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The Effect of Preceding Context on Inhibition: An Event-Related fMRI Study

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In this study we combined event-related fMRI with a parametric manipulation of the go nogo paradigm to examine the effect of preceding context on inhibitory processes. Nogo trials were preceded by either 1, 3, or 5 go trials and then compared to one another. Two distinct patterns of activation were associated with behavioral inhibition: First, the ventral prefrontal cortex, cingulate gyrus, and superior parietal regions showed a context effect with an increase in MR signal to nogo trials with increasing number of preceding go trials. Second, anterior regions in the supplementary and premotor cortex showed an increase in MR signal on the nogo condition after 5 preceding go trials, but not after only 1 or 3. A model using the BOLD response in our data was used to verify that the effect of context was not an artifact of the randomization scheme used in the design. © 2002 Elsevier Science (USA)

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Ventral prefrontal cortex has been implicated in behavioral inhibition, based on animal, clinical, and neuroimaging studies. Studies in nonhuman primates have demonstrated that lesions in ventral prefrontal cortex result in deficits in behavioral inhibition (Butters *et al.*, 1973; Iversen and Miskin, 1970), as have studies of patients with lesions in this region (Godefroy and Rousseaux 1996). Numerous imaging studies have shown that these areas are involved in response inhibition, using such paradigms as the go nogo and stop signal task (e.g., Casey *et al.*, 1997; Garavan *et al.*, 1999; Konishi *et al.*, 1999; Liddle *et al.*, 2001; Rubia *et al.*, 2000). More evidence that ventral prefrontal cortex is directly related to response inhibition was provided by Casey *et al.* (1997), who demonstrated that the volume of activity in this region correlated with correct performance on a go nogo task. However, imaging studies have shown that other areas are also activated during response inhibition, such as dorsolateral frontal cortex and regions of the anterior cingulate gyrus (e.g., Casey *et al.*, 1997; Garavan *et al.*, 1999; Konishi *et al.*, 1999; Liddle *et al.*, 2001). It has been suggested that these additional regions may not be involved in response inhibition per se, but reflect cognitive processes, related to other aspects of the task (Garavan *et al.*, 1999), such as maintaining other task relevant information, or monitoring conflict, respectively.

In the current study, we examined the effect of preceding context on inhibition by using a parametric manipulation: We varied the number of response trials preceding an inhibition trial in a variation of the go nogo paradigm. Areas that are critical for response inhibition should be activated at all levels of our manipulation, whereas noncritical areas may not be. One possible hypothesis is that the manipulation of context results in increasing task or response demands that will simply lead to more activation in the regions involved in the inhibition of a response. Alternatively, other brain regions, not typically reported in studies of response inhibition but implicated in maintaining context could be involved (e.g., dorsolateral prefrontal regions).

An advantage of a parametric manipulation such as the one described is that it will allow the comparison of groups, across different levels of task difficulty, if behavioral performance is indeed influenced by context. Previous developmental and clinical studies using the go nogo task have not controlled for differences in behavioral performance across tasks, which may be related to the differences in the pattern of activation reported between groups. Parametric manipulations have most often been used when testing for individual or group differences in more traditional working memory tasks (e.g., the *n*-back task Braver *et al.*, 1997; Thomas *et al.*, 1999) and not in inhibitory tasks.

In order to manipulate preceding context, we modified the go nogo task (e.g., Casey *et al.*, 1997). We parametrically manipulated the number of targets preceding every nontarget, so that either 1, 3, or 5 targets always preceded a nogo trial and maintained an overall target frequency of 75% across the entire experiment.

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We used a rapid mixed trial event-related functional magnetic resonance imaging (fMRI) design to link MR signal change to each individual trial type. The use of an event-related design, combined with the parametric manipulation of preceding context allows for the comparison of nogo trials to one another, rather than just comparing nogo trials to go trials. This manipulation allows one to tease apart systems involved in the representation of when not to respond rather than in the behavioral process of making a response or not. As we anticipated that the 12- to 16-s interval traditionally used in event-related designs would be too long to produce the desired behavioral inhibition (and too boring to ultimately use with children), we used a rapid mixed trial design for this fMRI study (Dale and Buckner, 1997).

METHODS

Paradigm. The subject's task was to press a button in response to visually presented stimuli, but to avoid responding to a rare nontarget. The task consisted of five runs, which lasted 3 min and 24 s each. Each run contained a total of 49 trials, with 75% go trials, resulting in a total of 60 nogo trials, 20 of each type (with 1, 3, or 5 preceding go trials). The order of presentation of the different types of nogo trials was pseudorandomized. In order to make this paradigm better suitable for use with children at a later date characters from the Pokemon cartoon series were used as stimuli. Stimulus duration was 500 ms. The interstimulus interval was 4 s.[1]

Subjects. Ten healthy right-handed adult subjects (mean age = 28.0 years, 5 male) were run in two versions of the go nogo paradigm.[1] Subjects were screened for any contraindications for an MRI. We obtained written consent from all subjects prior to scanning.

