

# Sensitivity of Prefrontal Cortex to Changes in Target Probability: A Functional MRI Study

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**Abstract:** Electrophysiological studies suggest sensitivity of the prefrontal cortex to changes in the probability of an event. The purpose of this study was to determine if subregions of the prefrontal cortex respond differentially to changes in target probabilities using functional magnetic resonance imaging (fMRI). Ten right-handed adults were scanned using a gradient-echo, echo planar imaging sequence during performance of an oddball paradigm. Subjects were instructed to respond to any letter *but* "X". The frequency of targets (i.e., any letter but X) varied across trials. The results showed that dorsal prefrontal regions were active during infrequent events and ventral prefrontal regions were active during frequent events. Further, we observed an inverse relation between the dorsal and ventral prefrontal regions such that when activity in dorsal prefrontal regions increased, activity in ventral prefrontal regions decreased, and vice versa. This finding may index competing cognitive processes or capacity limitations. Most importantly, these findings taken as a whole suggest that any simple theory of prefrontal cortex function must take into account the sensitivity of this region to changes in target probability. *Hum. Brain Mapping* 13:26–33, 2001. © 2001 Wiley-Liss, Inc.

**Key words:** prefrontal cortex; attention, inhibition; neuroimaging; fMRI

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## INTRODUCTION

Electrophysiological studies suggest the sensitivity of frontal regions to changes in the frequency or prob-

ability of an event [Sutton et al., 1965; Donchin and Coles, 1985; McCarthy et al., 1997]. This association has been argued most extensively in the context of the P300, an event-related potential (ERP) elicited by infrequent events. Neuroimaging studies [Grasby et al., 1993; Jonides et al., 1993; Cohen et al., 1994; McCarthy et al., 1994; Casey et al., 1995; Smith et al., 1995; Kawashima et al., 1996; Casey et al., 1997] together with physiological studies in monkeys [Niki, 1974; Mishkin and Manning, 1978; Goldman-Rakic, 1987; Fuster, 1988; Yajeya and Fuster, 1988] have largely focused on the involvement of frontal regions in higher cognitive

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processes such as working memory and inhibitory control. These studies provide better spatial resolution than do electrophysiology studies and suggest that different regions within prefrontal cortex are associated with different types of processing. For example, dorsolateral prefrontal cortex has been implicated in working memory [Goldman-Rakic, 1987; Fuster, 1988; Cohen et al., 1994; McCarthy et al., 1994; Smith et al., 1995], while more ventral regions of prefrontal cortex have been implicated in the suppression of prepotent responses as in the go/no-go task [Kawashima et al., 1996; Casey et al., 1997; Konishi et al., 1999]. Few imaging studies have examined the effects of manipulating target probability on these presumed prefrontal functions. One example of such an attempt is a recent study by McCarthy and colleagues [1997]. They showed that increased dorsolateral prefrontal activity was associated with infrequent events in an oddball paradigm using both electrophysiology and fMRI. The current study examined prefrontal activity as a function of changing target frequency (i.e., frequent and infrequent) in a modified version of an oddball paradigm.

The goal of this study was to determine if regions of prefrontal cortex differentially respond to changes in the probability of an event. Previously, we have examined prefrontal activity to frequent targets in a go/no-go version of the oddball paradigm [Casey et al., 1997]. In that study, either all trials within a block were targets (100%) or half the trials in a block were targets (50%). Thus target frequency did not vary from high to low but was constant within blocks of trials (i.e., either 50% or 100%). In the current study we manipulated the frequency of targets across trials allowing for high, moderate, and low frequencies of a target to occur throughout the experiment. We assumed that this manipulation would allow us to determine the relevance of target frequency to prefrontal function within a single task design.

Specifically, we assumed that rare targets would increase interference in the stimulus demands of the task and hypothesized that this would be associated with increased activity in dorsolateral prefrontal regions, but not ventral prefrontal regions. Rare target frequencies result in an increase in the number of nontarget relative to target stimuli. By frequently presenting the nontarget, "X", the representation of this stimulus should become highly salient, relative to the infrequent presentation of targets. We enhanced the extent of interference between targets and nontargets by having the targets consist of a large set of stimuli (i.e., A–Z, except X) occurring infrequently and having the nontarget be a single salient stimulus, the letter

"X". Increasing the salience of the nontarget (X) should result in increased interference between it and the set of target stimuli (A–Z, except X). Accordingly, we hypothesized that this type of interference (i.e., among stimuli) would result in increased activity in the dorsolateral prefrontal cortex. This hypothesis was based on the assumption that dorsolateral prefrontal cortex supports relevant stimulus information (e.g., any letter but X) against interference from competing sources over time [Goldman-Rakic, 1987; Cohen and Servan-Schreiber, 1992] and work by McCarthy et al. [1997] associating dorsolateral prefrontal cortex activity with infrequent targets.

