Dissociating top-down attentional control from selective perception and action

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Abstract

Research into the neural mechanisms of attention has revealed a complex network of brain regions that are involved in the execution of attention-demanding tasks. Recent advances in human neuroimaging now permit investigation of the elementary processes of attention being subserved by specific components of the brain's attention system. Here we describe recent studies of spatial selective attention that made use of positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and event-related brain potentials (ERPs) to investigate the spatio-temporal dynamics of the attention-related neural activity. We first review the results from an event-related fMRI study that examined the neural mechanisms underlying top-down attentional control versus selective sensory perception. These results defined a fronto-temporal-parietal network involved in the control of spatial attention. Activity in these areas biased the neural activity in sensory brain structures coding the spatial locations of upcoming target stimuli, preceding a modulation of subsequent target processing in visual cortex. We then present preliminary evidence from a fast-rate event-related fMRI study of spatial attention that demonstrates how to disentangle the potentially overlapping hemodynamic responses elicited by temporally adjacent stimuli in studies of attentional control. Finally, we present new analyses from combined neuroimaging (PET) and event-related brain potential (ERP) studies that together reveal the timecourse of activation of brain regions implicated in attentional control and selective perception. © 2001 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Selective attention is the ability to focus awareness on a portion of the vast array of potentially relevant stimuli in the environment. Attention can be directed voluntarily in a top-down manner, and visual attention can be focused on sensory stimuli based on attributes such as location, color, and/or higher-order form or object properties. Selective spatial attention (location selection) has been the subject of scientific investigation for more than a century. In the late 1800's, Hermann Von Helmholtz [61] provided experimental support for the idea that one could voluntarily focus awareness

upon a spatial location, even in the absence of eye movements (i.e. 'covert' spatial attention). More recently, Posner and colleagues [55] employed a simple paradigm that uses location expectancy to manipulate the focus of spatial attention. In the standard version of this paradigm a 'cue' stimulus occurs that provides information about where an upcoming 'target' stimulus is likely to occur, allowing participants to focus attention covertly (without saccades) upon the likely location prior to appearance of the target. Over the past 20 years, numerous variations of this paradigm have been used, and a wealth of experimental evidence now exists showing that selective spatial attention leads to faster and more accurate responses to stimuli at an attended location (see Pashler [50] for a review).

The mechanisms of covert spatial attention can be decomposed into a number of hypothetical, elementary

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mental operations. These may include but need not be limited to: disengaging attention from its current locus, moving attention to the desired location, selectively modulating the processing of new sensory inputs, and executing motor actions to target events [50,54]. Numerous studies in humans and animals have implicated a widespread set of cortical and subcortical brain regions in spatial attentional processing, leading to the view that attention is subserved by a highly specific but widely distributed attentional network [10,24,47]. The challenge is now to relate activity in specific parts of this attention network to particular component operations of attention.

Neuroimaging studies in humans, and lesion analysis in neurological patients and non-human primates, have shown that this spatial attention network may include the posterior parietal cortex [11,23,49,56] temporo-parietal junction [9,22], superior colliculus [47], thalamus [25,36,52], superior temporal sulcus [7,49,62], and regions of the frontal cortex [7,26]. While neuroimaging studies have identified the neural components of an attention-network in the healthy human brain, limitations in classical neuroimaging analysis methods have made it difficult to associate particular brain structures with specific attentional operations. Classical neuroimaging analysis methods often required tasks to be blocked over periods of many seconds or minutes. Within such block-design paradigms, top-down control and preparatory mechanisms are difficult to disentangle from the selective target processing that subsequently occurs as a result of attentional orienting. The advent of event-related methods of analysis in fMRI, however, has now enabled a more direct investigation of the neural substrates underlying the subcomponent processes of attention as for example, in the investigation of the neural mechanisms of top-down attentional control. In the next section we review recent evidence from our fMRI studies investigating the control circuitry of voluntary spatial attention.

2. Event-related fMRI study of attentional control and selective perception

2.1. Design and procedures

Recently, we used event-related functional magnetic resonance imaging (fMRI) to identify and dissociate the neural systems involved in top-down attentional control versus the subsequent selective processing of stimulus inputs [28]. In that study, a trial began with a cue presented at fixation for 500 ms that instructed participants where to covertly attend (randomly to the left or right; Fig. 1). Eye fixation was maintained on a central fixation cross during each trial. The cue consisted of overlapping isoluminant yellow and blue arrows point-

ing to opposite left and right field locations. This cue was used to control for simple sensory differences between leftward versus rightward directing cues. Each participant ($N = 6$) was instructed beforehand which color arrow was to be used to direct attention (half were instructed to use the blue arrow, half the yellow). After an interstimulus interval of either 1000 ms (17% of trials) or 8160 ms (83% of trials), checkerboard patterns were flashed bilaterally in the right and left visual fields (for 750 ms at a 4 Hz reversal rate). The task was to discriminate whether the checkerboard, at the attended location only, contained any gray checks or whether it was composed of only the standard white and black checks (a choice response was required on each trial). Flashing checkerboard patterns were used in order to ensure a strong response in visual processing regions of the brain [57], regardless of the presence or absence of the gray checks. The shorter ISI (1000 ms) was used to induce participants to shift attention as soon as the instructive cue appeared because the target could appear shortly after the cue. However, the hemodynamic response (responsible for the fMRI signal) is relatively slow to begin, peak and subside (on the order of seconds) in comparison to the underlying neural activity triggering the response (on the order of a few hundred milliseconds at most), and therefore the fMRI activity evoked by cue and target stimuli would overlap and be difficult to disentangle at the short ISI (but see Section 3.2 below for review of newer methods that allow for faster presentation-rate designs in fMRI). To avoid this and to permit cue and target activity to be distinguished, only the long ISI (8160 ms) trials were
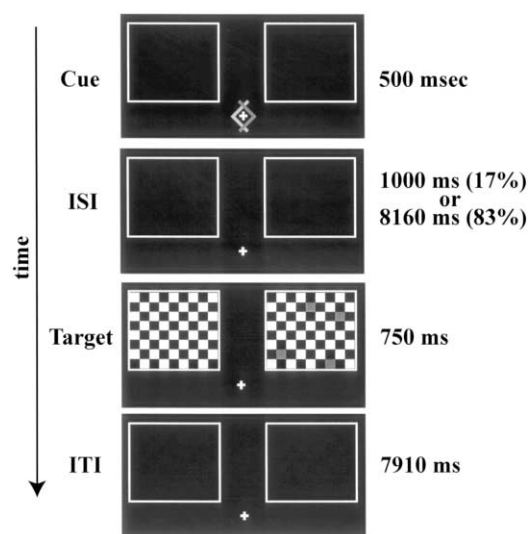

Fig. 1. Stimuli and procedure from Hopfinger et al. [28]. Cues consisted of overlapping isoluminant yellow and blue arrows that instructed subjects to covertly orient their attention to the location indicated. After a variable interstimulus interval (ISI), checkerboard target stimuli appeared within the outline boxes. The intertrial interval (ITI) was 7910 ms. See text for details.

analyzed in this study. We hypothesized that the cue-triggered activity would reflect those mechanisms involved in processing the cue stimulus, decoding the meaning of that stimulus, and most importantly, allocating attention covertly to the cued location. In contrast to these top-down control mechanisms, the target-related activity was expected to reveal the brain regions involved in sensory processing of the targets, selective modulation of the target processing by attention, and response generation.

2.2. Cue processing and top-down control

Brain regions active in response to the instructive cues included the intraparietal sulcus, superior temporal sulcus, and superior and mid-frontal regions near the frontal eye fields (Fig. 2, left column). These brain regions have previously been suggested to be involved in various aspects of spatially attentive behavior based on human and animal studies, but in the present experiment we were able to provide the additional information that these brain regions were activated only in response to the instructive cue stimuli. None of the foregoing regions were active in response to the target stimulus (versus baseline), nor were they active simply in response to the physical cue stimulus when non-instructive (two of the original participants were scanned during additional sessions wherein cues were either passively viewed, or were non-instructive with regard to location). Therefore it may be possible to interpret activity in these regions as neural correlates of attentional control processes.

