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Response control networks are selectively modulated by attention to rare events and memory load regardless of the need for inhibition

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ABSTRACT

Recent evidence has sparked debate about the neural bases of response selection and inhibition. In the current study, we employed two reactive inhibition tasks, the Go/Nogo (GnG) and Simon tasks, to examine questions central to these debates. First, we investigated whether a fronto-cortical-striatal system was sensitive to the need for inhibition per se or the presentation of infrequent stimuli, by manipulating the proportion of trials that do not require inhibition (Go/Compatible trials) relative to trials that require inhibition (Nogo/Incompatible trials). A cortico-subcortical network composed of insula, putamen, and thalamus showed greater activation on salient and infrequent events, regardless of the need for inhibition. Thus, consistent with recent findings, key parts of the fronto-cortical-striatal system are engaged by salient events and do not appear to play a selective role in response inhibition. Second, we examined how the fronto-cortical-striatal system is modulated by working memory demands by varying the number of stimulus-response (SR) mappings. Right inferior parietal lobule showed decreasing activation as the number of SR mappings increased, suggesting that a form of associative memory – rather than working memory – might underlie performance in these tasks. A broad motor planning and control network showed similar trends that were also modulated by the number of motor responses required in each task. Finally, bilateral lingual gyri were more robustly engaged in the Simon task, consistent with the role of this area in shifts of visuo-spatial attention. The current study sheds light on how the fronto-cortical-striatal network is selectively engaged in reactive control tasks and how control is modulated by manipulations of attention and memory load.

Introduction

Inhibitory control is a pervasive cognitive process. It is needed in the context of immediate threats such as stopping entry into the street in the face of an on-coming car, as well as to suppress urges so that we actively choose a more desirable response option over an alternative prepotent response. Not surprisingly, inhibitory control changes dramatically over development with robust individual differences in adulthood, and has been implicated in multiple forms of psychopathology including attention deficit hyperactivity disorder (Aron, 2011; Bhaijiwala et al., 2014) and obsessive-compulsive disorder (Tolin et al., 2014).

A central challenge to studying inhibitory control is that it comes in many flavors. A recent review by Aron provides a useful taxonomy, classifying inhibitory control along two key dimensions (Aron, 2011). The first dimension contrasts global control and selective control. In global inhibitory control tasks (Aron and Verbruggen, 2008), global inhibition of the motor system is required whenever a specific stimulus is presented, while in selective control tasks, the specifics of the stimulus determine the control needed to slow down the system to give enough time for one particular set of response tendencies to win out over another when conflict is detected (for detailed review, see Aron (2011).

The second dimension in Aron's taxonomy contrasts reactive and proactive control (Aron, 2011). In the former case, participants must inhibit a behavior in reaction to a specific stimulus *after* a response has been prepared. This type of control is often studied in a stop-signal paradigm where participants are instructed to stop a previously prepared response when a stop-signal is presented. Proactive control, by contrast, occurs where there is some advance control process that modulates behavior *before* the presentation of a response cue. Proactive control often implicates attentional or working memory processes that

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modulate control in task-appropriate ways. For instance, actively maintaining information in working memory (WM) can have inhibitory consequences, suppressing the influence of potentially distracting information.

Given the challenges of teasing apart different aspects of inhibitory control at the behavioral level, many studies have examined inhibitory control at the neural level. Data from both neurophysiology and fMRI have revealed a fronto-cortical-basal ganglia network critically involved in reactive control. This network includes the inferior frontal cortex (IFC), the pre-supplementary motor area (preSMA), the basal ganglia, and aspects of the motor system including thalamus and motor cortex (Aron et al., 2014a,b; Braver et al., 2001; Garavan et al., 2002, 2003; McNab et al., 2008; Menon et al., 2001; Mostofsky et al., 2003; Rae et al., 2015; Rubia et al., 2003; Simmonds et al., 2008). This same network may play a key role in 'braking' in proactive control tasks (Aron, 2011), but proactive control likely also involves other WM systems including the dorso-lateral prefrontal cortex (DLPFC) (Barber et al., 2013; Hester et al., 2004; McNab et al., 2008).

In the present report, we focus on a recent controversy regarding the neural systems that underlie reactive inhibitory control. A large body of evidence suggests that a fronto-cortical-striatal network is actively involved in inhibitory control, with a specific part of this network – rIFC and preSMA (Rae et al., 2015) – playing a braking function in reactive tasks. But a recent paper suggests that this fronto-striatal network is also engaged in attentionally-demanding conditions that do not have obvious inhibitory requirements (Erika-Florence et al., 2014). For instance, these researchers found increased activation in the rIFC network in response to infrequent cues across four task variants, even in tasks with no inhibitory demands. These data are consistent with prior studies that also suggested an attentional/WM role for the fronto-striatal network (Erika-Florence et al., 2014; Hampshire, 2015; Hampshire et al., 2010; McNab et al., 2008). More recently, Swick and Chatham have pointed out that tasks need to be designed such that they contain conditions matched for saliency and attentional demands amongst other elements (Swick and Chatham, 2014). Thus, at the heart of this controversy is whether there is a right-lateralized network for inhibitory control or a network involved in a broader class of control operations, including attention to rare events and the modulation of processing via task goals in working memory.

Here, we examine this controversy using two different reactive control tasks – one task that requires global reactive control – the GnG task – and one that requires selective reactive control – the Simon task. By studying tasks along the global-to-selective control dimension,[1] we hope to tap a range of tasks relevant to daily life that may have broad implications for populations with deficits in inhibitory control.

We examined two central questions about how the role of fronto-cortical-striatal system may differ during selective versus global reactive control. First, is the fronto-cortical-striatal system sensitive to the need for inhibition per se or the need for control on rare, attentionally-demanding trials? To address this question, we varied the response frequency of trials that do not require motoric inhibition (Go trials). In a frequent condition, participants completed a block of GnG trials with many Go trials and few Nogo trials. We contrasted performance in this condition with a block of trials with frequent Nogo trials and few Go trials. If fronto-cortical-striatal networks are sensitive to the inhibitory demands of the task, we expected to see greater activation on trials that require inhibition than during trials that do not require inhibition. By contrast, if fronto-cortical-striatal networks are sensitive to the need for control during rare, attentionally-demanding events, we expected to see greater activation during infrequent trials, regardless of whether these trials occurred during a frequent Go block or a frequent Nogo block. An important question is whether such effects generalize across tasks. Thus, the same participants completed a Simon task where the frequencies of Compatible and Incompatible trials were manipulated across blocks in an analogous fashion.

The second question we examined was whether activation of the fronto-cortical-striatal system is modulated by the need for inhibition per se or by the WM demands of the task. To examine this issue, we varied the memory load, while holding attentional demands constant (i.e., equal numbers of Go/Compatible and Nogo/Incompatible trials). In particular, we changed the number of stimulus-response (SR) mappings that participants had to maintain in both the GnG and Simon tasks. Previous studies have demonstrated that WM maintenance has a particular neural signature – activation increases as the WM load increases (Pessoa et al., 2002; Pessoa and Ungerleider, 2004; Todd and Marois, 2004). Thus, if WM is critically involved in these tasks, we would expect to see an increase in activation as the load increases within WM-specific regions of the fronto-cortical-striatal network. Data from several studies are consistent with this hypothesis. For instance, an increase in activation was observed within middle frontal gyrus, left middle temporal gyrus, thalamus, and rostral and dorsal ACC/preSMA as the memory load was increased in a GnG task (Hester et al., 2004).

Materials and methods

Participants

Twenty right-handed native English-speaking participants (age range 25±4 years; 9 women) took part in the experiment. All of them were students at the University of Iowa. All participants had normal or corrected vision. All participants signed an informed consent form approved by the Ethics Committee at the University of Iowa.

Procedure

The experimental paradigms were created using E-prime version 2.0 and were run on an HP computer (Windows 7). Participants were instructed that they would be given a set of response mappings that would be indicated before the start of each block. There were no practice trials, but participants were shown the sequence of events for a couple of trials to make sure they knew what they were going to do in the scanner.

In the GnG task, observers were asked to press a button when they saw a Go stimulus and withhold their response when they saw a Nogo stimulus (see Fig. 1B). In the Simon task, participants were asked to press the left button for one set of colors and the right button for a second set of colors (see Fig. 1C). On half the trials, stimuli were presented in the compatible hemifield (i.e., the color associated with a left button press was presented in the left hemifield), while on the other half of trials, stimuli were presented in the incompatible hemifield (i.e., the color associated with a left button press was presented in the right hemifield).

Stimuli were all the same shape and varied in color. The colors were equally distributed in CIELAB 1976 color space, a perceptually uniform color space and color-appearance model developed by the Commission Internationale de l'E´clairage. The shape was chosen from Drucker and Aguirre (Drucker and Aguirre, 2009). Colors used for the GnG task were separated by 30 degrees in color space from those colors used in the Simon task (see Fig. 1A). Within a task, the colors associated with specific responses (i.e., Go color and Nogo color) were chosen by going around the color wheel in a clockwise direction. The chosen colors were separated by 60 degrees in color space such that directly adjacent colors were associated with different response types. This prevents participants from adopting any sort of color category response strategy. Participants indicated the response for each trial using left and right

[1] Note that although the GnG and Simon tasks differ along this key dimension, these tasks can be conceptualized in other ways as well. For instance, the Simon task is often discussed as a 'resistance to interference' task. Critically, these different conceptualizations are not mutually exclusive.

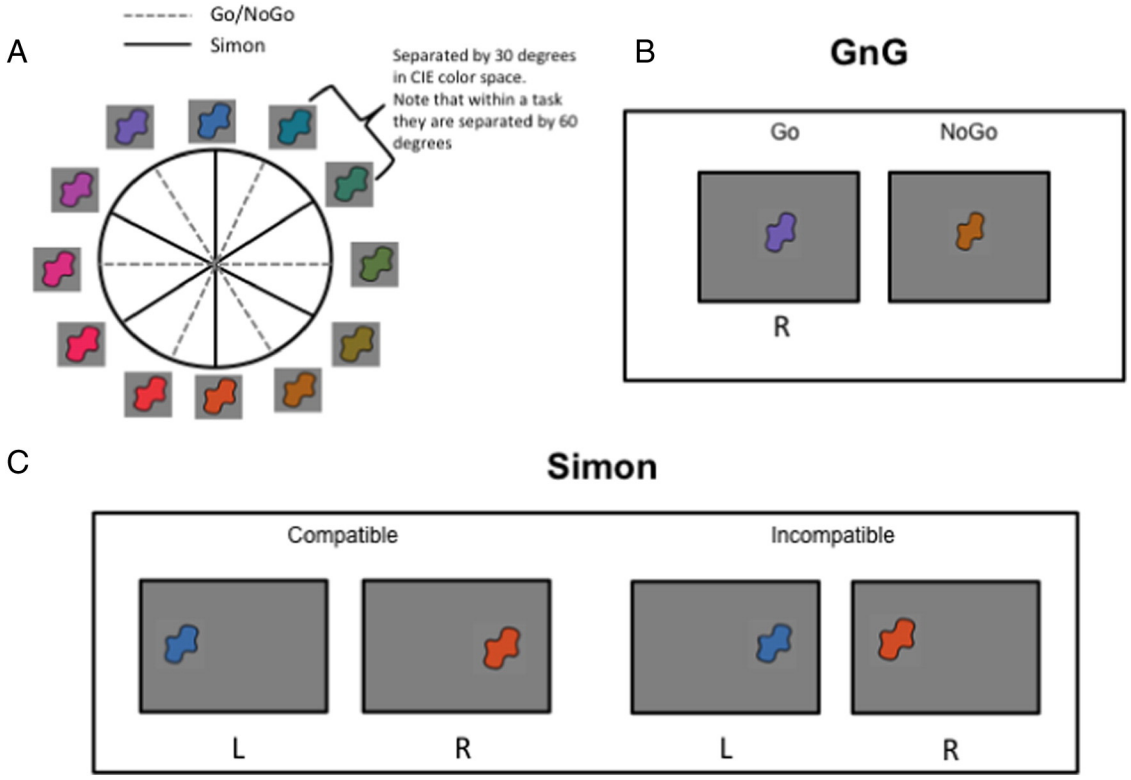

Fig. 1. (A) Colors of the stimuli used for both tasks. Colors used for the GnG task (dotted lines) were separated by 30 degrees in color space from colors used in the Simon task (solid lines). Colors used for different types of trials (i.e., Go or Nogo) within a task were separated by 60 degrees in color space. (B) Example of the stimuli and appropriate responses for the GnG task: the purple stimulus associated with a Go response should result in a right mouse button response whereas the orange stimulus associated with a Nogo response should result in no response. (C) Example of the stimuli and appropriate responses for the Simon task: the left button (L) should be pressed when the blue stimulus appears and the right button (R) should be pressed when the orange stimulus appears. These stimuli can appear in spatially Compatible locations (left display) or spatially Incompatible locations (right display).

manipulandam boxes. The first chosen color was determined randomly for each participant.

