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Research report

fMRI evidence that the neural basis of response inhibition is task-dependent

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Abstract

Event-related fMRI was used to investigate the hypothesis that neural activity involved in response inhibition depends upon the nature of the response being inhibited. Two different Go/No-go tasks were compared—one with a high working memory load and one with low. The 'simple' Go/No-go task with low working memory load required subjects to push a button in response to green spaceships but not red spaceships. A 'counting' Go/No-go task (high working memory load) required subjects to respond to green spaceships as well as to those red spaceships preceded by an even number of green spaceships. In both tasks, stimuli were presented every 1.5 s with a 5:1 ratio of green-to-red spaceships. fMRI group data for each task were analyzed using random effects models to determine signal change patterns associated with Go events and No-go events (corrected $P \leq 0.05$). For both tasks, Go responses were associated with signal change in the left primary sensorimotor cortex, supplementary motor area (SMA) proper, and anterior cerebellum (right>left). For the simple task, No-go events were associated with activation in the pre-SMA; the working memory-loaded 'counting' task elicited additional No-go activation in the right dorsolateral prefrontal cortex. The findings suggest that neural contributions to response inhibition may be task dependent; the pre-SMA appears necessary for inhibition of unwanted movements, while the dorsolateral prefrontal cortex is recruited for tasks involving increased working memory load.

Theme: Neural basis of behavior

Topic: Cognition

Keywords: Response inhibition; fMRI; Go/No-go; Supplementary motor area; Doroslateral prefrontal cortex; Working memory; Cerebellum

1. Introduction

'Response inhibition' refers to the suppression of actions that are inappropriate in a given behavioral context or that are unwanted because they interfere with the completion of a motor or cognitive task. Response inhibition is critical in preparation and selection of motor responses and is important for normal performance of a wide range of behavioral and cognitive tasks. Such tasks include processes involved in selective attention, which is, at least in

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part, dependent on the ability to inhibit attending to distracting or interfering stimuli.

Deficits in response inhibition are hypothesized to be important in the pathophysiology of several neuropsychiatric disorders including Tourette syndrome, obsessive–compulsive disorder, and attention deficit hyperactivity disorder (ADHD) [3,32,47]. In the latter, difficulty in inhibiting impulsive and off-task behavior is a defining characteristic of the disorder [3,47]. Furthermore, there is evidence for deficits in response inhibition across multiple domains in ADHD, including skeletomotor [13,27,60,64,65], oculomotor [58,59,48,10,45,46], and cognitive; the cognitive domain includes inhibition of any habitual, prepotent response governed by a rule that is held in working memory [4,24,25,62]. This is in addition to the most clinically salient domain of socioemotional disinhibition, which contributes to excessive impulsive behavior.

Consequently, there has been increasing interest in recent years in understanding the neural basis of response inhibition. Results from lesion studies in animals initially led investigators to conclude that the neural mediators of response inhibition are localized to ventral prefrontal regions [20,31], findings supported by observations of behavioral disinhibition associated with poor social judgment in adults with orbitofrontal lesions [22,40,66]. Yet this focus on disordered socioemotional response inhibition, while clinically salient and adaptable to animal models, neglects other varieties of response inhibition.

More recently, functional imaging, in particular functional magnetic resonance imaging (fMRI), has been used to study neural mechanisms involved in response inhibition [9,15,21,29,33,35,37,36,41,63,67,68]. A variety of tasks have been used, resulting in somewhat inconsistent results in mapping regions of activation involved in response inhibition. All studies concur that there is frontal involvement; however, the regions of activation reported within the frontal lobe have been extremely variable and not necessarily localized to ventral prefrontal regions. This has prompted some investigators [63] to consider a 'multiple domain' model of response inhibition [14], according to which the specific region of the frontal lobe involved in response inhibition may depend on the nature of the response being inhibited.

The multiple domain hypothesis of response inhibition has its basis in well-described functional subdivisions within the frontal lobes and their membership in circuits with specific subcortical regions [40,1] including (at a minimum) skeletomotor, oculomotor, dorsolateral prefrontal (DLPF), anterior cingulate, and orbitofrontal (medial and lateral) circuits [44]. There is considerable evidence that these different frontal regions/circuits govern different domains of response inhibition. Within skeletomotor circuits, the rostral portion of the supplementary motor area (SMA) has been identified as being important for preparation and inhibition of skeletomotor responses [2,30,42]. Frontal eye fields (FEF), supplementary eye fields (SEF), and DLPF regions have been shown to be important for inhibition of reflexive eye movements during an antisaccade task [7,11,26,49,50,53]. Dorsolateral and inferior prefrontal, as well as anterior cingulate cortices, appear to be important for cognitive tasks in which it is necessary to inhibit a prepotent response governed by a rule held in working memory [33,67,14]. As noted above, observations from adult lesion studies suggest that the orbitofrontal cortex (OFC) is important for inhibition of inappropriate behavioral/emotional responses [20,40], and there is evidence suggesting that inhibition mediated by OFC is specific to socioemotional decision making involving reward and response cost [14,5,6,56,57].

To elucidate the neural mechanisms critical to response inhibition, it would be advantageous to focus on the skeletomotor components solely involved in preparation and selection (including inhibition) of relatively simple actions, thus focusing on response inhibition in this specific domain and minimizing involvement of more complicated neural systems necessary for regulation of cognition and behavior.

One of the simplest paradigms used to study response inhibition is the Go/No-go task. Go/No-go paradigms involve the repeated delivery of a series of single cues that present in one-of-two distinct forms: a Go cue or a No-go cue. A subject is instructed to respond rapidly (usually with a button push) to the Go cues *only*. Response inhibition can be studied by inspection of data from the correct No-go trials (i.e. those where a No-go cue is met with a non-response). Tendency towards the errant response in No-go trials is increased by weighting the trial runs with a majority of Go cues (at a ratio of $\geq$3:1) in order to elicit a rapid, habitual response. Such weighting of trial types is intended to intensify the need for inhibitory brain function during the successful non-responses to 'No-go' trials.

