-oculogram (EOG) was recorded from tin electrodes attached to the outer canthi of each eye and above and below the left eye. The right cheek was grounded. EOG recordings were amplified ($\times 500$), low-pass filtered (0–40 Hz), digitized (1000 Hz) and processed by NeuroScan (Sterling, VA) hardware and software. Only those subjects who showed the expected reaction time pattern in both endogenous ($RT_{\text{valid}} < RT_{\text{invalid}}$) and exogenous ($RT_{\text{valid}} > RT_{\text{invalid}}$) conditions without moving their eyes within 1000 ms after the onset of the cue were asked to participate in the MRI experiment. Nineteen out of twenty-three tested subjects met these criteria. Of the four unsuccessful subjects, two did not show the expected RT pattern and two made occasional eye movements in the direction of the cue and/or target.

Fig. 2 gives the cue-locked EOG for the endogenous and exogenous condition for left- and rightward cues, averaged over the 19 successful subjects (black lines). As can be seen, no eye movements were recorded in response to a leftward or rightward cue, compared to when subjects did make an eye movement in response to the cue (gray lines).

MRI procedures

Brain imaging was performed on a Siemens 1.5 T Sonata scanner (Siemens Medical Systems, Erlangen, Germany) equipped with a head volume coil. An EPI sequence was used to image functional activation. Twenty oblique slices were collected per image covering the whole brain. Scanning parameters were: repetition time/echo time (TR/TE) = 2000/60 ms, flip angle (FA) = 90° , slice thickness = 6 mm, slice gap = 20%, acquisition matrix = 64×64 pixels, in-plane resolution = 3.125×3.125 mm. Images were on-line motion corrected.

After the functional imaging session, a 3-D structural scan was made for each subject using a T1-weighted MP-RAGE sequence. Scanning parameters were: TR/TE = 2700/3.97 ms, inversion time (TI) = 950 ms, FA = 8° , coronal slice thickness = 1.5 mm, no gap, acquisition matrix = 160×256 pixels, in-plane resolution = 0.977×0.977 mm.

A personal computer controlled the presentation of stimuli and acquisition of reaction times using ERTS software (Berlinger,

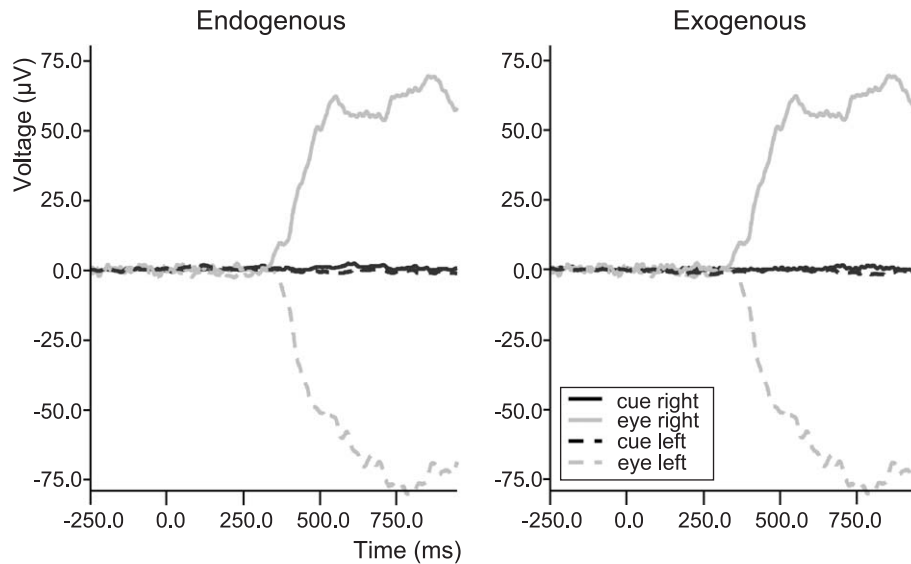


Fig. 2. Cue-locked EOG for the endogenous (left) and exogenous (right) orienting condition for rightward (solid black lines) and leftward (broken black lines) pointing cues, averaged over 19 subjects. Also shown is the cue-locked EOG to trials on which subjects were instructed to make an eye movement to the cued box (solid and broken gray lines). 1° of visual angle corresponds to a deflection of about 14 μ V.