In both tasks, the trial started with the presentation of the fixation cross for 2500 ms, followed by the stimulus presentation for 1500 ms. Participants were instructed to respond as quickly as possible. If a response was not entered in time (within 250 ms of stimulus presentation), 'No Response Detected' was displayed on the screen. The inter-trial interval was jittered between 1000 (50% of trials), 2500 (25%), or 3000 ms (25%). In the GnG task, the stimulus was always presented in the center of the screen; in the Simon task, the stimulus was presented at the center of the left or right hemifield (see Fig. 2).

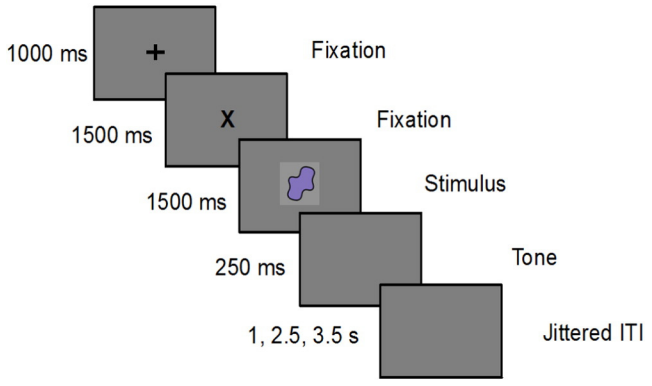

Fig. 2. Trial structure of the GnG and Simon tasks (GnG display is shown as an example). Note that the fixation turned from a '+' to an 'x' to keep the timing of events consistent with other tasks the same participants completed in other sessions not reported here.

Design

We conducted two parametric manipulations of each task – a Load manipulation and a Proportion manipulation. In the Load manipulation, the number of SR mappings was varied across three conditions – Load 2, 4, and 6. In the Load 2 condition of the GnG task, one stimulus was associated with a Go (button press) response and another with a Nogo response (no button press). In the Simon task, one stimulus was associated with a left button press and the other with a right button press. In the Load 4 condition of the GnG task, two stimuli were associated with a Go response and two other stimuli were associated with a Nogo response. In the Simon task, two stimuli were associated with a left button press and two stimuli were associated with a right button press. In the Load 6 condition of the GnG task, three stimuli were associated with a Go response and three other stimuli were associated with a Nogo response. In the Simon task, three stimuli were associated with a left button press and three other stimuli were associated with a right button press. For all manipulations of Load, 50% of the trials in the GnG task were Go trials and 50% were Nogo trials. Similarly, for the Simon task, 50% of the trials were Compatible trials and 50% were Incompatible trials.

For the Proportion manipulation, we varied the proportion of trials that did not require inhibition (Go trials, Compatible trials) relative to trials that required either inhibition of a response (Nogo trials) or inhibition of an incorrect SR mapping (Incompatible trials). In the 25% condition of the GnG task, 25% of the trials (36 trials) were Go trials and the remaining were Nogo trials (108 trials). In the Simon task, 25% of the trials (36 trials) were Compatible trials and the remaining were Incompatible trials (108). In the 50% condition of the GnG task, 50% of the trials were Go trials (72 trials) and the remaining were Nogo trials. In the Simon task, 50% of the trials were Compatible trials (72 trials), and the remaining were Incompatible trials. Finally, in the

75% condition of the GnG task, 75% of the trials were Go trials (108 trials) and the remaining were Nogo trials. In the Simon task, 75% of the trials were Compatible trials (108 trials) and the remaining were Incompatible trials. The Load was maintained at 4 stimulus-response mappings across all manipulations of Proportion.

Participants completed five total runs on the GnG scanning day: Load 2 (50% Go, 50% Nogo), Load 4 (50% Go), Load 6 (50% Go), 25% condition (25% Go trials at Load 4), and the 75% condition (75% Go trials at Load 4). Participants completed five runs on the Simon scanning day: Load 2 (50% Compatible), Load 4 (50% Compatible), Load 6 (50% Compatible), 25% condition (25% Compatible trials at Load 4), and the 75% condition (75% Compatible trials at Load 4). There were eight possible orders, randomly selected for each day: 6-4-2-25-75, 6-4-2-75-25, 2-4-6-25-75, 2-4-6-75-25, 25-75-2-4-6, 75-25-2-4-6, 25-75-6-4-2 or 75-25-6-4-2. The order of the scanning days (GnG first versus Simon first) was counterbalanced across participants.

Image acquisition and processing

A 3T Siemens TIM Trio magnetic resonance imaging system with a 12-channel head coil located at the Magnetic Resonance Research Facility at the University of Iowa was used. Anatomical T1 weighted volumes were collected using an MP-RAGE sequence. Functional BOLD imaging was acquired using an axial 2D echo-planar gradient echo sequence with the following parameters: TE=30 ms, TR=2000 ms, flip angle=70°, FOV=240×240 mm, matrix=64×64, slice thickness/gap=4.0/1.0 mm, and bandwidth=1920 Hz/pixel. Each run was approximately 15 minutes and collected 454 volumes.

Head movement was restricted using foam padding inserted between the observer's head and the head coil. Both tasks were presented using E-prime software and a high-resolution projection system. The stimuli were subtended at a visual angle of 3.2–4.2 degrees. Responses were recorded by a manipulandum strapped to the participants' hands. The timing of the presented stimuli was synchronized to the trigger pulse from the MRI scanner.

Data were analyzed using Analysis of Functional NeuroImages (AFNI) software. Standard preprocessing was used that included slice timing correction, outlier removal, motion correction, and spatial smoothing (Gaussian FWHM=8mm). First-level analyses consisted of constructing a general linear model using *afni_proc* with regressors for motion, drifts in baseline, and ten regressors of interest for each task. In the GnG task, the regressors of interest were onset of the stimulus presentations for Go and Nogo trials at Loads 2, 4 and 6 and at Proportions 25% and 75%. Similarly, in the Simon task, the regressors of interest were onset of the stimulus presentations for Compatible and Incompatible trials at Loads 2, 4 and 6 and at Proportions 25% and 75%.

To analyze the group-level data, we used the percent signal change maps for each regressor in two three-factor ANOVAs designed to identify group-level effects associated with the Load and Proportion manipulations. The factors for the Load ANOVA were Task (GnG, Simon), Type (Go/Compatible, Nogo/Incompatible), and Load (2, 4 and 6). The factors for the Proportion ANOVA were Task (GnG, Simon), Type (Go/Compatible, Nogo/Incompatible), and Proportion (25%, 50%, 75%). Note that the Type factor grouped trials that do not require any form of inhibition (Go/Compatible) and trials that require some form of inhibition (inhibition of a motor response on Nogo trials, and inhibition of an incorrect SR mapping on Incompatible trials). Although in the latter case we effectively group two different senses of inhibition, it is important to note that differences between them could emerge in regions that show a significant Task × Type interaction.

Group level analyses were done using AFNI's *3dMVM* function. Resultant functional images of main effects and interactions were corrected for family-wise errors using 3dClustSim (corrected at alpha <0.05, corresponding to a cluster size threshold of and a cluster threshold of >27 voxels i.e 1158 ml). Centers of mass for the resulting significant clusters are reported in later tables. If effects shows clusters that were large and could be broken into more regions, they were intersected with an atlas and then re-labeled. *3dROIStats* was then used to compute the average percent signal change for each subject across all conditions for each cluster identified as significant within the main effect or interaction. For example, if a cluster in the right inferior parietal lobule showed a main effect of Load, an average percent signal change was calculated for each subject across all voxels in that cluster for Loads 2, 4, and 6. Paired two-tailed t-tests were performed on these average percent signal change values. The threshold for these t-tests were maintained at $p<0.05$. Note that no further correction for multiple comparisons was performed given that a correction was already carried out at the level of the omnibus ANOVAs. Moreover, the goal of these t-tests was primarily descriptive in nature – to help describe the pattern of data underlying the ANOVA effect in question.

ROI-based analyses were also carried out within 10 mm spherical regions defined using coordinates from previous reports. The goal was to investigate whether the need for Inhibitory control as the Proportion of each trial type was manipulated elicited activation in targeted ROIs including right inferior frontal cortex (IFG) – (Hampshire, 2015), pre-supplementary area (PreSMA) – (Hampshire et al., 2010) and right superior temporal gyrus (STG) and right inferior parietal lobule (IPL) – collectively referred to as the right temporo-parietal junction (Corbetta et al., 2000). A 3-factor (Task, Type, Proportion) ANOVA was computed within this mask using a voxel-wise correction with $p<0.01$. Voxels that showed a main effect or interaction were clustered, and we computed an average percent signal change for the relevant effect. Paired two-tailed t-tests were performed on these average percent signal change values with $p<0.05$. Note that average percent signal change within each ROI was also calculated for each subject. A three-factorial ANOVA on data from each ROI revealed no significant main effects or interactions.

Results

Behavioral results

Only correct trials were analyzed as accuracy was over 86% for both tasks and all conditions (see Table 1).

For the GnG task, two (Load, Proportion) one-factor repeated measures ANOVAs were conducted on reaction times (RTs) for Go trials. Results from the ANOVA examining the effect of Proportion (25%, 50%, 75%) on RTs revealed a main effect of Proportion, $F(2,38) = 6.546$, $p<0.005$. Post-hoc comparisons using t-tests with revealed that RTs were significantly slower when 25% of the trials were Go trials as compared to when 75% of the trials were Go trials, $p<0.005$ (Fig. 3A). Results from the ANOVA examining the effect of Load (2, 4, 6) revealed a main effect of Load, $F(2,38) = 48.892$, $p<0.001$. Post-hoc comparisons revealed that RTs increased with increasing Load for all pairwise comparisons, $p<0.001$ (Fig. 3B).

For the Simon task, results from a two-way ANOVA with Proportion (25%, 50%, 75%) and Compatibility (Compatible, Incompatible) as factors revealed a main effect of Compatibility on RTs, $F(1,19) = 14.251$, $p<0.005$, with greater RTs for Incompatible trials than for Compatible trials (Fig. 3C). A second two-way ANOVA with Load (2, 4, 6) and Compatibility as factors revealed a main effect of Load on RTs, $F(2,38) =$

Table 1
Percentage (%) of correct trials for Go, Compatible and Incompatible trials. Overall accuracy of 86.5 % and above was achieved.