In its simple, 'classical' form, the Go/No-go task lends itself to the study of motor response inhibition because it minimizes cognitive and behavioral demands; however, many of the designs used in previous fMRI studies of Go/No-go involved additional cognitive and attentional factors, complications that have contributed to a range of activation patterns being reported [9,21,29,36,41,63,68].

Some fMRI studies of Go/No-go used a block design approach [9,68,61] in which brain activation associated with response inhibition was determined using a model contrasting blocks containing both Go and No-go events (usually in a 1:1 ratio, as opposed to 3–5:1 ratios often used in clinical and research settings outside the scanner) with blocks consisting entirely of Go events. The argument for using this approach is that by contrasting the mixed block versus the Go-only block one can isolate activation related to response inhibition. The problem is that the two blocks differ in more than just response inhibition: the mixed block requires a different level of vigilance than does the Go-only block. Furthermore, the mixed block

requires increased need to engage neural systems involved in recognizing the cue and making a decision based on what is shown. It is therefore difficult to conclude that brain activation reported when using a block design approach is specific to response inhibition.

More recently, investigators have published fMRI studies of Go/No-go using event-related designs [15,21,29,36,41], which allow for targeted analysis of activation associated with successful non-response (inhibition of response) to a No-go cue. In one study, however, investigators used a complex task in which subjects were required to decide between two possible No-go cues based on previous events occurring up to several seconds prior to the No-go trials of interest [21]. Performance was, therefore, highly dependent on working memory, which might explain why activation associated with successful 'No-go' non-response appeared to be widely distributed throughout the brain, most pronounced in frontal and parietal regions, including the right middle and inferior frontal gyri, the left inferior parietal lobule, and the right angular gyrus. In other event-related studies with simpler Go/No-go tasks [29,36,41] investigators often used long interstimulus intervals: 8 [41], 18 [29], and 32–40 s [36]. The long interstimulus intervals allowed for hemodynamic recovery between individual events associated with the BOLD signal but also yielded paradigms that required relatively low frequency motor responses and inhibitions, rendering it dissimilar to paradigms used in clinical and investigative settings outside the scanner.

For the current study, we decided to examine the neural basis of response inhibition using event-related analysis of fMRI data acquired during the performance of two Go/No-go tasks. We first used a 'simple' Go/No-go task in which cues were presented at a rapid rate (once every 1.5 s) that increased demand on systems involved in motor response preparation and inhibition. A single type of Go cue and a single type of No-go cue were used (as opposed to tasks used in most previous fMRI studies in which there was a single type of No-go cue amongst many types of Go cues). With this simple scheme we hoped to isolate motor response inhibition by minimizing the influence of complex cognitive and behavioral variables. These results were contrasted with those from a 'counting' Go/No-go task with a high working memory load. This task was similar to the simple Go/No-go task except that it required subjects to inhibit responding only to those red spaceships preceded by an odd number of green spaceships. Response inhibition therefore depended on holding in working memory the number of green spaceships that preceded each red spaceship. We hypothesized that presentation of No-go stimuli in the simple task would be associated with activation in brain regions involved in the preparation and inhibition of simple motor responses (e.g. SMA); activation associated with presentation of No-go stimuli in the counting task would include brain regions involved in working memory (e.g. DLPFC).

2. Methods

2.1. Subjects

Subjects in this study were 48 right-handed adult volunteers who reported no history of mental health problems. The sample equally represented males and females. The age range of the males was 27.4±5.7 years and for the females it was 27.5±4.8 years. A subsample of 28 also completed a counting Go/No-go task. Of the 28, 13 were male with an age distribution of 27.1±4.1 years, 15 were female with an age distribution of 27.0±5.1 years. The study was approved by the Johns Hopkins Medical Institutional Review Board and the experiment was undertaken with the understanding and written consent of each subject.

2.2. Paradigms

All 48 subjects completed a simple Go/No-go task; 28 also completed a counting Go/No-go task. Subjects viewed the projected, computer-controlled paradigms on a screen at the head of the scanner via a 45° angled mirror affixed to the MRI head coil. Subjects responded by pressing a button with their right index finger, using a button box held in the right hand.

2.3. Simple Go/No-go task

Cues consisted of drawings of green (Go) and red (No-go) spaceships (see Fig. 1). Subjects were instructed to push the button as quickly as possible in response to green spaceships only. A short practice run of 11 trials was completed to verify that each subject understood the directions.

Immediately after the practice run, fMRI acquisition was carried out during two paradigm runs lasting 4 min and 50 s each. During each run the subject encountered 123 green cues, 27 red cues, and four long (10-s) rest phases. The stimuli were presented one at a time in pseudo-random order with the following constraints: no more than two red cues could appear in a row, no fewer than three green cues could appear in a row, and a red cue could not appear immediately after one of the 10-s rests or at the onset of data acquisition. The cue presentation patterns were weighted towards serial Go cues (82%) to maximize a subject's tendency toward a button press, even at the appearance of the No-go cues. Patterns used for the two runs were different in order to dampen between-run learning effects. The precise timing of the stimuli presentation was the following: each spaceship appeared for 200 ms, each inter-trial interval was 1300 ms, and each rest phase had a duration of 10 s. In between cues and during long rests the subject was continuously shown a central fixation marker that they had been instructed to focus upon throughout the scan. The rest phases were

