

Hemodynamic and Electrophysiological Study of the Role of the Anterior Cingulate in Target-Related Processing and Selection for Action

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Abstract: A number of experiments requiring attention or other complex cognitive functions have found substantial activation in the anterior cingulate cortex (ACC). Some of these studies have suggested that this area may be involved in “selection for action,” such as for selecting to respond to a target stimulus. Here, positron emission tomography (PET) and event-related potentials (ERPs) were used to study the effects of target probability during a demanding visual spatial attention task, in which the target percentage was either low (2%, 1 per ~26 sec) or high (16%, 1 per ~3.5 sec). As expected, ERPs to detected targets evoked large, bilaterally distributed P300 waves. The PET showed strong activation of the ACC, particularly dorsally, during all the attend conditions relative to passive. However, these PET activations did not significantly differ between the few-target and many-target conditions, showing only a small trend to be larger in the many-target case. Such results indicate that the bulk of the ACC activation does not reflect selection for action per se, while also suggesting that the ACC is not a likely source of the P300 effect. The current data, however, do not argue against the ACC serving a role in maintaining a vigilant or anticipatory state in which one may need to select for action, or in continually or repeatedly (i.e., for each stimulus) needing to resolve whether to select to act or to not act. *Hum Brain Mapping* 8:121–127, 1999. © 1999 Wiley-Liss, Inc.

Key words: attention; P300; PET; positron emission tomography; ERP; event-related potentials

INTRODUCTION

A number of PET and functional MRI neuroimaging studies involving tasks requiring attention or other complex cognitive functions have found substantial activation in the anterior cingulate cortex (ACC) [Pardo et al., 1990; reviewed in Posner and Raichle, 1994]. Various theories have been proposed to explain the frequent activation of the ACC in these tasks, includ-

ing attention-related activity for performing nonroutine procedures [LaBerge, 1990]) and control of behavioral output by facilitating execution of appropriate responses and/or inhibiting execution of inappropriate ones [Paus et al., 1993]. Some of the neuroimaging studies have supported the notion that the ACC may be particularly active when there are many stimuli that require a response (e.g., targets), suggesting that the anterior cingulate may be particularly important for “selection for action” [Posner et al., 1988; Posner and Raichle, 1994]. In an experiment consistent with this view, Pardo et al. [1991] showed that sustained attention for detecting very infrequent pauses or intensity

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decrements of continuous somatosensory or visual stimuli activated parietal cortex and dorsolateral prefrontal cortex, but not the anterior cingulate. On the other hand, Murtha et al. [1996] showed that just anticipation of the onset of a task can lead to some anterior cingulate activation, even without any stimuli needing to be presented. However, no studies have explicitly studied the effect of target frequency on anterior cingulate activation while holding other factors (such as arousal or difficulty) constant.

In addition to the need to clarify the relationship between target frequency, selection for action, and ACC activation, there is also a need to understand the timing of target-related brain processes. However, because the blood-flow and other blood-feature modulations measured in hemodynamically based neuroimaging studies change so slowly, such studies provide little characterization of the *timing* of information processing in the brain. Event-related potentials (ERPs), on the other hand, which reflect the rapidly changing electrical activity in the brain evoked by a stimulus or cognitive event, provide high temporal resolution images of neuronal populations engaged in information processing. Moreover, because ERPs measure such fast-changing signals, ERP studies typically capitalize on the capability of selectively averaging the evoked activity time-locked to different event types, such as targets versus nontargets, from *within* the same run. Such studies have demonstrated clear, target-selective ERP activations. For example, if one attends to a particular region of space while a series of target and nontarget stimuli are presented in random sequence to several locations in the visual field, *all* stimuli (both targets and nontargets) presented in the attended region elicit an enhanced positive electrical wave ("the P1 effect") at ~100 msec over occipital scalp contralateral to the direction of attention. However, detected targets in the attended region *also* elicit the large "P300" wave (350–700 msec) relative to nontargets in the attended region (typically preceded by a negative wave, "N2b", between 250–300 msec) [Heinze et al., 1990]. Despite the clear target-specificity of these effects, specifying their neural sources has been difficult.

