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Representation of response alternatives in human presupplementary motor area: Multi-voxel pattern analysis in a go/no-go task

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ABSTRACT

A debate exists as to the role of the presupplementary motor area (preSMA) in cognitive control. Recent findings suggest that preSMA plays a central role in conflict resolution and encodes response alternatives as opposed to simply the presence of conflict. Evidence of neuronal heterogeneity within preSMA of non-human primates suggests that univariate analysis of functional MRI data may not provide adequate resolution to fully characterize cognitive control-related responses. Here, multi-voxel pattern analysis (MVPA) is employed to examine the distributed patterns of activity in preSMA associated with both successful go responses and no-go inhibitions. In a go/no-go task, univariate analysis showed undifferentiated activation of preSMA in response to both go and no-go stimuli. However, when an anatomically-defined preSMA ROI was subjected to MVPA, a significant difference in the activation pattern encoded by go as compared to no-go stimuli was observed. These differences in preSMA activation are consistent with the ongoing maintenance and manipulation of stimulus–action representations.

1. Introduction

Response inhibition is an effortful process involving the suppression of a habitual response and the selection of an alternative, controlled action. Across a wide range of studies, the medial frontal cortex (MFC) has been implicated in this type of cognitive control (Ridderinkhof, Nieuwenhuis, & Braver, 2007; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). The network involved in response inhibition has been previously characterized (Aron, 2007; Chambers et al., 2006; Nachev, Kennard, & Husain, 2008; Swann et al., 2012), and consists of right inferior frontal gyrus (rIFG), presupplementary motor area (preSMA) and subthalamic nucleus (STN). However, there are ongoing questions as to the distinct role each of these regions play in response inhibition (Duann, Ide, Luo, & Li, 2009).

The functional responsibility of preSMA within this network remains unclear (Greenhouse, Swann, & Aron, 2012; Stuphorn & Emeric, 2012). One difficulty in ascribing a specific response inhibition-related function to preSMA is the tendency for the literature to treat the MFC as a unified processing locus, an assumption which has been challenged by diffusion tensor imaging results demonstrating dissociable clusters within the broader MFC (Beckmann, Johansen-Berg, & Rushworth, 2009). In addition, preSMA has been shown to be more closely associated with prefrontal areas (Picard & Strick, 2001) and can be parcellated into anterior and posterior regions, with different functionality ascribed to each (Kim et al., 2010; Zhang, Ide, & Li, 2012).

At a cognitive level, many alternative functions have been ascribed to preSMA as a part of the wider MFC (Ridderinkhof et al., 2007). Both conflict monitoring (Botvinick, Braver, Barch, Carter, & Cohen, 2001) and task set maintenance (Petersen & Posner, 2012) functions have been proposed. Additionally, preSMA has been implicated in the process of deciding among potential action alternatives for task performance (Ridderinkhof, Forstmann, Wylie, Burle, & van den Wildenberg, 2011; Ridderinkhof et al., 2004). Support for a conflict monitoring function is seen in studies showing increased preSMA activation with no-go stimulus presentation (Nee, Wager, & Jonides, 2007; Swick, Ashley, & Turken, 2011), although recent evidence suggests that the activations previously ascribed to conflict monitoring may be more closely associated with time on task (Grinband et al., 2011) or the setting of response thresholds (Chen, Scangos, & Stuphorn, 2010).

As has been discussed elsewhere (Simmonds, Pekar, & Mostofsky, 2008), the absence of preSMA activation in response to the presentation of a go stimulus is not a consistent finding across all studies of response inhibition and cognitive control. A significant subset of the neuroimaging literature examining

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response inhibition tasks report preSMA activation for both executed and inhibited motor responses. A number of studies also describe an overlap in activation within the MFC, and preSMA specifically, evoked by both go and no-go stimuli (Humberstone et al., 1997; Kiehl, Smith, Hare, & Liddle, 2000; Liddle, Kiehl, & Smith, 2001; Mostofsky et al., 2003).

