ELSEVIER

Neuropsychologia 42 (2004) 379–386

NEUROPSYCHOLOGIA

www.elsevier.com/locate/neuropsychologia

What is odd in the oddball task? Prefrontal cortex is activated by dynamic changes in response strategy

Scott A. Huettel*, Gregory McCarthy

Brain Imaging and Analysis Center, Box 3918, Duke University Medical Center, Durham, NC 27710, USA

Received 5 July 2002; accepted 29 July 2003

Abstract

In the "oddball" target detection task, subjects respond to target stimuli that occur infrequently and irregularly within a series of standard stimuli. Although detection of these targets reliably evokes transient activity in prefrontal cortical regions, it has not been established whether this activity is due to selection of an infrequent response or to changes in response strategy. We investigated this issue using a novel variant of the oddball task that incorporated the Simon effect, while measuring hemodynamic brain activity in prefrontal cortex using functional magnetic resonance imaging (fMRI). Subjects viewed a series of circles and squares that required left and right button presses, respectively. On 90% of trials ("standard" trials), the stimuli were presented in the same visual hemifield as the hand of response, but on 10% of trials ("strategy-change" trials) they were presented in the opposite visual hemifield. Significant activation to the infrequent strategy-change trials was found in the anterior middle frontal gyrus (MFG), the posterior inferior frontal gyrus (IFG) and adjacent insular cortex, and in the anterior cingulate gyrus (ACG). These regions, which correspond to previous reports of oddball-related activation, were consistent across subjects. Behavioral results supported our interpretation that subjects potentiated a position-based response strategy, which was inhibited on the strategy-change trials. Activity within the MFG and ACG was much greater on error trials than on correct trials, while IFG activity was similar between error and correct trials. We conclude that the dorsolateral prefrontal cortex (dlPFC) is associated with dynamic changes in the mapping of stimuli to responses (e.g. response strategies), independently of any changes in behavior.

Keywords: FMRI; dlPFC; Attention; Response selection; Working memory; Target detection

1. Introduction

Detection of an infrequent target stimulus evokes widespread neural activity that is reflected in both electrophysiological and hemodynamic measures. In the commonly used "oddball" paradigm, subjects identify infrequent "target" stimuli within a series of rapidly presented "standard" stimuli. For example, in a visual oddball task, there might be a 95% chance for a square to be presented and a 5% chance for a circle. When the targets (e.g. circles) appear, the subject must make a response, such as pressing a button or updating a mental count. The oddball task and its variants have been used in more than 1000 published electrophysiological studies (Herrmann & Knight, 2001; Picton, 1992), and recent studies have adopted the oddball design within event-related functional magnetic resonance imaging (fMRI). This popularity is a direct result of its success in evoking robust and reliable phenomena that have been used as markers of cognitive function (Polich, 1999).

Detection of a target elicits systematic fMRI activation in prefrontal and parietal cortices (Casey et al., 2001; Clark, Fannon, Lai, & Benson, 2001; Clark, Fannon, Lai, Benson, & Bauer, 2000; Kirino, Belger, Goldman-Rakic, & McCarthy, 2000; Linden et al., 1999; McCarthy, Luby, Gore, & Goldman-Rakic, 1997; Stevens, Skudlarski, Gatenby, & Gore, 2000; Strange, Henson, Friston, & Dolan, 2000). Because the prefrontal cortex (PFC) activation, like that measured electrophysiologically (Daffner et al., 2000; Desmedt, Debecker, & Manil, 1965; Picton, 1992; Sutton, Braren, Zubin, & John, 1965), appears to be insensitive to stimulus modality or method of responding (Kirino et al., 2000), these regions have been associated with context-dependent control of behavior, consistent with evidence from other experimental designs (Knight & Grabowecky, 2000; Miller & Cohen, 2001). However, the oddball task, like any other complex paradigm, likely evokes activation in a network of brain regions representing various cognitive components of the task. Thus, despite the oddball task's surface simplicity, the particular cognitive processes performed by the active prefrontal cortex regions are not well established.

* Corresponding author. Tel.: +1-919-681-9527; fax: +1-919-681-7033.
E-mail address: scott.huettel@duke.edu (S.A. Huettel).

0028-3932/$ – see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neuropsychologia.2003.07.009

One possible model for PFC function in the oddball task is that it selects among possible responses. When a new response is required, as to the target stimuli, PFC must inhibit the previous response and select the correct new one. But, when a subject makes the same response repeatedly, as to the standard stimuli, that action becomes efficiently coded and can be made in the absence of prefrontal control. A second model contends that PFC accesses, inhibits, or changes behavioral strategies, instead of behavior itself. In any experimental task, subjects form response strategies based upon the expected pattern of stimuli and required responses. For the oddball design task, because most stimuli are non-targets, subjects predict that non-targets are likely and thus set up a response strategy that is biased toward them. When a target occurs, the subjects must inhibit this response strategy so that they can correctly respond to the target.