	Percentage of correct trials (%)			
	Go	NoGo	Compatible	Incompatible
Load 2	96.5	99.7	91.5	94.2
Load 4	96.7	97.6	92.3	92.0
Load 6	93.1	94.1	86.5	86.8
Prop 25	93.5	97.1	91.8	93.9
Prop 75	94.6	97.9	93.1	92.1

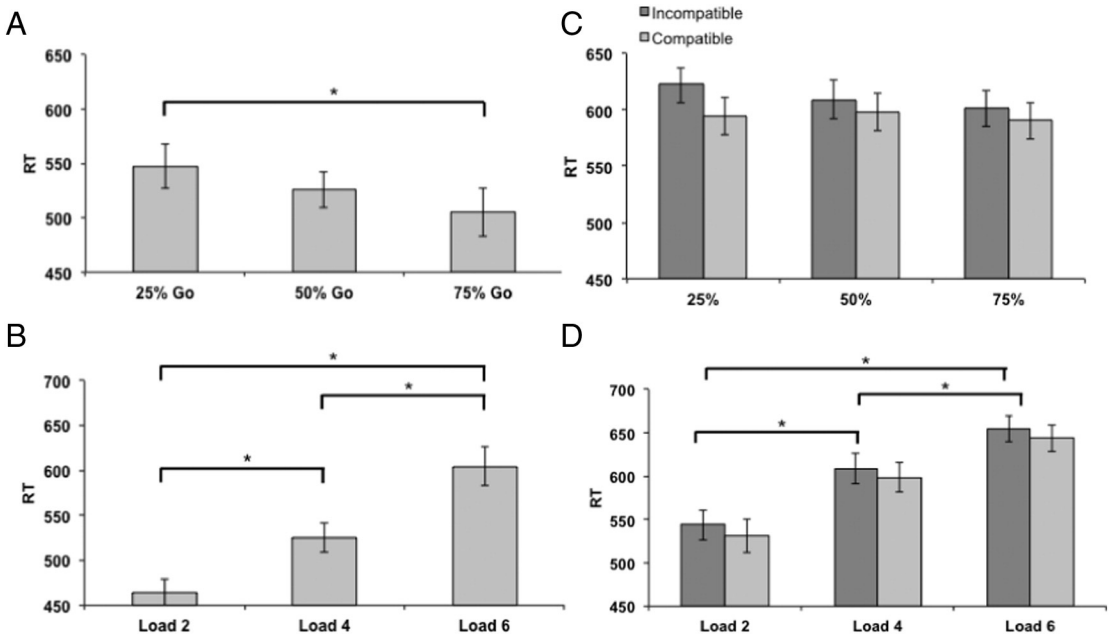

Fig. 3. (Top) Effect of Proportion on RTs for (A) Go trials. RTs at 25% were significantly higher than at 75%. (B.) Compatible and Incompatible trials. RTs to Incompatible trials were greater than for Compatible trials. (Bottom) Effect of Load on RTs for (C.) Go trials. RTs increased with increase in number of stimulus-response (SR) mappings. (D.) Compatible and Incompatible trials. RTs increased with increase in number of SR mappings across Compatible and Incompatible trials. Across all Loads, RTs to Incompatible trials were greater than to Compatible trials.

46.785, $p<.001$, with increasing RTs as load increased. Post-hoc comparisons revealed that all pairwise Load comparisons differed significantly, $p<0.001$ (Fig. 3D). There was also a main effect of Compatibility, $F(1,19) = 10.384$, $p<0.005$ with greater RTs for Incompatible trials than for Compatible trials. Note that the interaction between Load and Compatibility was not significant.

Overview of fMRI analysis approach

We analyzed the fMRI data using two omnibus ANOVAs. The first three-way ANOVA focused on the Proportion manipulation to examine whether Inhibitory control areas are sensitive to the need for control on infrequent trials. This ANOVA included Proportion (25%, 50%, 75%), Type (Go/Compatible, Nogo/Incompatible), and Task (GnG, Simon) as within-subject factors. Our central question is addressed by examining main effects of Proportion and Proportion-related interactions. The second ANOVA focused on the Load manipulation to examine whether particular brain regions show an increase in activation as the number of SR mappings increases consistent with the neural signature of WM. This ANOVA included Load (2, 4, 6), Type (Go/Compatible, Nogo/Incompatible), and Task (GnG, Simon) as within-subject factors. Here, our central question is addressed by examining main effects of Load and any Load-related interactions.

Critically, the omnibus ANOVAs have common factors of Type and Task even though they involve largely independent sets of data. This allows us to partition all effects that do not involve the Proportion or Load factors into two key categories: Task-general effects (e.g., Type main effects) and Task-specific effects (e.g., Task main effects and Task-related interactions). The latter effects reveal the brain systems critically involved in global reactive control versus selective reactive control. Note that, Nogo trials do not require a response whereas Incompatible trials do require a response. Thus, Type × Task interactions may also reflect differences in the amount of motor output.

How is brain activity modulated as the proportion of each Type is varied?

The Proportion × Type × Task ANOVA yielded significant Proportion × Type and Proportion × Task interactions, but no other significant Proportion-related effects after family-wise correction.

Proportion × Type interactions. When Go/Compatible trials were infrequent (25% condition), there was robust activation on these trials relative to Nogo/Incompatible trials in bilateral insula, right putamen, and right thalamus (see Table 2 and Fig. 4). By contrast, as Nogo/Incompatible trials became less frequent (75% condition), there was a robust increase in activation on these trials relative to Go/Compatible trials in the same regions. Indeed, in right putamen, the pattern completely reversed across the Proportion manipulation, showing robust activation on infrequent trials, regardless of whether they required inhibition. Thus, activation in these regions reflects the need for control on infrequent types rather than the need for inhibition per se.

Proportion × Task interactions. There was a significant Proportion × Task interaction in the thalamus (see Table 3 and Fig. 5), indicating that there were different demands placed on the need for control in the two tasks. In particular, the need for control was greatest in the GnG task in the 25% condition where the infrequent trials required an active response (i.e., the Go trials). Thus, the thalamus is responsive to the need for control on infrequent trials when a response is needed (vs. Nogo trials). The Simon task requires an active response on both Compatible and Incompatible Types. Here we see the greatest modulation of thalamic activity in the 75% condition when Incompatible trials were infrequent, that is, when an infrequent response must be activated *and* this response requires inhibition of a strongly prepotent response.

ROI-based analyses. Whole-brain analyses did not yield significant differences in activation for regions in right IFG and pre-SMA as the need for control was varied. It is possible effects in these canonical

Table 2
Regions activated for Proportion × Type interaction ($p<0.05$, corrected).

Cluster Region	Hemi	BA	Talaraich (RAI) (mm)			Size (ml)	F(4,76)
			x	y	z		
Insula	L	13	29.1	−9.5	7	4630	8.03
	R	13/47	−33.9	−14	3.6	3473	9.32
Thalamus	R	-	−2.6	18.7	5	3773	8.28
Putamen	R	-	−26.8	10.7	−3	1372	7.60

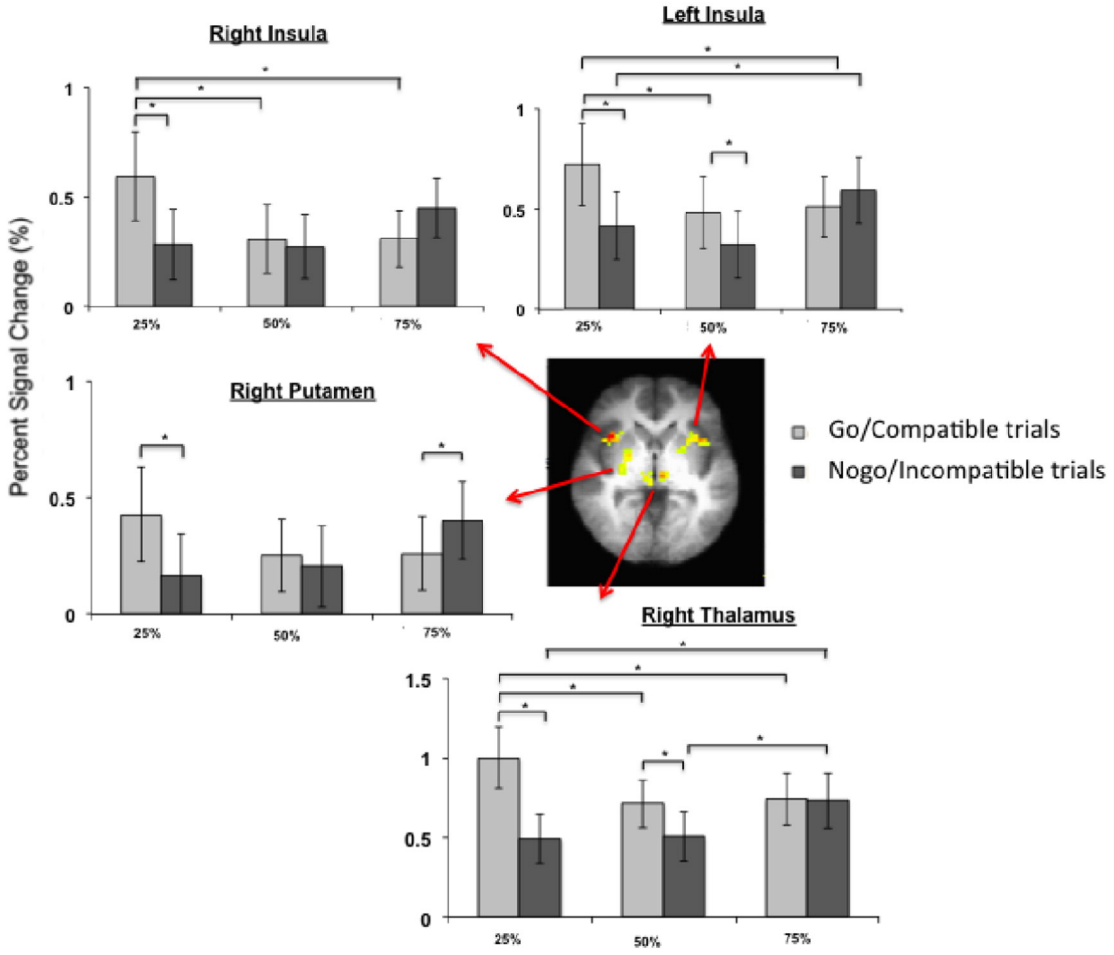

Fig. 4. Bar plots showing average percent signal change ± S.E.M. across Go/Compatible trials and Nogo/Incompatible trials at Proportions of 25 %, 50 % and 75 %. Significance at $p < 0.05$ is denoted by '*'.

inhibitory-control regions were weak and might not have survived whole-brain correction for multiple comparisons. Thus, we conducted a ROI-based analysis, examining activity in right IFG, preSMA, and right TPJ. Results from a three-factorial ANOVA revealed a significant Type × Proportion interaction in the right STG and a significant Task × Proportion × Task interaction in the right middle temporal gyrus (MTG). Fig. 6a shows the Type × Proportion effect for right STG. This area followed the same pattern reported in the whole brain analyses: there was greater activation on Go/Compatible trials in the 25% condition and there was an increase in activation on Nogo/Incompatiable trials as these trials became less frequent in the 50% and 75% conditions. This trend was also observed in right MTG, but only for the GnG task (see Fig. 6b). Note that there were no significant effects in the right IFC and preSMA ROIs.

How is brain activity modulated as the memory load increases?

The Load × Type × Task ANOVA revealed main effects of Load and Load × Type interactions. No other Load-related effects reached significance after family-wise correction.

Table 3
Region activated for an interaction between Proportion and Task (p<0.05, corrected).

Cluster Region	Hemi	BA	Talaraich (RAI) (mm)			Size (ml)	F(4,76)
			x	y	z		
Thalamus	R	-	−10	2.3	12	1501	7.53

Main effects of load. Activation in the right inferior parietal lobule was largest for a Load of two items and decreased with an increase in Load (Table 4 and Fig. 7). This pattern is the opposite of what is typically observed in studies of WM. This suggests that the SR mappings in these tasks are not actively maintained in WM. It is possible that another form of memory such as associative memory is responsible for remembering the task rules. We return to this possibility in greater detail below.