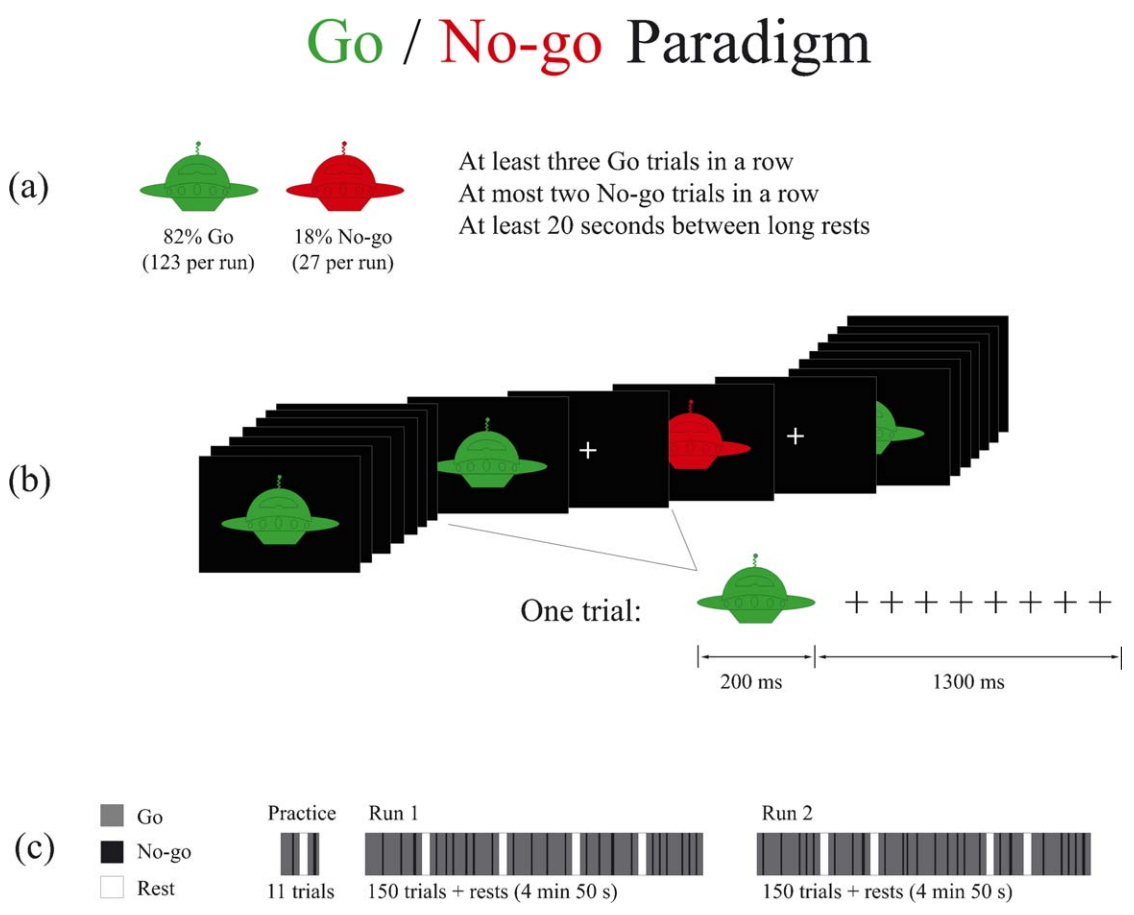

Fig. 1. Schematic of behavioral paradigm for the simple Go/No-go task. (a) The constraints used to determine frequency and ordering of the Go and No-go cues. (b) An isolated sub-stream of trials and a single trial. (c) A timeline for the entire fMRI experimental session.

included to allow a recovery period for the hemodynamic response associated with the steady and rapid stream of Go or No-go trials. Paradigm programming and display was done using E-prime (Psychology Software Tools, Pittsburgh, PA, USA) running on Windows 98.

2.4. Counting Go/No-go task

The design of the counting Go/No-go task was similar to that of the simple Go/No-go task except that subjects were instructed to push a button (with their right index finger) as quickly as possible in response to green spaceships and to red spaceships preceded by an even number of green spaceships. The number of green spaceships before a red spaceship ranged from three to six, and the task was balanced for the two types of red spaceships. Subjects completed four runs of the counting Go/No-go task; the simple and counting Go/No-go tasks were thereby balanced for the total number of No-go stimuli (54). A simple practice involving three separate scenarios—an even trial, an odd trial, and one of each—was completed by each participant prior to scanning.

2.5. Scan procedure

Scanning was carried out in a 1.5 Tesla ACS-NT Powertrack 6000 MRI scanner (Philips Medical Systems) using body coil transmission and quadrature end-capped head coil reception. Coronally orientated volumes were acquired every 2.5 s using single shot echo planar imaging. Each volume was composed of 4 mm slices (with 0.5 mm inter-slice gap); coverage ranged from 29 slices (from just anterior to the frontal pole to the middle cerebellum) to 41 slices (providing whole brain coverage). Image matrix was 64×64 voxels each voxel was 3.59×3.59×4.5 mm. TE was 40 ms and flip angle was 90°.

2.6. Image processing and data analysis

All post acquisition image processing was carried out using Matlab (v5.3–6.1) (Mathworks, Natick, MA, USA) and SPM99 (http://www.fil.ion.ucl.ac.uk/spm/). DICOM (Digital Imaging and Communications in Medicine) images from the scanner were converted to Analyze format and then time corrected to adjust for within volume time of acquisition differences [8], realigned, and smoothed [18]

using a Gaussian kernel that was half the resolution of the acquisition matrix ($7\times7\times9$ mm^3). Prior to estimation, the data were spatially normalized to Montreal Neurological Institute (MNI)-labeled space [16], resampled into voxels of (2 mm)^3, and temporally smoothed. The temporal smoothing can be broken down as follows: a high-pass filter cutoff of 32–36 s (0.031-0.028 Hz) was applied, and low pass filtering was achieved by convolving with the SPM hemodynamic response function (~0.34 Hz) [19].