In addition, differences in functional activation have been observed between preSMA and more rostral anterior cingulate cortex (Milham & Banich, 2005; Schulz, Bédard, Czarnecki, & Fan, 2011). These differences suggest that preSMA encodes response alternatives, while rostral anterior cingulate cortex may be more sensitive to the presence of conflict or the outcomes of prior actions (Rushworth & Behrens, 2008). Recent conceptualizations suggest that response inhibition is analogous to a choice between go and no-go responses, as opposed to stopping what would otherwise be an executed motor response (Mostofsky & Simmonds, 2008). Viewed within this theoretical framework, a role for preSMA in adjudicating among action selection or task set rules (Ridderinkhof et al., 2011) becomes more tenable. That is, preSMA may be involved in the representation and maintenance of task sets and response alternatives as a final step before motor program execution (Banich, 2009).

Single unit recordings of non-human primates performing response inhibition tasks provide insight into potential sources of this observed overlap in preSMA activation. A recent review (Stuphorn & Emeric, 2012) posits that neurons in preSMA are involved in both initiating and inhibiting motor responses via modulations of baseline neuronal activity. In addition, single-cell recordings have illustrated heterogeneous neuronal populations within the primate preSMA analog, where individual cells that respond to either go or no-go stimuli are located in close proximity (Isoda & Hikosaka, 2007). Direct evidence of sensitivity to the presence of conflict has been seen in only a small subset of neurons recorded across multiple studies (Nakamura, Roesch, & Olson, 2005; Ito et al., 2003).

The discrepancies between human and primate findings have led to a debate as to the applicability of drawing cross-species conclusions (Cole, Yeung, Freiwald, & Botvinick, 2009; Schall & Emeric, 2010). However, recent evidence suggests that the organization of human and primate frontal cortex are more similar than that previously believed (Sallet et al., 2013). Given the heterogeneity of neuronal populations in both the primate (Isoda & Hikosaka, 2007; Nakamura et al., 2005) and human (Bush et al., 2002) medial frontal cortex, traditional univariate analyses of fMRI—which collapse across a large number of neurons—may not be sufficiently sensitive to illustrate differences between the neural representations of stimulus–action associations in preSMA.

Here we used multi-voxel pattern analysis (MVPA) to examine the distributed patterns of activity associated with both successful go and no-go responses in preSMA. MVPA differs from conventional univariate analyses in that it can detect differences between conditions at an information-based, as opposed to an activation-based, level (Kriegeskorte, Goebel, & Bandettini, 2006) and can thus reveal additional information about patterns of activity across many voxels (Haynes & Rees, 2006; Kamitani & Tong, 2005). This method is better suited to detect distributed coding of task-relevant information (Mur, Bandettini, & Kriegeskorte, 2009) and has the ability to characterize differentiations in brain activity between conditions unavailable in univariate analyses (Jimura & Poldrack, 2012).

If preSMA activation seen in response to go stimuli reflects a partial engagement of the same inhibition process more directly associated with no-go stimuli, then the pattern of activation observed should be undifferentiated between go and no-go stimuli. While a partial engagement of the inhibition process in response to go stimulus presentation would lead to a reduced level of preSMA activation, it would result in a similar pattern of encoded information in response to both sets of stimuli. If instead preSMA plays a role in adjudicating among response alternatives (Banich, 2009; Brown, 2009; Ridderinkhof et al., 2011), then the observed activation elicited by go stimuli should be dissociable from the activation elicited by no-go stimuli. A differentiated response representation between go and no-go stimuli would lead to similar levels of preSMA activation but would result in distinct patterns of encoded information. Such an observable, but differentiated, response pattern in preSMA would be evidence of its direct role in choosing among potential action affordances in a goal-directed manner.