Load × Type interactions. A broad network of regions showed significant Load × Type interactions (see Table 5 and Figs. 8 and 9). This network included the bilateral cerebellum, bilateral superior temporal gyrus, right transverse temporal gyrus, right parahippocampal gyrus, right lingual gyrus, right fusiform gyrus, right insula, and right cuneus/posterior cingulate cortex.

In the right transverse temporal gyrus, left superior temporal gyrus, right insula, and bilateral cerebellum, there was a significant decrease in activation as the Load increased, consistent with the general pattern observed in the right inferior parietal lobule for the main effect of Load. Here, however, the decrease over Load only occurred for the Go/Compatible trials – there was no significant change in activation as the Load increased on Nogo/Incompatible trials. We also directly compared activation on the Go/Compatible and Nogo/Incompatible trials at each Load. Here, all regions showed significantly greater activation on Go/Compatible trials at Load 2 relative to Nogo/Incompatible trials. Greater activation on Go/Compatible trials versus Nogo/Incompatible trials was also evident at Loads 4 and 6 in the right transverse temporal gyrus and right fusiform gyrus.

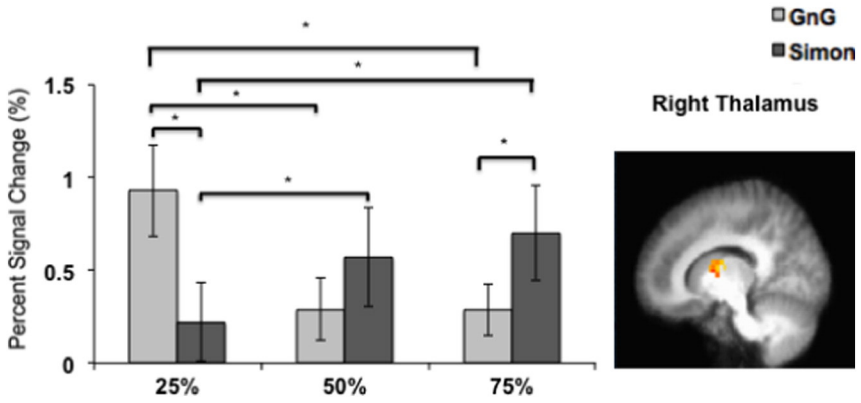

Fig. 5. Bar plots showing average percent signal change ± S.E.M. for GnG and Simon tasks at Proportions of 25%, 50% and 75%. Note, Go and Nogo trials were pooled together for the GnG task and Compatible and Incompatible trials were pooled together for the Simon task. Significance at $p < 0.05$ is denoted by '*'.

Once again, these results are not consistent with the hypothesis that the SR mappings are actively maintained in WM. Further, the differential activation on Go/Compatible trials suggests that these mappings are represented differently than mappings during Nogo/Incompatible trials. It is possible, for instance, that the mappings during the Go trials are stored in an associative memory that varies systematically by Load, while the mappings during Nogo trials are not remembered. We return to this possibility in the Discussion.

Do the demands of trial Type generalize across tasks?

Across the two omnibus ANOVAs, there was a broad network of brain regions that showed a common Type main effect in both analyses with greater activation on Go/Compatible versus Nogo/Incompatible trials. This network included bilateral transverse temporal gyrus, bilateral insula, bilateral superior temporal gyrus, left cingulate gyrus, left inferior parietal lobule, left precentral gyrus, bilateral medial frontal gyrus, right cerebellum, left putamen and bilateral thalamus (see Table 6). An example pattern of activation is shown in Fig. 10B for the left transverse temporal gyrus. This region showed greater activation on Go/Compatible trials when there were no inhibitory demands, suggesting that this region is actively involved in response selection and/or generation.

Note that the spatial pattern of results showed good overlap across the two omnibus ANOVAs. An example is shown in Fig. 10A. Yellow colors show voxels with a significant Type main effect in both ANOVAs, while red colors show voxels with an effect that was unique to one ANOVA or the other. Given the robust overlap, we only show significant findings in Table 6 for clusters that intersect across both ANOVAs.

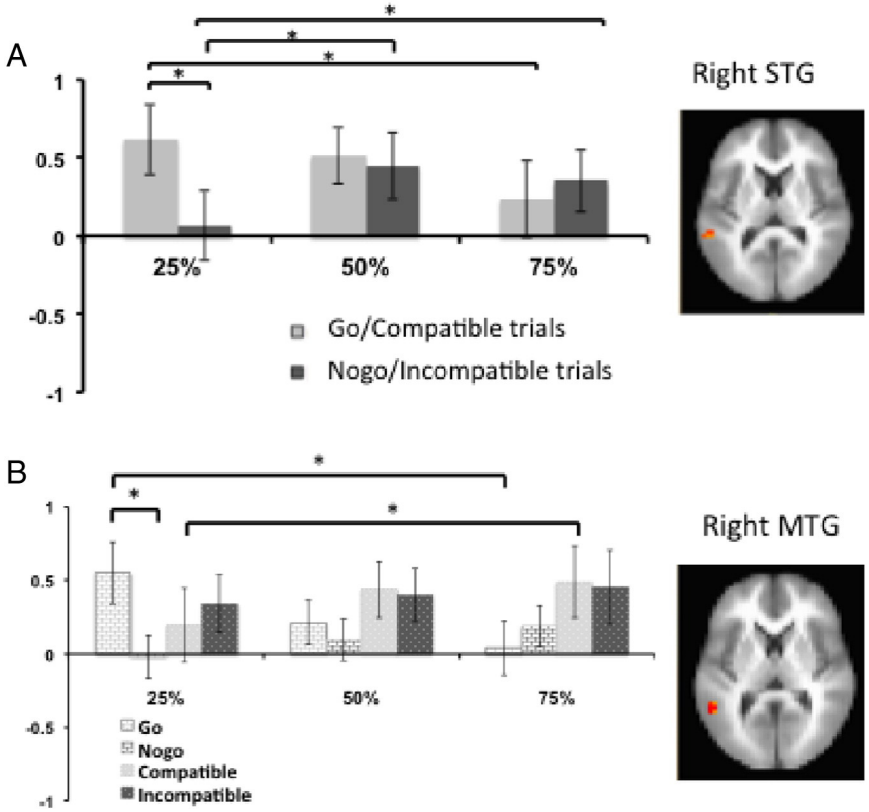

Fig. 6. Bar plots showing average percent signal change ± S.E.M. ROIs for (a) Right superior temporal gyrus (b) Right middle temporal gyrus. Significance at $p < 0.05$ is denoted by '*'.

Table 4
Region activated for the main effect of Load (p<0.05, corrected).

Cluster Region	Hemi	BA	Talaraich (RAI) (mm)			Size (ml)	F(2,38)
			x	y	z		
Inferior Parietal Lobule	R	13/41	−44.2	32	22.3	1415	11.49

Table 5
Regions activated for Load × Type interaction (p<0.05, corrected).

Cluster Region	Hemi	BA	Talaraich (RAI) (mm)			Size (ml)	F(4,76)
			x	y	z		
Cerebellum	L	-	−6	45	−13	5317	8.82
Transverse Temporal Gyrus	R	41/13	−44.2	25.9	12	2144	8.44
Cuneus / Posterior Cingulate Cortex	R	30	−10.9	67.8	13.3	1758	7.68
Cerebellum	R	-	−35.3	52.5	−23	1715	7.49
Insula	R	-	−33	−4.3	5	1629	8.33
Superior Temporal Gyrus	L	41	41.5	34	7.1	1501	8.21
	R	13	−45.3	47.3	18.2	1286	9.61
Parahippocampal Gyrus	R	30	−24	−19	46	1029	8.18
Lingual Gyrus	R	19	16	−49	−1	300	10.10
Fusiform Gyrus	R	37	−37	25	−7.5	129	7.00

What patterns of brain activity are specific to each task?

The two omnibus ANOVAs revealed two sets of task-specific effects: significant Task main effects and significant Task × Type interactions. Given that the latter results relate to the Type main effects discussed in the previous section, we discuss these effects first and then conclude with the Task main effect.

Task × Type interactions. A broad network of regions showed clusters with significant Task × Type interactions. An example for the left insula is shown in Fig. 11B. Go trials elicited greater activation than Nogo trials, with comparable activation on Compatible and Incompatible trials. As with the Type main effect described above, there was robust spatial overlap in results from the two omnibus ANOVAs. Fig. 11A shows an example of the overlap between these regions.

Table 7 shows the full set of results for clusters that intersected across both ANOVAs. The areas showing common activation across both ANOVAs were left transverse temporal gyrus, left insula, left superior temporal gyrus, left inferior parietal lobule, left postcentral gyrus, bilateral medial frontal gyrus, right cerebellum, left putamen and bilateral thalamus. In all of these regions, there was significantly stronger activation on Go trials than on Nogo trials. There was stronger activation for Go trials than Compatible trials in left insula, left postcentral gyrus, right cerebellum, left putamen and left thalamus. Incompatible trials elicited greater activation than Nogo trials in the left transverse temporal gyrus, left insula, left IPL, bilateral medial frontal gyrus, right cerebellum, left putamen and bilateral thalamus. Note that, these results were consistent across both ANOVAs.

What is driving the Task × Type interactions? Recall that activation decreased as the number of Go/Compatible S-R mappings increased (Load main effect), and this effect was particularly robust on Go/Compatible trials (Load × Type interaction). It is possible we are seeing a related effect here. In GnG, there were 1, 2, or 3 stimuli that required an active response. In Simon, there were 2, 4, or 6 stimuli that required a response. The Task × Type interaction might reflect this difference across tasks, with greatest activation on the Go trials given that there are few SR mappings where a response is required, weaker activation in Simon given that there are many SR mappings where a response is required, and weakest activation on Nogo trials because no response was required. Thus, there appears to be weaker engagement of motor-related areas as the number of stimuli that require a manual response across tasks is increased.

Task main effect. The Simon task elicited positive activation in bilateral lingual gyri whereas activation was negative for the GnG task. This result was consistent across both ANOVAs (see Table 8 and Fig. 12). Increased lingual gyri activation has been previously linked to shifts of visuo-spatial attention to the contralateral hemifield of stimulation. The Simon task places a heavy burden on control of spatial attention, because on Compatible trials, spatial attention can facilitate responding while on Incompatible trials, spatial attention can delay correct responding. Increased lingual gyri activation may reflect heightened sensitivity to spatial information in the Simon task. By contrast, stimuli in the GnG task were always presented in the center of the display and Go responses were mapped to a single response button. Both of these factors could have resulted in attenuated activation in the lingual gyri in the GnG task.

Discussion

Previous studies investigating inhibitory control have shown that a distributed fronto-cortical-striatal system is involved in response inhibition and response selection including IFG/IFJ, DLPFC, pre-SMA, SMA, insula, IPL, motor and pre-motor cortices, and sub-cortical regions such as the caudate, putamen, and thalamus. The present study used two reactive control tasks – GnG and Simon – to investigate whether this broad network is sensitive to the inhibitory demands of the task or the need for control as attentional and WM demands are varied.

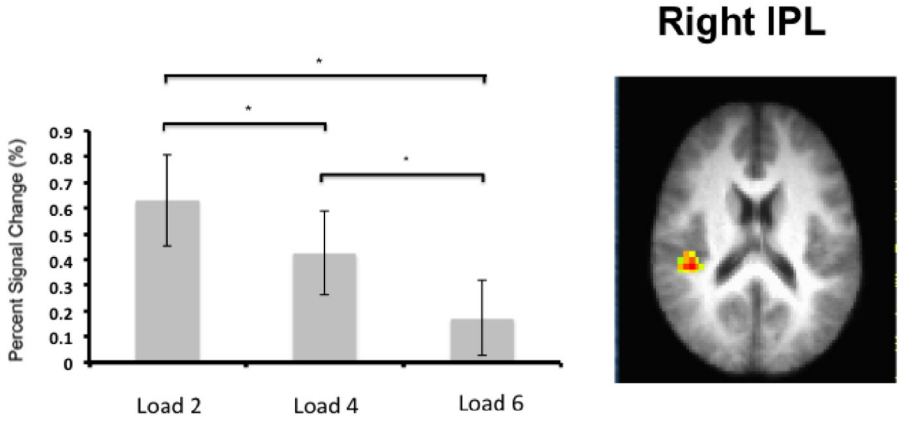

Fig. 7. Bar plots showing average percent signal change ± S.E.M. for Loads 2, 4 and 6 (p<0.05, uncorrected). Note, that beta values were computed by pooling across Type and Task. Significance at p < 0.001 is denoted by '*'.