Go and No-go associated brain activation was assessed using an 'event-related' analytic design [34]. SPM99 was used to construct and test the fit of the image data to a general linear model [17] that accounted for the effects associated with rare incorrect responses (commissions on No-go trials and omissions on Go trials) and specifically tested for and created statistical maps corresponding to the time-course of correct Go and No-go trial execution by the subject. For the counting task, the general linear model included separate regressors for correct No-go responses, Go responses to green spaceships, and Go responses to red spaceships as well as those for rare incorrect responses. The implicit baseline for these effects corresponds to the periods during which subjects viewed the central fixation cross-hair (rest periods). Voxel-wise *t*-maps were constructed for each of the subjects as a first level analysis and the amplitude maps were then carried to a second level analysis to test for significant group effects using a Gaussian random field theory corrected $P\leq0.05$ [69] and a cluster threshold of >5 voxels. The two level strategy described is equivalent to a random effects analysis in that the analysis is dominated by intersubject variance (as opposed to interscan variance) in order to provide a better idea of the average activation of a given population [28]. The location of voxels significantly associated with Go or No-go execution were summarized by their local maxima separated by at least 8 mm, and by converting the maxima coordinates from MNI to Talairach coordinate space using the formulas provided by Matthew Brett (http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html). These coordinates were finally assigned neuroanatomic and cytoarchitectonic labels using the Talairach Daemon [39] (http://ric.uthscsa.edu/projects/talairachdaemon.html).

To assess the magnitude and single subject applicability of the significant Go and No-go effects observed, all of the first level individual *t*-maps were reviewed with a statistical threshold of uncorrected $P\leq0.001$ and a cluster threshold of 2. This liberal threshold was chosen to increase sensitivity to any effects apparent in single subjects. To summarize the correspondence between single subject and group derived data overlap in activated voxels was also calculated between each subject and the group data.

For each of the individual tasks (simple and counting Go/No-go), two additional statistical comparisons (treating the two tasks separately) were conducted using a combination of the individual Go and No-go effects. The first of such comparisons tested for regions where there was a significant difference between Go and No-go effects. This was done to address whether Go effects were significantly greater than No-go effects in one case, and whether the converse differential effects (i.e. No-go greater than Go) were significant in a separate analysis. The second combination-based statistical comparison was a 'cognitive conjunction' [54] of Go and No-go effects. A conjunction analyses was used to highlight regions where both Go and No-go effects appeared to be significantly positive. All combination-based effects were the result of random effects analyses where the first-level contrast images from each subject were brought to a second-level analysis in order to determine significant group effects with restricted influence from within subject variance. For the conjunction analysis, orthogonalization was with respect to Go events as they represented the most frequently sampled regressor.

Finally, a paired *t*-test was used to examine the difference between No-go activation in the simple Go/No-go task and that in the counting Go/No-go tasks. Each pair consisted of an individual's No-go contrasts for the counting and simple Go/No-go tasks. Only the 28 participants who completed both tasks were included in this analysis.

3. Results

3.1. Subject performance

All subjects successfully completed the scanning without difficulty. For the simple Go/No-go paradigm, mean reaction time on correct Go trials was 339 ± 95 ms, mean number of commission errors was $7.6\pm8.6\%$, and mean number of omission errors was $0.2\pm0.4\%$. For the counting Go/No-go paradigm, mean reaction time on correct Go trials was 341 ± 72 ms, mean number of commission errors was $9.9\pm8.5\%$, and mean number of omission errors was $0.4\pm0.6\%$. Standard *t*-tests did not reveal any significant differences in mean reaction time, commission errors or omission errors across the two tasks.

For the counting task there were three reaction times to consider, that for red Go trials, that for even green spaceships, and that for odd green spaceships. The construction of the task is such that participants always respond after seeing an even number of green spaceships, regardless of the color of the next spaceship. To ensure that subjects were attending to the color of the stimulus following an even number of green spaceships, analysis of variance (ANOVA) was used to examine for differences in mean reaction times across red Go, odd green, and even green trial types. The mean reaction time for red Go trials was 474 ± 119 ms, for odd green trials was 345 ± 78 ms, and for even green trials was 327 ± 73. ANOVA across the three trial types was significant ($P<0.0001$). Fisher's post-hoc analyses revealed that mean red Go trial reaction time

was significantly longer than that for both odd and even green trials (both at $P<0.0001$). Reaction times for each of the green trial types, however, were not significantly different ($P=0.5$) and were therefore not treated differently in the fMRI data analysis.

3.2. fMRI results

3.2.1. Simple Go/No-go task

Table 1 summarizes the main group Go and No-go effects for the simple Go/No-go task that were observed using the event-related, random effects analytic procedures described above. Fig. 2 provides a pictorial depiction of those same effects.

As expected, Go-effects were observed in the left primary sensorimotor cortices (BA3/4) and SMA (BA6) contralateral to the finger used for the button press (i.e. right index finger used by all subjects). Activation associated with the occurrence of Go trials was also seen in the cerebellum. Anterior cerebellar activation was seen on the right, ipsilateral to the finger used for the button press; a more posterior-lateral region of activation was seen bilaterally.

Within the cerebral cortex, main effects of No-go were localized to the medial wall of the superior frontal gyrus (BA6). The region of activation appeared to overlap in part, but not entirely, with SMA activation observed in association with Go trials (see Fig. 2). No-go activation had a greater extent rostral to the coronal plane of the anterior commissure and was thus centered in the region referred to as the pre-SMA [42,52]. No-go effects also included bilateral cerebellar activation in a region corresponding to bilateral cerebellar activation seen with Go stimuli.

3.2.2. Counting Go/No-go task

Table 2 summarizes the main group Go and No-go effects for the counting Go/No-go task. Based on results from behavioral data presented above, Go effects were assessed by examining activation associated with presentation of the green spaceships. Consistent with observations from the simple task, Go-effects were observed in the left primary sensorimotor cortices (BA3/4) and SMA (BA6) contralateral to the finger used for the button press, and bilaterally in the cerebellum. Additional Go effects were seen in the left thalamus and right middle occipital gyrus.