1992). Visual stimuli were back-projected (Liesegang dv305, Düsseldorf, Germany) onto a screen that was viewed by the subjects through an angled mirror positioned on top of the head coil. The distance from the eyes to the screen was 135 cm. Subjects responded by pressing a fiber-optic button (Lumitouch Photon Control, Burnaby, Canada) with their right index finger. Before functional imaging began, subjects practiced one endogenous and one exogenous block to get familiar with the response button and their position in the scanner. After practice, subjects performed eight blocks of each orienting condition with targets and three blocks of each condition without targets. The order of conditions was counterbalanced across subjects; blocks without targets will not be discussed in this paper.

MRI data analysis

Preprocessing and statistical analysis of MRI data was performed using BrainVoyager 4.9 software (Brain Innovation, Maastricht, The Netherlands). The first two volumes of each run were discarded to avoid differences in T1 saturation. The remaining functional volumes were first corrected for slice acquisition order. Then, low-frequency drifts were removed with a temporal high-pass filter (1/50 Hz), and the data were temporally and 3-D spatially smoothed with a Gaussian kernel (FWHM 3 s/6 mm).

Functional volumes were manually coregistered with the individual 3-D structural scans. The 3-D scans were then transformed into Talairach space (Talairach and Tournoux, 1988) and the parameters for this transformation were applied to the coregistered functional data, creating 4-D functional data sets in Talairach space (see, e.g., Goebel et al., 2001).

A multirun/multisubject design matrix was created specifying events (trials) for each run and subject (Friston et al., 1995). Events started at cue-onset and lasted 1000 ms. Error-trials, i.e., trials on which subjects responded either incorrectly, too fast (<150 ms) or too slow (>600 ms), were excluded. There were two types of events in each orienting condition: cued trials (target and catch) and neutral trials (target and catch). To generate predictors for the

multiple-regression analysis, the event time series were convolved with a delayed γ function ($\delta = 2.5$ s; $\tau = 1.25$ s) to model the hemodynamic response (Boynton et al., 1996). Voxel time series were z-normalized for each run, and additional predictors accounting for baseline differences between runs were included in the design matrix.

The statistical analyses were performed in two steps: first for the whole brain and then specifically for a number of regions of interest (ROIs). The goal of the first analyses was to find brain regions that were more active in one orienting condition than in the other. Responses to cued trials in each orienting condition were compared after subtraction of the corresponding control trials (i.e., $[\text{cue}_{\text{endo}} - \text{neutral}_{\text{endo}}] - [\text{cue}_{\text{exo}} - \text{neutral}_{\text{exo}}]$). A random-effects multiple-regression analysis was performed, with a threshold at $P = 10^{-3}$ and a minimum cluster size of 0.05 ml (uncorrected for multiple comparisons). This threshold was chosen to minimize Type II errors (false negatives). The goal of the second whole-brain analysis was to identify brain regions that reflected attentional shifts in both orienting conditions. To this end, all cued trials were compared against all neutral trials (i.e., $[\text{cue}_{\text{endo}} + \text{cue}_{\text{exo}}] - [\text{neutral}_{\text{endo}} + \text{neutral}_{\text{exo}}]$). Again, a random-effects multiple-regression analysis was performed with a threshold at $P = 10^{-4}$ and a minimum cluster size of 0.10 ml (uncorrected). This more conservative threshold was chosen to minimize Type I errors (false positives).

The goal of the subsequent ROI analyses was to compare endogenous and exogenous orienting in detail in those brain regions that reflected attentional shifts. To this end, significantly active regions from the second whole-brain analysis were defined as ROIs. For each ROI, beta weights, corrected for serial correlations, were obtained separately for each subject, orienting condition (endogenous, exogenous), and trial type (cued, neutral). The betas for neutral trials were then subtracted from the betas for cued trials, yielding two corrected betas (one for each orienting condition) for each subject and ROI. These betas reflect the strength of the neural response to cues in each orienting condition, controlled for visual stimulation, target

detection, motor response and arousal. These corrected betas were then compared between orienting conditions by paired t tests over subjects. To verify that the obtained betas were indeed sensitive to attentional shifts, the corrected betas were pooled over orienting conditions and tested against zero over subjects (which is identical to comparing cued betas against neutral betas). The significance threshold for these ROI analyses was set to $P = 0.05$.