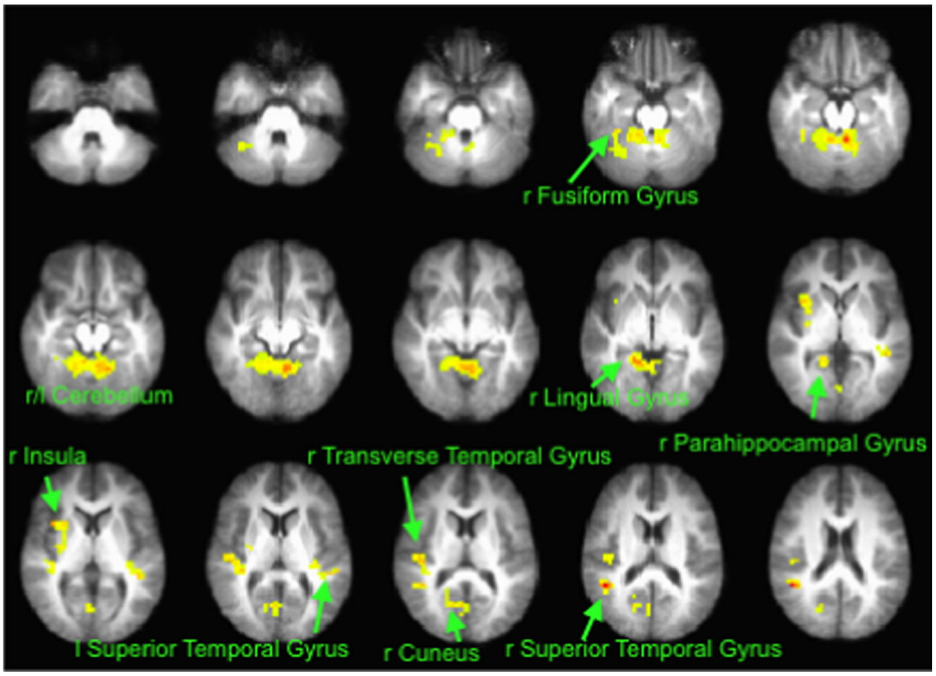

Fig. 8. Regions activated for an interaction between Load and Type. Significance at $p < 0.05$ is denoted by '*'.

Below, we discuss findings that emerged from our multi-factorial ANOVAs and then discuss how these regions work together to carry out cognitive control.

A cortical-subcortical circuit is activated by the need for control on rare events

Previous fMRI studies have shown robust IFC (Aron, 2011; Liddle et al., 2001; Munakata et al., 2011; Simmonds et al., 2008; Wager et al., 2005), insula (Dodds et al., 2011; Wager et al., 2005), and subcortical activation (Kelly et al., 2004; Liddle et al., 2001; Wager et al., 2005) in reactive inhibitory control tasks such as the GnG task. After findings from recent work, Aron and colleagues updated their claims to report that rIFG was activated by a stop signal or an unexpected event and engaged a brake by slowing down, pausing or completely stopping an action (Aron et al., 2014a,b). Most studies, however, have probed response control by employing a smaller number of trials that require inhibition than trials that do not (Kelly et al., 2004; Mostofsky et al., 2003; Wager et al., 2005). This confounds inhibitory control with modulation of response selection processes on rare, attentionally-demanding events. Thus, in the present study, we varied the proportion of trials to probe whether cortical and subcortical activation was specific to the need for inhibition on Nogo and Incompatible trials, or whether these networks were robustly active on attentionally-demanding rare events regardless of the need for inhibition. Results show that bilateral insula, right putamen, and right thalamus were active on infrequent trials, regardless of whether these trials require or do not require inhibition and regardless of whether the task required 'global' or 'selective' control.

Results showing insula activation on rare, attentionally demanding trials are consistent with previous studies that have identified this area as part of a salience network (Menon and Uddin, 2010; Sridharan et al., 2008; Uddin, 2015). The insular cortex facilitates detection of target stimuli amongst distractors in oddball paradigms, suggesting this

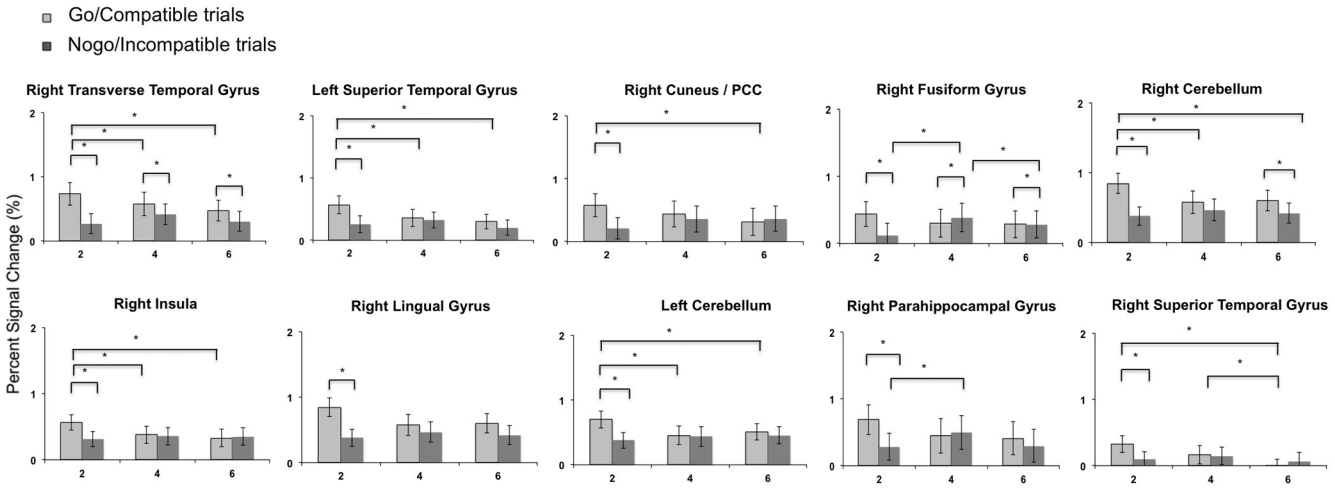

Fig. 9. Bar plots showing average percent signal change ± S.E.M. for the interaction between Load and Type. Significance at $p < 0.05$ is denoted by '*'.

Table 6
Regions activated for a main effect of Type for the intersection between the Proportion and Load ANOVAs ($p<0.05$, corrected). Only regions with clusters > 2 voxels (86 ml) are presented and discussed.

Cluster Region	Hemi	BA	Size (ml)	Talaraich (RAI) (mm)			Load F(X,Y)	Proportion F(X,Y)
				x	y	z		
Transverse temporal gyrus	L	41	472	42.6	25	10	28.25	27.11
	R	41	129	−40.2	25.5	10	18.44	25.70
Insula	L	13	7546	38.1	13.5	13.9	40.57	34.44
	R	13	472	−43	28.4	17.4	22.91	23.83
	L	13	43	33.2	1	6.5	34.67	18.37
Superior temporal gyrus	L	41	858	44.1	29.8	15.6	38.76	30.75
	R	41	257	−46.2	27.6	15.4	27.92	28.49
Cingulate Gyrus	L	24	300	6.7 2	2.3	35	32.52	29.91
Inferior parietal lobule	L	13	129	43.8	32.4	24	45.26	24.56
Precentral Gyrus	L	13	129	44.6	−0.5	6.5	39.51	31.87
Medial Frontal Gyrus	L	6	600	3.3	6.9	49.9	35.16	27.67
	R	6	300	−2.6	5.7	48.9	29.92	24.79
Cerebellum	R	19	1115	−20.6	57.3	−15.1	46.26	22.73
	R	37	5274	−23.1	45.8	−18.2	51.11	28.54
Putamen	L	-	557	26.5	9.6	2	33.66	20.46
Thalamus	L	-	2958	11.7	18.8	10.3	27.34	31.66
	R	-	515	11.7	18.8	10.3	25.41	24.82

area plays a role in salience detection (Crottaz-Herbette and Menon, 2006; Downar et al., 2000). The insular cortex jointly with the IFC has also been implicated in switching between the default mode network and the central executive network in saliency-detection tasks that spanned the visual and auditory modalities (Sridharan et al., 2008). This is consistent with a review of insular cortex function by Menon and colleagues who suggested that the function of the insula is to detect salient events and to switch between large-scale networks when salient events are detected via strong coupling between the insula, the anterior cingulate cortex, and the motor system (Menon and Uddin, 2010).

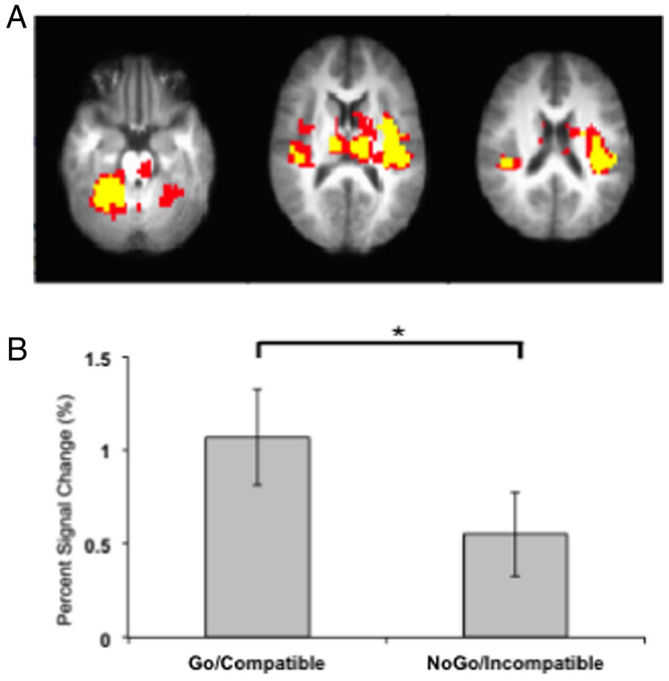

Fig. 10. (A) Regions activated for a main effect of Type for the Proportion and Load ANOVAs. Regions common across both the Proportion and Load ANOVAs are shown in yellow. Regions unique to the Proportion or Load ANOVAs are shown in red. (B) Canonical bar plot of left transverse temporal gyrus but also representative of all activated regions reported in Table 6. Significance at $p < 0.05$ is denoted by '*'.