Conversely, we assumed that frequent targets would increase interference in the response demands of the task (i.e., when to respond or not) and hypothesized that this would activate ventral regions of prefrontal cortex but not dorsal prefrontal regions. Frequent targets result in an increase in the number of responses relative to nonresponses. When a response is required frequently to a target, the representation of that response is activated repeatedly, making the response more salient. The salience of the response interferes with the task demands of not responding to an X. If a response is required infrequently, as with rare targets, the representation of that response is not activated repeatedly and therefore does not compete or interfere with the task demands of not responding to an X. Accordingly, we hypothesized that this type of interference (between responses) would result in increased activity in the ventral prefrontal cortex. This prediction was based in part on the presumed role of ventral prefrontal cortex in suppression of prepotent responses as in the go/no-go task [Kawashima et al., 1996; Casey et al., 1997; Konishi et al., 1999].

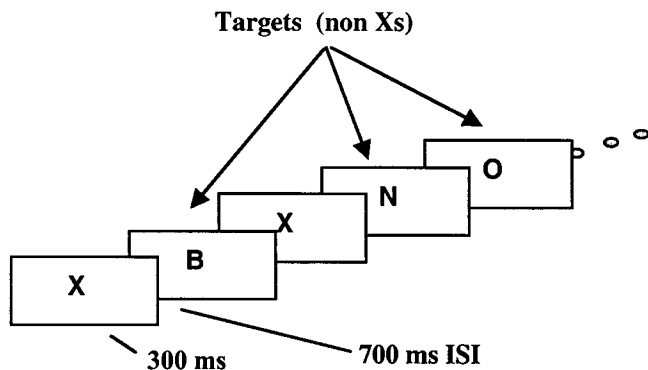
## MATERIALS AND METHODS

### Subjects

Ten right-handed adult subjects (18–41 years old) were recruited from the Pittsburgh area and were paid \$50 for their participation in the study. Data from one male subject was excluded due to excessive in-plane head motion of more than .5 voxels.

### Behavioral task

Subjects were presented with a sequence of single letters, one at a time, at the center of the visual display and were instructed to respond to any letter except X. The stimuli were presented for 300 ms with an inter-stimulus interval of 700 ms (refer to Fig. 1). Target



**Figure 1.**

An illustration of the behavioral task with the stimulus parameters and timing of events.

probability varied between 10% and 60% in 120-sec oscillations. Each subject performed five runs of two oscillations and each run lasted 240 sec (i.e., 240 trials). Stimulus presentation was controlled by a Macintosh computer using Psyscope [Cohen et al., 1993], a rear projection screen, and an Infocus projector system. Subjects responded by pressing a designated button on a specially constructed handheld fiber-optic response box, connected to a transducer via fiber optic cables to the Macintosh. Both reaction times and accuracy were collected.