In a previous article [Woldorff et al., 1997], we reported results from a combined PET/ERP study showing that highly focused lateralized spatial attention within the lower visual field enhanced early activity in contralateral dorsal occipital cortex. These effects were interpreted as showing that the early visual spatial attention effects followed the retinotopic organization of the early visual sensory pathways.

In the present article, we present PET and ERP data examining the target-related activity and target frequency effects during this same demanding spatial attention task. The main questions we address are: (1) How does the ACC activation vary as a function of target frequency in an attentionally demanding task? Selection-for-action theory suggests that ACC activation will increase with increasing target frequency. (2) Using block-design PET in which target frequency and attention direction are independently varied, will the target frequency manipulation result in hemodynamic activation differences that can then be mapped to the target-selective, high-temporal-resolution, ERP effects recorded from the same individuals? More specifically, if ACC activity increases with more targets, is this area a likely neural source for the large P300 ERP wave?

METHODS

Stimuli and Task

In two separate sessions, subjects ($n=10$, 18–41 yr, all right-handed, four male) performed the same visual attention task while either ERPs or PET scans of their brain activity were recorded. In all conditions, subjects fixated on a small cross in the center of the screen (50 cm away) while bilateral stimuli of 150-msec duration were rapidly presented (stimulus onset asynchronies = 250–750 msec) in the lower visual field. Each stimulus consisted of two small reversing checkerboards, one in each lower visual field, each having either one, two, or no small dots (Fig. 1). In the active attention conditions, subjects covertly attended to a designated side of the bilateral stimuli and pressed a button with the right hand upon detecting checkerboard arrays on that side with two dots ("targets"). Those with only one or no dots in the array on that side were thus nontargets, or "standards."

There were five conditions: (1) attend left, with many targets [16%] (2) attend right, with many targets [16%], (3) attend left, with few targets [2%], (4) attend right, with few targets [2%], and (5) passive viewing (with 2% irrelevant targets). With 16% targets, there was on average one target (on each side) per every ~3.5 sec; at 2%, there was one every ~26 sec. In preliminary runs, the target difficulty was adjusted for each subject, for each visual field, by changing the contrast and/or the size of the dots, so that highly focused attention was required, but such that target detection accuracy was around 90%. These parameters were then used for both the ERP and PET runs.

The present report focuses on the effects of the target frequency manipulation.

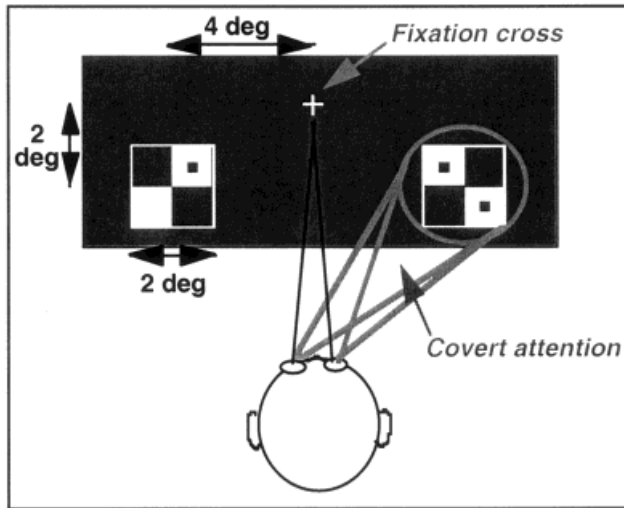


Figure 1.

Schematic diagram of the bilateral stimulus and task, indicated for an attend-right condition during an occurrence of a two-dot target array on that side.

ERP Recordings. EEG was continuously recorded during forty 90-sec runs (eight in each condition) from 64 scalp sites (sample rate per channel: 400 Hz, bandpass: 0.01–100 Hz), including several for recording eye movements for later rejection of artifact-contaminated trials. Averaged ERPs to the standards and targets under the various attention conditions were extracted by selective averaging. Repeated-measures analyses of variance (ANOVAs) of the peak and mean amplitude of ERP components across specified latency ranges were performed.