2. Methods

2.1. Participants

Sixteen neurologically healthy, right-handed subjects (7 female, aged 19–37 years) consented to participate in a study approved by the Human Subjects Review Board at George Mason University. All subjects had either normal or corrected-to-normal vision.

2.2. Task design

The experimental task was created with Presentation (Neurobehavioral Systems Inc, Albany, CA). Participants were instructed to press a button when presented with the go stimulus (letter X) and withhold from pressing the button when presented with the no-go stimulus (letter A). The letters subtended 2.76° to the left and right of center, and 2.33° above and below the center of the screen. Across the entire experiment, the go stimulus trials were presented 432 times and the no-go stimulus trials were presented 90 times (17% of go total). In addition, null trials consisting of a black screen with no stimulus displayed were shown 132 times (25% of the go plus no-go stimulus totals). The order of presentation for the go, no-go, and null trials were randomized both across runs and between participants. A single experimental trial consisted of a centrally presented crosshair that was visible for 200 ms; a black screen for 50 ms; one of the three stimuli (go, no-go, null) presented in the center of the screen for 200 ms; and a black screen for 2500 ms. The entire experiment included 6 task runs of 7 min each (approximately 42 min total) with short breaks between runs.

2.3. Trial matching

In each run, two subsets of the total correct go trials equivalent in number to the correct no-go trials were randomly selected for each participant. The first subset of go trials was used for comparisons to the no-go trials. The second subset of correct go trials (matched go trials) was compared to the initial subset of go trials in the MVPA as described below as a control analysis. The additional go trials (remaining go trials) not included in the two described subsets were modeled in the GLM, but were not analyzed further.

2.4. Imaging procedure

fMRI data were collected using a Siemens 3T Allegra scanner at the Krasnow Institute for Advanced Study at George Mason University. Visual stimuli were displayed on a rear projection screen and viewed by participants via a mirror mounted on the head coil. The following parameters were used to acquire functional gradient-echo echoplanar images in the axial orientation: 33 slices (4 mm thick, 1 mm gap); repetition time (TR)/echo time (TE)=2000/30 ms; flip angle=70°; 64×64 matrix with 3.8×3.8 mm^2 in-plane resolution; field of view=240 mm. In each run 200 volumes were collected. Two T1 whole-head high resolution anatomical structural scans were gathered using a three-dimensional, magnetization-prepared, rapid-acquisition gradient echo (MPRAGE) pulse sequence (160 1 mm-thick slices, 256×256 matrix, field of view 260 mm, 0.94 mm^2 voxels, TR/TE=2300/3 ms).

2.5. fMRI data analysis

Preprocessing of fMRI data included removal of the first four volumes from each run to compensate for the time required to reach equilibrium magnetization. The fMRI Expert Analysis Tool (FEAT) software tool of the fMRI of the Brain Software Library (FSL) toolbox (www.fmrib.ox.ac. uk/fsl/) was used for fMRI analysis. The fMRI time series were high-pass filtered at 128 s, and motion corrected. No smoothing was applied at this stage of analysis. Volume-based fMRI

data remained in each participant's native functional space throughout preprocessing in FSL.

For each run, the onset and duration of each stimulus presentation was modeled, creating five regressors as follows: (1) correct no-go response inhibitions; (2) an equivalent number of randomly selected correct go responses (go trials); (3) a second equivalent number of randomly-selected correct go responses (matched go trials) used in the MVPA analysis as described below; (4) the remaining correct go responses (remaining go trials); and (5) all erroneous responses or inhibitions to no-go and go stimuli respectively. The five regressors were convolved with a gamma function (SD 3; lag 6) to estimate the response to the stimuli separately for each condition. In addition, the temporal derivative and parameters from motion correction were added to the model. Pre-whitening was also used to remove temporal autocorrelation of the fMRI time series. In addition, two contrasts of interest, correct go vs. correct no-go and correct go vs. matched go, were calculated for each run. Contrast-of-the-parameter estimate (COPE) images were calculated, and the estimates were averaged over the six functional runs. These averaged COPE images were then projected onto the Freesurfer-generated surface of each individual. For the mapping of cortical areas involved in task performance across participants using univariate analysis, COPE images were transformed into MNI space, and smoothed with a 5 mm full width at half-maximum (FWHM) Gaussian kernel. For the multivoxel pattern analysis, fMRI data remained in native space and was not smoothed.