The inferior parietal cortex has been suggested to be involved in spatial attention on the basis of cellular recordings in animals [5] and prior block-design imaging studies in humans [8,12,23,49]. The present study suggests that subregions of the inferior parietal cortex support attentional control mechanisms, which may include spatial shifting of the attentional focus. While the superior parietal lobe did show activity to the cue stimulus, it was also found to be active in response to the target stimuli, and to the cue stimuli when they were passively viewed. Although some previous studies have implicated the superior parietal lobe in spatial attention mechanisms [11,56], our results do not provide support for a specific role in attentional control via central symbolic cues. Although the superior temporal sulcus has been found to be active in studies of spatial attention [8,49] and lesions to it result in neglect-like symptoms in non-human primates [62], its role in attention has remained unclear. Here, we provide evidence that it is involved in preparatory processing to the cue, suggesting that it may be involved in an aspect of attentional control and not simply involved in higher-order aspects of target processing. Regions of the frontal lobe near the frontal eye fields (FEF) also showed activity specific to processing of the instructive cue stimuli (not to the non-instructive cue stimuli). While the FEF has previously been shown to be involved in voluntary overt eye movements, e.g. [8], our data provide evidence that this region of the FEF may also be involved in voluntary covert attention, (possibly especially so under conditions where fixation must be maintained at a location other than where covert attention is shifting, c.f. the human 'foveal fixation system' [53]) Finally, regions of the superior frontal gyrus anterior to the FEF, previously implicated in working memory functions [15,30,35] were also selectively active to the cue stimulus.

2.3. Target processing and response generation

The target events as compared with the cue events evoked activity in a highly distinct network of brain regions (Fig. 2, right column). These regions included bilateral regions of the supplementary motor area, extending into the mid-cingulate gyrus, bilateral ventro-lateral prefrontal regions, and the precentral and postcentral gyri, as well as visual cortex. We will briefly review each in turn.

Regions surrounding the anterior cingulate have been suggested to be involved in attentional control [54]. Our results suggest that the mid-cingulate/SMA regions we found active here are not involved in aspects of attentional control related to preparatory processing. Rather these regions may be involved in aspects of target processing, likely including processes such as discriminating a complex stimulus, monitoring response generation processes, and executing the appropriate response [40,51]. Regions of the inferior-lateral frontal lobes, ventral to the regions activated by the cue, were also found to be active to the target stimuli. Our results are consistent with recent models that suggest this region of the frontal lobe may be involved in inhibitory control processing during task performance [31]. In this study, the bilateral presentation of the target stimuli, when only one side needed to be attended, requires inhibition of perceptual representations generated by the unattended side, and this may rely on lateral inferior frontal cortex. This is, of course, merely speculation and direct tests are now required.

In addition to the foregoing, the targets also elicited activity in the precentral gyrus and postcentral gyrus. The subjects were required to make a motor response to the targets to indicate the presence or absence of the gray checks that defined the to-be-detected stimuli. As a result, activity in motor cortex and somatosensory cortex is expected. Similarly, analysis of the physical features of the target stimuli would be expected to activate visual cortex, and this too was observed. The interesting aspect of the activity in visual cortex was how it was affected by the direction of spatial attention; this is discussed in the next section.
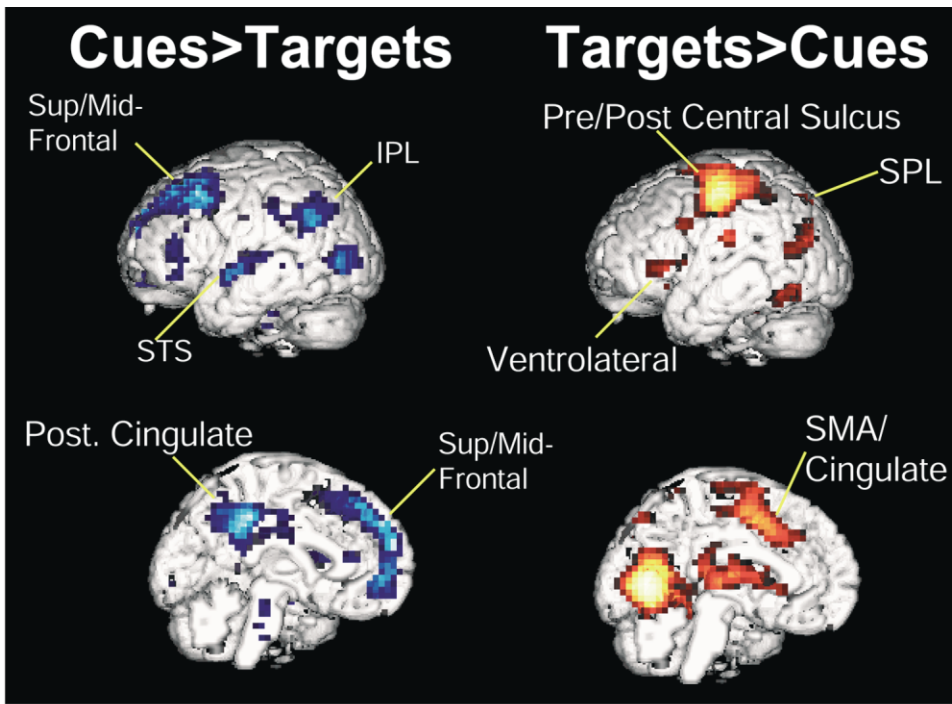
Fig. 2. Statistical parametric maps showing significant differences (maximun of labelled regions, $P < 0.001$, corrected) between cue and target processing overlaid onto a 3D rendered brain (results from group analysis; $N = 6$). Top panels show the lateral surface of the left hemisphere, bottom panels show the medial surface. The left column shows areas more active to cue processing than target processing, including the intraparietal sulcus (IPS), superior temporal sulcus (STS), posterior cingulate (Post. Cingulate), and regions of the mid-superior medial and lateral frontal lobe. The right column presents areas more active to target processing than to cue processing, including the superior parietal lobule (SPL), ventrolateral prefrontal cortex, and the supplementary motor area (SMA) stretching into the cingulate. Modified from Hopfinger et al. [28]. Reprinted with permission. Copyright Nature Neuroscience, 2000, Nature America.
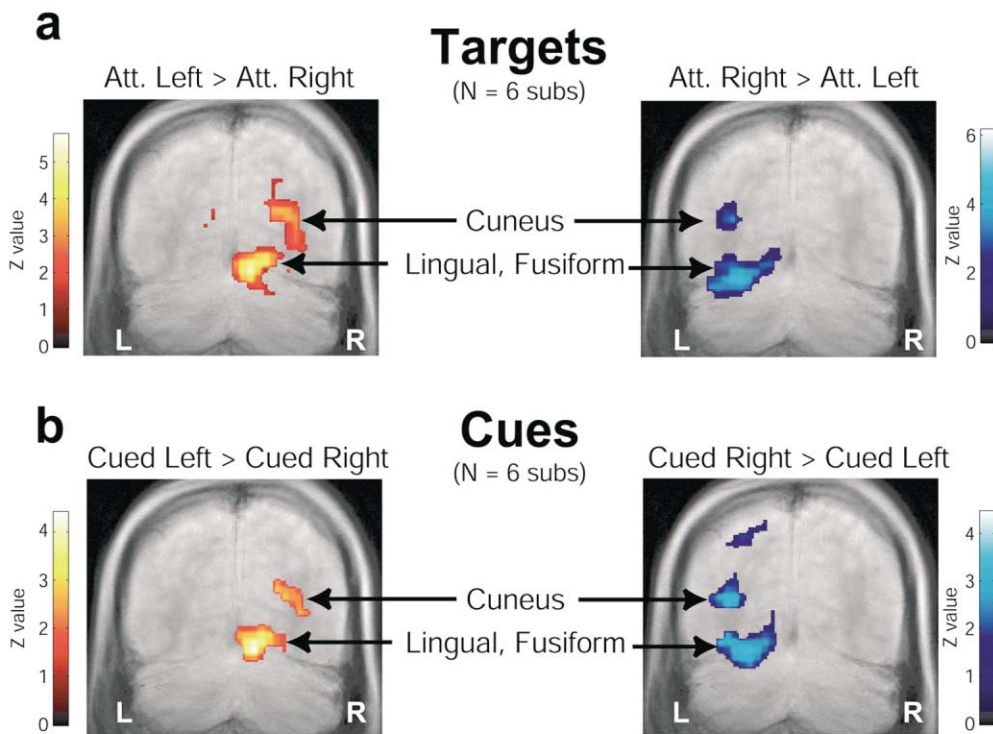