PET. Brain blood flow was measured with O^{15} -labeled water administered as an intravenous bolus of 50–70 mCi. Each subject underwent a series of 10 PET blood-flow scans, two in each condition, performed in a counterbalanced order. Following global normalization, the individual scan images were motion-corrected [Woods et al., 1992], 3D-interpolated, and spatially normalized into Talairach coordinate space [Fox et al., 1988; Talairach and Tournoux, 1988; Lancaster et al., 1995]. Like-condition scans were then averaged across subjects, and the resultant grand-averaged scans from relevant pairs of conditions subtracted. Change Distribution Analysis [Fox et al., 1988] was used to assess the statistical significance of outliers identified in the averaged subtraction images. Z-score PET blood-flow change images were derived, thresholded ($121 < 2.0$), and then overlaid on the spatially normalized, grand-averaged MRI images from the same subjects.

MRI Scans. All subjects had high-resolution (1 mm X 1 mm X 1.6 mm) MRI scans obtained from an 1.9T Elscint MRI scanner. These were acquired using 3D-acquisition, T1-weighted, gradient-echo pulse sequences, with parameters TR=33msec, TE=7.9msec, flip angle=25 deg. The MRI scans were also spatially normalized into Talairach coordinate space for coregistration with the PET scans and to enable grand-averaging.

RESULTS

ERP effects

As previously reported [Woldorff et al., 1997], the ERPs showed a significantly enhanced positive wave (P1 effect) between 80–150 msec for all stimuli (i.e., both standards and targets), in all the attention conditions relative to the passive condition, over occipital areas contralateral to the direction of attention. These attention effects were not different between the many-target and few-target conditions, providing evidence that sustained attention was similar across these conditions.

The selective averaging of the ERPs showed clear differential processing given to targets (as compared to the nontargets) at the longer latencies: Targets in the active attention conditions, relative to the standards, elicited large (5–15 uV) P300 waves (400–800 msec) ($P < .001$) (Fig. 2a), which were preceded by N2b waves that were largest over occipital cortex contralateral to the direction of attention ($P < .01$) (not shown). The P300s in the 2% target conditions were larger (per target event) than those in the 16%-target conditions (Fig. 2a), by ~ 25% in peak amplitude ($P < .001$) and by around 70% in integrated area under the curve (mean amplitude) ($P < .001$), consistent with the well-known P300 probability effect [Hillyard and Picton, 1987]. The irrelevant “targets” in both the passive conditions and on the unattended side during the active conditions did not differ from the standards in those conditions, eliciting no P300s or other target-related activity (not shown).

PET effects

Also as previously reported [Woldorff et al., 1997], the active attention conditions relative to passive showed strong activity in the contralateral dorsal occipital areas (Brodmann Areas [BA] 18/19), which was similar in the many-target and few-target conditions. Moreover, dipole modeling of the early ERP P1 attention effects indicated that these dorsal occipital