Cortical surfaces were reconstructed from the average of the two MPRAGE scans of each participant using Freesurfer software (surfer.nmr.mgh.harvard.edu/). This automated processing involved motion correction and averaging of the two structural images, removal of non-brain tissue, intensity normalization, and segmentation to create a representation of the pial surface.

Surface-based analysis was employed in an effort to restrict the anatomically defined regions of interest described below to cortical gray matter. In addition, surface models lend themselves to surface-based registration (SBR) techniques, which in theory are better suited to account for differences in cortical folding pattern across participants (Fischl, Sereno, Tootell, & Dale, 1999). A surface-based one-sample group mean analysis with factors of stimulus type (no-go vs. go) was conducted. Results were viewed on the average inflated cortical surface with a height threshold of $p=0.001$ and a cluster size threshold of $p=0.05$ (with cluster size p-value corrected for multiple comparisons using Monte Carlo simulation conducted in FreeSurfer via mri_glmfit-sim).

2.6. Mapping regions of interest

Anatomical regions of interest (ROI) labels were created on each participant's reconstructed cortical surface for preSMA using anatomical landmarks derived from descriptions of supplementary motor area anatomy (Mayka, Corcos, Leurgans, & Vaillancourt, 2006; Nachev et al., 2008). The boundaries of the preSMA ROI were as follows: anterior—a line perpendicular to the anterior/posterior commissure axis aligned with the anterior commissure; posterior—70% of the distance from the anterior boundary to the paracentral sulcus; dorsal—the midline of the brain; ventral—the cingulate sulcus (Fig. 1). The posterior boundary was moved forward from the paracentral sulcus to exclude the supplementary eye fields and supplementary motor area from the preSMA ROI. For subsequent MVPA, all voxels within the preSMA ROI in the left (average size 94.4 voxels, se=7.3) and right (69.1, 5.0) hemispheres were used.

A control ROI was created in the ventral occipital cortex in the area of overlapping peak activation for the go and no-go conditions. Approximated mirrored vertices on the left (−26, −87, −14) and right (26, −81, −8) hemispheres were identified and dilated to create a hexagonal ROI on the FreeSurfer average cortical surface (FsAverage). This dilated occipital ROI was then projected from FsAverage onto each subject's derived cortical surface via mri_label2vol. Fig. 2 illustrates the individual cortical surface ROI for three representative subjects. Across subjects, this occipital ROI encompassed a mean of 80.5 (3.5) voxels in the left hemisphere and 74.9 (4.6) voxels in the right hemisphere.

2.7. Multi-voxel pattern analysis

MVPA was performed in Matlab (Mathworks, Nattick, MA) using linear support vector machine (SVM) classification implemented via the LIBSVM library (Chang & Lin, 2011). Analysis procedures followed those recommended by Etzel, Gazzola, and Keysers (2009). Parameter estimates of activation within all voxels of each subject's anatomically-defined preSMA ROI or occipital control ROI were used. Voxel values were z-normed (mean=0, SD=1) within each class (go vs. no-go; or go vs. matched go) prior to classification. SVM prediction accuracies were compared for go vs. no-go activation and go vs. matched go activation separately. The parameter estimate data was split into a training set consisting of data from five experimental runs and a testing set consisting of data from one remaining experimental run. The within-participant classification accuracy of the SVM was then calculated for the testing set. This procedure was repeated six times per subject, using a leave-one-out cross-validation methodology so that each run served as the testing set once per participant. Prediction accuracy of the SVM (number of correct predictions/number of total predictions) was calculated for each cross-validation and then averaged across cross-validations to obtain an overall prediction accuracy value for the classification of activation within the preSMA ROI for each participant. To assess the statistical significance of the classification accuracy at the group level, a two-step procedure was used. First, the observed null classification accuracy was determined for each participant using permutation testing. Go and no-go labels were randomly assigned to data from each experimental run. SVM was run as described above, and classification accuracy was recorded. This process was repeated for 5000 permutations for each participant, and the mean of this null distribution was calculated. The same procedure was used to compute the null distribution for the go vs. matched go classification. Second, the classification accuracies for each participant for the comparisons of interest, go vs. no-go and go vs. matched go, were then subjected to a paired-sample t-test against each participant's mean null classification accuracies derived from the permutations distribution.