Fig. 3. *Caption overleaf.*

2.4. Selective attention effects and preparatory processing

In this study, we were also able to investigate the effects of the spatial focus of selective attention on target processing by comparing activations for the bilateral targets when participants were attending the left visual field versus the right visual field. Previous ERP studies in humans and intracranial recordings in non-human primates have shown that focused selective spatial attention produces a relative enhancement of processing within visual processing regions for attended versus ignored-location stimuli, e.g. [60,17,41,48]. In the current fMRI study, a ventral region within the lingual/fusiform gyri and a more dorsal region in the cuneus showed selective attention effects, evidenced by enhanced activity contralateral to the attended hemifield (Fig. 3, top). This finding of attention effects in extrastriate areas was expected, and agrees with numerous previous findings, e.g. [25,44,65]. However, the present study went a step further and investigated the preparatory processing that was occurring within visual cortical regions before the target stimuli appeared.

A statistical contrast between cues directing attention to the left versus right (and vice versa) revealed a relative increase in activity in the visual cortex of the hemisphere contralateral to the attended hemifield, prior to the onset of the targets. Importantly, these regions overlapped with the regions where attention effects were subsequently found in response to the target stimuli (Fig. 3, bottom). Because this differential activity was found in response to the cue and before target processing, it provides support for models of attention that posit a preset gain-control mechanism that enhances the excitability of visual cortical neurons coding the attended regions of space prior to any target, e.g. [27] and is in line with related findings from other neuroimaging work c.f. [6,16,32,33], and single-cell studies in monkeys [38]. These results suggest that attention may act to bias neuronal excitability to produce modulations of sensory areas prior to target onset, in such a way as to produce the enhanced responses to subsequent stimuli impinging on those neurons. These attention related effects, in cortical regions corresponding to those that will respond to the upcoming target stimuli, provide evidence that one aspect of top-down control is to bias the activity in cortical regions where selective processing will subsequently occur.[1]

While this study has provided new evidence that dissociates some of the brain regions involved in attentional control from those involved in selective attentional processing, further work is needed to identify the precise computations being performed by these networks. Orienting attention and selective visual processing are but two of the multiple subprocesses that are likely reflected in our cue-related and target-related activations. In the following section we present additional results that aid in the interpretation of these attention-related activations, and outline a few current methods for linking component processes of attention more precisely to regional brain activity.

3. Multiple brain activations in neuroimaging studies of attention

An issue in the functional imaging of selective attention, and for neuroimaging in general, is the interpretation of the multiple regions found to be active in any given task. Neuroimaging results are typically used to produce static pictures of all the brain regions involved in a task. While the spatial precision of functional imaging is excellent, and is continuing to improve, it is also well documented that the timing is inadequate for studies of many cognitive functions, which occur on a much more rapid time-scale. Even when the experimen-

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[1] The biasing effect could be accomplished by various means. For example, a transient differential enhancement of activity in visual regions coding the to be attended spatial locations (such as we found) may modify the potential excitability of those neurons for a brief time, leading to selective processing for subsequent attended stimuli. Another possible mechanism would be an increase in the baseline firing rates of neurons, possibly resulting in attention effects on target processing due to additivity of the baseline and stimulus evoked responses. The non-human primate single-unit study by Luck and colleagues [38] found such a sustained enhancement of the baseline firing rates of neurons in visual cortex. However, they found that the conditions that produced the most robust enhancement in baseline firing rates (before target onset) were not the conditions that produced the strongest attention effects on subsequent target-evoked processing. Therefore, a direct causal relation between the biasing of activity in response to cue stimuli and subsequent attention effects on target processing has not yet been shown; rather further research is required in order to better understand the exact relation of these effects.

Fig. 3. Results from group analysis ($N = 6$) showing selective attention effects in visual processing regions overlaid on an averaged proton density MRI scan (slice at $y = -64$). (A) Top panels show regions with differential activity for target processing as a function of where attention was focused. Left panels show regions showing greater target-related activity for attend left than attend right; right panels shows regions exhibiting greater activity for attend right then attend left. Target processing was significantly enhanced ($P < 0.001$ corrected) contralateral to the direction of attention in ventral lingual/fusiform regions and in a more dorsal region of the cuneus. (B) Bottom panels show attention effects in response to the attention-directing cue stimuli. Cue-induced activity was also greater ($P < 0.001$, uncorrected) contralateral to the direction of attention, and the effects were in regions that closely overlapped with where the attention effects were seen in response to the target stimuli (compare with upper panels). Reprinted with permission from Hopfinger et al. [28] Nature Neuroscience, 2000, copyright Nature America.

tal design is such that only one hypothetical component of the task is eliciting the activations, there are typically numerous brain regions involved in that component, as would be expected in most complex cognitive processes.

3.1. Separating component processes using event-related designs

Our previous study illustrated one method of dissociating the networks of brain regions revealed in most attention studies, by contrasting cue-related and target-related activations. This was a simple extension of the typical experimental design utilized in neuroimaging studies, isolating the mental phenomena of interest by way of designing experiments that separate the sub-component processes involved in that phenomenon. The use of event-related fMRI designs now allows the dissociation of processes that had previously been difficult to separate using standard neuroimaging paradigms. For example, in our study, we were able to separate the preparatory influences of top-down control in visual processing regions from the selective processing that occurs later. However, as noted above, our network of cue-related brain areas probably still contributes to a number of distinct mental processes. Further experiments are needed to identify the contributions of each brain region to more specific mental processes. However, the experimental design of studies would be limited in their effectiveness if they had to proceed at the relatively slow pace of our previous study. We used a cue-to-target interval of ~ 8 s, in order to accommodate for the relatively sluggish nature of the hemodynamic response, which typically peaks 6–8 s after the neural events which trigger it. Using long intervals between events of interest does allow successive activations to be isolated, however, there are also limitations that arise when using such designs.

First of all, inherent in the slow-rate method is the limitation of only being able to isolate activities that are separated by many seconds. Second, slowing the task to a rate at which hemodynamic responses are easily separable may change the task itself, and thereupon lead to differences in how subjects perform the task in comparison to well-established behavioral or electrophysiological (event-related potential; ERP) paradigms. Care must be taken in the interpretation of data that result from paradigms that have been changed significantly from accepted and well-understood designs. Previously, we laid out a 'frames of reference' approach for combining ERPs with functional imaging [42]. The logic of that approach is that by using identical experimental designs, physical stimuli, and participants (the 'experimental,' 'sensory,' and 'biological' frames, respectively), the results from neuroimaging and ERP sessions can be compared on the basis that they should be related to the same underlying mental process. The utilization of fast-

rate methods for fMRI analysis is essential for this enterprise.