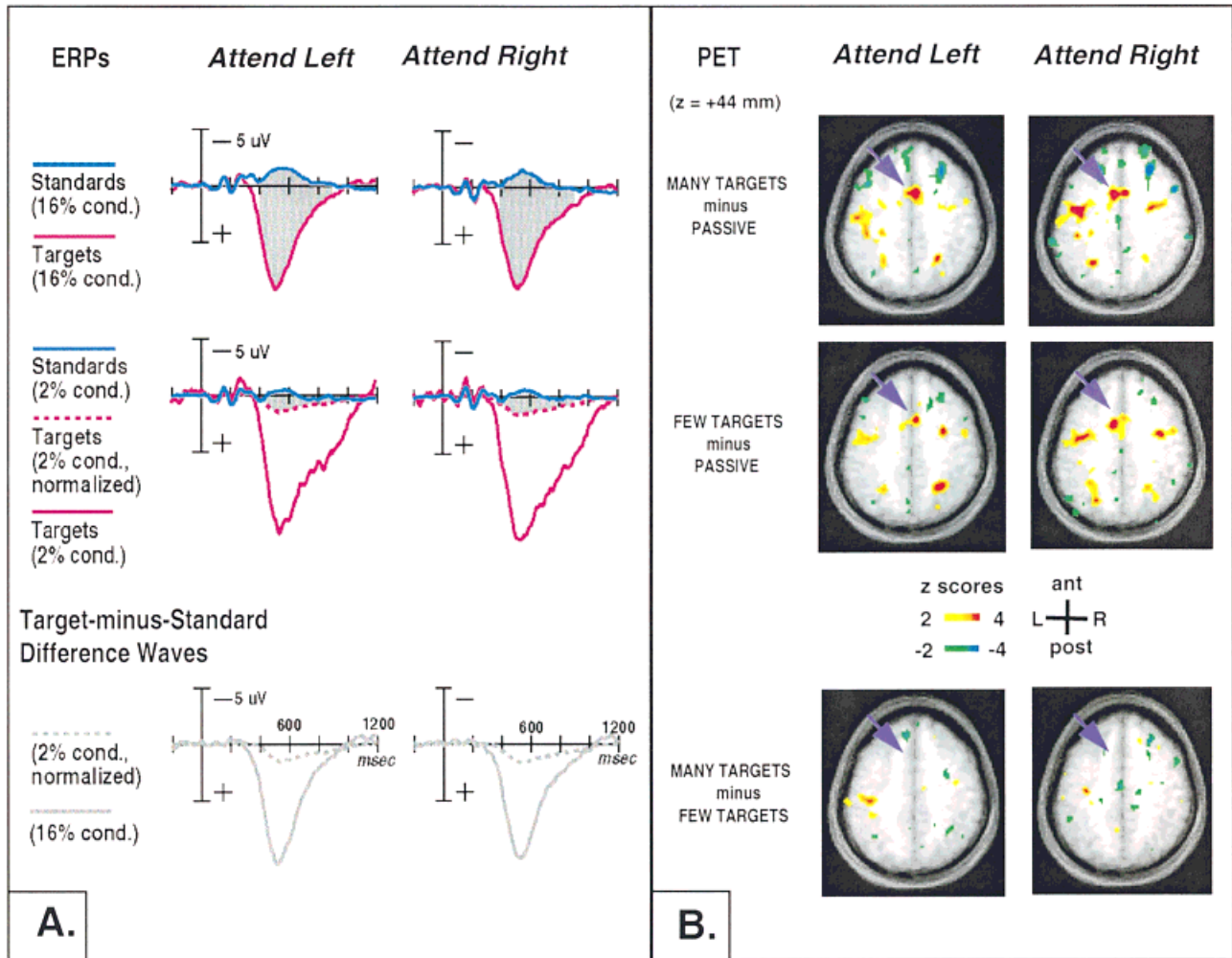


Figure 2.

(A). Overlay of the ERPs and ERP difference waves to standard and target stimuli for the different conditions at midline parietal site Pz, all grand-averaged across the 10 subjects in the study. **Top row:** Overlay of the ERPs to the attended target and standard stimuli during the 16%-target conditions. Note the large P300 wave to the targets peaking at ~550 msec (shaded area). **Second row:** Overlay of the ERPs to the attended target and standard stimuli during the 2%-target condition, along with a number-normalized version of the target ERP (i.e., normalized by $1/8 = .125$, because there are 8 times fewer target responses, relative to the corresponding 16% condition, that would be integrated across the run by the PET measure). The number-normalized P300 response, representing the relative size of the integrated P300 activity in this

condition, is shaded. **Third row:** Overlay of the corresponding target-minus-standard difference waves for the 16% condition and normalized target-minus-standard difference wave for the 2% condition, showing the large difference in the total integrated P300 activity that occurred between the two conditions. **(B).** Grand-average z-score PET images ($n = 10$) overlaid on the grand-averaged, spatially normalized MRI images from the same subjects at the level of the dorsal anterior cingulate ($z = 44$ mm). Note the strong activation of the dorsal ACC for both the many and few target conditions, relative to passive. Note also that the magnitude of this activation was fairly similar for the many and few target conditions, such that there was no residual significant difference in a direct contrast between the two (bottom).