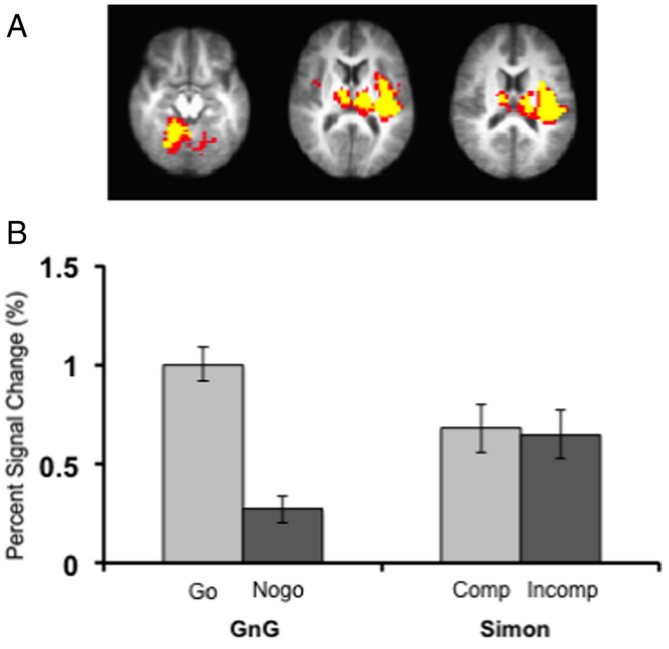

Fig. 11. (A) Regions activated by an interaction between Type and Task for the Proportion and Load ANOVAs. Regions common across both the Proportion and Load ANOVAs are shown in yellow. Regions unique to the Proportion or Load ANOVAs are shown in red. (B) Canonical bar plot of left insula but also representative of all activated regions reported in Table 7, showing average beta coefficient values representative of all Go and Compatible (Comp) trials and Nogo and Incompatible (Incomp) trials for GnG and Simon tasks. Significance at $p < 0.05$ is denoted by '*'.

A recent study tried to dissociate the functional roles of the right inferior frontal cortex and anterior insula, which have both been implicated in inhibitory control (Cai et al., 2014). Their meta-analysis of 70 published studies employing the stop-signal task and GnG suggested that the right anterior insula is important for saliency detection but rIFC is important for inhibitory control. By contrast, the right insula and IFC were reported to not be uniquely engaged in inhibitory control; rather, that these areas belonged to a distributed network engaged in attentional and working memory processes (Erika-Florence et al., 2014). Consistent with this, insular cortex was robustly activated in

Table 7
Regions activated for an interaction between Task and Type for the intersection between the Proportion and Load ANOVAs ($p<0.05$, corrected). Only regions with clusters > 2 voxels (86 ml) are presented and discussed.

Cluster Region	Hemi	BA	Size (ml)	Talaraich (RAI) (mm)			Load F(X,Y)	Proportion F(X,Y)
				x	y	z		
Transverse Temporal Gyrus	L	41	557	39.9	26.6	10	24.99	20.26
Insula	L	13	7203	37	15.3	14.9	32.79	26.07
	L	13	86	33.2	−0.6	6.5	23.78	20.40
Superior Temporal Gyrus	L	41	1029	43.1	30.2	15.3	28.53	22.82
Inferior Parietal Lobule	L	13	129	43.8	32.2	24	33.15	26.15
Postcentral Gyrus	L	40	129	51.4	25.5	15.5	33.57	18.62
Medial Frontal Gyrus	L	6	643	3.1	5.3	49.9	26.83	23.84
	R	-	343	−1.8	6.2	49.8	23.37	18.52
	R	-	2015	−20.2	59.2	−15.1	19.70	26.23
Cerebellum	R	-	5917	−19.7	47.4	−16.5	25.98	30.48
	R	-	214	−7.7	46.5	−13.6	23.79	25.63
Putamen	L	-	1372	24.8	4.7	4.3	20.25	17.37
Thalamus	L	-	3173	12.9	19	10.5	21.42	25.36
	R	-	986	−11	12.8	13.4	19.21	27.09

Table 8
Regions activated for the main effect of Task for the Proportion (left column) and Load (right column) ANOVAs (p<0.05, corrected).

Cluster Region	Hemi	BA	Proportion ANOVA					Load ANOVA				
			Talaraich (RAI) (mm)			Size (ml)	F(1,19)	Talaraich (RAI) mm)			Size (ml)	F(1,19)
			x	y	z			x	y	z		
Lingual Gyrus	L	19	14	64.3	−8.1	5874	16	11.1	67.7	−7.2	1243	14
	R	19	−15.4	70.9	−4.2	2015	17	−13.9	73.4	−5.2	1158	15

the present study whenever rare, attentionally-demanding stimuli were presented. Further support comes from Sharp and colleagues who observed activation in a region they classify as IFG/Insula which showed activation during unexpected events that required stopping or continuing a motor response in a stop-signal task (Sharp et al., 2010).

Evidence from Chatham, Swick and colleagues has suggested that a region close to the anterior insula in the right ventrolateral prefrontal cortex may be involved in context-monitoring of the environment for behaviorally-relevant signals and not motoric stopping per se as evidenced by similar activation on stop trials and trials where a double go response was required (Chatham et al., 2012a,b). Interesting follow-up work by the same group investigating the effects of contextual monitoring in children has shown that practice-based context monitoring improved response inhibition in children more than practice-based motoric stopping (Chevalier et al., 2014). Following this work and in response to rebuttals from Swick and Chatham (2014) and Erika-Florence et al. (2014), Aron (2014b) argue that rIFC activation in the double go trials could still be a result of a brake that does not slow the response. They further argue that 'externally-triggered' braking is inextricably linked to salience detection.

In agreement with Hampshire and colleagues, however, we found that no part of the right IFC was specially activated relative to the need for inhibitory control or the need for control on rare / infrequent trials (Erika-Florence et al., 2014; Hampshire, 2015; Hampshire et al., 2010). It is possible that rIFG is only selectively activated in reactive inhibition tasks where a prepared motor response has to be cancelled or the brakes applied in response to a sudden-onset cue as in the stop-signal task. We note that the reactive inhibition tasks used here, by contrast, placed heavy demands on response selection processes as each stimulus was selectively mapped to a particular response.

As with insular cortex, we found that the right putamen displayed an increase in activation in response to the need for control on salient / infrequent trials. The putamen forms part of the striatum, which is known to connect to the cortex through pallidal, nigral and thalamic structures and also receive input via organized projections (Alexander et al., 1986). The putamen has been implicated in cognitive functions pertaining to stimulus-response and habit learning whereas its structural counterpart, the caudate nucleus, is important for processing underlying goal-directed behavior (Grahn et al., 2008). The putamen has also been shown to co-activate with motor and sensorimotor areas (Alexander and Crutcher, 1990; Parent and Hazrati, 1995). We suggest the putamen plays a role in the detection of infrequent stimulus-response mappings and helps to regulate response selection by modulating motor circuits.

Right thalamus activation was also modulated by the need for control on rare, attentionally-demanding trials. This is consistent with previous studies showing that thalamic functions include planning and monitoring of response selection and acting like a relay between cortico-subcortical structures (Karnath et al., 2002; Sherman and Guillery, 2002). Further, neuronal projections from the thalamus to the striatum are known to pass information about shifts in attention after the onset of salient stimuli. A recent study suggests that this modulation might occur via feed-forward connections that relay information from the thalamus to the putamen and then to relevant motor circuitry (Ding et al., 2010).

In addition to results showing thalamic activation on rare trials, we also found differential thalamic activation across the two tasks, with greater activation on Go trials in the GnG task when these trials were rare, and greater activation on Incompatible trials in the Simon task when these trials were rare. This pattern of activation likely reflects the different demands placed on the motor system in these two tasks. The GnG task only requires a motor response on Go trials. Thus, the strong thalamic activation on rare Go trials suggests that the thalamus is selectively engaged on attentionally-demanding trials that require a motor response. In the Simon task, this is the case on both types of trials because a motor response is always required in this task. Here, the stronger thalamic activity on rare, Incompatible trials likely reflects the need for additional control to suppress responding to the spatial aspects of the stimulus and focus on the color of the stimulus.

Interestingly, the thalamic activation reported here is consistent with a study by Zhang et al. (2008) who used partial correlations on resting state scans to extract the connectivity patterns of five parcellated ROIs with the thalamic nuclei. In the present study, thalamic regions near the medial dorsal nucleus showed a significant Proportion × Type effect. Zhang et al. (2008) reported connectivity between this area and prefrontal cortex. Such connections could support the modulation by attentionally-demanding stimulus events observed here. By contrast, thalamic regions near the ventral anterior nucleus showed a significant Proportion × Task effect. Zhang et al. (2008) reported connectivity between this area of the thalamus and motor and premotor

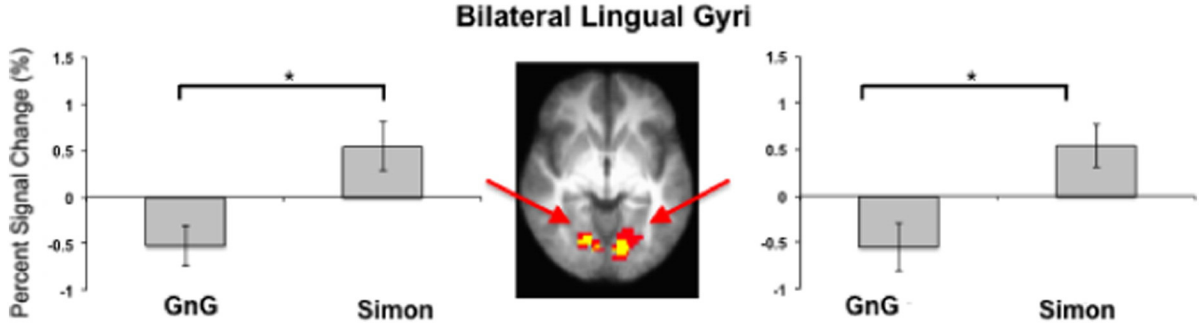

Fig. 12. Bar plots showing average percent signal change ± S.E.M. in the left and right lingual gyri. Regions common across both the Proportion and Load ANOVAs are shown in yellow. Regions unique to the Proportion or Load ANOVAs are shown in red. Significance at $p < 0.05$ is denoted by "*".

cortex. Such connections are consistent with our findings showing modulation of ventral anterior thalamus by both attentional demands and demands on motor output.

An interesting result that emerged from our ROI analyses is the significant interaction between Proportion and Type in the right STG. This area showed effects similar to those observed in whole-brain analyses from the insular-putamen-thalamic network with greater activation on infrequent trials. A long of line of research from Corbetta and colleagues have proposed that a ventro-parietal network with a specific focus on the right TPJ acts as a 'circuit-breaker' to direct attention to a relevant stimulus that is outside of the current focus (Corbetta et al., 2000; Corbetta and Shulman, 2002). Further research has demonstrated that similar effects occur when using visual and auditory stimulation and not just with changes in spatial information (Braver et al., 2001; Downar et al., 2000, 2001). In line with proposals by Corbetta and colleagues, we suggest that the insular network is responsible for detecting infrequent / salient events, and then lateralized TPJ serves as an 'alerting system', directing attention away from the current set of task rules (i.e., away from the frequent events). It is interesting that MTG only showed a modulation of activity in the GnG task. Thus, parts of TPJ appear to be selectively engaged in tasks that activate or inactivate motor responses. It is important to note that these results did not emerge in the whole-brain analysis; thus, additional work will be needed to tease apart interactions between the insular network and TPJ.

In summary, our manipulation of the proportion of trials that require inhibition revealed a pattern activation in the insula, putamen, thalamus, and TPJ that indicated these regions are sensitive to rare and infrequent stimuli, rather than to the need for inhibitory control. A central question moving forward is precisely how these regions modulate response selection system in the brain. It is possible that the activation patterns observed here reflect active global inhibition or down-regulation of the motor system in the face of the need for control on rare events (Erika-Florence et al., 2014). That is, insula, putamen, and thalamus might be slowing down response processes in the face of rare events to facilitate accurate response selection, with TPJ working to actively shift attention to competing alternatives. It is also possible, however, that insula, putamen, and thalamus are enhancing processing or up-regulating response selection areas in the face of response conflict on rare, attentionally-demanding events (Erika-Florence et al., 2014). That is, these brain areas might boost activation in response selection regions on rare events when conflict is detected. Note that existing models of response inhibition and response selection such as the model by Weicki and Frank have only feed-forward connections between cortical areas and subcortical regions of the basal ganglia (Wiecki and Frank, 2013). It will be important in future theoretical work to understand how reciprocal connectivity might enable down-regulation vs. up-regulation and to tease apart differential predictions for these two alternatives.