3.2. New directions: fast-rate event-related fMRI

As noted above, the very slow time course of the fMRI hemodynamic response results in considerable temporal overlap between the event-related responses unless the stimuli are presented very slowly. One way to deal with this overlap is to randomize the presentation of the various event types in ways analogous to those developed for ERPs [63], such that the average overlap is about the same for the different types. Thus, in a contrast between two event types, the hemodynamic overlap effectively subtracts away, leaving only the differential event-related activity [14]. An extension of this idea involves randomizing the various event types not just with each other, but also with 'no-stimulus' events, which are points in time during the stimulus sequence randomized just as if they were stimulus events although no stimulus actually occurs [14,20]. This randomization results in the averaged overlap being about the same for the no-stim trials as for the stimulation-present trials, so that a comparison to no-stim 'responses' subtracts out the overlap from preceding events. This approach has been shown to work well in event-related fMRI experiments at rates of one event per every 2 s [14], and even as fast as one event per every 500 ms [4] (however, see Friston et al. [19] and Huettel and McCarthy [29] for some possible caveats about such an approach).

The fast-rate study by Burock and colleagues [4] has shown that event-related fMRI experiments can produce reliable results at presentation rates of up to one stimulus every 500 ms. While this study measured only simple visual responses to a large pattern stimulus, it nonetheless provides promising evidence that closely spaced hemodynamic responses can be differentiated. Such a finding suggests that fMRI studies of attention may be conducted at rates comparable to that used in behavioral studies. Indeed, Woldorff and colleagues [64] have recently conducted an fMRI study using a paradigm similar to our previous event-related fMRI design, but with much shorter cue-target SOAs and intertrial intervals, thereby avoiding some of the concerns of event-related designs listed above.

As noted above, one way to perform fast rate fMRI studies is to include so-called 'no-stim' trials that introduce a jitter to the timing of the stimuli, and allows the overlapping activity from temporally adjacent trials to be estimated and subtracted away. In addition to the use of 'no-stim' trials, an important advance of the Woldorff et al. study [64] was to extend this approach to trial types that include compound-events, constructed in a hierarchical design. There were three main trial types: (1) compound cue-plus-target trials (including all combina-
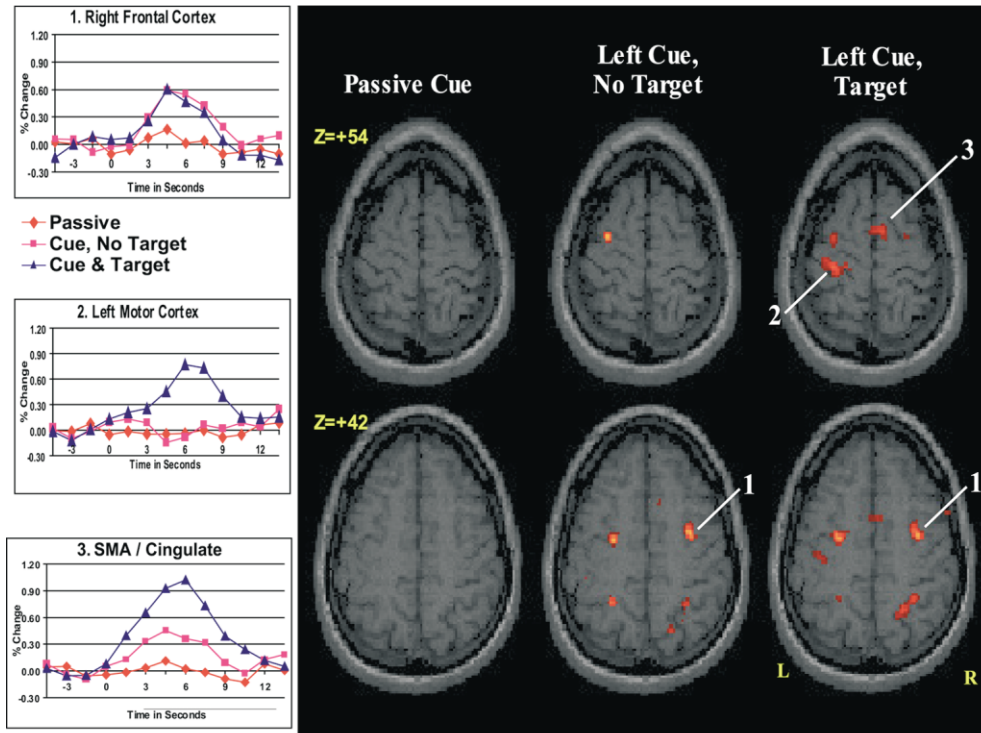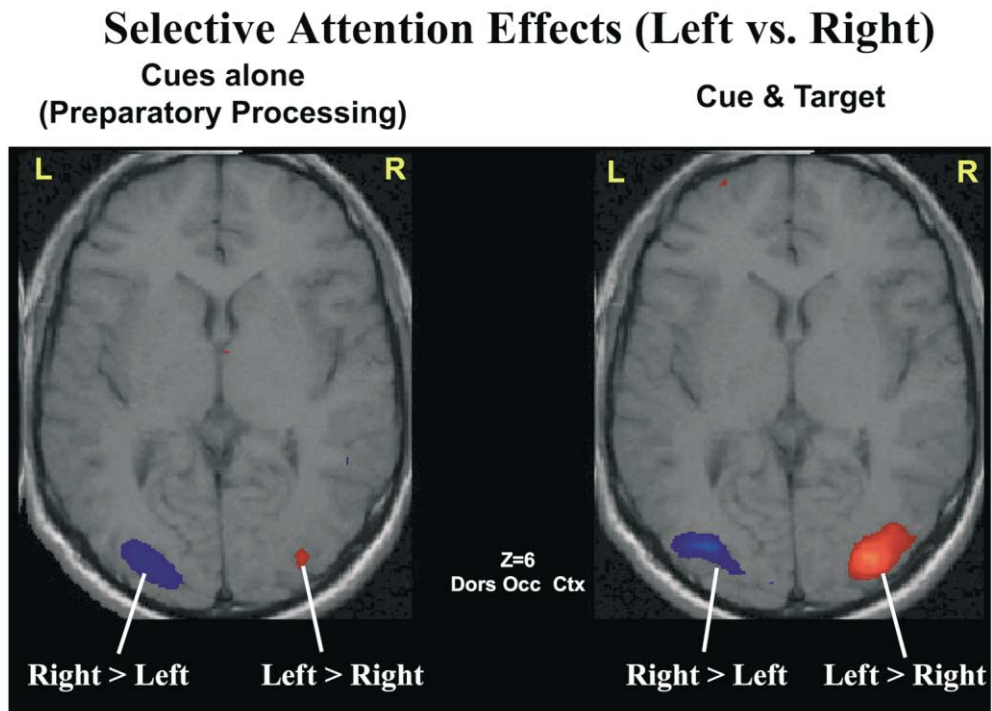
Fig. 4. *Caption overleaf.*

Fig. 5. *Caption overleaf.*

tions of left cues, right cues, left targets, and right targets); (2) cue-only trials (left, right, or passive); and (3) 'no-stim' trials that contained no stimuli at all. After subtracting out the 'responses' to no-stim trials, activity on the cue only trials should provide evidence of attentional control mechanisms (for the right or left cues) plus sensory processing of the cues (for left, right, and passive cues). The compound cue-plus-target trials would show all of the forgoing activity, plus the activity induced by target processing. The onset-to-onset interval for these various trial types was 4.5 s and the TR was 1.5 s. The cue to target interval was 900 or 1900 ms (compared to the ∼8 s intervals we used previously). The target stimuli in this study were faint visual dots presented in the lower left or right visual hemifield. The target dots were made faint in order to make the detection task difficult (and thus requiring of attention) and to minimize unilateral sensory stimulation, in order to emphasize other non-sensory aspects of target processing.