PET locations were likely sources of these attention effects [Woldorff et al., 1997]. Thus these effects, like the focal early ERP positivity effect, would appear to be associated with sustained attention rather than with target detection. In addition, such results suggest that in a contrast between attending to a side when there

were many targets and attending to that same side when there were few targets, the effects of the sustained lateralized attention would approximately cancel, leaving mainly the effects of target frequency.

Figure 2b shows the PET effects of target frequency at the level of the dorsal anterior cingulate. In particu-

TABLE I. Talairach coordinates of centroids of activation increases in the dorsal anterior cingulate as a function of conditional contrasts

	x	y	z	z score	<i>p</i> value
Attend left					
Few targets minus passive	6	4	46	4.1	.0001
	0	4	38	2.9	.002
Many targets minus passive	6	2	46	4.3	.0001
	-4	4	38	3.6	.0001
Many targets minus few targets	no signif. ACC activ.				
Attend right					
Few targets minus passive	6	4	48	3.0	.001
	-8	-2	46	4.0	.0001
	-2	0	40	4.0	.0001
Many targets minus passive	6	4	48	4.3	.0001
	-6	4	36	4.0	.0001
Many targets minus few targets	no signif. ACC activ.				

lar, the dorsal anterior cingulate *was very active in both the many- and few-target conditions* relative to passive. There appeared to be a trend for this activity to be slightly larger for the many-target condition, but this was not significant. Indeed, in a direct contrast between the many and few target conditions, no portion of the ACC reached significance (Fig. 2b bottom). Table I shows the Talairach coordinates of the locations of these activations.

In contrast, and as a control, some areas that are more closely associated with motor output, such as somatomotor cortex (see Fig. 2b) and portion of the cerebellum (right anterior lateral and the vermis), did show more activity in the many-target conditions than in the few-target conditions, as might be expected for such areas when more motor activity (i.e., more button pressing) occurred.

DISCUSSION

The PET results in this experiment showed strong activation of the dorsal ACC during all attention conditions relative to passive. However, the magnitude of this effect did not significantly differ between the few- and many-target conditions. This was despite the few-target conditions containing only ~2 targets in each PET run vs. 8 times that number in the many-target conditions. These results indicate that the bulk of the ACC activation does not reflect selection for action per se. That is, most of the ACC activity, at least in an attentionally demanding task, is neither reflective

nor proportional to the number of times in which the subject needed to select an action. In this experiment, there were mainly just two areas that seemed to be significantly and robustly activated with more targets: the left somatomotor cortex and portions of the cerebellum, areas often associated with motor output.

The selectively averaged ERPs showed clear target-specific activity. The targets elicited a large, robust, bilaterally distributed P300 wave, preceded by a smaller contralateral N2b wave, neither of which is closely associated with motor output. Presumably, there was also some premotor negative-wave activity due to the button pressing, but this was heavily masked by the P300.

In the many-target conditions, there were eight times as many targets — and therefore eight times as many P300s — as in the few-target conditions. However, in the many-target minus few-target PET subtractions, there did not appear to be any corresponding focal blood-flow effects that would indicate likely sources of these P300s, despite the very large size and signal-to-noise ratio of this wave. The lack of significant target-probability effect in the ACC, for example, indicated it was not a likely source for the P300. The two main areas showing significant activity difference in the many-target minus few-target contrast also seemed unlikely sources. The motor area that was activated seems unlikely because it was left-lateralized (due to the use of the right hand for the motor response), whereas the P300 is bilaterally symmetric. As for the cerebellum, its highly folded structure seems unlikely to be a geometry whose activity would spatially summate and produce large, open-field waves that would be well recorded at a distance [Hillyard and Picton, 1987].