Activation in the response selection network decreases as the memory load increases

Previous studies have suggested that response selection and inhibition arises from distributed cortical and subcortical networks involved in attention and working memory. For instance, several studies have demonstrated that frontal and parietal cortices are robustly activated in both inhibitory control and working memory tasks (Barber et al., 2013; Bunge et al., 2001; Hester et al., 2004; Kelly et al., 2006; McNab et al., 2008; Mostofsky et al., 2003; Perlstein et al., 2003). In particular, McNab and colleagues used conjunction analysis and showed right inferior frontal gyrus activation across two working memory and two inhibition tasks (McNab et al., 2008). Similarly, Barber et al. (2013) showed that the dorsolateral prefrontal cortex was recruited in two GnG tasks when working memory was required to inhibit a response.

To address how working memory demands affect fronto-cortical-striatal control systems, we modulated the need for control in two reactive inhibition tasks by varying the memory load, while holding the attentional demands constant (i.e., Go/Compatible and Nogo/Incompatible trials were equally frequent). If the fronto-cortical-striatal network is sensitive to the attentional and WM demands of the task, we expected to see the same areas activated by the attentional manipulation also active as the memory load was varied. The Load manipulation also speaks to the nature of the memory representation underlying response selection in these tasks. Previous studies have demonstrated that WM maintenance has a particular neural signature – activation increases as the WM load increases (Pessoa et al., 2002; Todd and Marois, 2004). Thus, if WM was critically involved in these tasks, we would expect to see an increase in activation as the load increased within WM-specific regions of the fronto-cortical-striatal network. For instance, Hester et al. (2004) found an increase in activation as the memory load was increased in a GnG task within middle frontal gyrus, left middle temporal gyrus, thalamus, and rostral and dorsal ACC/preSMA (for related results, see Bunge et al. (2001).

Interestingly, results from IPL in the current study showed the opposite pattern – activation in the right IPL *decreased* as the memory load increased. Previous studies suggest that IPL is responsible for processing sensory and motor information (Andersen, 2011; Andersen et al., 1985; Fogassi et al., 2005; Fogassi and Luppino, 2005; Hyvarinen, 1981). Functional sub-divisions of the monkey IPL have distinguished areas 7a and 7b in the monkey cortex responsible for visual and visuomotor functions respectively. One hypothesis, the vasomotor integration hypothesis suggests that IPL combines information from sensory and motor nodes - for detailed review, see Andersen (2011). This is consistent with our findings showing modulation of IPL activation as the number of stimulus-response mappings was varied.

Anatomical tracing experiments have identified many connections from the IPL to other cortical regions, including the superior temporal region, parahippocampal area, cingulate cortex, and the insula (Andersen, 2011). Interestingly, in the current study, these regions along with the transverse temporal gyrus, cerebellum, and lingual gyrus showed the same pattern of activation as rIPL but only for trials that did not require inhibition. Specifically, these regions showed significantly greater activation on Go/Compatible trials than Nogo/Incompatible trials at Load 2, and as the load increased, activation on Go/Compatible trials decreased. It is possible that the absence of a load effect on Nogo/Incompatible trials in these regions reflects weak memory traces on these trials. Recent behavioral work suggests that response inhibition reduces attention to stimuli, yielding weaker memory traces at encoding and retrieval (Chiu and Egner, 2015).

The current study showed decreasing activation with increasing number of SR mappings in the right IPL. On the other hand, Hester et al. (2004) showed the opposite pattern of activation. Why do these results differ? There are several differences across studies that might explain our findings. Hester et al. (2004) used a verbal working memory task rather than a visual working memory task. Thus, it is possible that there are important differences in how these two working memory systems are engaged in response selection and inhibition tasks. In addition, Hester et al. (2004) only examined effects of memory load in a GnG task where the Nogo trials were infrequent. It is possible that their findings reflect an interaction between attentional and working memory processes not observed here given that we held the attentional demands constant across load conditions. Finally, we note that results from Hester et al. (2004) were mixed in that several fronto-cortical-striatal areas showed either no change in activation as the load increased or a *decrease* in activation as the load increased as reported here (e.g., in the cerebellum).

Clearly, our findings are not consistent with the typical neural signature observed in studies of working memory that activation increases as the load increases. An alternative possibility is that our results reflect the engagement of an associative memory system rather than a working memory system. For instance, in Wiecki and Frank's model of response selection and inhibition, SR mappings are stored in an associative

memory (Wiecki and Frank, 2013). More SR mappings make it harder to resolve the competition among different associative weights, slowing down decision-making and enabling conflict-monitoring networks to exert control. It is possible that such effects yield a *decrease* in the BOLD response as the memory load is increased because growth of activation is limited by enhanced competition. Future work will be needed to examine the possibility.

Note that our region of interest in the right IPL lies in the vicinity of right STG and MTG, which were activated when Proportion was manipulated. Corbetta et al. (2000) demonstrated two regions of activation in the vicinity of right TPJ (right STG, right IPL) while reorienting attention towards novel stimuli. In the current study, we did not explore the effects of manipulating Load whilst manipulating Proportion; instead, we maintained Proportion at 50% in all Load conditions. It is possible we might see interactions between right IPL and STG/MTG when both factors are manipulated together.

A distributed cortico-subcortical system is engaged by motor output demands

Go/Compatible trials elicited greater activation than Nogo/Incompatible trials within a host of cortical and subcortical regions. The broad network of regions showing this pattern is known to be involved in managing sensory-motor mappings as well as motor planning and control. For instance, the insula, putamen, and thalamus are involved in detecting salient stimuli and activating appropriate motor circuitry in response to stimulation (Cai et al., 2014; Menon and Uddin, 2010; Uddin, 2015). Similarly, IPL has been associated with visuo-spatial attention, managing SR mappings, and processing sensory and motor information (Andersen et al., 1985, 1990; Mattingley et al., 1998). Further, medial frontal gyrus (Rushworth et al., 2004; Talati and Hirsch, 2005) and cerebellum have been implicated in associative learning as well as motor selection, planning, and coordination (Stoodley and Schmahmann, 2010; Timmann et al., 2010).

Interestingly, activation in these same areas was also modulated by the Task. In particular, there was greater activation on Go trials relative to Nogo trials in the GnG task. There was also greater activation on Go trials relative to compatible trials in the Simon task. Further, Incompatible trials also elicited greater activation than Nogo trials. One primary difference between the tasks is that there is a motor response only on Go trials in the GnG task, but a motor response is required on every trial in the Simon task. Consequently, there would be fewer competing motor options in the GnG task, and more competing motor options in the Simon task. If motor planning / motor control areas are particularly sensitive to the amount of competition between *motor responses*, then this would explain the difference across tasks because there are more response options in the Simon task where a weaker hemodynamic response was observed.

Lingual gyrus shows differential activation across tasks reflecting shifts of spatial attention

Bilateral lingual gyrus was activated for the Simon task but showed suppressed activation for the GnG task. The lingual gyrus is involved in basic visual processing and has been implicated in inhibitory control (Braet et al., 2009; Menon et al., 2001; Odlaug et al., 2014; Schulz et al., 2004) but its role has not been well explored. Some studies have suggested that the lingual gyrus might be involved in visuo-spatial attention (Hopfinger et al., 2000; Mangun et al., 1998). For instance, activation was observed in the lingual gyrus in a task where participants had to pay attention to a stimulus presented in the contralateral hemifield (Mangun et al., 1998) . Similarly, lingual gyrus was also activated when a stimulus was presented in the contralateral hemisphere, an effect that was strengthened when tactile stimulation was administered to the same side as visual stimulation (Macaluso et al., 2000). Using effective connectivity, they reported back-projections between right IPL and lingual gyrus and suggested that tactile information could be passed on from postcentral gyrus to the lingual gyrus via IPL.

One of the primary differences between the GnG and Simon tasks is that shifts of spatial attention are required in the Simon task, whereas stimuli are always presented centrally in the GnG task. Moreover, the Simon task requires modulation of spatial attention because on incompatible trials, one must suppress the irrelevant spatial information. We suspect the differential engagement of lingual gyrus reflects this differential engagement of spatial attention across the two tasks. In light of evidence from Macaluso et al. (2000), future work should explore causal connectivity between the lingual gyrus and IPL/post-central gyrus because all of these areas were robustly active in the present study.

To summarize and conclude, this study addresses issues that are currently a source of debate in the field of response selection and inhibition. Our findings clearly show modulation of insular cortex, putamen, and thalamus in response to rare, salient events rather than as a function of inhibitory demands. We suggest that the insular cortex is involved in the detection of salient or infrequent events. In concert with the putamen and thalamus, detection then modulates motoric circuits with the thalamus acting as a relay to pass information to other cortico-subcortical structures. In addition, coupling with TPJ helps shift the focus of attention toward the infrequent task rules. Perhaps in concert with such effects, lingual gyrus plays a role in shifting visuo-spatial attention to task-relevant features when this is required by the task. Our findings further suggest that a form of associative memory underlies response selection across a broad motor planning network that includes insula, parahippocampal gyrus, STG, and cingulate cortex. The right IPL appears to play a central role in this selection process or serves as a central relay among these regions, which reportedly all have anatomic connections to this critical response selection area.

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Conflict of interest

The authors have no conflict of interest.

References

Alexander, G.E., Crutcher, M.D., 1990. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci. 13, 266–271.
Alexander, G.E., DeLong, M.R., Strick, P.L., 1986. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu. Rev. Neurosci. 9, 357–381.
Andersen, R.A., 2011. Inferior parietal lobule function in spatial perception and visuomotor integration. Supplement 5: Handbook of physiology, the nervous system, higher functions of the brain: *ICompr Physiol*pp. 483–518.
Andersen, R.A., Essick, G.K., Siegel, R.M., 1985. Encoding of spatial location by posterior parietal neurons. Science 230, 456–458.
Andersen, R.A., Asanuma, C., Essick, G., Siegel, R.M., 1990. Corticocortical connections of anatomically and physiologically defined subdivisions within the inferior parietal lobule. J. Comp. Neurol. 296, 65–113.
Aron, A.R., 2011. From reactive to proactive and selective control: developing a richer model for stopping inappropriate responses. Biol. Psychiatry 69, e55–e68.
Aron, A.R., Verbruggen, F., 2008. Stop the presses: dissociating a selective from a global mechanism for stopping. Psychol. Sci. 19, 1146–1153.
Aron, A.R., Robbins, T.W., Poldrack, R.A., 2014a. Inhibition and the right inferior frontal cortex: one decade on. Trends Cogn. Sci. 18, 177–185.
Aron, A.R., R., T. W., Poldrack, R.A., 2014b. Right inferior frontal cortex: addressing the rebuttals. Front. Hum. Neurosci. 8.
Barber, A.D., Caffo, B.S., Pekar, J.J., Mostofsky, S.H., 2013. Effects of working memory demand on neural mechanisms of motor response selection and control. J. Cogn. Neurosci. 25, 1235–1248.
Bhaijiwala, M., Chevrier, A., Schachar, R., 2014. Withholding and canceling a response in ADHD adolescents. Brain Behav. 4, 602–614.
Braet, W., Johnson, K.A., Tobin, C.T., Acheson, R., Bellgrove, M.A., Robertson, I.H., Garavan, H., 2009. Functional developmental changes underlying response inhibition and error-detection processes. Neuropsychologia 47, 3143–3151.