Finally, event-related time courses of activation were computed for each ROI, orienting condition, trial type and subject. Time courses lasted from -2 to 12 s relative to cue presentation, they were averaged over replications and each was referenced (percent signal change) to its pre-cue baseline. For each orienting condition, time courses evoked by neutral trials were subtracted from those evoked by cued trials, again to control for differences between tasks. For each ROI, the amplitudes (averaged over post-cue values) and peak latencies of these corrected time courses were compared between orienting conditions by paired t tests over subjects at threshold $P = 0.05$.

Results

Behavioral performance

Sixteen out of nineteen subjects showed the expected reaction time pattern in the MRI experiment in both the endogenous ($RT_{\text{valid}} < RT_{\text{invalid}}$) and exogenous ($RT_{\text{valid}} > RT_{\text{invalid}}$) condition. The behavioral and MRI data of these 16 subjects were further analyzed. RTs shorter than 150 ms or longer than 600 ms, and incorrect responses (i.e., no response on target trials or a response on catch trials) were considered as errors. Errors were observed on 2.1% (endogenous condition) and 2.2% (exogenous condition) of the trials. Only correct trials were further analyzed.

Fig. 3 gives the RTs for the endogenous and exogenous orienting condition as a function of validity for both the EOG and MRI experiment. The RTs for each orienting condition were analyzed by

Table 1

Results of the whole-brain analysis (cue–neutral)

Region (BA)	Side	x	y	z	Mean T	Volume (ml)
<i>Frontal</i>						
SMA/ACC (6/32)	M	2	9	41	5.61	1.37
IFG (9)	R	50	7	28	5.53	0.20
Premotor (6)	L	-24	-9	56	6.13	0.67
Premotor (6)	R	31	-12	57	5.55	0.30
<i>Parietal</i>						
PC (7)	M	-2	-50	42	5.48	0.13
TPJ (22/40)	R	52	-44	27	5.45	0.35
<i>Occipital</i>						
Cuneus (19)	M	-2	-77	33	5.71	0.43
<i>Subcortical</i>						
Cerebellum	M	-4	-72	-34	5.47	0.12

For each region, the coordinates of the center of the activation in Talairach space, the mean T_{15} value and the volume of activated tissue are given. L = left hemisphere; R = right hemisphere; M = medial (extending into both hemispheres); BA = Brodmann area; SMA = supplementary motor area; ACC = anterior cingulate cortex; IFG = inferior frontal gyrus; PC = precuneus; TPJ = temporo-parietal junction.

a multivariate analysis of variance with experiment (EOG, MRI) and validity (valid, invalid, neutral) as factors. In both orienting conditions, there was no difference between experiments, but a highly significant effect of validity (for endogenous: $F_{2,14} = 97.59$, $P < 0.001$; for exogenous: $F_{2,14} = 66.95$, $P < 0.001$). For endogenous orienting, RTs were faster to valid ($RT_{\text{valid}} - RT_{\text{neutral}} = -19.4$ ms, $F_{1,15} = 46.84$, $P < 0.001$) and slower to invalid ($RT_{\text{invalid}} - RT_{\text{neutral}} = 21.0$ ms, $F_{1,15} = 36.80$, $P < 0.001$) compared to neutral trials. For exogenous orienting, RTs were slower to valid ($RT_{\text{valid}} - RT_{\text{neutral}} = 11.8$ ms, $F_{1,15} = 11.17$, $P = 0.004$) and faster to invalid ($RT_{\text{invalid}} - RT_{\text{neutral}} = -21.4$ ms, $F_{1,15} = 42.91$, $P < 0.001$) than to neutral trials.