In relating the ERP and PET activations, it is critical to consider that PET integrates activity across the entire PET run. In the many-target blocks, there were clearly many (8x) more P300s than in the few-target blocks. However, to relate this difference in number to the corresponding integrating PET hemodynamic data, one must consider that P300s to targets are larger when they occur less frequently [Hillyard and Picton, 1987]. Indeed, in the present experiment, the P300 amplitude was ~25% larger in the few vs. many-target conditions, and the total integrated activity under the P300 curve was ~70% larger. Thus, even if we assume that the total P300 activity per target in the 2% condition was as much as *twice* as large as the total P300 activity per target in the 16% condition, there would still be four times as much integrated P300 activity (at least electrically) in the 16% condition. Apparently, however, even such a large difference in electrical activity did not produce a clear, focal, significant difference in

blood-flow, at least as evaluated with the block-design approach in this PET experiment.

The current results would seem to underscore a fundamental limitation of block-design approaches to at least some of the questions posed in this study. More specifically, because the PET required such an approach, the experiment required designing a target-activity difference between blocked conditions while holding other factors constant. Our central interest in this experiment, however, was in a difference *between event types—namely, targets vs. nontargets—within the same run*. ERP experiments have typically capitalized on the ability to extract such event-specific activations by means of selective averaging, but only relatively recently has such an approach been shown to be eminently viable with hemodynamic imaging. Indeed, it has become clear that an extremely powerful way to measure event-specific hemodynamic neural activity is with event-related fMRI [reviewed in Rosen et al., 1998], which, with appropriate design and analysis considerations, can be performed even at rather fast ISIs [Burock et al., 1998]. An event-related fMRI study of target processing was first performed by McCarthy et al. (1997), who reported target-selective activity in lateral prefrontal and in parietal areas in a foveally presented visual “oddball” detection task. (McCarthy’s study did not include any image slices through the anterior cingulate.) Our preliminary event-related fMRI results using the lateralized visual spatial attention task presented in this report appear to confirm the target-specific activity found by McCarthy et al. [1997]. More generally, however, it is clear that the event-related fMRI approach will provide an extremely effective means for extracting such target-selective and other event-specific hemodynamic activity. In addition, even though the time course of these event-related hemodynamic responses is still rather slow (peaking at ~5 sec or so) relative to the true neuronal processing, their event-specificity means they can be much more effectively mapped to the corresponding, high-temporal-resolution, event-related potential (or event-related magnetic field) activations.

It may be important to note that, although not significant, there was a trend for the ACC activation to be slightly larger in the many-target conditions than in the few target ones. As discussed above, the strong activation in the few-target conditions (when there were only ~2 targets in the entire PET run) means that the bulk of the ACC activity observed cannot reflect selection for action per se. On the other hand, given the block design used here, we cannot rule out that there could be small *additional transient* increases in this area when targets occur (or slightly greater transient activ-

ity for targets than for standards), adding up over time to slightly greater integrated activity in the many-target conditions than in the few-target ones. A combined application of block and event-related fMRI may be required to disentangle the sustained and event-related activity patterns in the ACC.

In summary, the present experiment indicates that the integrated activity in the anterior cingulate does not vary significantly with target frequency, and thus the bulk of the activity seen in this brain region in an attentionally demanding task cannot reflect selection of action per se. Our current data, however, do not argue against the possibility that the anterior cingulate might be important in *maintaining a sustained vigilant or anticipatory state in which one may need to continually be ready to select for action* (although if this were the case it is not clear why ACC activation was not seen in the Pardo et al. [1991] study of vigilance). Another possibility is that the ACC activation seen in the present study is subserving the repeated need, on each and every stimulus (i.e., standards *and* targets), *to resolve whether to act or to not act*. Regardless, our present results also suggest that the anterior cingulate is not a major source of the large P300 ERP wave elicited by detected targets. In the future, the event-related fMRI approach seems likely to be the most powerful way to relate event-related blood-flow changes to event-related electrophysiological activity, such as for studying the functional neuroanatomy and timing of target-specific brain activity and mechanisms.

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