No-go effects in the counting task (Fig. 2) included activation in the medial wall of the superior frontal gyrus (BA6), consistent with the region defined as the pre-SMA. However, in contrast to observations from the simple task, the primary area of No-go activation in the counting task was localized to the right DLPFC (middle frontal gyrus, BA9 and BA46). Additional activation was observed in the right inferior parietal lobe and right insular cortices.

3.2.3. Within-task differential effects and conjoint effects

For the simple Go/No-go task, Go effects were significantly larger (corrected $P\leq0.05$) than the corresponding No-go effects in the left primary sensorimotor cortex. No regions of the brain demonstrated No-go effects that were significantly greater than Go effects. Conjunction of Go and No-go effects (corrected $P\leq0.05$) yielded four clusters of significance, in the left primary sensorimotor cortex, the left rostral SMA and in both the right and left cerebellum.

For the counting Go/No-go task, Go effects were again significantly larger (corrected $P\leq0.05$) than the corresponding No-go effects in the left primary sensorimotor cortex; Go effects were also significantly larger in the occipital cortex and right cerebellum. No-go effects were significantly larger than Go effects (corrected $P\leq0.05$) in the right DLPFC, right inferior parietal lobule, and insular cortex.

3.2.4. Between-task differential effects

The paired *t*-test comparison (corrected $P\leq0.05$) of No-go effects between tasks for counting>simple (Fig. 3) yielded regions of activation in the right DLPFC (middle frontal gyrus, BA9) consistent with some of those regions seen in analysis of No-go effects within the counting task. The counting>simple contrast also yielded activation in

Table 1
Primary Go and No-go effects for simple Go/No-go paradigm

Effect	*x*	*y*	*z*	*t*	Cluster size (vox)	Hem	Structure	Single subject overlap
Go	24	−48	−21	12.1	864	R	Anterior lobe of cerebellum	26
	−48	−19	51	11.6	1513	L	Pre/Postcentral gyri	46
	−8	5	51	9.66	328	L	Superior frontal gyrus (BA6)	13
	−32	−55	−21	8.84	160	L	Anterior lobe of cerebellum	15
No-go	−36	−55	−16	9.5	190	L	Posterior lobe of cerebellum	11
	−4	7	55	8.0	425	L	Superior frontal gyrus (BA6)	12
	32	−50	−21	7.8	192	R	Anterior lobe of cerebellum	11

Cluster foci of highest *t*-value is reported for activation seen in both Go and No-go at corrected $P=0.05$, cluster threshold 5. Coordinates are in Talairach space. 'Hem' refers to Hemisphere. Single subject overlap was defined for each cluster using an effective radius in mm, treating the cluster size as a spherical volume. If the vector distance to an individual's activation cluster was less than the effective radius, the cluster was deemed to overlap.