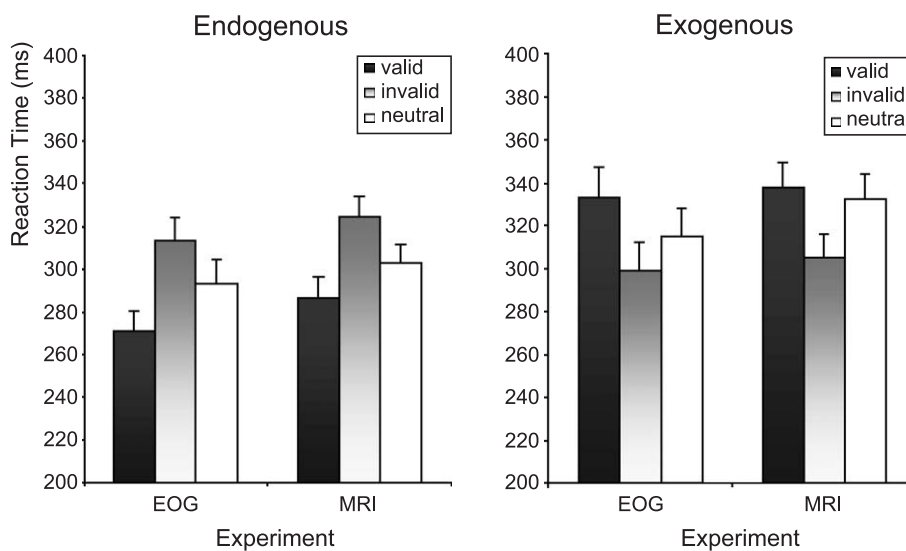


Fig. 3. Mean reaction times for the endogenous (left) and exogenous (right) orienting condition as a function of validity (valid, invalid, neutral) and experiment (EOG, MRI). Plotted are the results of the 16 subjects who showed facilitation in the endogenous condition and IOR in the exogenous condition in both the EOG and MRI session. Error bars indicate standard error of the mean.

fMRI whole-brain analyses

The whole-brain comparison between endogenous and exogenous orienting (i.e., $[\text{cue}_{\text{endo}} - \text{neutral}_{\text{endo}}] - [\text{cue}_{\text{exo}} - \text{neutral}_{\text{exo}}]$) revealed significantly more activation only in the right middle occipital gyrus (BA 18; Talairach coordinates: 29, -83, -10) for the endogenous condition. This difference was due to a relative deactivation of this area in the exogenous contrast ($\text{cue}_{\text{exo}} - \text{neutral}_{\text{exo}}$), which was probably caused by a stronger activation of this part of visual cortex by the central cue compared to the peripheral cue. As such, this activation does not reflect an attention-related difference, but is the result of visual stimulation caused by the neutral cue that served as control in the exogenous orienting condition. No other difference was found between endogenous and exogenous orienting. To ensure that the absence of a difference was not due to the adopted statistical method, we

also compared the orienting conditions using a fixed-effects multiple-regression analysis. Again, there was a low occipital effect (BA 18; Talairach coordinates: 30, -82, -9) at $P = 0.05$, cluster size 0.05 ml, but no other difference, even if the statistical threshold was lowered to $P = 0.80$ (corrected for multiple comparisons). As both group analyses may have obscured effects because of poor overlap between active regions in different subjects, we also analyzed each subject individually. No consistent difference (defined as a difference on a particular gyrus or sulcus in more than two subjects) was found in these analyses between the two orienting conditions.

As the first whole-brain analyses did not reveal relevant differences between endogenous and exogenous orienting, the cued trials of both orienting conditions were pooled and compared against neutral trials (i.e., $[\text{cue}_{\text{endo}} + \text{cue}_{\text{exo}}] - [\text{neutral}_{\text{endo}} + \text{neutral}_{\text{exo}}]$) to identify brain regions reflecting attentional shifts.