Scan acquisition. EPI BOLD images were acquired in 24 axial slices on a 1.5 T GE Signa scanner, covering most of the brain (TR = 2000, TE = 40, 64 × 64, 4-mm slice thickness, 3.125 × 3.125-mm in-plane resolution). Anatomical Spin Echo images were also collected (TR = 500, TE = min, 256 × 256, FOV = 20, 4-mm slice thickness) in the same locations as the functional slices. Stimuli were presented using the integrated functional imaging system (IFIS) (PST, Pittsburgh), which uses a LCD video display in the bore of the MR scanner and a fiberoptic response collection device.

Analysis. AIR (Automated Image Registration) version 3.08 (Woods *et al.*, 1992) was used for motion correction, image smoothing (2 mm), and cross registration of data. A voxelwise, multifactorial ANOVA was performed pooling data into a 10 (subjects) × 4 (trial type - go trials and nogo trials preceded by 1, 3, or 5 go trials) design, averaging across all 5 runs. Two scans were included in the ANOVA for each trial, at 4 and 6 s after stimulus presentation. Regions of three or more contiguous voxels ($P < 0.005$) were identified (Forman *et al.*, 1995). Only correct trials were analyzed. Images were warped into stereotaxic space using AFNI (Cox, 1996) to localize regions of activity, based on the coordinate system of the Talairach atlas (Talairach and Tournoux, 1988).

RESULTS

Behavioral. None of the subjects were explicitly aware that the nontarget always followed 1, 3, or 5 targets (i.e., never 2 or 4) based on self-report at the end of the study. Average accuracy on the nogo trials was 95.5%. Average reaction time on go trials was 559 ms. The number of errors on the nogo trials increased with number of preceding go trials (2.5%, 5%, 6%, $P < 0.05$).

FMRI. Three general patterns of change in MR signal were observed (see Table 1 and Fig. 1). Two of these patterns reflected the contextual manipulation. In general, the MR signal to nogo trials increased with number of preceding go trials. Areas in the inferior frontal gyrus (BA 9/44 and 44/46), cingulate gyrus (both anterior and posterior) (BA 32 and 23/31) and superior parietal cortex (BA 7) showed an increase in MR signal after three preceding go trials, whereas regions in the superior and middle frontal gyri (BA 6/8) did not show an increase in MR signal until after five preceding go trials. Primary motor cortex (BA 4) showed a decrease in activation for all three nogo conditions compared to go trials.

MODELING

The behavioral increase in the number of errors on nogo trials with increasing number of preceding go trials confirms our assumption that inhibition becomes more difficult as the demands on response inhibition increase (i.e., inhibiting after having made more responses consecutively). Several regions showed an in-

[1] We performed a comparison of two versions of our task: (1) One with a fixed interstimulus interval (ISI) of 4 s; and (2) one with a jittered ISI, which varied between 3 and 5 s with a mean of 4 s. The results were very similar for both versions: Accuracy and reaction time were comparable, and both paradigms produced similar patterns of activation. However, activation was more robust for the fixed than the jittered design. Therefore, the results reported in this paper are those for the fixed design. Differences in robustness are hypothesized to be related to "off-peak" sampling in the jittered presentation, resulting in reduced power. Alternatively, the regular, predictable presentation rate associated with the fixed design (stimulus appears every 4 s) may result in a more compelling behavioral set, making inhibition harder to accomplish, and resulting in a more robust activation in the areas associated with performance of this task.

TABLE 1

Patterns of Activation for the Comparison of Go Trials to Nogo Trials, Preceded by 1, 3, or 5 Go Trials

Pattern in figure 2	Area	Brodmann	Side	Talairach	Max F
A	Inferior frontal gyrus	9/44	Right	(36, 23, 28)	7.51
		44/46	Left	(−30, 25, 23)	13.37
	Anterior cingulate gyrus	32	Right	(7, 37, 29)	9.01
	Posterior cingulate gyrus	23/31	Right	(8, −39, 26)	10.07
		23/31	Left	(−11, −44, 25)	7.30
	Superior parietal lobule	7	Left	(−17, −67, 41)	7.02
B	Superior frontal gyrus	6	Right	(9, 6, 57)	8.78
		8	Left	(−11, 37, 45)	8.18
	Middle frontal gyrus	6/8	Left	(−42, 0, 44)	7.96
C	Primary motor	4	Left	(−42, −28, 57)	12.29

Note. Patterns correspond to Fig. 1.

crease in MR signal as a function of increasing number of preceding targets (i.e., the effect of context). These regions may be recruited more as interference in the task demands increase (i.e., withholding a response after having made several responses).