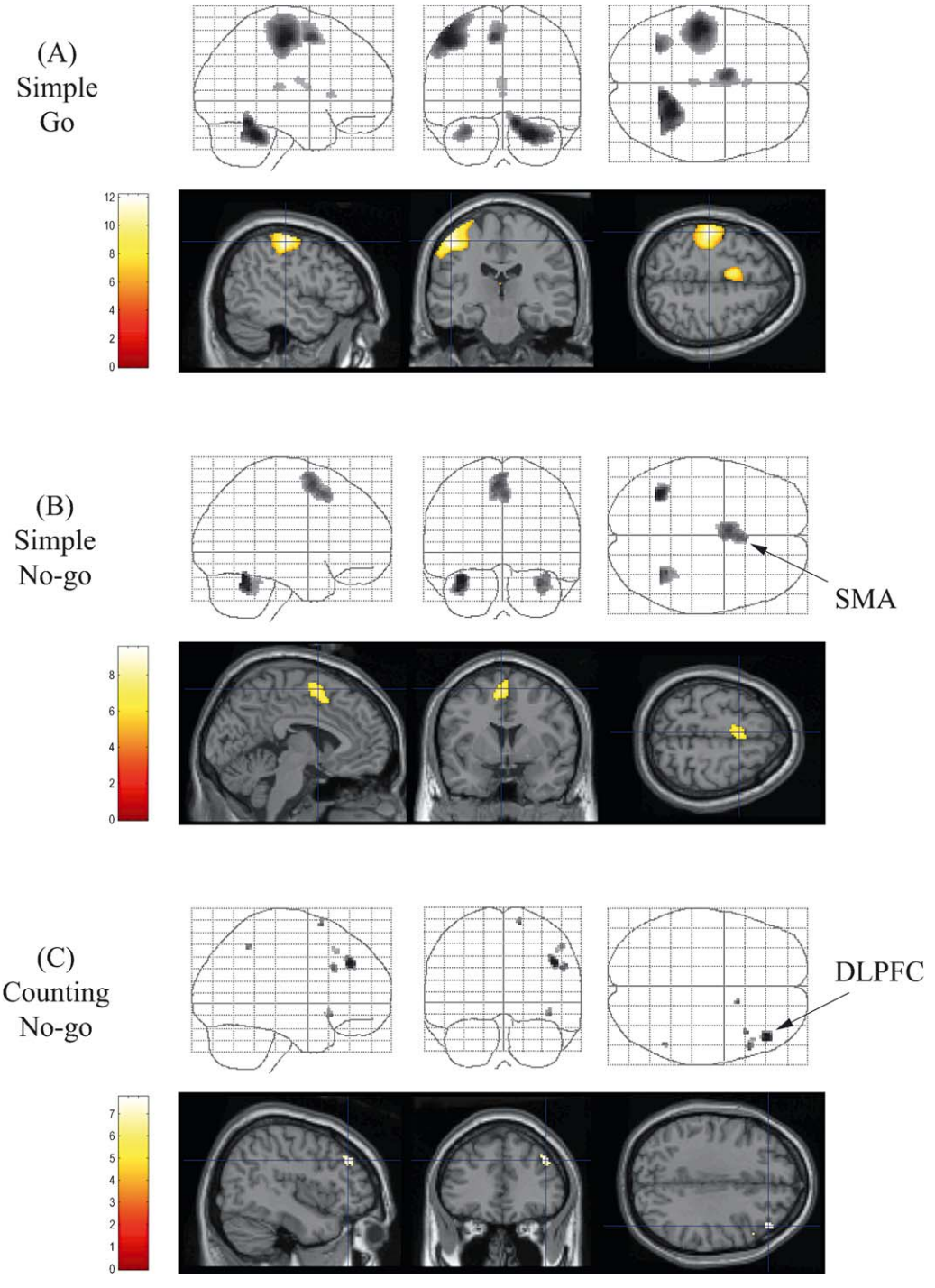

Fig. 2. Effects for both simple and counting Go/No-go tasks. Transparent and sectional brain maps showing regions where the time courses were significant covariates of fMRI signal changes for simple Go (A), simple No-go (B), and counting No-go (C) trials. These results are based on a random effects analysis of 48 subjects for the simple task, 28 for the counting task, all using a corrected threshold $P \leq 0.05$, cluster size larger than five. Neurologic convention is used (i.e. right=right hemisphere; projections looking rightward or into the page). Main effects of simple Go and No-go are visible in the left SMA. Isolated Go effects are also apparent in the cerebellum (right>left) and the left (contralateral to motor action) primary sensorimotor cortex. Sectional images for Go highlight activation in the primary sensorimotor cortex; those for No-go highlight activation in the SMA (BA 6). For the counting No-go, the primary main effect is visible in the right DLPFC (middle frontal gyrus); activation is also seen in the right SMA, inferior parietal lobule and insula. Sectional images highlight activation in the DLPFC (middle frontal gyrus).

Table 2
Primary Go and No-go effects for counting Go/No-go paradigm

Effect	*x*	*y*	*z*	*t*	Cluster size (vox)	Hem	Structure	Single subject overlap
Go	22	−95	8	13.5	5378	R	Middle occipital gyrus	26
	−6	−7	6	10.2	746	L	Thalamus	14
	−38	−17	49	9.1	309	L	Precentral gyrus	9
	−4	7	53	8.2	187	L	Superior frontal gyrus (BA 6)	18
No-go	44	36	29	7.74	50	R	Middle Frontal gyrus	6
	50	23	27	6.84	12	R	Middle Frontal gyrus	2
	14	15	62	6.78	5	R	Superior frontal gyrus (BA 6)	7

Cluster foci of highest *t*-value is reported for activation seen in both Go and No-go at corrected $P=0.05$, cluster threshold 5. Coordinates are in Talairach space. 'Hem' refers to Hemisphere. Single subject overlap was defined for each cluster using an effective radius in mm, treating the cluster size as a spherical volume. If the vector distance to an individual's activation cluster was less than the effective radius, the cluster was deemed to overlap.

the right inferior frontal gyrus and pre-SMA. The opposite comparison (simple No-go>counting No-go) yielded regions of activation bilaterally in the primary sensorimotor cortex (L>R) and in the left paracentral lobule.

3.2.5. Single subject correspondence to group data

For both tasks, single subject Go effects generally were consistent with the group analyses although some variability was present. With regard to single subject replication of Talairach defined regions for the simple task (Table 1), this agreement was observed in 96% of the subjects for the contralateral primary sensorimotor cortex (pre/post central gyri). Single subject correspondence for other Go effects observed in group analysis were 54% for the ipsilateral cerebellum, 31% for the contralateral cerebellum, and 21% for the SMA (BA 6).

Single subject No-go effects were not as consistent with the group effects. For the simple task, 25% of individuals demonstrated No-go associated activation within the activation field in the SMA (BA 6) observed in the group analyses. For the counting task (Table 2), 29% of individuals demonstrated No-go associated activation within the DLPFC (middle frontal gyrus); 25% of individuals demonstrated activation within the SMA (BA 6).

4. Discussion

In this study adults performed two Go/No-go tasks during fMRI as a means of examining neural mechanisms underlying motor response inhibition, a simple Go/No-go task in which the cognitive and behavioral variables were minimized, and a counting Go/No-go task in which inhibition of a motor response was dependent upon a rule held in working memory. Activation associated with presentation of Go stimuli was fairly consistent across both