Although preliminary, the results of this study are promising. Fig. 4 shows data from a single subject in this design. A medial region of the right superior frontal cortex, similar to the cue-induced activity in our previous experiment, was active in response to the instructional cues (Fig. 4, area 1). Note that this area showed little or no response to the passive cues (see time course curves for area 1), and shows the same amount of activity for the instructional cue stimuli as for the compound cue-plus-target stimuli, suggesting that the activity in this medial frontal area is driven primarily by the cues, and therefore may reflect an aspect of attentional control processes. In contrast, the left motor cortex (area 2, Fig. 4) shows activity only in response to the compound cue-plus target events, and likely reflects response-related activity to the target stimuli (subjects pressed the button with the right hand). In addition, the SMA/cingulate region we de-

scribed in our previous study again shows activation in response to the target stimuli (Fig. 4, area 3).

This study also allowed for the investigation of selective attention effects related to cue versus target processing. The attention effects on target processing in this study were seen in dorsal occipital regions (Fig. 5, right), in line with previous reports of selective attention effects in relation to the retinotopic organization of posterior visual areas [59,65]. That is, in our earlier study [28] we presented stimuli to the upper visual field and observed target-related activity in the ventral visual cortex, but here the stimuli were presented to the lower visual field, and hence the target-related activity was observed in dorsal regions owing to the now well-known mapping of the visual field onto visual cortex. Importantly, those regions also showed differential activity in response to the cue stimuli alone (Fig. 5, left). Although preliminary, these results provide additional support for the finding that attention acts to bias activity within the visual processing regions corresponding to the location of expected target stimuli, as also shown in Fig. 3 (see also [16,32,33]). These preliminary findings hold significant promise for allowing experimental designs to be implemented in fMRI research that closely parallel the well-developed paradigms previously used in behavioral and ERP studies of selective attention.

3.3. Combining neuroimaging with electrophysiology

Given that many cognitive events of interest occur on a sub-second time scale, the sluggishness of the hemodynamic response remains a limiting factor in neuroimaging studies of cognition. Even if fast-rate fMRI techniques can ultimately allow a separation of processes occurring 500 ms apart [4], numerous component mental processes of interest cannot be separated with this type of temporal resolution. Therefore, it remains

Fig. 4. Preliminary data from a single representative subject in a fast-rate, short cue-target SOA, fMRI study of cued visual spatial attention [64]. Horizontal slices show areas of significant activation ($t > 2.75$, $P < 0.005$ uncorrected) overlaid on T1-weighted structural images. Three trial types are shown: passive cue versus no-stim (left images), left cue-only versus no-stim (middle images), and left cue-plus-target versus no-stim (right images). Three regions of significant activation are labeled on the images; they include the medial right frontal cortex (labeled 1), the left motor cortex (labeled 2) and a region of the supplementary motor area (SMA) extending into the cingulate (labeled 3). The corresponding time courses of the hemodynamic responses from these regions (relative to the no-stim trials) are shown in the graphs in the left column. Significant activity was observed in frontal and parietal areas when the cues were task relevant. The time courses for right medial frontal cortex (area 1) showed highly similar activity for both the cue-only and cue-plus-target trials, but little activity for passive-cue trials. This area is close to the superior frontal cortex/frontal eye fields recently reported by Hopfinger et al. [28] and Corbetta et al. [9] to be activated during the initiation (i.e. control) of visual spatial attention in long-SOA experiments. In contrast, left motor cortex (2) showed activity only for the cue-plus-target trials, reflecting the execution of the motor command to the targets. The SMA/cingulate region (3) also showed strong activity for cue-plus-target trials, with cue-only trials activating this region to a lesser degree.

Fig. 5. Preliminary grand-averaged ($N = 10$) data from the fast-rate fMRI experiment [64], showing selective attention effects (attend right versus attend left) for the cue-only trials and the cue-plus-target trials. Regions showing greater activity for attention to the left versus to the right are shown in red, regions showing greater activity for attention to the right than the left are shown in blue ($P < 0.01$, uncorrected). In line with previous results for lower visual field stimuli [65], target processing is enhanced in dorsal occipital regions contralateral to the direction of attention (right panel), consistent with the retinotopic organization of the sensory pathways. Preparatory processing can also be observed in these same regions, as selective attention effects on cue-only processing (left panel) produced differential activity in these regions on trials in which no target occurred.
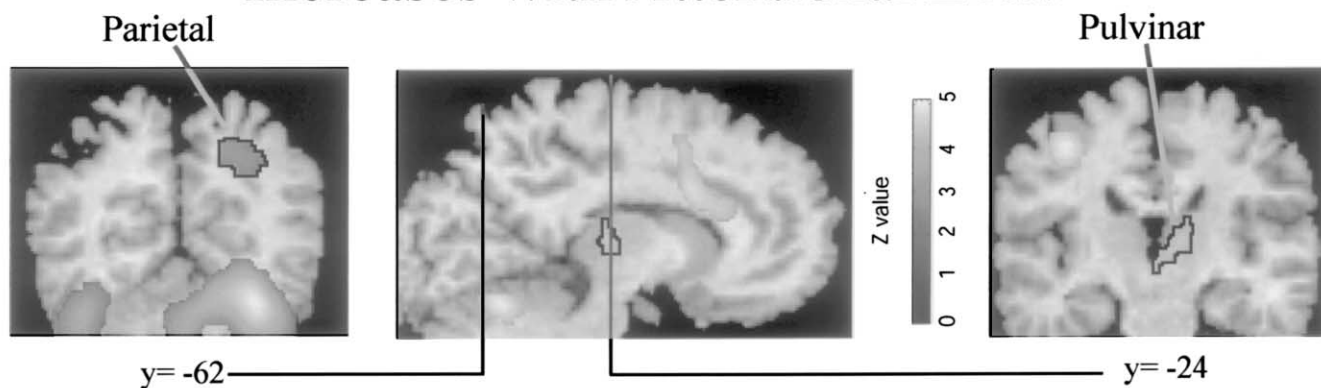
Fig. 6. Results of parametric PET analysis (from data originally reported in Mangun et al. [44], $N = 11$) showing regions in which regional cerebral blood flow increased systematically and monotonically from passive viewing, to detecting simple luminance increments, to discriminating complex forms. Activations are overlaid on a standardized brain, showing coronal slices (left and right panels), and a saggital section (middle panel). Stereotactic coordinates refer to the standardized space used in SPM96 (Wellcome Department of Cognitive Neurology, University College London), based upon the atlas of Talairach and Tournoux [58]. Regions showing increased activity (maps thresholded at $Z = 2.33$, $P < 0.01$ uncorrected) with increasing attentional load included a region in the right parietal lobe (left panel) and a region of the pulvinar (right panel).

unlikely that fMRI experimental data alone will provide the necessary temporal resolution needed to provide detailed accounts of all the neural mechanisms of attention.

Previously, we and others have shown the utility of combining neuroimaging with scalp recorded event-related brain potentials (ERPs) in studies of visual selective attention, e.g. [25,44,45,65]. While ERPs are often limited in their ability to specify the precise intracranial locations of the neural generators of the scalp-recorded potentials, they nonetheless provide measures of neural activity in real time, and therefore complement the strengths and weakness of functional neuroimaging [21]. Specifically, the temporal activity patterns of brain activations defined by positron emission tomography (PET) or fMRI might be determined more precisely if they could be linked to ERP activity at specific instances of time. This temporal information is essential for a full understanding of the attention mechanisms reflected in PET or fMRI activations. An example from a study in our laboratory provides evidence of the strength of this combined methodological approach in furthering our understanding of the brain dynamics supporting attentional operations.

Recently we re-analyzed a portion of a study that had combined PET and ERPs (initially reported in Mangun et al. [44]). Participants ($N = 11$) were required to maintain fixation upon a centrally located cross, while pairs of symbols within each visual field were simultaneously flashed bilaterally (50 ms duration, 250–550 ms interval between successive bilateral onsets) to the right and left upper visual fields. In separate blocks, participants were instructed to either covertly attend to the pair of symbols on the left, covertly attend to the pair on the right, or

to simply passively view the stimuli. There were also three types of instructions. Participants were instructed on some blocks to press a button whenever the two symbols matched (a difficult discrimination), on other blocks to press a button whenever a small dot appeared somewhere within the area where the symbols were flashing (a simple detection task), or simply to passively view the stimuli in yet other blocks. Participants completed PET and ERP sessions on separate days. MRI scans were also obtained from each participant.