We wanted to exclude the possibility that this increase in MR signal might be based on an artifactual summation of blood oxygen level-dependent (BOLD) responses due to our randomization scheme. In order to check this, we modeled our randomization scheme using the model of hemodynamic response function proposed by Boynton *et al.* (1996):

$$h(t) = (t/\tau)^{(n-1)} e^{-(t/\tau)}/\tau\,(n-1)!$$

Modeling methods. In order to fit the model to our data, we chose a total of 14 regions of interest (ROI) from our dataset that showed an increase in MR signal to nogo trials relative to go trials. We plotted the BOLD response for these regions to all three types of nogo trials (see Fig. 2).

We fit the model to the various BOLD curves to empirically determine the values of n and τ for each BOLD curve separately. The model was then combined with the randomization scheme, using the empirically determined values of n and τ. This resulted in models for the average BOLD response to a nogo trial after 1, 3, or 5 preceding go trials in all 14 regions. As the results were comparable for all regions, the values

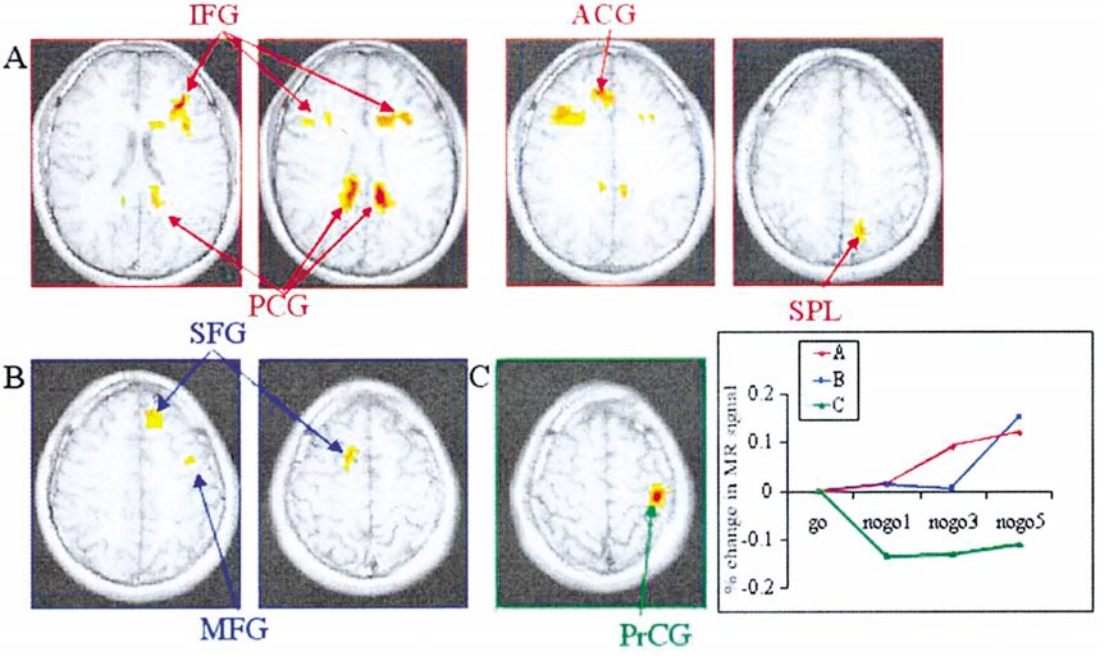

FIG. 1. (A) Brain regions showing the context effect; (B) Brain regions showing an increase in activation only to nogo trials following 5 go trials. (C) Brain regions showing a response to the go trials. (D) Three patterns observed for the comparison of go trials to nogo trials after 1, 3, or 5 preceding go trials.

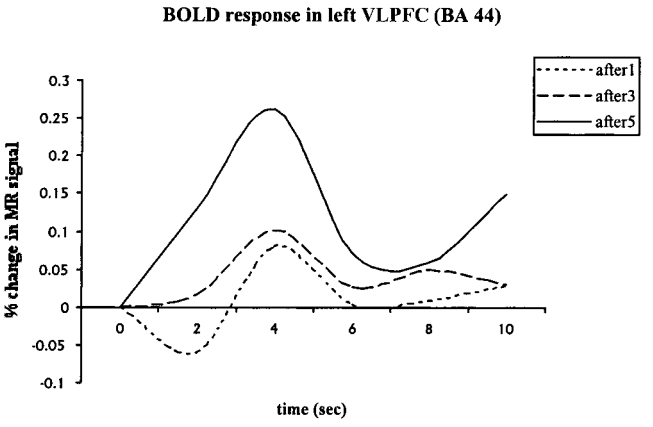

FIG. 2. Example of a BOLD response, plotted for a region of interest that responded to context.

from the overall average BOLD curve are further reported here.