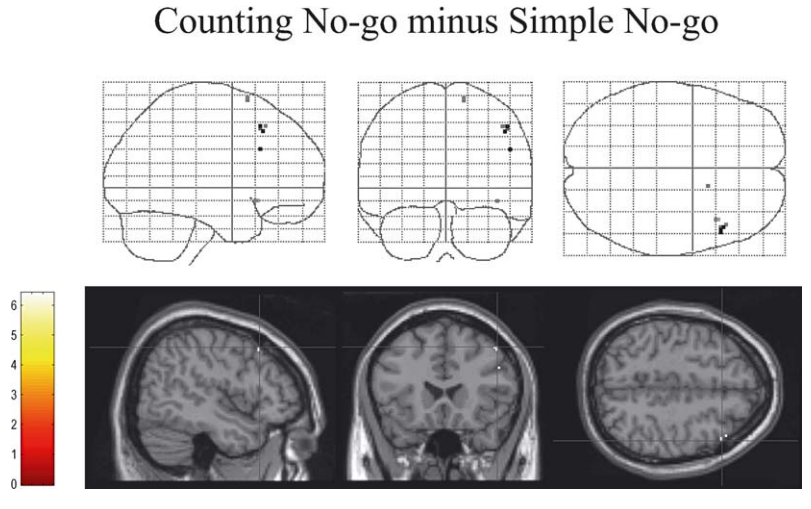

Fig. 3. Effects for paired *t*-test comparison of No-go effects between counting and simple Go/No-go tasks. Results are based on a random effects analysis of 28 subjects who completed both tasks (corrected $P\leq0.05$). Transparent and sectional brain maps show regions where the time courses were significant covariates of fMRI signal changes in which No-go activation in the counting task was greater than that seen in the simple task. Neurologic convention is used (i.e. right=right hemisphere; projections looking rightward or into the page). Main effects of counting No-go>simple No-go are primarily seen in the right DLPFC (middle frontal gyrus, BA9); effects are also seen in the right inferior frontal gyrus and pre-SMA. Sectional images highlight activation in the right DLPFC.

tasks. No-go effects, however, were clearly distinct: for the simple Go/No-go task, activation was localized to the pre-SMA; the counting task elicited additional No-go activation in the right dorsolateral prefrontal cortex. The findings are consistent with our a priori hypotheses and lend support to a multiple domain model of response inhibition [63] in that they suggest that a circumscribed region within the skeletomotor circuit is necessary for inhibition of a motor response under conditions minimizing superimposed cognitive processes, whereas recruitment of the DLPFC is necessary under conditions in which working memory is necessary to guide inhibition of the response.

Unlike most previous fMRI studies of Go/No-go tasks, this study utilized an event-related design in which cues were presented at a relatively rapid rate (every 1.5 s), consistent with how the task is administered in clinical and investigative settings outside the scanner. As applied to the simple Go/No-go task, the rapid presentation of cues served to increase demand on the systems involved in motor response preparation and inhibition; this, combined with the use of a simple design with a familiar color cue–response association (green for Go; red for No-go), allowed us to minimize the influence of cognitive demands (e.g. working memory) and thereby investigate the systems involved in inhibition of a motor response.

Results for the simple Go/No-go task reveal partially overlapping patterns of activation associated with presentation of (and response to) Go and No-go cues. Presentation of Go cues (and resulting motor response) was associated with activation in contralateral (left) primary motor and sensory cortices, the left SMA, and bilateral cerebellum; all of these regions are known to be important for execution of voluntary movement [51]. We were able to detect robust, event-specific activation associated with motor response to a visual cue despite the rapid (1.5 s ISI), non-jittered presentation of the Go trials. Our task design, which incorporated intermittent long (10 s) rest intervals as well as No-go events into the paradigm, probably enhanced our ability to detect changes in regional brain activation associated with motor response to Go cues.

Regarding apparent Go specificity of the signal changes detected with the simple Go/No-go task, statistical contrast between Go and No-go events revealed an area of significance in the primary motor cortex where Go effects were larger than No-go effects. These results suggest that Go events (simple motor actions) are, as expected, specifically associated with primary motor cortex activation [51].

Activation associated with the occurrence of No-go events (and resulting inhibition of motor response) during the simple task was observed in a specific region localized to the anterior (rostral) portion of the SMA. Investigators using single-cell recording methods in studies of primates [42] have referred to this region as the pre-SMA, distinguishing it from the more caudal SMA proper. This labeling convention has also been adapted by those summarizing the extensive literature on motor regions studied in human functional imaging experiments [52]. The distinction was based on findings of neuronal activity occurring between a stimulus and a motor response in the pre-SMA during a delayed reaction trial, suggesting that this region is involved both in preparation (which might also include inhibition) and execution of a motor response. Activity in the SMA proper, on the other hand, was associated with the movement itself, suggesting that this region is dedicated to motor execution.

The contrast of No-go effects to Go effects in the simple task, did not yield any brain voxels in the pre-SMA demonstrating such No-go dominance at corrected *P*-values. Conjunction analysis between No-go and Go, however, did confirm that Go and No-go events are both associated with signal changes in the pre-SMA. Such commonality supports this region's relevance in motor response preparation, an important component of which involves initiating selected motor responses, while inhibiting initiation of others.

Data from other studies [2,30,11,61] provide evidence for pre-SMA involvement in motor response inhibition. Direct stimulation of the anterior medial wall of the frontal lobe has been shown to inhibit ongoing voluntary motor activity and prevent initiation of a movement [30]. In fMRI studies, SMA activation has been observed during antisaccade and antipointing tasks, both of which require inhibition of a prepotent response [11]; and the SMA was one of the primary regions of activation observed in a conjunctive analysis addressing common activation sites across two different response inhibition tasks [63]. Furthermore, by coupling the temporal resolution offered by EEG with the spatial resolution offered by fMRI, investigators were able to demonstrate that an 'intermediate' region of the SMA is crucial in triggering a motor action by release of inhibition of the primary motor area, arguing for its role in motor response inhibition [2].

If the pre-SMA is involved in both motor inhibition and response preparation as suggested by Matsuzaka et al. [42], it may be that our difficulty in distinguishing between these components during Go/No-go is related to limitations in temporal resolution associated with fMRI. The approach taken by Ball et al. [2], with coupling of EEG and fMRI, would therefore be useful in resolving the role of the pre-SMA in inhibition of a motor response to a No-go cue. We speculate that better temporal resolution would reveal the pre-SMA to be involved in both motor response preparation and inhibition, albeit at different points in time.