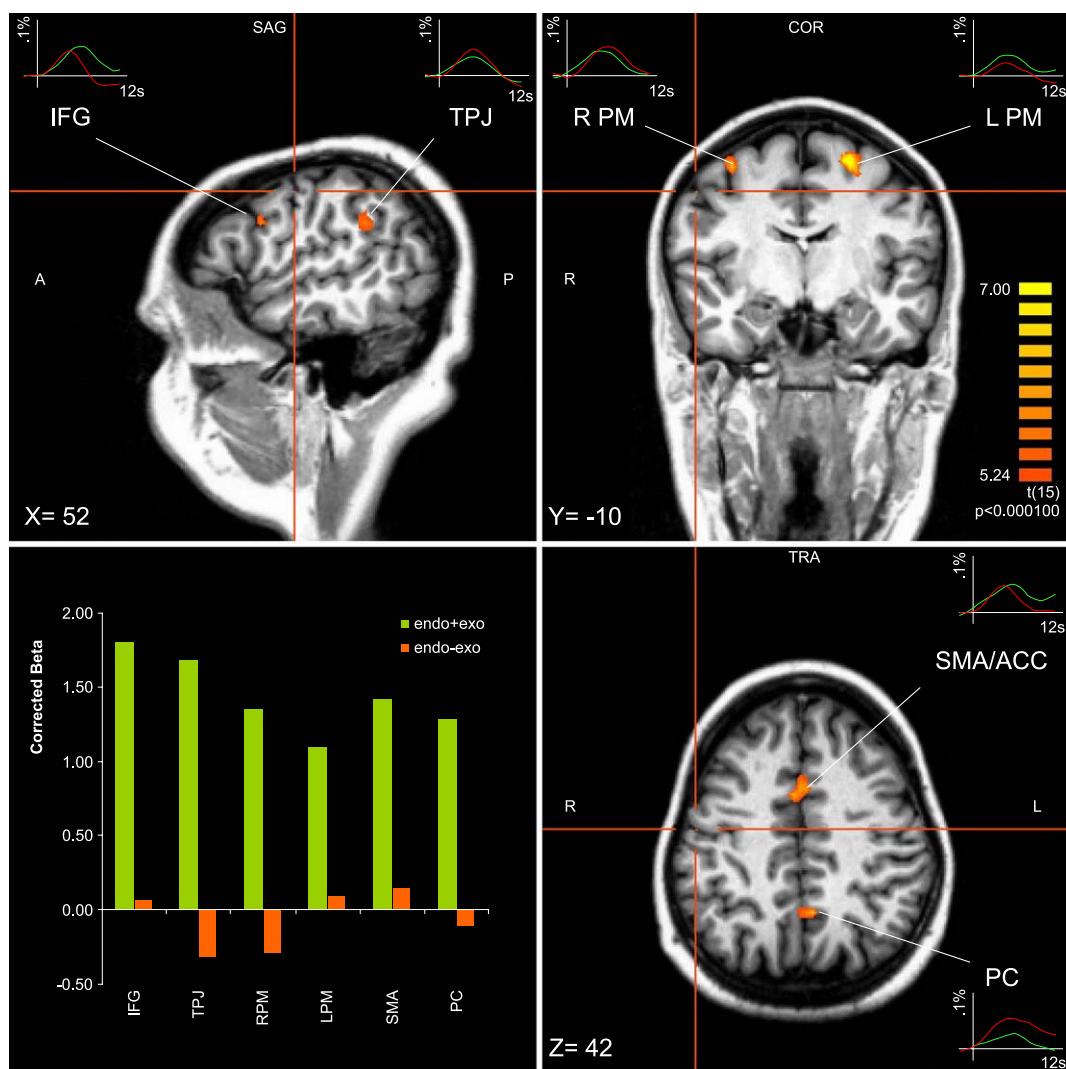


Fig. 4. Group activation maps (16 subjects) and event-related time courses of the hemodynamic responses to the cues (i.e., cue-neutral) in both orienting conditions displayed on the anatomical scan in Talairach space of one of the subjects. Not shown are activations in cuneus and cerebellum. The views are sagittal, coronal and transversal at $x = 52$, $y = -10$, $z = 42$ mm. The lower left panel shows the summed (green bars) and differential (orange bars) response to endogenous and exogenous cues, corrected for between-block confounds and serial correlations, separately for each active region. The time courses show the event-related response for each orienting condition (red traces = exogenous; green traces = endogenous) from -2 to 12 s relative to cue-onset, referenced to pre-cue baseline.

Table 1 gives the Talairach coordinates, the volume and the average T value of the regions that were significantly active in this comparison. Fig. 4 shows these regions and their time courses of activation on an anatomical scan in Talairach space of one of the subjects.

Frontal activations

Lateral premotor cortex (BA 6), including frontal eye fields (FEF), was activated bilaterally. At the chosen threshold, the right-sided premotor activity consisted of two foci. Because of the close proximity of the two foci, they were taken together and were treated as a single region of activation. In the right hemisphere, the inferior frontal gyrus (IFG, BA 9) was significantly activated. Medial frontal activity involved the supplementary motor area (SMA, BA 6) and the anterior cingulate cortex (ACC, BA 32).

Parietal activations

Posterior parietal cortex was activated bilaterally. Peaks of activation were found in the precuneus (PC, BA 7) and the right temporo-parietal junction (TPJ, BA 40). The precuneus activity was located medially and extended into both hemispheres. Activity in the right TPJ was centered on the supramarginal gyrus and extended into the superior part of the temporal lobe.

Occipital activations

Occipital activation was observed in the cuneus (BA 19). This activation consisted of two separate foci, which (because of their close proximity) were taken together in further analyses.

Subcortical activations

We found cerebellar activity that was located medially.