3. Results

3.1. Behavior

Accuracy was significantly higher for go trials (mean accuracy=97.13%, SE=0.01) than no-go trials (81.5%, 0.03) ($t(15)=5.84$,

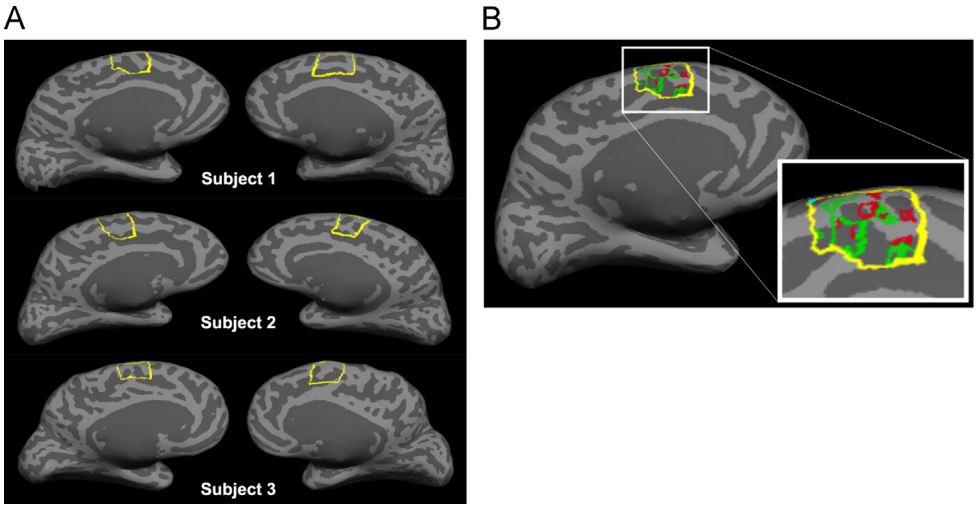

Fig. 1. preSMA region of interest. (A) Representative anatomical preSMA ROIs in yellow from three participants and (B) ROI defined in yellow; go (green) and no-go (red) activations (unsmoothed) within ROI also displayed for a single subject. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