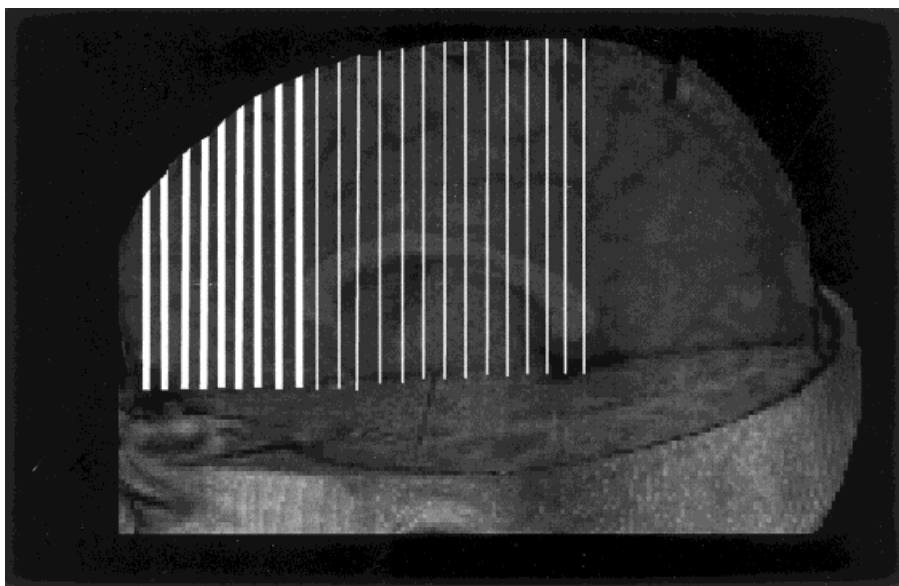
### Scanning procedures

All subjects were screened carefully for any metal implants or contraindications for a MRI and then acclimated to the scanner environment in a simulator

that mimics the scanner in appearance and sound. Images were acquired on a 1.5T GE scanner modified by Advanced NMR (Wilmington, MA) and a head coil. A set of T1-weighted sagittal images was acquired using a spoiled gradient sequence (spin echo, TE 18, TR 500) for localization and prescription of coronal slices. A second set of T1-weighted coronal images (spin echo, TE 18, TR 500, 4-mm skip 0) was acquired covering the whole brain. Next, five sets of T2\*-weighted coronal images (4-mm skip 0) were acquired using an echo planar imaging (EPI) gradient echo sequence (EPI-ISGR) with TE 40, TR 5000, and a flip angle of 90°. Each of five sets of images consisted of 52 repetitions of 23 slice locations (Fig. 2).

### Image analysis

Each subject's images were realigned in 3D space using Wood's automated image registration (AIR) algorithm [Woods et al., 1992]. All subjects' data were then registered to one representative subject's brain and pooled. Each 5-sec scan consisted of five 1-sec behavioral trials. Scans were divided into those with high (e.g., > two targets out of five trials), moderate (two targets out of five trials), and low (e.g., < two targets out of five trials) target probabilities. The first two 5-sec scans of each of five runs were excluded from the analysis to allow the hemodynamic response to peak. Further we collected two 5 sec scans at the end of each run to assess the signal change for the last 10 trials (i.e., 52 repetitions per run). Thus we analyzed 80 scans per probability condition (high, moderate, and low), and the mean percentage of targets in each



**Figure 2.**

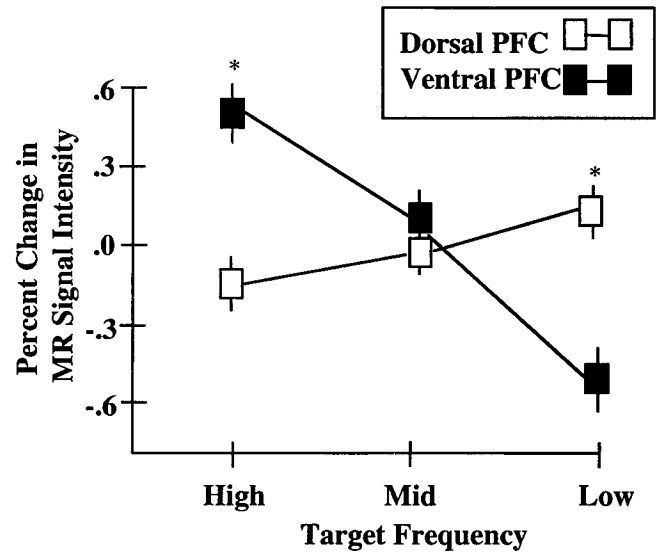
Sagittal view of acquired slice locations. Bold lines indicate the slice locations used for the analysis of the current study.