Our findings from the simple Go/No-go task are similar to those from another event-related fMRI study [29] in which region of interest (ROI) analyses performed on the medial prefrontal cortex revealed that SMA-proper activation was associated with presentation of Go cues, whereas pre-SMA activation was associated with both presentation

of Go and of No-go cues. However, other investigators using event-related Go/No-go designs [15,21,36,41] reported activation in a variety of frontal/prefrontal regions, and in the aforementioned study [29] the initial analyses, conducted prior to ROI analyses, revealed widely distributed patterns of activation. Most of these studies incorporated elements that increased the cognitive requirements beyond that of the simple Go/No-go task used in the current study. Prefrontal activation in one of these event-related Go/No-go studies [21] may be attributable to the use of a complex task that was dependent on working memory (Subjects were required to decide between two possible No-go cues based on events occurring up to several seconds prior). In the other event-related studies [15,29,37,41] investigators used simpler Go/No-go tasks; however, in three of these studies the Go and No-go cues used were numbers [29], letters [41], and cartoon character images [15] which might have increased the demand for working memory load compared with our use of familiar cue–response associations of green for Go and red for No-go.

To determine if additional working memory load would require the recruitment of additional prefrontal regions, we tested subjects using a second, counting Go/No-go task. The design was very similar to that of the simple Go/No-go task, except that one needed to utilize information held in working memory in order to guide inhibition of the motor response. Consistent with our hypotheses, the right DLPFC, which has been shown to be critical for working memory [12,23], was the primary region of activation associated with presentation of No-go cues in the counting task and in the differential 'No-go minus Go' contrast. Furthermore, the right DLPFC was the primary region of activation in the between-task differential contrast of counting No-go minus simple No-go.

In both the simple and the counting Go/No-go task, presentation of No-go cues elicited activation in the pre-SMA. Since inhibition of a skeletomotor response is basic to both tasks, the findings suggest that the pre-SMA is necessary for inhibition of all actions and that recruitment of prefrontal regions occurs as tasks increase in complexity. It is evident that the DLPFC is recruited when response inhibition is governed by a rule held in working memory; similarly, we speculate that OFC may be recruited when motor response is governed by motivational information related to response and reward cost. Anatomic organization within the SMA supports this hypothesis. The SMA proper, involved in initiation and execution of a motor response, is connected with the primary motor cortex and primary/secondary sensory areas; in contrast, the pre-SMA receives afferents from frontal and parietal association areas (including the DLPFC and OFC) and sends direct efferents to premotor regions (including the SMA proper) but *not* to the primary motor cortex [42,38,55]. The anatomic organization supports a pre-SMA role in selection (which includes inhibition) of motor actions that, dependent on task demand (i.e. domain of response inhibition), can be further guided by cognitive and emotional information provided by afferents from association areas.

There were differences in No-go activation within the pre-SMA between the simple and counting Go/No-go tasks; No-go activation during the simple task was centered in the left pre-SMA, whereas activation in the counting task was centered in the right pre-SMA (as was that seen in the contrast of counting>simple No-go). The findings suggest that region-specific activation within the pre-SMA may be task dependent; left pre-SMA activation in the simple Go/No-go task may be related to left hemisphere dominance for motor preparation/execution, whereas right pre-SMA activation in the counting Go/No-go task appears to be linked to recruitment of other regions within the right hemisphere, in particular the right DLPFC.

Low inhibitory task demand is an unlikely explanation for the lack of prefrontal activation during the simple Go/No-go task. The paradigm had a high ratio of Go to No-go cues that intensified the need for inhibitory brain function during successful non-responses to No-go trials. Furthermore, the rate of errors of commission (7.6%) in our subjects is consistent with the error rate obtained by other studies [21,37,41], and was not significantly different from the rate seen in the counting task.

It should also be noted that other event-related studies may have observed prefrontal activation because their statistical or brain sampling methods were less rigorous or less applicable to a wider population than those used in our study. For example, most of the previous event-related studies cited in this paper [15,36,41] did not explicitly utilize a random effects model, and only two [21,41] explicitly used a *P*-value corrected for multiple comparisons. These differences in analytic approach open the possibility to the presence of type I errors in previous studies showing prefrontal activation or to the possibility of a type II error in our investigation; the former appears more likely given the large number of subjects in our study and our use of random effects analysis. With respect to sampling, Konishi et al. [36] limited their acquisition to the slices 10–40 mm above the AC–PC plane. While this sub-sampling increases signal to noise in portions of the prefrontal cortex, it also has the disadvantage of missing completely much of the superior and inferior brain including both the SMA and the cerebellum.

Cerebellar findings from the simple Go/No-go task paralleled those seen in the SMA: activation of the right anterior cerebellar cortex was associated with Go events; bilateral activation in an area posterior and lateral to that observed with Go events was associated with both Go and No-go events. These findings suggest that more medial cerebellar activation is associated with motor execution specific to Go events; more lateral activation is related to preparation (and possibly inhibition) of the motor response. This medial/lateral dissociation in the anterior cerebellar

cortex is similar to the rostral/caudal dissociation seen in the SMA; an observation consistent with mapping of frontal-cerebellar circuits [43] showing parallel projections from the dentate nucleus to (via the thalamus) motor and premotor regions in the cerebral cortex.

Single subject analysis only partially agreed with the group results of this investigation (see last column of Tables 1 and 2). Agreement was most apparent in the contralateral sensorimotor and ipsilateral cerebellar activation associated with the Go response. No-go effects, however, were more variable across subjects offering empirical support of the notion that universal (i.e. that seen in most individuals) response inhibitory brain activation is considerably more subtle than universal signal changes associated with motor execution. It is also possible that Go effects were more robust because the number of such trials was more than three times that for No-go.

Despite the variability in the single subject data, our application of random effects models to group analyses allows for insight into mechanisms underlying response inhibition in the general population. Our findings appear to indicate that a circumscribed region within the skeletomotor circuit (pre-SMA) is necessary for inhibition of a motor response, whereas recruitment of the DLPFC is necessary under conditions in which working memory is necessary to guide inhibition of the response. Systematic study using tasks with additional cognitive and emotional/behavioral components would help to map out the domain-specific roles of other frontal regions and circuits (e.g. OFC).

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