Modeling results. Under the null hypothesis that there was no effect of context (i.e., the amplitude of the BOLD curve following a nogo was the same for all three levels of the nogo), the model predicted no artifactual effect of context for either design.

DISCUSSION

Overall, this study demonstrated an effect of preceding context on behavior and pattern of brain activity. The number of errors made by subjects to nogo trials increased as a function of the number of preceding go trials. Similarly, brain regions implicated in response inhibition showed increased activity as the number of preceding go trials increased. Brain regions traditionally linked to manipulations of context, memory load, or task demands, such as dorsolateral prefrontal cortex (Braver *et al.*, 1997) were not activated by the context manipulation, rather the brain regions included inferior frontal cortex and the anterior cingulate gyrus. Two distinct patterns of activation were observed for regions that responded to the context manipulation (see Table 1 and Fig. 2). The ventrolateral prefrontal cortex (BA 9/44 and 44/46), the cingulate gyrus (BA 32 and 23/31) and superior parietal cortex (BA 7) increased their activation to nogo trials as a function of the number of preceding go trials. These regions may be maintaining the task or response demands as interference from the go trials increases, in a similar manner to that suggested for dorsolateral prefrontal regions (Braver *et al.*, 1997; Thomas *et al.*, 1999).

Activity in anterior supplementary and premotor cortex increased only to nogo trials that followed 5 go trials, but not fewer. At least one imaging study using a go nogo paradigm has reported activation of premotor areas to nogo trials. That event-related fMRI study (using 18-s intervals) reported activity in anterior premotor areas to nogo trials (Humberstone *et al.*, 1997). Single cell recording studies have also described cells in premotor cortex that respond to withholding a response (Watanbe, 1986). One possible explanation for activity in this region is that it reflects preparation for a motor response prior to stimulus onset. Perhaps after a certain number of responses or threshold, the system is primed to make a motor response as evidenced by the activity in these premotor regions that is then overridden when a nontarget appears. In this paradigm, subjects had 4 seconds between trials, allowing them plenty of time to prepare for the next event, particularly if the expectation for or probability of a target/response was high. Similar patterns of activity and interpretations of premotor activity have been reported during working memory tasks, suggesting either preparation of a motor response or practice effect (Braver *et al.*, 1997; Petersen *et al.*, 1998; Thomas *et al.*, 1999). Either of these interpretations is consistent with the current findings.

Overall, our results show the feasibility of using context manipulations to vary task difficulty in an inhibitory task. As such, this task may be used when comparing groups with different levels of accuracy on the go nogo task as it will allow the comparison of subjects at the same level of performance, but different level of task demand. This manipulation will prove critical in studies comparing age groups and psychiatric conditions (e.g., ADHD).

It should be noted that at least two other studies have manipulated target frequency in a go nogo task (DeZubicaray *et al.*, 2000; Casey *et al.*, 2001). However, these tasks used blocked designs in acquisition or analysis of the data. Both studies report a distributed network of regions, including regions of the dorsolateral prefrontal cortex, that show linear increases as a function of number of targets and nontargets. Since these studies used block designs where the probability of go trials was manipulated per block, varying between 10 and 100%, the signal change associated with a single nogo trial could not be examined as blocked designs do not allow the isolation of the trial of interest (i.e., the nogo), but rather involve collapsing across trial types. Furthermore error trials cannot be easily excluded from these designs.

In sum, we have demonstrated both a behavioral and biological effect of preceding context on inhibition using a version of a traditional inhibitory task. We replicated previous work demonstrating the importance of the ventral prefrontal cortex in performance of this task and implicated other regions as well (cingulate and parietal cortex). All of these regions were sensitive to preceding context, but more dorsolateral prefrontal regions often described as critical for maintaining context were not sensitive to this manipulation. This finding suggests that dorsal and ventral prefrontal cortex may both be sensitive to preceding context, but differ

according to the contextual information maintained. In the current study, the relevant behavioral response was perhaps more important than the stimulus information that is typically manipulated in tasks implicating more dorsal prefrontal regions. Finally, our behavioral task and experimental design manipulations have implications for future studies. We showed that manipulating the number of preceding targets affected task difficulty as indicated by overall accuracy. This finding suggests that parametric manipulations of preceding context may be a useful approach for titrating task difficulty when studying subjects of different ages or different clinical populations.

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