probability condition was approximately 60%, 30%, and 10%, respectively. A 9 (subjects) × 3 (high, moderate, and low target probabilities) ANOVA was performed on the pooled data with subject as a random factor, and areas of significant activation were identified that satisfied a contiguity threshold of three contiguous pixels with  $P < .005$  [Forman et al., 1995]. Post hoc t-tests were performed on the condition (high, moderate, and low target probabilities) means to determine the direction of change in MR signal intensity. Images were warped into stereotaxic space using AFNI [Cox, 1996]. The time series for significant regions of activation were calculated by averaging across subjects (9) and runs (5). For the purpose of this study, activity was examined in the prefrontal cortex from the genu of the corpus callosum to the frontal pole to exclude motor areas in the analysis (refer to Fig. 2). This area represents prefrontal regions of 17 mm < Y < 55 mm in Talairach stereotaxic space. Localization of activity to specific gyri (i.e., superior, middle, inferior, and orbital) in the prefrontal cortex was based on the coordinate system of the Talairach atlas [Talairach and Tournoux, 1988] and confirmed by two independent raters using a standard brain atlas [Duvernoy, 1991]. Inter-rater reliability was .98. The results are presented by individual gyri and by region (i.e., ventral and dorsal prefrontal cortex). Ventral prefrontal activation was defined as activity of the inferior frontal gyrus and/or orbital frontal gyrus and dorsal prefrontal activation was defined as activity of the superior frontal gyrus and/or middle frontal gyrus. The conditional means of MR signal intensity for each significant cluster (identified by gyri) was averaged within the dorsal prefrontal region and likewise within the ventral prefrontal region. Percent change in MR signal intensity for each cluster was calculated as the difference of the condition mean (high, moderate, or low target probabilities) from the overall mean and then divided by the overall mean. These percent differences were then averaged across clusters falling in dorsal or ventral prefrontal regions.

## RESULTS

Behaviorally, mean accuracy rate and mean reaction time did not differ significantly for rare and frequent target probabilities. Mean accuracy rate across the entire experiment was 92% or greater.<sup>1</sup> The imaging

<sup>1</sup>The mean reaction times and mean accuracies across subjects for the high, middle, and low target probability conditions were 427, 449, and 456 msec and 96%, 94%, and 93%, respectively.



\*  $p < .05$

Figure 3.

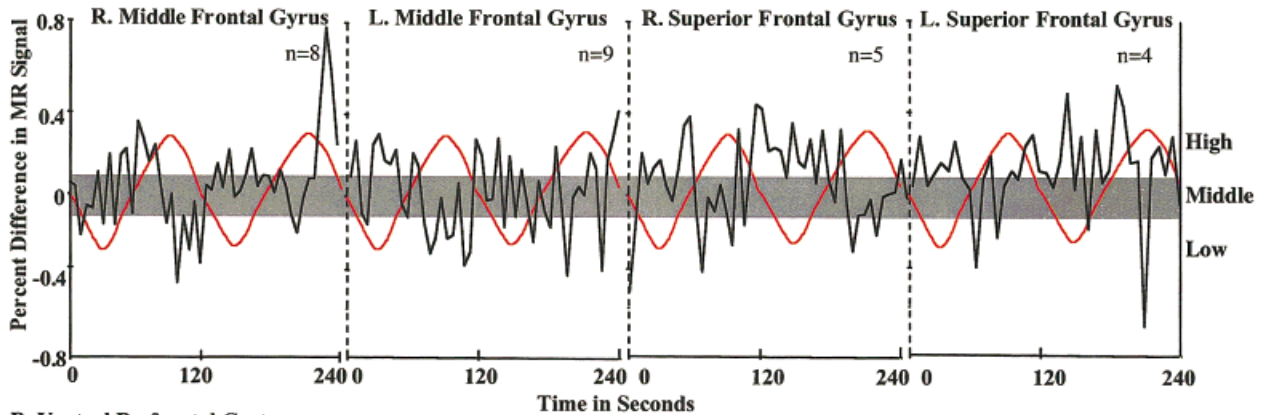
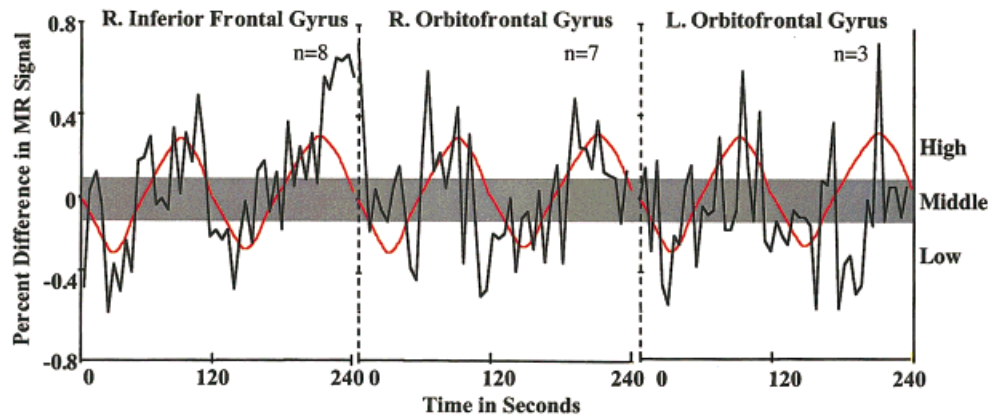
Percent change in MR signal as a function of high, moderate, and low target frequency in ventral and dorsal prefrontal cortex (PFC).