Previously, we had directly contrasted attend-left versus attend-right conditions to examine the effects of selective attention on visual processing [44]. However, there are numerous attention-related processes engaged within a task that do not depend upon the precise locus of spatial attention, but rather are engaged regardless of where attention is directed (e.g. see cue activations in Fig. 2). The purpose of the present analysis was to investigate the brain regions involved in these non-directionally-sensitive aspects of attention. Furthermore, recent studies of attentional 'load' [37] have shown that the allocation of attentional resources is not an all-or-none phenomenon, but rather depends on factors such as perceptual and task difficulty. Therefore, we performed a 'parametric' style analysis [18] across the three task-types of the current study to investigate regions of the brain in which activity changed systematically and monotonically with increasing task difficulty, or recruitment of attentional resources. For the purposes of this analysis, we interpreted the passive viewing condition as being the least attention-demanding 'task,' the detection of simple luminance targets as the next most attention demanding, and the symbol discrimination task as having the highest attentional load.
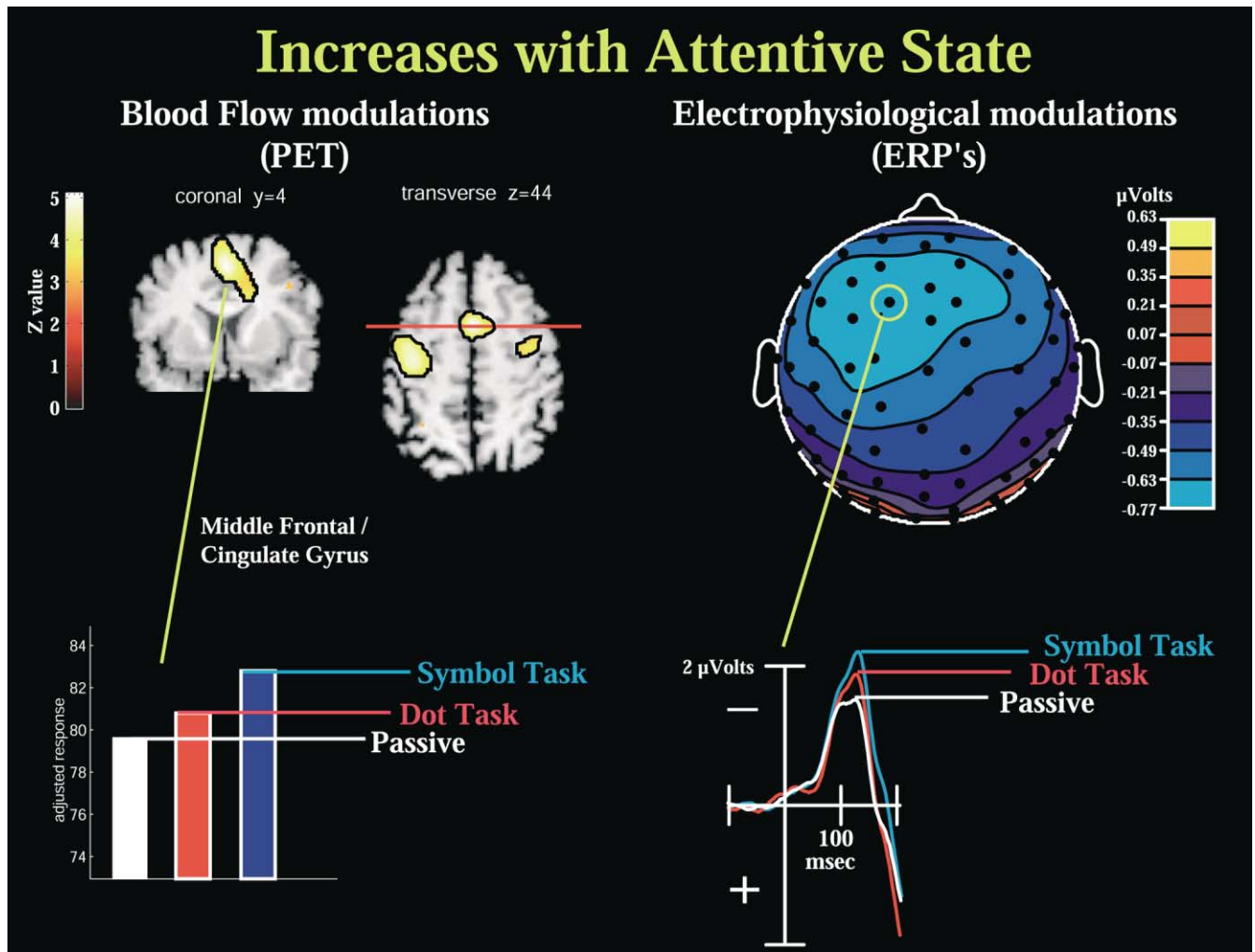
Fig. 7. Parametric analyses of PET effects and corresponding ERP effects with increasing levels of task difficulty. The coronal section at left is taken at the anterior–posterior level indicated in the horizontal section displayed to the right. At the bottom left, the pattern of activation for the SMA/cingulate activation (stereotactic coordinates 0, 4, 44; $Z = 5.10$) is shown graphically (the y-axis 'adjusted response' refers to blood flow measurements after all scans were scaled to have a mean whole brain level of 50 ml/min/dl, and after removal of confounding factors). At bottom right, the ERP waveform from a single fronto-central electrode site is displayed for the three levels of the task. An increase in the anterior N1 ERP component (peaking at about 140 ms) can be seen with increasing task difficulty. The scalp distribution of this effect is shown at top right, by plotting the difference map for the symbol task minus the passive viewing condition. Adapted from [43] with permission from Lippincott, Williams, & Wilkins, 2000.

Multiple brain regions that had not shown selective attention effects in the previous direction-specific analyses were revealed by the current analysis as being involved in aspects of attentional engagement. For example, this analysis revealed activation in the right pulvinar (stereotactic coordinates 10, − 24, 8; $Z = 3.57$; $P < 0.001$ uncorrected for multiple comparisons; Fig. 6) and in parietal regions (left: − 36, 56, 52, $Z = 3.63$; right: 22, − 62, 40, $Z = 3.13$) that our previous analysis of selective attention effects had not revealed. These regions of cortex have previously been implicated in attention [12,36,49] and here we show that they are engaged to a greater extent as the task difficulty increases, possibly involved in the recruitment or allocation of attentional resources. In particular, the pulvinar

has been hypothesized to be involved in attention tasks, especially when filtering of irrelevant information is needed [36]. Our findings accord with this hypothesis, as activity in the pulvinar increased across task conditions as the need for more effective filtering of unwanted information increased.