These two possibilities are indistinguishable in the canonical oddball design because the infrequent target stimulus is (by definition) associated with a similarly infrequent response. Every time a target appears, it not only requires inhibition of the previous response, if any, and initiation of a new response, but also requires inhibition of any biasing strategy induced by its infrequency. However, these concepts are not inexorably confounded, as manipulation of response strategy independent of response changes, would allow them to be distinguished. If response strategy changes evoked no dlPFC activation when unassociated with a response change, then the first possibility would be supported. If response-strategy changes evoked dlPFC activation, even when not contingent upon response changes, then the second possibility would be supported.

We modified the standard oddball design to answer this question: are response changes necessary for evocation of dlPFC activation? Two stimuli, a circle and a square, were presented one at a time over many trials, requiring left and right button presses respectively. On most trials, the stimuli were presented on the same side of fixation as the hand of the response. Since response time is facilitated when stimulus position is compatible with response hand, as demonstrated by the Simon effect (Simon & Small, 1969), we hypothesized that a "position" response strategy would be potentiated. But, when the stimuli were presented oppositely from the required response hand (e.g. a circle on the right), we expected that subjects would inhibit the position strategy and change to the correct "shape" strategy. Thus, the infrequent, odd events in the current design are not response-change trials, but strategy-change trials.

2. Materials and methods

2.1. Subjects

The subject sample consisted of 15 healthy adults (age = 23 ± 8 years; 8 females, 7 males). No participant reported any history of neurological injury or disease. Participants provided written informed consent in accordance with the policies of the Duke University Institutional Review Board.

2.2. Experimental task

The experimental task required subjects to classify rapidly presented stimuli on the basis of their shape (see Fig. 1). On each trial, a single circle or square was presented for 500 ms. The shapes subtended about 3° of visual angle (absolute size: ~2.5 cm; distance from eyes: ~50 cm), and were presented either on the left or the right side of the screen, about 8° from fixation. Consecutive stimuli were separated by a 3000 ms stimulus-onset asynchrony. Each experimental run consisted of 122 stimuli (about 6 min), and subjects participated in between 8 and 10 runs (mean 9.33).

The task required subjects to press a button with the left hand when a circle was presented and to press a button with the right hand when a square was presented. Subjects were instructed to respond as quickly as possible while maintaining a low error rate. On 90% of the experimental trials, the stimuli were presented on the same side of the screen as the hand of response. We refer to these trials

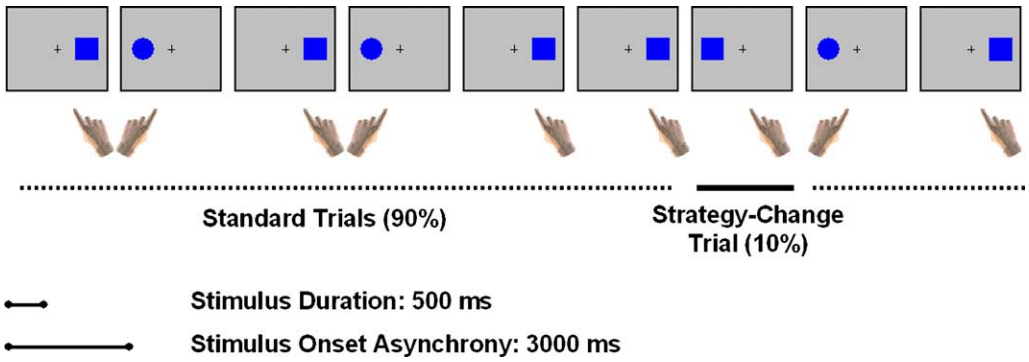

Fig. 1. A schematic representation of the experimental design. On each trial, subjects pressed a left-hand button if a circle was presented and a right-hand button if a square was presented. On standard trials (90%), the shapes were presented on the same side of the display as the hand of the response, but on strategy-change trials (10%), the shapes were presented on the opposite side of the display. Each stimulus was presented for 500 ms, and the interval between stimuli was 3000 ms onset-to-onset.

as "standard" trials. However, on 10% of the trials, the stimuli were presented on the opposite side of the screen as the hand of the response. We refer to these trials as "strategy-change" trials, because they require subjects to inhibit use of a position-based strategy and to employ a shape-based strategy. Circles and squares were presented equally often, and the order of stimuli was randomized across trials. On average, there were 117 strategy-change trials per subject. The mean interval between successive strategy change trials was 9.3 stimuli (S.D. 9.0 stimuli).

2.3. Acquisition of fMRI data

Functional images encompassing PFC were acquired using T2*-weighted echoplanar MRI (TR, 1000 ms; TE, 40 ms; flip angle, 81°; voxel size, 3.75 mm × 3.75 mm × 5 mm) on a GE NV/i 1.5T scanner (General Electric Medical Systems, Waukesha, WI). The images were sensitive to blood-oxygenation-level dependent (BOLD) contrast. To sample brain activity at the high temporal resolution necessary to fully characterize the fMRI hemodynamic response, our imaging volume was restricted to 12 5-mm slices, chosen perpendicular to the line connecting the anterior and posterior commissures (AC and PC). We focused on PFC because of previous research implicating it in the processing of infrequent target stimuli. Due to the constraints upon our imaging volume, no fMRI data were recorded from parietal, temporal, or occipital cortices. High-resolution T1-weighted spin-echo images were acquired at the same slice locations to aid in anatomical comparisons across subjects.