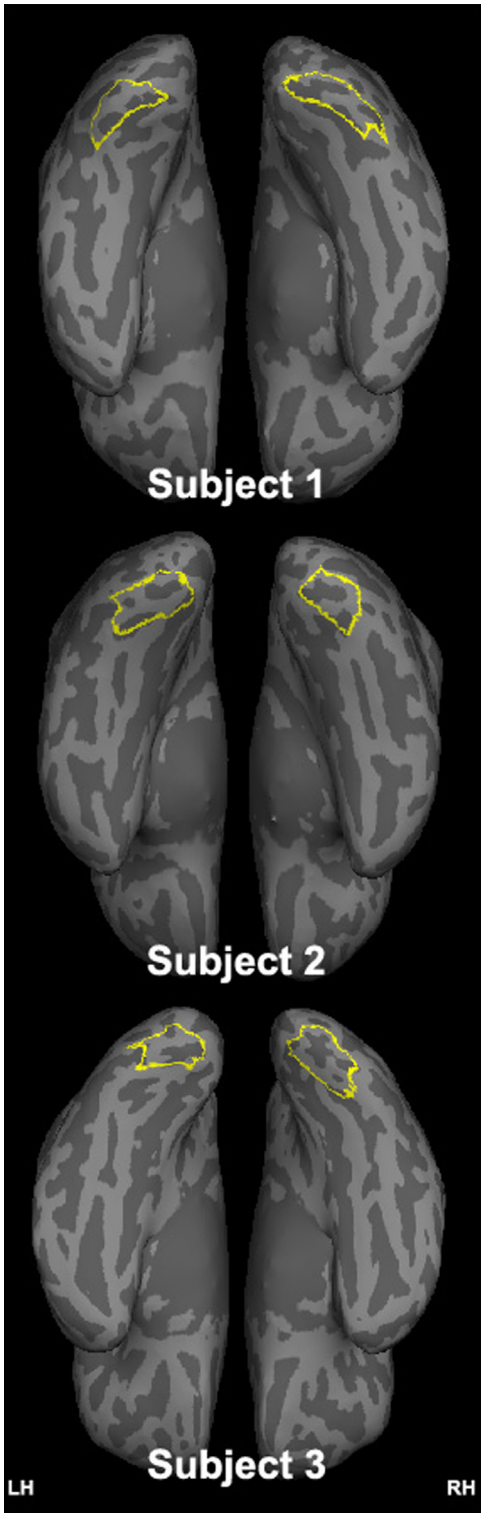

Fig. 2. Occipital region of interest. Representative ventral occipital ROIs in yellow from three participants. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

$p<0.001$). The mean reaction time (RT) for correct go trials was 361 ms (15.4). Accurate no-go trials did not elicit a response therefore RT was not analyzed. No difference in mean RT was observed among the two subsets of go trials used in further fMRI analysis (go trials, matched go trials) and the remaining, unanalyzed go trials: go trials (359.6 ms, 5.38); matched go trials (358.4, 15.46), and unanalyzed go trials (364.6, 14.81) across all subjects ($F(2,30)=1.971$, $p=0.166$, $d=0.362$).

3.2. fMRI

3.2.1. Univariate analysis

Significant activation of a network of brain areas previously associated with response inhibition was observed for no-go vs. baseline and the no-go vs. go contrast. Specifically, no-go stimuli evoked greater activation in the right inferior frontal cortex, right intraparietal lobule (IPL) and precuneus. Of note, there were no differences observed in the direct contrast of no-go and go activation in both the preSMA and the ventral occipital cortex. In order to determine if these results reflected significant but equivalent preSMA and occipital activation, the two stimulus conditions were compared. Relative to baseline, go and no-go stimuli each elicited an increase in preSMA and occipital activation (Fig. 3). Table 1 summarizes the main group no-go vs. go stimulus effects that were observed using the univariate analytic procedures.

Within the anatomically-defined preSMA ROI, average extracted percent signal change values did not significantly differ between no-go and go activation for either hemisphere. A 2 (stimulus type) × 2 (hemisphere) repeated measures ANOVA was performed on the average extracted percent signal change with the anatomically defined preSMA ROIs for each participant. No significant main effect of stimulus type ($F(1,15)=0.807$, $p=0.383$, $d=0.463$), hemisphere ($F(1,15)=0.01$, $p=0.921$, $d=0.496$), or their interaction ($F(1,15)=1.99$, $p=0.178$, $d=0.728$) was observed (Fig. 4). The primary no-go activation, while greatly overlapping the go activation, was centered slightly more rostrally, in agreement with prior results (Mostofsky et al., 2003). Exploratory analysis using a less stringent statistical threshold ($p<0.05$, uncorrected) also failed to show significant activation in the area of overlapping activation within the preSMA ROI for the contrast between no-go and go activation.