Finally, a fixed-effects multiple-regression analysis of the same contrast (i.e., $[\text{cue}_{\text{endo}} + \text{cue}_{\text{exo}}] - [\text{neutral}_{\text{endo}} + \text{neutral}_{\text{exo}}]$) revealed the same areas, with the exception that cuneus and cerebellum did not quite reach significance at $P = 0.05$ (corrected for multiple comparisons), cluster size 0.10 ml.

fMRI regions-of-interest analyses

For each of the eight areas of activation found in the previous whole-brain analyses (see Table 1), the voxel time series were pooled and subjected to the same multiple-regression analysis, separately for each subject. The resulting betas, corrected for serial correlations, were tested over subjects for each ROI separately to compare in detail attentional shifts and differences between attentional shifts in the two orienting conditions. The results are given in Table 2 and are displayed in the lower left panel of Fig. 4. Paired sample t tests (with α set to 0.05) did not reveal significant differences between endogenous and exogenous orienting in any of the eight active regions (smallest $P = 0.21$; orange bars in Fig. 4), but each region responded significantly to the presentation of a spatial cue (compared to neutral cues; largest $P = 0.002$; green bars in Fig. 4).

Finally, for each region, the peak latencies and post-cue amplitudes of the event-related time courses of activation were compared. In correspondence with the multiple-regression analyses, none of the amplitudes differed significantly between orienting conditions (smallest $P = 0.23$), but there was a significant difference in peak latency between the time courses evoked by exogenous (at 4.7 s; red trace) and endogenous (at 6.9 s; green trace) cues in the right inferior frontal gyrus ($T_{15} = 3.04$, $P = 0.008$). In all

Table 2

Results of the regions-of-interest analyses

Regions (BA)	Side	(endo–exo)		(cue–neutral)	
		T	P	T	P
<i>Frontal</i>					
SMA/ACC (6/32)	M	0.32	0.76	4.40	<0.001
IFG (9)	R	0.16	0.88	4.66	<0.001
Premotor (6)	L	0.31	0.76	4.29	<0.001
Premotor (6)	R	−0.87	0.40	4.01	0.001
<i>Parietal</i>					
PC (7)	M	−0.31	0.76	3.71	0.002
TPJ (22/40)	R	−0.94	0.36	5.26	<0.001
<i>Occipital</i>					
Cuneus (19)	M	−1.32	0.21	7.01	<0.001
<i>Subcortical</i>					
Cerebellum	M	0.55	0.59	5.49	<0.001

For each region, T_{15} and P values are given of the differential (endo–exo) and summed (cue–neutral) hemodynamic response to endogenous and exogenous cues, corrected for serial correlations and between-block confounds. Abbreviations as in Table 1.

other areas, the event-related time courses peaked in both conditions between 5.5 and 6.7 s (smallest $P = 0.35$).

Discussion

The present study demonstrates that a common network of brain regions is involved in endogenous and exogenous orienting. We addressed some of the concerns with previous imaging studies (Corbetta et al., 1993; Kim et al., 1999; Nobre et al., 1997; Rosen et al., 1999), which made interpreting the reported results difficult. First, we used an event-related design that allowed us to look specifically at spatial attention *shifts* rather than spatial attention *tasks*. Second, by only using subjects who showed the desired RT pattern in both conditions, we ensured that we imaged typical endogenous and exogenous attention shifts. Third, all subjects were selected in a prior EOG experiment by their ability to keep their eyes fixated during critical moments of a trial. As EOG and MRI experiment were identical in all respects, we were confident that subjects did not make eye movements during the MRI experiment. The fact that no significant RT differences were observed between the EOG and MRI session showed that the two sessions were indeed highly comparable. Finally, we used random-effects (as well as fixed-effects) analyses to generalize the findings and enhance their reliability.

When comparing endogenous and exogenous orienting directly while controlling for between-task confounds, we found no difference in brain activity except for a low occipital effect caused by the physical difference between the exogenous cues (central–peripheral). This was true independent of the adopted statistical method (random- or fixed-effects). Based on monkey research and neurological patient studies (Milner et al., 1978; Rafal et al., 1988; Robinson and Kertzman, 1995), the superior colliculus (SC) may have been activated in this contrast, which was, however, not the case. As the SC is a small subcortical structure, the volume of activation in this area was probably too small to be detected by the present study. The fact that none of the previous imaging studies

(Corbetta et al., 1993; Kim et al., 1999; Nobre et al., 1997; Rosen et al., 1999) reported activation in the SC supports this conclusion. When comparing brain activity evoked by spatial cues (both endogenous and exogenous) to brain activity evoked by neutral cues, we found a large-scale network of frontal, parietal and temporal areas that has been linked previously to spatial orienting and visual attention (e.g., Corbetta and Shulman, 1998; Corbetta et al., 2002; Gitelman et al., 1999; Hopfinger et al., 2000; Mesulam, 1981). This network consisted of regions in the right inferior frontal gyrus (IFG), medial frontal cortex [supplementary motor area (SMA) and anterior cingulate cortex (ACC)], bilateral premotor cortex including frontal eye fields (FEF), right temporo-parietal junction (TPJ) and bilateral precuneus. Other activation was found in the medial cuneus and cerebellum.