2.4. Analysis

Our experimental analyses examined changes in brain activation associated with the infrequent strategy-change events. Data were initially corrected for order of acquisition within a TR using spline interpolation (custom MATLAB functions). Then, epochs were identified around each strategy-change trial that consisted of 19 time points, from 5 time points before the trial through 13 time points afterward. For each subject, these epochs were excised from the overall stimulus sequence and an averaged epoch was created. Active voxels were identified by correlating the averaged epoch response of each voxel to an empirical reference waveform (Huettel & McCarthy, 2000). The significance of the correlation was evaluated at each voxel by *t*-test. As a control comparison, we conducted a similar analysis that identified epochs around an equal number of randomly selected standard stimuli.

For comparison of activation across subjects, we aligned all subjects' data to a reference brain image from one of the experimental subjects using custom MATLAB functions. Initial translation by hand matched gross anatomy across subjects, so that all subjects had the same anatomical features in the same slices. Eight slices were common across all subjects, so all further analyses report data from these slices (slice centers: 10 mm through 45 mm anterior to the AC). Then, two-dimensional rotation and scaling were used to map each slice in each subject to the corresponding slice of the reference image. This procedure takes advantage of the fact that all subjects' data were acquired perpendicular to the AC–PC line, so that effective coregistration can be performed even on this partial-brain imaging volume.

Random-effects analyses were performed to identify voxels with significant activation across subjects. At each voxel, the t values of the correlation coefficient across subjects were used as dependent measures of effect size, and a t-test was conducted on those t values. We set the significance threshold, for differences from a distribution of mean zero, to $P < 0.01$. All regions of activity discussed below passed a cluster-size threshold of four functional voxels. This analysis allows generalization of the current results to the population from which our subject sample was drawn.

3. Results

3.1. Behavior

Response time and percentage of correct responses were compared across all trial types (see Fig. 2). Responses were not recorded for one subject due to an equipment failure, and all behavioral analyses use the remaining 14 subjects. Subjects were more accurate to standard trials than to strategy-change trials (97% versus 81%; $t(13) = 5.89$; $P < 0.00001$), and this effect was present for every subject both for circles and for squares. When responding correctly, subjects responded faster to standard trials than to strategy-change trials (481 ms versus 611 ms; $t(13) > 15.0$; $P < 0.00001$), and this effect was also present for all subjects both for circles and for squares. But, when subjects made errors, their response times were slower to standard trials than to strategy-change trials (650 ms versus 431 ms; $t(9) = 4.62$; $P < 0.001$), and this effect was present for all but one subject. We additionally analyzed strategy-change trials as a function of whether a response change was required from the previous trial. Error rates did not differ between response changes and response repetitions (80% versus 82%; $t(13) = 0.31$; $P > 0.10$). Nor were there any differences in response time, whether across all trials (539 ms versus 517 ms; $t(13) = 1.51$; $P > 0.10$), for correct responses (613 ms versus 608 ms; $t(13) = 0.63$; $P > 0.10$), or for incorrect responses (449 ms versus 427 ms; $t(11) = 1.01$; $P > 0.10$).

There were no significant differences between responses to the circles (left button press) and the squares (right button press) either in response time ($t(13) = 0.60$; $P > 0.10$) or error rate ($t(13) = 1.32$; $P > 0.10$). There were also no significant differences between the stimuli for response time to correct standard trials ($t(13) = 0.37$; $P > 0.10$) or for response time to incorrect strategy-change trials ($t(10) = 0.41$; $P > 0.10$), which were both associated

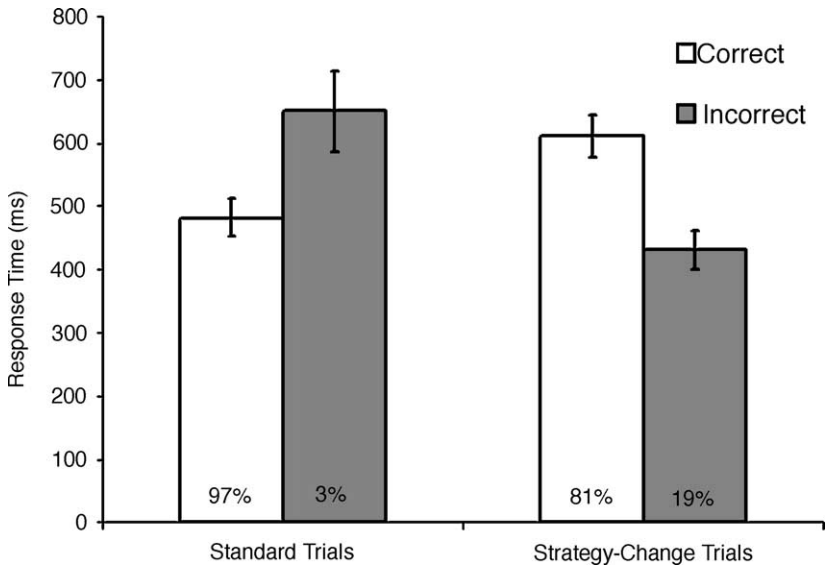

Fig. 2. Effects of trial type upon response time and accuracy. Response time is shown on the *y*-axis, and percentage of responses is shown at the bottom of each column. The error bars reflect the standard error of the mean for each trial type. On standard trials, response time was faster for correct responses than for incorrect responses, while on strategy-change trials response time was faster for incorrect responses than for correct responses.