A particularly strong modulation across tasks was found in a region of the supplementary motor area, extending into the mid-cingulate gyrus (0, 4, 44; $Z = 5.10$, $P = 0.001$, corrected for multiple comparisons; Fig. 7). This area is similar to the area activated by the target stimuli in our event-related fMRI experiments described above [28,64]. Although these event-related fMRI studies were able to attribute this activity to target processing (as opposed to cue-invoked prepara-
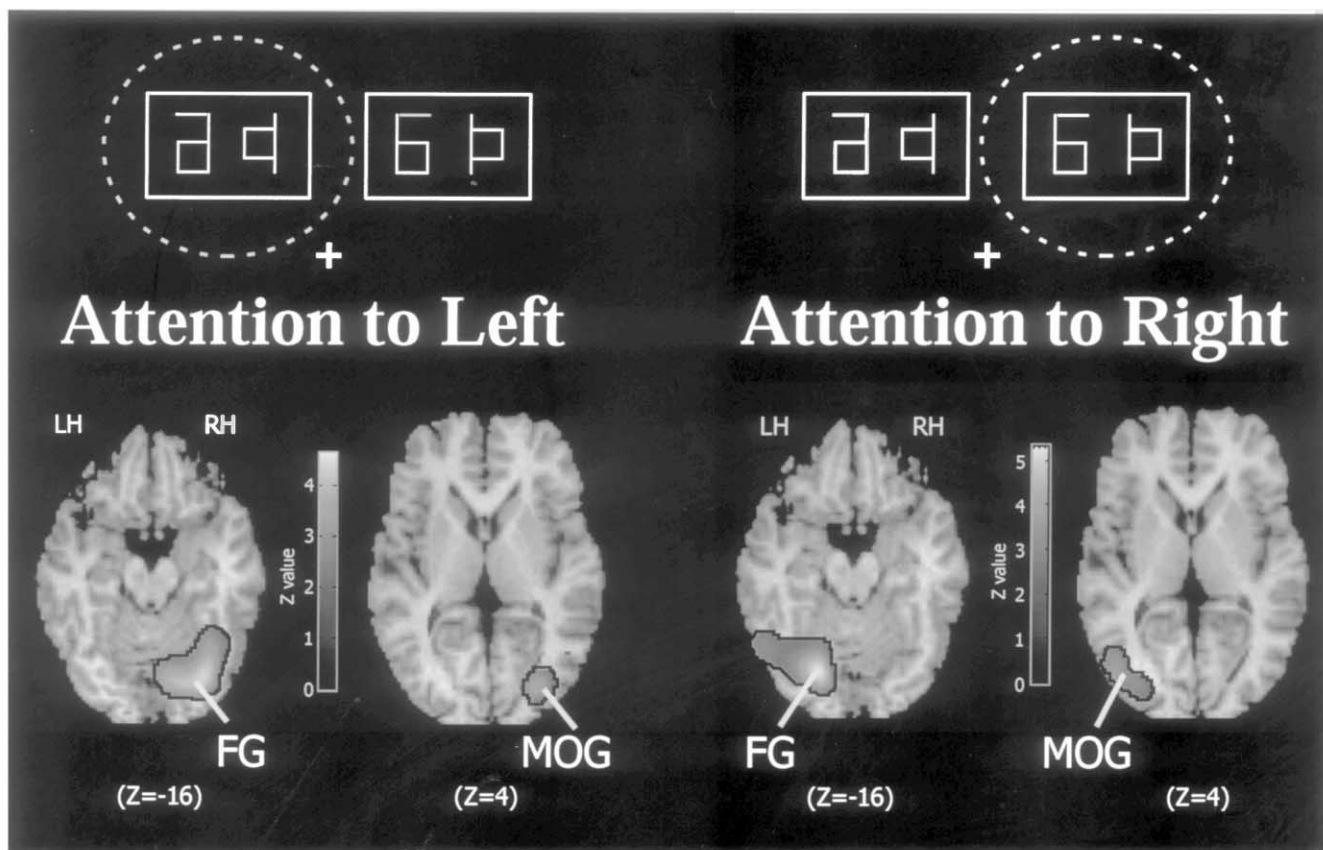
Fig. 8. Top. Stimuli consisted of a fixation cross and two white outline rectangles in the upper visual field that were present throughout all trials. Bilateral arrays of non-sense symbol pairs were flashed within the outline boxes for a duration of 50 ms., with a stimulus onset asynchrony of 250–550 ms. Participants covertly attended to the left or right, as instructed in separate experimental blocks. The dashed line circles here indicate the direction of covert attention. In separate blocks the participants either detected a small luminance increment (a small dot presented infrequently within the outline boxes) at the attended location, detected symbol matches for the pair at the attended location, or passively viewed the stimuli. Bottom. Group-averaged changes in regional cerebral blood flow (activation) during attention to left versus right visual field stimuli. The activations are overlaid onto horizontal sections of a standardized brain (maps are thresholded at $P < 0.01$, uncorrected). The sections pass through ventral visual areas at lower slices ($z = -16$), and at slightly higher slices ($z = 4$). Activations (outlined in black for clarity) in the hemisphere contralateral to the attended field were observed in the posterior fusiform gyrus (FG) and middle occipital gyrus (MOG). After Mangun et al. [44], with permission, Human Brain Mapping, Copyright 1997, Wiley.

tory processing), they could not precisely specify when the activity was occurring. Therefore, from the fMRI data alone, it is difficult to infer the stage of processing at which this area of the brain is involved in target processing. However, our combined PET/ERP study can shed light on this, via the temporal resolution of ERP effects. Specifically, we were able to examine the ERP data for activity that varied with task difficulty, in addition to testing for parametric modulations in the PET data. A negative polarity peak, occurring at ∼100 ms latency after target onset and recorded at scalp locations overlying the SMA/Cingulate region, was found to show a monotonic increase with increasing attentional load (Fig. 7). Although we will not provide electrical modeling of the intracranial currents associated with this ERP activity, the scalp distribution of this ERP effects is very consistent with a generator in midline anterior regions of the brain. This correspondence between the PET and ERP effects, combined with the spatial position of these effects, suggests that this region of cortex is active ∼100 ms following the presentation of the target. This information can be used to constrain the interpretation of the operation(s) being performed by this region, for example by excluding the possibility that it is only involved in a final response generation after perceptual analyses have been thoroughly completed. Rather, our data suggest that this region of the brain is active well before a response is actually executed, extending the suggestion from recent event-related fMRI studies [34,40] that the more caudal regions of the anterior cingulate may be involved in on-line monitoring of response and task difficulty, evaluating when higher levels of control are needed to avoid erroneous responses.
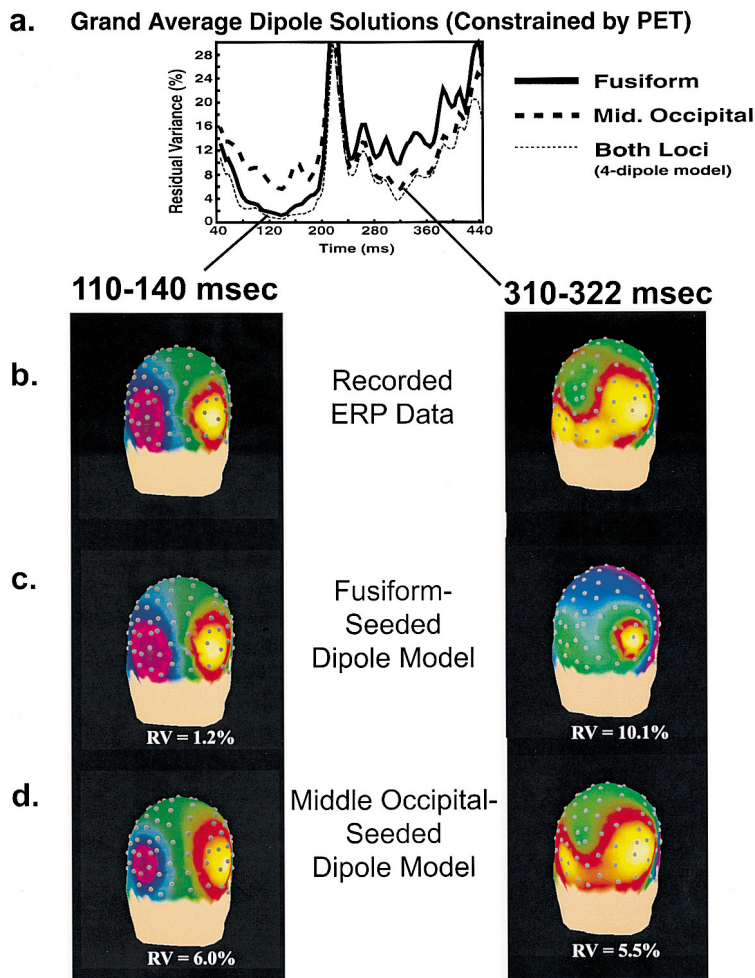
Fig. 9. Data from combined PET and ERP study (Mangun et al. [44]). (A) Graph depicting the percentage of scalp voltage variance not accounted for ('Residual Variance') when measuring the goodness of fit between dipole models and the observed ERP scalp distribution for the attend left minus attend-right difference waveform (note that a lower value on the residual variance graph represents a better goodness of fit). Dipole models were constrained by the PET activations (left and right fusiform gyri, and left and right middle occipital gyri) elicited by the attend left versus attend right comparison. The Fusiform gyrus model (indicated by the solid line in the graph) produced a better fit than the middle occipital model (1.2 versus 6.0%, respectively) in the latency range of 110–140 ms, corresponding to the P1 ERP attention effect. In contrast, at a latency range of 310–322 ms, the middle occipital gyrus model (indicated by the thick dashed line) produced a better fit than did the fusiform model (5.5 versus 10.1%). (B–D) Recorded topographic maps of attention effects (B) corresponding to the attend left minus attend-right difference waveform, and model data topographic maps (C–D) for dipoles placed at the location of the PET defined fusiform gyrus attention effects (C) or the location of the PET defined middle occipital gyrus attention effects (D). The maps are for the time period of the P1 component (110–140 ms) in the left column, and for a later sustained positivity (310–322 ms) in the right column. The difference between the recorded and model data, expressed as percent residual variance (RV), is shown below each model head. The view of the heads is from the rear (left on left). The locations of electrodes are indicated by gray disks.