Having found this network of brain areas reflecting attentional shifts, we compared endogenous and exogenous orienting for each active area in detail. The amount of activation evoked by each type of cue, controlled for differences between tasks, was compared by direct tests over subjects. There was no significant difference between exogenous and endogenous orienting in any of the active regions. The comparison of activation due to endogenous and exogenous orienting in the TPJ was especially interesting, as this area has been linked to both endogenous (Rafal and Henik, 1994) and exogenous orienting (Bartolomeo and Chokron, 2002; Bartolomeo et al., 2001; Corbetta et al., 2000). Although we observed slightly more activation in the TPJ following an exogenous cue, this difference was not statistically significant. Note that in the fMRI study by Corbetta et al. (2000), exogenous orienting was defined as the detection of an unattended but task-relevant target, whereas in the present study the exogenous condition consisted of involuntary orienting toward a task-irrelevant cue. A difference between exogenous and endogenous orienting was observed in the peak latency of the event-related hemodynamic responses in the right inferior frontal gyrus. This may be related to a genuine difference in the timing of the attentional shifts, but it may also be a Type I error (as these tests were all thresholded at $P = 0.05$). At present, this effect needs further replication before it can be interpreted with confidence.

Although the behavioral data of the present study showed the typical difference between endogenous and exogenous orienting, the underlying network of brain areas reflecting attentional shifts was identical in both conditions. This implies that the differences found previously in imaging studies using blocked designs [either bilateral superior frontal cortex (Corbetta et al., 1993), or left posterior parietal cortex (Kim et al., 1999; Nobre et al., 1997) or bilateral temporo-occipital cortex (Kim et al., 1999), or right dorsolateral prefrontal cortex (Rosen et al., 1999)] may have been due to differences between the tasks employed rather than genuine differences between the two types of orienting. Among those differences between tasks may be expectation, arousal, effort, and mnemonic, behavioral and other demands (e.g., Fletcher and Henson, 2001; Rosen et al., 1998). Other possible causes for the reported differences may include other-than-intended cognitive processes, differential eye movements and/or the adopted statistical methods. It seems unlikely that a lack of power can account for the absence of a difference between endogenous and exogenous orienting in the present study, for four reasons. First, we used 16 subjects in our analysis, which is more than three of the four previous imaging studies that did find differences (Kim et al., 1999; Nobre et al., 1997; Rosen et al., 1999). Second, all subjects showed the typical RT pattern,

indicating that the two orienting conditions differed in terms of the relative contribution of endogenous and exogenous orienting. Third, liberal thresholds were used in the comparisons between endogenous and exogenous orienting ($P = 0.001$ for the whole-brain analysis and $P = 0.05$ for the ROI analysis). Finally, the comparison between cued and neutral trials did reveal the expected attentional network (Corbetta and Shulman, 1998; Corbetta et al., 2002; Gitelman et al., 1999; Hopfinger et al., 2000; Mesulam, 1981), independent of the adopted statistical method. It may be argued that the endogenous cueing condition may not be purely endogenous, as an arrow may elicit automatic tendencies to orient in its direction after a few trials of practice. Similarly, the exogenous cueing condition may contain an endogenous component, as subjects potentially reorient their attention endogenously to the center box after it has been captured by a peripheral cue. However, although both orienting conditions may consist of a subtle combination of endogenous and exogenous processes, they are still likely to differ in the ratio of endogenous and exogenous components given the types of cues and validities we used in the present study.

To conclude, we found no difference in brain activation between endogenous and exogenous attentional orienting when controlling for task factors and eye movements. Instead, both forms of orienting activated the same fronto-parietal network that mediates spatial orienting and visual attention. We conclude that in healthy humans, given the present task conditions, endogenous and exogenous orienting are subserved by the same large-scale neural network.

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