with the frequent response strategy. However, right-button-press responses were significantly faster than left-button-press responses for both correct strategy-change trials ($t(13) = 2.71$; $P < 0.05$) and incorrect standard trials ($t(7) = 2.86$; $P < 0.05$), both of which were associated with response changes from the standard strategy. Given that a majority of our sample was right handed, these results were consistent with the idea that subjects more readily shift to a dominant-hand response than to a non-dominant-hand response. However, as the reverse effect was not observed in any of the three subjects who reported being left-handed, more specific interpretations will require future study.

3.2. fMRI

Significant activation to trials requiring a change in response strategy was found across subjects in three primary regions within prefrontal cortex: the anterior middle frontal gyrus (MFG), the posterior inferior frontal gyrus and insula (IFG/INS), and the anterior cingulate gyrus (ACG). The pattern of activation observed is shown in Fig. 3. Anterior

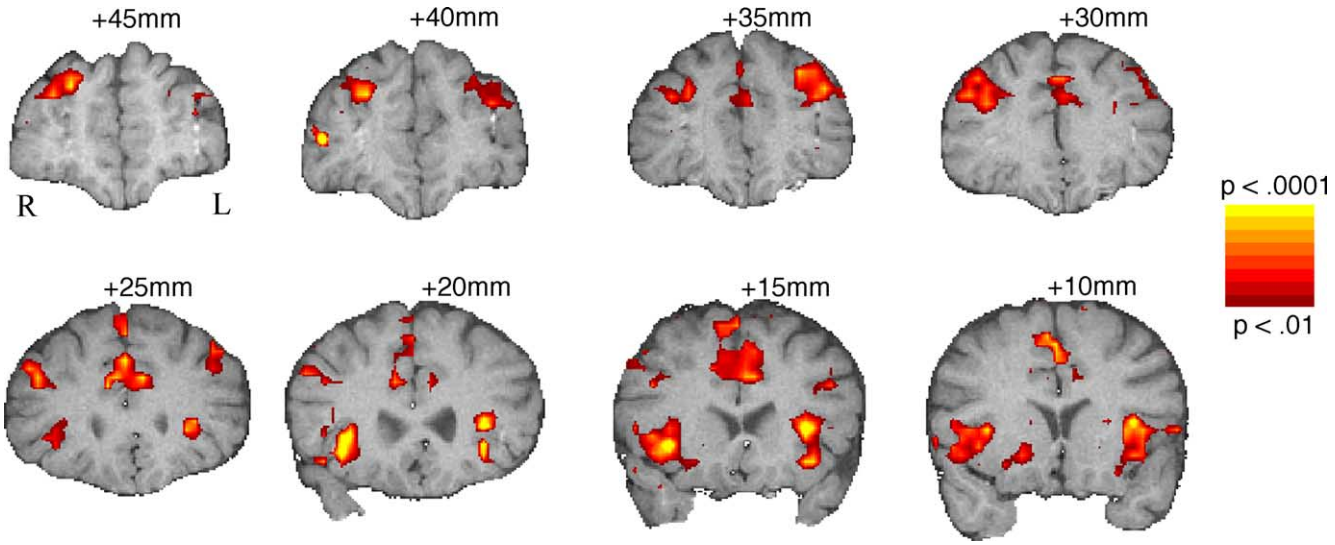

Fig. 3. The pattern of fMRI activation evoked by strategy change trials. Shown are coronal slices through prefrontal cortex, with an activation overlay indicating areas with significant activation to the strategy change trials as indicated by the random effects analysis (see text for details). All slices are presented in radiologic convention. Readily apparent are bilateral activation foci in the anterior middle frontal gyrus, the posterior inferior frontal gyrus/insula, and the anterior cingulate gyrus. Additional smaller foci were identified in the putamen and in the medial frontal gyrus.

MFG activation was observed bilaterally, although there was a right-hemisphere bias in the spatial extent of activation. Maximal significance values were observed at 35 mm (left hemisphere) and 40 mm (right hemisphere) anterior to the AC. Posterior IFG activation was also found bilaterally, with more active voxels in the right hemisphere than the left, and with maximal significance values observed around 15 mm anterior to the AC for both hemispheres. The ACG was analyzed as a single midline region, as there were no apparent laterality effects, and maximal significance was observed around 15 mm anterior to the AC.

Beside these three primary areas of activation, contiguous clusters of more than four active voxels were identified in only two regions: the putamen (+10 mm) and medial frontal gyrus (+25 mm), both in the right hemisphere. Lowering the alpha threshold to 0.05 revealed no additional areas of activation, and the putamen and medial frontal gyrus activations were clearly evident and remained lateralized at the lower threshold.