results are presented in Figures 3 and 4 and Table I. Seven clusters of significant activation were identified. Each cluster is identified by location (e.g., gyrus), maximum F ratio, size in voxels, and percent change in signal in Table I. As predicted, dorsal prefrontal activity increased when the target frequency was low and ventral prefrontal activity increased when target frequency was high. There was an inverse relation between dorsal and ventral prefrontal activity whereby when activity in dorsolateral prefrontal cortex increased, activity in ventral prefrontal cortex decreased and vice versa. This pattern of results is depicted in Figure 3. To illustrate that the change in MR signal intensity corresponded to the experimental manipulation, the time course for the change in MR signal as a function of target frequency is depicted in Figure 4 for all seven clusters separately.

## DISCUSSION

The overall goal of this study was to determine if regions of prefrontal cortex differentially respond to changes in target probability. Specifically, we assumed that rare targets would increase interference in the stimulus demands of the task and that this would be associated with increased activity in dorsolateral prefrontal regions. Conversely, we assumed that frequent targets would increase interference in the re-



**A. Dorsal Prefrontal Cortex****B. Ventral Prefrontal Cortex****Figure 4.**

Time course of change in MR signal intensity averaged across subjects ( $n$ ) as a function of target frequency for (a) dorsal prefrontal cortex and (b) ventral prefrontal cortex. MR signal change is plotted in black and target probability is plotted in red. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

response demands of the task (i.e., when to respond) and would activate ventral regions of prefrontal cortex. Our results appear to be consistent with our predictions in that rare targets were associated with dorsolateral prefrontal cortex activity and frequent targets were associated with activity in ventral regions of prefrontal cortex.

The most robust activation was observed during frequent targets in ventral prefrontal cortex. One confound of the current task design is the greater number of responses in the frequent versus rare target conditions. Accordingly, one may interpret the observed ventral prefrontal activity as merely reflecting the increase in number of motor responses. However, our previous study using a similar paradigm controlled for the number of motor responses (by slowing the stimulus presentation rate) and the same ventral prefrontal areas were activated [Casey et al., 1997]. Fur-

ther, in our previous study, an increase in number of false alarms (i.e., more motor responses) was related to a decrease in overall ventral prefrontal activity, suggesting that those subjects who performed worse and made extra motor responses activated ventral prefrontal cortex less. Finally, in an event-related fMRI study using a go/no-go task, Konishi et al. [1999] showed ventral prefrontal activity during the no-go trials. Taken together, our current results and previous findings are consistent with the idea that the ventral prefrontal cortex is involved in successful representation of the response demands of the task. Alternatively, the results may be interpreted as the ventral prefrontal region being recruited simply to inhibit a response [Diamond, 1990; Fuster, 1997; Roberts et al., 1998]. If this were the case, one would expect this region to be activated during the low target probability when a number of responses are being inhibited,

**TABLE I. Location and magnitude of prefrontal activation during performance of the go no-go task**

Regions of interest	Brodmann's area	Talairach			Mean % difference	Maximum F-value	Cluster size in voxels
		X	Y	Z			
<i>Dorsal Prefrontal Regions</i>							
R. Superior Frontal Gyrus	8	2	18	54	-.26	15.40	5
L. Superior Frontal Gyrus	8	-13	25	44	-.22	5.80	4
R. Middle Frontal Gyrus	9/46	36	34	26	-.22	8.36	8
L. Middle Frontal Gyrus	9/46	-49	33	34	-.20	5.31	9
<i>Ventral Prefrontal Regions</i>							
R. Inferior Frontal Gyrus	47	51	42	-8	.64	15.41	8
R. Orbitofrontal Gyrus	11	18	34	-7	.98	15.40	7
L. Orbitofrontal Gyrus	11	-16	33	-13	1.22	25.68	3

but in that condition we show a decrease in ventral prefrontal activity. Accordingly, our data appear more consistent with Cohen and Servan-Schreiber's [1992] theory of prefrontal cortex being involved in supporting the representation of relevant task demands. When response competition is high, ventral prefrontal cortex helps maintain the relevant response demands of the task thereby suppressing the representation of the competing response.