Braver, T.S., Barch, D.M., Gray, J.R., Molfese, D.L., Snyder, A., 2001. Anterior cingulate cortex and response conflict: effects of frequency, inhibition and errors. Cereb. Cortex 11, 825–836.
Bunge, S.A., Ochsner, K.N., Desmond, J.E., Glover, G.H., Gabrieli, J.D., 2001. Prefrontal regions involved in keeping information in and out of mind. Brain 124, 2074–2086.
Cai, W., Ryali, S., Chen, T., Li, C.S., Menon, V., 2014. Dissociable roles of right inferior frontal cortex and anterior insula in inhibitory control: evidence from intrinsic and task-related functional parcellation, connectivity, and response profile analyses across multiple datasets. J. Neurosci. 34, 14652–14667.
Chatham, C.H., Claus, E.D., Kim, A., Curran, T., Banich, M.T., Munakata, Y., 2012a. Cognitive control reflects context monitoring, not motoric stopping, in response inhibition. PLoS One 7, e31546.
Chatham, C.H., Claus, E.D., Kim, A., Curran, T., Banich, M.T., Munakata, Y., 2012b. Cognitive control reflects context monitoring, not motoric stopping, in response inhibition. PLoS One 7, e31546.
Chevalier, N., Chatham, C.H., Munakata, Y., 2014. The practice of going helps children to stop: the importance of context monitoring in inhibitory control. J. Exp. Psychol. Gen. 143, 959–965.
Chiu, Y.C., Egner, T., 2015. Inhibition-induced forgetting: when more control leads to less memory. Psychol. Sci. 26, 27–38.
Corbetta, M., Shulman, G.L., 2002. Control of goal-directed and stimulus-driven attention in the brain. Nat. Rev. Neurosci. 3, 201–215.
Corbetta, M., Kincade, J.M., Ollinger, J.M., McAvoy, M.P., Shulman, G.L., 2000. Voluntary orienting is dissociated from target detection in human posterior parietal cortex. Nat. Neurosci. 3, 292–297.
Crottaz-Herbette, S., Menon, V., 2006. Where and when the anterior cingulate cortex modulates attentional response: combined fMRI and ERP evidence. J. Cogn. Neurosci. 18, 766–780.
Ding, J.B., Guzman, J.N., Peterson, J.D., Goldberg, J.A., Surmeier, D.J., 2010. Thalamic gating of corticostriatal signaling by cholinergic interneurons. Neuron 67, 294–307.
Dodds, C.M., Morein-Zamir, S., Robbins, T.W., 2011. Dissociating inhibition, attention, and response control in the frontoparietal network using functional magnetic resonance imaging. Cereb. Cortex 21, 1155–1165.
Downar, J., Crawley, A.P., Mikulis, D.J., Davis, K.D., 2000. A multimodal cortical network for the detection of changes in the sensory environment. Nat. Neurosci. 3, 277–283.
Downar, J., Crawley, A.P., Mikulis, D.J., Davis, K.D., 2001. The effect of task relevance on the cortical response to changes in visual and auditory stimuli: an event-related fMRI study. Neuroimage 14, 1256–1267.
Drucker, D.M., Aguirre, G.K., 2009. Different spatial scales of shape similarity representation in lateral and ventral LOC. Cereb. Cortex 19, 2269–2280.
Erika-Florence, M., Leech, R., Hampshire, A., 2014. A functional network perspective on response inhibition and attentional control. Nat. Commun. 5, 4073.
Fogassi, L., Luppino, G., 2005. Motor functions of the parietal lobe. Curr. Opin. Neurobiol. 15, 626–631.
Fogassi, L., Ferrari, P.F., Gesierich, B., Rozzi, S., Chersi, F., Rizzolatti, G., 2005. Parietal lobe: from action organization to intention understanding. Science 308, 662–667.
Garavan, H., Ross, T.J., Murphy, K., Roche, R.A., Stein, E.A., 2002. Dissociable executive functions in the dynamic control of behavior: inhibition, error detection, and correction. Neuroimage 17, 1820–1829.
Garavan, H., Ross, T.J., Kaufman, J., Stein, E.A., 2003. A midline dissociation between error-processing and response-conflict monitoring. Neuroimage 20, 1132–1139.
Grahn, J.A., Parkinson, J.A., Owen, A.M., 2008. The cognitive functions of the caudate nucleus. Prog. Neurobiol. 86, 141–155.
Hampshire, A., 2015. Putting the brakes on inhibitory models of frontal lobe function. Neuroimage 113, 340–355.
Hampshire, A., Chamberlain, S.R., Monti, M.M., Duncan, J., Owen, A.M., 2010. The role of the right inferior frontal gyrus: inhibition and attentional control. Neuroimage 50, 1313–1319.
Hester, R., Murphy, K., Garavan, H., 2004. Beyond common resources: the cortical basis for resolving task interference. Neuroimage 23, 202–212.
Hopfinger, J.B., Buonocore, M.H., Mangun, G.R., 2000. The neural mechanisms of top-down attentional control. Nat. Neurosci. 3, 284–291.
Hyvarinen, J., 1981. Regional distribution of functions in parietal association area 7 of the monkey. Brain Res. 206, 287–303.
Karnath, H.O., Himmelbach, M., Rorden, C., 2002. The subcortical anatomy of human spatial neglect: putamen, caudate nucleus and pulvinar. Brain 125, 350–360.
Kelly, A.M., Hester, R., Murphy, K., Javitt, D.C., Foxe, J.J., Garavan, H., 2004. Prefrontal-subcortical dissociations underlying inhibitory control revealed by event-related fMRI. Eur. J. Neurosci. 19, 3105–3112.
Kelly, A.M., Hester, R., Foxe, J.J., Shpaner, M., Garavan, H., 2006. Flexible cognitive control: effects of individual differences and brief practice on a complex cognitive task. Neuroimage 31, 866–886.
Liddle, P.F., Kiehl, K.A., Smith, A.M., 2001. Event-related fMRI study of response inhibition. Hum. Brain Mapp. 12, 100–109.
Macaluso, E., Frith, C.D., Driver, J., 2000. Modulation of human visual cortex by crossmodal spatial attention. Science 289, 1206–1208.
Mangun, G.R., Buonocore, M.H., Girelli, M., Jha, A.P., 1998. ERP and fMRI measures of visual spatial selective attention. Hum. Brain Mapp. 6, 383–389.
Mattingley, J.B., Husain, M., Rorden, C., Kennard, C., Driver, J., 1998. Motor role of human inferior parietal lobe revealed in unilateral neglect patients. Nature 392, 179–182.
McNab, F., Leroux, G., Strand, F., Thorell, L., Bergman, S., Klingberg, T., 2008. Common and unique components of inhibition and working memory: an fMRI, within-subjects investigation. Neuropsychologia 46, 2668–2682.
Menon, V., Uddin, L.Q., 2010. Saliency, switching, attention and control: a network model of insula function. Brain Struct. Funct. 214, 655–667.
Menon, V., Adleman, N.E., White, C.D., Glover, G.H., Reiss, A.L., 2001. Error-related brain activation during a Go/NoGo response inhibition task. Hum. Brain Mapp. 12, 131–143.
Mostofsky, S.H., Schafer, J.G., Abrams, M.T., Goldberg, M.C., Flower, A.A., Boyce, A., Courtney, S.M., Calhoun, V.D., Kraut, M.A., Denckla, M.B., Pekar, J.J., 2003. fMRI evidence that the neural basis of response inhibition is task-dependent. Brain Res. Cogn. Brain Res. 17, 419–430.
Munakata, Y., Herd, S.A., Chatham, C.H., Depue, B.E., Banich, M.T., O'Reilly, R.C., 2011. A unified framework for inhibitory control. Trends Cogn. Sci. 15, 453–459.
Odlaug, B.L., Chamberlain, S.R., Derbyshire, K.L., Leppink, E.W., Grant, J.E., 2014. Impaired response inhibition and excess cortical thickness as candidate endophenotypes for trichotillomania. J. Psychiatr. Res. 59, 167–173.
Parent, A., Hazrati, L.N., 1995. Functional anatomy of the basal ganglia. II. The place of subthalamic nucleus and external pallidum in basal ganglia circuitry. Brain Res. Brain Res. Rev. 20, 128–154.
Perlstein, W.M., Dixit, N.K., Carter, C.S., Noll, D.C., Cohen, J.D., 2003. Prefrontal cortex dysfunction mediates deficits in working memory and prepotent responding in schizophrenia. Biol. Psychiatry 53, 25–38.
Pessoa, L., Ungerleider, L.G., 2004. Neural correlates of change detection and change blindness in a working memory task. Cereb. Cortex 14, 511–520.
Pessoa, L., Gutierrez, E., Bandettini, P., Ungerleider, L., 2002. Neural correlates of visual working memory: fMRI amplitude predicts task performance. Neuron 35, 975–987.
Rae, C.L., Hughes, L.E., Anderson, M.C., Rowe, J.B., 2015. The prefrontal cortex achieves inhibitory control by facilitating subcortical motor pathway connectivity. J. Neurosci. 35, 786–794.
Rubia, K., Smith, A.B., Brammer, M.J., Taylor, E., 2003. Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. Neuroimage 20, 351–358.
Rushworth, M.F., Walton, M.E., Kennerley, S.W., Bannerman, D.M., 2004. Action sets and decisions in the medial frontal cortex. Trends Cogn. Sci. 8, 410–417.
Schulz, K.P., Fan, J., Tang, C.Y., Newcorn, J.H., Buchsbaum, M.S., Cheung, A.M., Halperin, J.M., 2004. Response inhibition in adolescents diagnosed with attention deficit hyperactivity disorder during childhood: an event-related FMRI study. Am. J. Psychiatry 161, 1650–1657.
Sharp, D.J., Bonnelle, V., De Boissezon, X., Beckmann, C.F., James, S.G., Patel, M.C., Mehta, M.A., 2010. Distinct frontal systems for response inhibition, attentional capture, and error processing. Proc. Natl. Acad. Sci. U. S. A. 107, 6106–6111.
Sherman, S.M., Guillery, R.W., 2002. The role of the thalamus in the flow of information to the cortex. Philos. Trans. R. Soc. Lond. B Biol. Sci. 357, 1695–1708.
Simmonds, D.J., Pekar, J.J., Mostofsky, S.H., 2008. Meta-analysis of Go/No-go tasks demonstrating that fMRI activation associated with response inhibition is task-dependent. Neuropsychologia 46, 224–232.
Sridharan, D., Levitin, D.J., Menon, V., 2008. A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. Proc. Natl. Acad. Sci. U. S. A. 105, 12569–12574.
Stoodley, C.J., Schmahmann, J.D., 2010. Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing. Cortex 46, 831–844.
Swick, D., Chatham, C.H., 2014. Ten years of inhibition revisited. Front. Hum. Neurosci. 8, 329.
Talati, A., Hirsch, J., 2005. Functional specialization within the medial frontal gyrus for perceptual go/no-go decisions based on "what," "when," and "where" related information: an fMRI study. J. Cogn. Neurosci. 17, 981–993.
Timmann, D., Drepper, J., Frings, M., Maschke, M., Richter, S., Gerwig, M., Kolb, F.P., 2010. The human cerebellum contributes to motor, emotional and cognitive associative learning. A review. Cortex 46, 845–857.
Todd, J.J., Marois, R., 2004. Capacity limit of visual short-term memory in human posterior parietal cortex. Nature 428, 751–754.
Tolin, D.F., Witt, S.T., Stevens, M.C., 2014. Hoarding disorder and obsessive-compulsive disorder show different patterns of neural activity during response inhibition. Psychiatry Res. 221, 142–148.
Uddin, L.Q., 2015. Salience processing and insular cortical function and dysfunction. Nat. Rev. Neurosci. 16, 55–61.
Wager, T.D., Sylvester, C.Y., Lacey, S.C., Nee, D.E., Franklin, M., Jonides, J., 2005. Common and unique components of response inhibition revealed by fMRI. Neuroimage 27, 323–340.
Wiecki, T.V., Frank, M.J., 2013. A computational model of inhibitory control in frontal cortex and basal ganglia. Psychol. Rev. 120, 329–355.
Zhang, D., Snyder, A.Z., Fox, M.D., Sansbury, M.W., Shimony, J.S., Raichle, M.E., 2008. Intrinsic functional relations between human cerebral cortex and thalamus. J. Neurophysiol. 100, 1740–1748.