Examination of a similar analysis of standard trials revealed no voxels with significant activity in any of the regions that showed significant activity to the strategy-change targets. However, there was a semi-circle of significant activity in ventral orbitofrontal cortex within the area of susceptibility-induced signal loss on the functional images. To verify that this activity was an artifact of the high variability in that region, we re-ran the control analysis on a second set of randomly selected standard trials. In the second control analysis, there were no groups of significant voxels that passed the cluster-size threshold anywhere within the imaging volume. We therefore conclude that strategy change trials, but not standard trials, evoke activity within the set of prefrontal regions shown in Fig. 3.

To investigate consistencies in this pattern of activation across subjects, we investigated whether each subject exhibited significant activation in three regions of interest (ROIs): anterior MFG, posterior IFG/INS, and ACG. The random-effects group analysis was used as a logical mask to determine the boundaries of the ROIs. The significance threshold for each subject was set at $t > 2.57$ ($P < 0.01$). For the anterior MFG ROI, a cluster of significant voxels was found in 13 of 15 subjects (9 bilateral, 2 left-only, 2 right-only). Likewise, in the posterior IFG ROI, significant activation was found in 13 of 15 subjects (8 bilateral, 5 right-only). For the ACG, significant activation was found in 10 of 15 subjects.

To investigate the potential contribution of error processing to the observed activation pattern, we separated the strategy-change trials according to whether the subject responded correctly or incorrectly, and repeated the above analyses for each response independently. When only correct trials were examined, significant activity was found in the posterior IFG bilaterally. Activity in the anterior MFG and ACG, though present, was greatly reduced in spatial extent compared to analysis of all trials. When only incorrect trials were examined, there was significant activity in the ACG, posterior IFG, and anterior MFG, as observed across all trials, as well as a new focus of activity in right posterior MFG (+10 mm) that was not present when all trials were considered. For each region examined, the peak amplitude of activity was significantly greater (*t*-tests; all $P = 0.01$) for incorrect trials compared to correct trials. The foci of activity in the putamen and medial frontal gyrus were both evident when examining the incorrect trials, and the putamen activity was also present for correct trials.

We additionally evaluated whether there were differences in activity for strategy-change trials depending upon whether they required a response change from the previous trial. For example, if a circle on the left was followed by a circle on the right, subjects must change the response strategy but not the response. However, if a circle on the left was followed by a square on the left, both the response strategy and the response must change. As for the behavioral data, response changes had little effect upon the results. The same three regions (aMFG, pIFG, and ACG) active in the combined data were active regardless of whether a response change was required. A ROI analysis verified that previous response did not significantly affect peak hemodynamic amplitude within any region (*t*-tests; all $P > 0.05$). It is interesting to note that clear activity in the right putamen was observed for strategy-change trials on which the response repeated from the previous trial, but not for response changes. No medial frontal gyrus activity was observed in either condition.

In summary, infrequent stimuli that require a different response strategy than used on standard stimuli evoke transient activity in regions within frontal cortex, including the anterior MFG, the posterior IFG, and the ACG. Though activity in these regions is observed regardless of whether the subject responds correctly, hemodynamic amplitude is greater on error trials. The activity in these regions does not depend, however, on whether a response change is required from the previous trial.

4. Discussion

The current study provides strong evidence that the oddball effect observed in prefrontal cortex does not require one behavioral response to be executed more frequently than another. Instead, the standard pattern of prefrontal activity can be evoked by an infrequent event that requires a different stimulus-response mapping than used for standard trials.

The behavioral results confirmed that response-strategy changes occurred independently of response changes. Although the infrequent strategy-change trials did not differ in their response requirements from standard trials, they significantly affected subjects' behavior. The measured difference in response time between standard and strategy-change trials (about 135 ms) was similar in magnitude to the difference between standard and target trials as reported in previous oddball tasks (Kirino et al., 2000), and the preceding response had no effect on response time to the strategy-change

trials. Furthermore, the pattern of response times across conditions indicates that subjects formed a preferential response strategy that was inhibited on strategy-change trials. For standards, correct responses were much faster than incorrect responses, but on strategy-change trials, incorrect responses were faster, suggesting that inhibiting the frequent response strategy required additional processing time. Of note is the finding that response time was shorter for correct responses to standard than for incorrect responses. Such a result is atypical, in that errors in discrimination tasks are usually associated with very rapid responding (e.g. before the stimulus has been correctly identified). One possible explanation is that on the error trials, subjects failed to use position information and instead attempted to use the shape information. As identifying shape would be more difficult than responding based on the very different positions, a shape-discrimination strategy would be slower and more error-prone (for trials where position gives correct information).