The observed increase in dorsolateral prefrontal cortex with the low target probability presumably reflects the importance of maintaining relevant stimulus information against interference from competing non-target stimuli. The dorsolateral activity is consistent with ERP and fMRI findings reported by McCarthy et al. [1997] using infrequent targets in a similar oddball paradigm. In the current study, the percent change in MR signal for the dorsal areas, although significant, was modest. The modest increase in signal in more dorsal prefrontal regions may be due to the lack of demand in maintaining stimulus information on-line since the only stimulus of real significance was "X". Other studies [e.g., Braver et al., 1997] have shown that the percent change in MR signal in dorsolateral prefrontal cortex increases monotonically as a function of increasing memory load from one to four items. In our current study, we have the equivalent of a memory load of one item in terms of the relevant item of information (X), but the target set actually includes 25 letters (all letters of the alphabet except X).

The decrease in dorsal prefrontal activity and increase in ventral prefrontal activity is suggestive of competing cognitive processes. A similar inverse relationship has been reported in at least one other neuroimaging study to date using positron emission tomography [Drevets and Raichle, 1998]. In that study the authors report decreases in areas implicated in

emotional processing (e.g., amygdala and orbitofrontal cortex) during demanding cognitive tasks and conversely, decreases in areas implicated in cognitive processing (e.g., dorsolateral prefrontal cortex) during emotion related tasks. Given the similarities of the prefrontal regions activated in that study relative to the current one, one may argue that the ventral prefrontal activity observed in the current study reflects an emotional component to the task. Clearly, the word "no" has social relevance and so it might seem plausible that an emotional response would occur when an individual did something they were asked not to do (i.e., do not respond to X) as in the case of making a false alarm. However, in the current study, there was no significant difference in the number of false alarms during conditions of rare (93% accuracy) and frequent targets (96%) and so this interpretation appears insufficient to explain the inverse relation between dorsal and ventral prefrontal activity. Alternatively, these data may be suggestive of competing cognitive processes or bottlenecks in the processing stream of cognition associated with capacity limitations.

A limitation of the current study is the confound introduced by the use of a blocked design over an event-related design. As such, each condition includes blocks of trials with targets and nontargets and thus any change observed in the MR signal intensity cannot be linked to a specific event (no-go vs. go trials). Accordingly, our interpretation of increases and decreases in ventral and dorsal prefrontal regions, respectively, are confounded. Clearly, event-related fMRI studies that take into consideration the previous context of trials (e.g., number of targets preceding a nontarget or vice versa) will more adequately address how regions of the prefrontal cortex respond differentially to changes in target probabilities.

The purpose of this study was to determine if regions of prefrontal cortex respond differentially to changes in target probabilities. We showed that even within the same task, the manipulation of target probability changes the neural systems involved in performing the task. Any theory of prefrontal cortex function must therefore account for the sensitivity of the prefrontal cortex to changes in target probability. Clearly the notion that prefrontal regions are specialized according to spatial vs. object working memory [Goldman, 1994] or for complex information manipulation versus simple maintenance and retrieval [Petrides, 1994; Owen, 1997] do not adequately address the findings of the current study. The same type of stimuli (letters) and task instructions were provided regardless of whether the target was rare or frequent and task difficulty was not different between these conditions. What appeared to change over the course of the study was the type of interference (i.e., the stimulus or response demands of the task). Thus our results appear most consistent with a role of the prefrontal cortex in supporting task-relevant information from interference similar to that proposed by Cohen and Servan-Schreiber [1992]. Specifically, the dorsolateral prefrontal cortex appears more involved when there is interference in stimulus demands, while the ventral prefrontal cortex appears more involved when there is interference in the response demands of the task. However, our results are not conclusive as an event related fMRI study would more directly link changes in MR signal to a specific type of event (target versus nontarget).

## CONCLUSION

In sum, we show two interesting results with the simple manipulation of target probability. First, this study demonstrates that even within the same task using the same stimulus type and instructions, the manipulation of target probability changes the cognitive and neural systems involved in performing the task. Dorsal prefrontal activity increases as a function of low target frequency and ventral prefrontal cortex increases as a function of high target frequency. Accordingly, any simple theory of prefrontal cortex function must therefore account for the sensitivity of the prefrontal cortex to changes in target probability. Further, we showed an inverse relation between activity in the dorsal and ventral prefrontal regions with decreases in one corresponding to increases in the other. This pattern of activity may provide evidence for competing cognitive processes and insight to biological

mechanisms underlying bottlenecks in the processing stream of cognition or capacity limitations.

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