3.4. Functionally constrained electrophysiological models

In closing we will describe one additional new analysis performed on the Mangun et al. [44] data, involving inverse dipole modeling. As reported previously [44], the effect of selective attention on the ERPs to target stimuli was a relative enhancement of the P1 component, while the PET effect was increased blood flow in two separate loci within visual cortex contralateral to the attended side. One activation was observed in the posterior fusiform gyrus, while another was found more laterally in the middle occipital gyrus (Fig. 8). Previ-

ously, we have argued that covariations across experimental manipulations can be used to infer a correspondence between attention effects seen in neuroimaging results and attention effects on specific components of the ERP waveform [44]. Here we use the brain loci identified by PET to constrain our modeling of the ERP data [25,65].

Mathematical modeling of ERP sources often models the brain, skull, and scalp as three concentric spheres of different, but homogenous conductivity [1,67]. However, more recently, the spherical models have been augmented by realistic head models that allow for a

more accurate modeling of the propagation of brain electrical activity [13,66]. For the present data, we used a boundary element approach [2,3,39,46] in a realistic head model. The details of the brain, skull, and scalp anatomy were derived from anatomical MR images of the participants. The ERP data were coregistered with the MR-derived realistic head model by fitting the 3-D electrode array (digitized from each participant's head during recording) to the MR image surface using a minimization algorithm and fiducial landmarks.

With two candidate regions (fusiform and middle occipital gyrus) in each hemisphere defined by our PET activations, it was possible to seed dipoles to either the left and right fusiform gyri, the left and right middle occipital gyri, or to all four loci, and to ascertain which of these produced the best model of the recorded ERP data, in particular during the time range corresponding to the P1 attention effect.[2] We found that when dipoles were placed in the fusiform gyrus, the model provided a better explanation (i.e. lower residual variance (RV)) for the recorded data in the time range from 110 to 140 ms than did placement of the dipoles in the more lateral PET activations in the middle occipital gyrus (Fig. 9, top graph). Although both the fusiform model and the middle occipital model bear a superficial similarity to the recorded data in the 110-140 ms latency range (Fig. 9, left column), subtle differences in the magnitudes and scalp locations of maxima and minima can be discerned, with the fusiform model providing a better fit during this time range (1.2% RV versus 6.0% RV). Furthermore, as the graph in Fig. 9 indicates, the 4-dipole model was only slightly better than the fusiform model alone, suggesting that activity in the middle occipital gyrus did not likely contribute much, if at all, to the activity recorded during this latency range. This time range conforms closely to the P1 ERP attention effect, and provides further evidence that the fusiform attention effect is occurring at this time, as we proposed previously [25,44].

Although the possibility exists that activity in both the fusiform and middle occipital gyri contributes to the P1, evidence from our modeling suggest that the middle occipital gyrus may instead be active at slightly longer latencies. In addition to the data from the 4-dipole

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[2] Note that a 4-dipole model should always produce a better fit than either of the 2-dipole models, simply due to the fact that the extra dipoles will be able to account for at least a portion of the remaining residual variance, regardless of where that activity was actually produced. We present the 4-dipole model simply to indicate the best fit that could be expected at these time ranges given only occipital location dipoles. Specifically, the fits overall are generally not as good at longer latencies, presumably due to more widespread brain activity at those latencies. Therefore, in order to distinguish between the timecourse of activities in these relatively close-proximity regions, we are interested in the relative fits of the fusiform versus middle occipital dipole models at each point, not simply the absolute residual variances.

model described above suggesting that fusiform activity alone can account for the activity at 110–140 ms, the inverse pattern was observed at a later latency range. Specifically, the lowest residual variance for the middle occipital dipole model occurred at a later time, in the 310–322 ms latency range, corresponding to a sustained bilateral posterior positivity (Fig. 9). During this later time range, the middle occipital dipole model produced a better solution than did the fusiform dipole model (5.5% RV versus 10.1% RV; Fig. 9, top graph and right column). In addition, the 4-dipole model was only slightly better than the middle occipital dipole model alone, suggesting that the fusiform did not likely contribute much to the activity recorded at this latency range. Furthermore, although the RV for the middle occipital model is only slightly better at this time range than for the P1 time range, a visual inspection of the graph in Fig. 9 illustrates that it is a good fit relative to the overall ability of occipital sources to account for activity in this latency range (the poorer overall fits are likely due to additional activity in more anterior brain regions). Together, these findings provide further support for our prior conclusion that activity in the region of the fusiform is related to attentional modulations of early sensory processing, and extends this result by showing that activations in more lateral regions of visual cortex may be related to attentional modulations at longer latencies, in line with the sequential organization of the ventral visual processing stream [59]. These results also provide an illustration of the ability of a combined ERP and functional imaging approach for elucidating the temporal sequence of brain activity.

4. Conclusions

The advent of new analysis methods for brain imaging has ushered in an exciting time for the study of the neural mechanisms of selective attention. Hypothesized elementary operations contributing to attentive behaviors can now start to be linked to distinct underlying brain circuitry. Our event-related fMRI studies have begun to dissociate some of the circuitry involved in attentional control from the brain processing involved in subsequent attentional modulation of stimulus processing. Regions in the intraparietal sulcus, superior temporal sulcus, and dorsal frontal cortex were implicated in an attentional control circuit that may bias activity in the visual processing regions of cortex representing attended regions of space, prior to the appearance of the target stimuli. The fast-rate event-related fMRI study [63] extends these findings within a paradigm that more closely resembles those used previously in behavioral and ERP studies. This should permit more direct links to be made between cognitive models of attention and neurobiological mechanisms.

Despite these advances, however, functional imaging remains unavoidably limited in temporal precision. By integrating functional imaging with ERP recording, we have shown how a more precise timing of neuroimaging-defined brain activity can be approached. For example, activation within a region of the mid-cingulate/ SMA was associated with scalp-recorded neural activity at a specific latency (~ 100 msec) after target presentation. Additionally, attention effects in multiple extrastriate areas were attributed to processing at distinct latencies using dipole modeling of ERP activity in realistic head models. Future studies using this integrative approach to address preparatory mechanisms of attention should provide further evidence about how top-down cognitive mechanisms modulate visual perception.

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