The fMRI results, in turn, demonstrated that the activation pattern in PFC for changes in response strategy is similar to that previously identified in standard oddball designs for changes in responses. Kirino and colleagues found that detection of infrequent targets evoked bilateral activation in the anterior MFG and posterior IFG, with stronger activation in the right hemisphere, in the same slice locations as found in the present study (Kirino et al., 2000). However, no activation was reported in the ACG, which was strongly activated in the present study. Similarly, other fMRI studies using the oddball task have consistently reported MFG activation (Casey et al., 2001; Clark et al., 2000, 2001; McCarthy et al., 1997; Stevens et al., 2000), while cingulate activation has been reported in some, but not all, studies (Clark et al., 2000; Menon, Ford, Lim, Glover, & Pfefferbaum, 1997; Stevens et al., 2000). The presence of ACG activation is consistent with the resolution of response conflict processes, with which the ACG has been associated in many studies (MacDonald, Cohen, Stenger, & Carter, 2000; Turken & Swick, 1999). We have previously shown that these regions are active when subjects must change from a potentiated response to a non-potentiated response, independently of whether that inhibition results in a response change or a response repetition (Huettel, Mack, & McCarthy, 2002). In that earlier study, PFC activity was evoked by violations of short repeating patterns or longer alternating patterns. However, responses in the current study were potentiated by overall response-strategy infrequency, not local sequences of stimuli. We suggest that changing of response strategy is independent of the context by which that response strategy is created and evokes activity in these prefrontal regions. This interpretation is consistent with previous electrophysiological studies demonstrating that P300 amplitude changes with stimulus sequence (Munson, Ruchkin, Ritter, Sutton, & Squires, 1984; Squires, Wickens, Squires, & Donchin, 1976).

In addition to PFC, the putamen was transiently active to strategy-change trials, specifically those that repeated the preceding response. Similar putamen activity has been found for violations of a temporal pattern (Huettel et al., 2002). More difficult to interpret is the suggestion of medial frontal gyrus activity to strategy-change trials. We note that the superior portion of the medial frontal gyrus lies adjacent to the sagittal sinus, which is the major draining vein for the superior cerebrum. Since the BOLD signal measured in fMRI depends largely on venous changes (and secondarily on local capillary changes), apparent neuronal activity may be mislocalized to distal veins. Further studies using methods less sensitive to venous drainage could be useful in evaluating activity in this region.

4.1. Selection processes in PFC

It is important to recognize that for this experimental task, like the standard oddball paradigm, the subject's response strategy is underdetermined and may change over trials. On each trial, there are two forms of evidence to which the subject may attend: shape and position. Both are highly predictive of the correct response, even though on 10% of trials position provides incorrect information. So, for subjects to maximize both speed and accuracy of processing, they must monitor both stimulus dimensions and adjust their response strategy over trials. While our results demonstrate transient prefrontal activity associated with the infrequent stimulus-response mapping, it cannot be established from these data alone whether such activity results from selection of the appropriate strategy before responding, from detection and recognition of the infrequent mapping during the trial, or from changes in expectation following the response.

One possible summary framework is that the prefrontal cortex is responsible for adjustment of behavioral strategies based on new information, which could be provided by an unexpected stimulus or by top–down evaluation of response errors (Miller, 2000). We note that the analysis of error trials revealed that they evoke activity within the same set of regions as active on correct trials. The cingulate gyrus, in particular, has been shown to play a critical role in error detection (Carter et al., 1998; Kiehl, Liddle, & Hopfinger, 2000), and has been implicated within models for PFC function as important for integrating feedback information into plans for behavior (Miller & Cohen, 2001). While we found greatly increased ACG activity on error trials, consistent with previous reports, significant ACG activity was observed even when no overt error was made. This suggests that the ACG also contributes to the prevention of errors through online monitoring of cognition, which may reflect a separate cognitive process also localized to anterior cingulate cortex (Ullsperger & von Cramon, 2001).

An interesting contrast can be drawn between the strategy-change trials in the present design and the task-irrelevant "novels" that are frequently included in oddball designs. Here, however, infrequent strategy change trials evoke significant PFC activation, regardless of whether a similar or different button press is required. In a typical three-stimulus

oddball design (Kirino et al., 2000), visually striking novels (e.g. photographs of objects) that require the same button press as the standards do not evoke similar PFC activation. To account for the absence of activity to novels, we speculate that subjects in oddball tasks bias their response strategies toward the frequent standard stimuli. If the standards require no response, then an appropriate strategy would be "do nothing"; if the standards required a particular button press, then the strategy might be "prepare to press the right button". As novels are not inconsistent with the basic strategy, the dlPFC remains inactivated. Similarly, subjects in the current task adopt a basic response strategy that does not include the strategy-change trials: "respond left to stimuli on the left, and respond right to stimuli on the right". We conclude that the particular response strategy adopted by the subject determines whether dlPFC will be active to infrequent stimuli.

These results also serve to tie the oddball paradigm to other tests of dlPFC function. DLPFC activation has been associated with a diverse set of cognitive processes, including actively maintaining information in working memory (Braver et al., 1997; Cohen et al., 1997; D'Esposito, Postle, & Rypma, 2000; Duncan & Owen, 2000; McCarthy et al., 1994), changing behavior according to task demands (MacDonald et al., 2000; Sohn, Ursu, Anderson, Stenger, & Carter, 2000), or representing past events, current goals, and future predictions (Knight & Grabowecky, 2000; Miller, 2000). In fact, early fMRI studies using the oddball task (McCarthy et al., 1997) interpreted the observed dlPFC activation as resulting from the first of these alternatives, working memory. But, as working memory tasks typically include active responding to stimuli, more recent work has argued that dlPFC is associated with dynamic response selection (Huettel et al., 2002; Rowe, Toni, Josephs, Frackowiak, & Passingham, 2000). We suggest that selection processes, such as the inhibition of inappropriate response plans and activation of context-appropriate behaviors, are common across diverse cognitive tasks.

4.2. Limitations of the study

An important limitation of the current study lies in the restricted imaging volume, which spans most of prefrontal cortex but does not include regions in posterior cortex. Lateral parietal cortex has been frequently implicated in target detection paradigms including the oddball task (Clark et al., 2000; Linden et al., 1999; McCarthy et al., 1997; Stevens et al., 2000; Strange et al., 2000). Further evidence for its importance comes from electrophysiological studies of the P300b target-detection waveform, which appears to have a largely parietal source and is greatly impaired by parietal lesions (Knight & Grabowecky, 2000; Picton, 1992). It is possible, therefore, that the prefrontal cortex and parietal cortices play different roles in the control of behavior. One possible division may be that prefrontal cortex may be associated with more executive or goal-directed behavior, while parietal cortex may be associated with the establishment of percept–action relations. Another limitation lies in the use of the Simon effect for introducing an nominally irrelevant, but predictive, stimulus property. This manipulation induced subjects to use position information as part of their response strategy, but it necessarily confounds strategy change with stimulus-response compatibility. While these two concepts are intertwined, in that each represents the inhibition of potentiated response, they may reflect different cognitive processes. Overcoming an arbitrary stimulus-response mapping learned during the course of a relatively short experiment may require a different mechanism compared to supplanting well-practiced spatial congruency mappings. So, an important direction for future research will be to investigate how prefrontal cortex and related brain regions mediate different types of strategy changes.

The current results constrain interpretations of prefrontal function by showing that behavioral changes are not required to evoke transient prefrontal cortex activity. We conclude that prefrontal cortex activity in the oddball task is associated not with changes in behavior, but with dynamic changes in response strategy.

Acknowledgements

We thank Dr. Martin McKeown for assistance with partial-brain coregistration, and Cynthia Liu, Jonathan Smith, Richard Sheu, and Evan Gordon for assistance in data analysis. This research was supported by the US Department of Veterans' Affairs, and by NINDS-41328, and NIDA-16214. Dr. McCarthy is a VA Research Career Scientist.

References

Braver, T. S., Cohen, J. D., Nystrom, L. E., Jonides, J., Smith, E. E., & Noll, D. C. (1997). A parametric study of prefrontal cortex involvement in human working memory. *Neuroimage*, *5*(1), 49–62.

Carter, C. S., Braver, T. S., Barch, D. M., Botvinick, M. M., Noll, D., & Cohen, J. D. (1998). Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science*, *280*(5364), 747–749.

Casey, B. J., Forman, S. D., Franzen, P., Berkowitz, A., Braver, T. S., & Nystrom, L. E. et al., (2001). Sensitivity of prefrontal cortex to changes in target probability: a functional MRI study. *Human Brain Mapping*, *13*(1), 26–33.

Clark, V. P., Fannon, S., Lai, S., & Benson, R. (2001). Paradigm-dependent modulation of event-related fMRI activity evoked by the oddball task. *Human Brain Mapping*, *14*(2), 116–127.

Clark, V. P., Fannon, S., Lai, S., Benson, R., & Bauer, L. (2000). Responses to rare visual target and distractor stimuli using event-related fMRI. *Journal of Neurophysiology*, *83*(5), 3133–3139.

Cohen, J. D., Perlstein, W. M., Braver, T. S., Nystrom, L. E., Noll, D. C., & Jonides, J. et al., (1997). Temporal dynamics of brain activation during a working memory task. *Nature*, *386*(6625), 604–608.

Daffner, K. R., Scinto, L. F., Calvo, V., Faust, R., Mesulam, M. M., & West, W. C. et al., (2000). The influence of stimulus deviance on electrophysiologic and behavioral responses to novel events. *Journal of Cognitive Neuroscience*, *12*(3), 393–406.

Desmedt, J. E., Debecker, J., & Manil, J. (1965). Demonstration of a cerebral electric sign associated with the detection by the subject of a tactile sensorial stimulus. The analysis of cerebral evoked potentials derived from the scalp with the aid of numerical ordinates. *Bulletin de l Academie Royale de Medecine de Belgique*, *5*(11), 887–936.

D'Esposito, M., Postle, B. R., & Rypma, B. (2000). Prefrontal cortical contributions to working memory: evidence from event-related fMRI studies. *Experimental Brain Research*, *133*(1), 3–11.

Duncan, J., & Owen, A. M. (2000). Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends in Neurosciences*, *23*(10), 475–483.

Herrmann, C. S., & Knight, R. T. (2001). Mechanisms of human attention: event-related potentials and oscillations. *Neuroscience and Biobehavioral Reviews*, *25*(6), 465–476.

Huettel, S. A., Mack, P. B., & McCarthy, G. (2002). Perceiving patterns in random series: Dynamic processing of sequence in prefrontal cortex. *Nature Neuroscience*, *5*(5), 485–490.

Huettel, S. A., & McCarthy, G. (2000). Evidence for a refractory period in the hemodynamic response to visual stimuli as measured by MRI. *NeuroImage*, *11*(5), 547–553.

Kiehl, K. A., Liddle, P. F., & Hopfinger, J. B. (2000). Error processing and the rostral anterior cingulate: an event-related fMRI study. *Psychophysiology*, *37*(2), 216–223.

Kirino, E., Belger, A., Goldman-Rakic, P., & McCarthy, G. (2000). Prefrontal activation evoked by infrequent target and novel stimuli in a visual target detection task: An event-related functional magnetic resonance imaging study. *Journal of Neuroscience*, *20*(17), 6612–6618.

Knight, R. T., & Grabowecky, M. (2000). Prefrontal cortex, time, and consciousness. In M. S. Gazzaniga (Ed.), *The new cognitive neurosciences* (pp. 1319–1339). Cambridge, MA: MIT Press.

Linden, D. E., Prvulovic, D., Formisano, E., Vollinger, M., Zanella, F. E., & Goebel, R. et al., (1999). The functional neuroanatomy of target detection: An fMRI study of visual and auditory oddball tasks. *Cerebral Cortex*, *9*(8), 815–823.

MacDonald, A. W., Cohen, J. D., Stenger, V. A., & Carter, C. S. (2000). Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science*, *288*(5472), 1835–1838.

McCarthy, G., Blamire, A. M., Puce, A., Nobre, A. C., Bloch, G., & Hyder, F. et al., (1994). Functional magnetic resonance imaging of human prefrontal cortex activation during a spatial working memory task. *Proceedings of the National Academy of Sciences of United States of America*, *91*(18), 8690–8694.

McCarthy, G., Luby, M., Gore, J., & Goldman-Rakic, P. (1997). Infrequent events transiently activate human prefrontal and parietal cortex as measured by functional MRI. *Journal of Neurophysiology*, *77*(3), 1630–1634.

Menon, V., Ford, J. M., Lim, K. O., Glover, G. H., & Pfefferbaum, A. (1997). Combined event-related fMRI and EEG evidence for temporal-parietal cortex activation during target detection. *NeuroReport*, *8*(14), 3029–3037.

Miller, E. K. (2000). The prefrontal cortex and cognitive control. *Nature Reviews Neuroscience*, *1*(1), 59–65.

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience*, *24*, 167–202.

Munson, R., Ruchkin, D. S., Ritter, W., Sutton, S., & Squires, N. K. (1984). The relation of P3b to prior events and future behavior. *Biological Psychology*, *19*(1), 1–29.

Picton, T. W. (1992). The P300 wave of the human event-related potential. *Journal of Clinical Neurophysiology*, *9*(4), 456–479.

Polich, J. (1999). P300 in clinical applications. In E. Niedermeyer, & F. L. d Silva (Eds.), *Electroencephalography, basic principles, clinical applications, and related fields* (pp. 1073–1091). Baltimore: Urban and Schwarzenberg.

Rowe, J. B., Toni, I., Josephs, O., Frackowiak, R. S., & Passingham, R. E. (2000). The prefrontal cortex: Response selection or maintenance within working memory? *Science*, *288*(5471), 1656–1660.

Simon, J. R., & Small Jr., A. M. (1969). Processing auditory information: Interference from an irrelevant cue. *Journal of Applied Psychology*, *53*(5), 433–435.

Sohn, M., Ursu, S., Anderson, J. R., Stenger, V. A., & Carter, C. S. (2000). The role of prefrontal cortex and posterior parietal cortex in task switching. *Proceedings of the National Academy of Sciences of the United States of America*, *97*(24), 13448–13453.

Squires, K. C., Wickens, C., Squires, N. K., & Donchin, E. (1976). The effect of stimulus sequence on the waveform of the cortical event-related potential. *Science*, *193*, 1142–1145.

Stevens, A. A., Skudlarski, P., Gatenby, J. C., & Gore, J. C. (2000). Event-related fMRI of auditory and visual oddball tasks. *Magnetic Resonance Imaging*, *18*(5), 495–502.

Strange, B. A., Henson, R. N., Friston, K. J., & Dolan, R. J. (2000). Brain mechanisms for detecting perceptual, semantic, and emotional deviance. *Neuroimage*, *12*(4), 425–433.

Sutton, S., Braren, M., Zubin, J., & John, E. R. (1965). Evoked-potential correlates of stimulus uncertainty. *Science*, *150*(700), 1187–1188.

Turken, A. U., & Swick, D. (1999). Response selection in the human anterior cingulate cortex. *Nature Neuroscience*, *2*(10), 920–924.

Ullsperger, M., & von Cramon, D. Y. (2001). Subprocesses of performance monitoring: a dissociation of error processing and response competition revealed by event-related fMRI and ERPs. *Neuroimage*, *14*(6), 1387–1401.