Similar results were observed in the occipital ROI. Average extracted percent signal change values did not significantly differ between no-go and go activation in either hemisphere (Fig. 5). A 2 (stimulus type) × 2 (hemisphere) repeated measures ANOVA within the occipital ROI showed no significant main effect of stimulus type ($F(1,15)=0.008$, $p=0.93$, $d=0.046$), hemisphere ($F(1,15)=3.714$, $p=0.07$, $d=0.995$), nor a significant interaction ($F(1,15)=0.284$, $p=0.60$, $d=0.275$) (Fig. 5).

3.2.2. Multi-voxel pattern analysis.

MVPA-based class prediction accuracy for the no-go vs. go comparison was significantly greater than the null classification accuracy derived from permutations testing in the left preSMA ROI (mean no-go vs. go accuracy 60.42%, SD=13.78; permuted null classification accuracy=49.96%, SD=0.156) ($t(15)=3.06$, $p=0.008$, $d=1.580$), while the right preSMA ROI failed to reach significance when compared to the null classification accuracy derived from permutations testing (no-go vs. go accuracy=57.29%, SD=18.23; permuted null classification accuracy=50.03%, SD=0.183) ($t(15)=1.59$, $p=0.13$, $d=0.821$).

In the occipital ROI, MVPA-based class prediction accuracy for the no-go vs. go comparison failed to reach significance in either the left occipital ROI (mean accuracy 55.2%, $t(15)=1.17$, $p=0.260$, $d=0.604$) or the right occipital ROI (mean accuracy 50.52%, $t(15)=0.170$, $p=0.867$, $d=0.088$) when compared the permuted null distribution in each hemisphere respectively.

No significant above-chance class predictions were observed for the control analysis (go trials vs. matched go trials) of the preSMA ROI in either the left (mean accuracy 48.21%, $t(15)=0.327$, $p=0.749$, $d=0.169$) or right (mean accuracy 50.00%, $t(15)=0.00$, $p=1.00$, $d=0.00$) hemispheres when compared to the permuted null classification accuracies. Additionally, control analysis of the

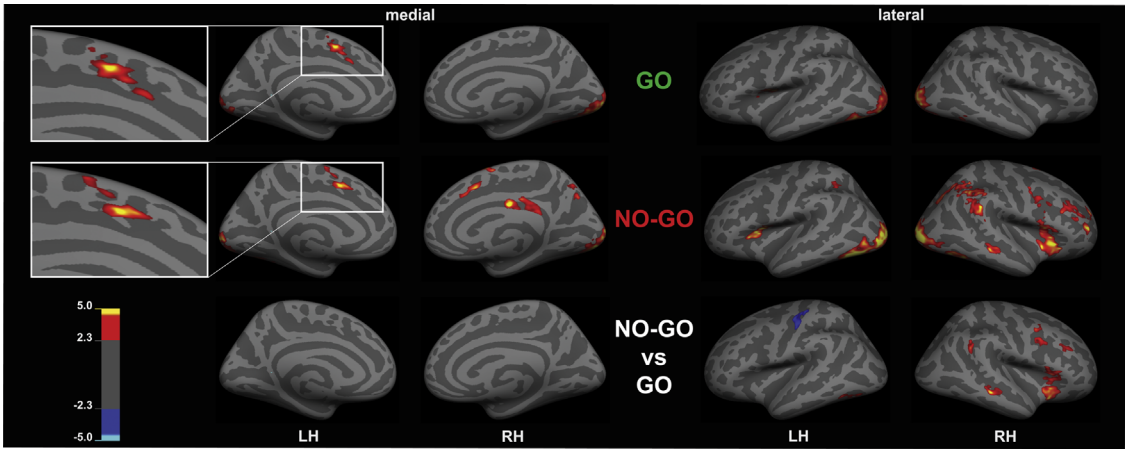

Fig. 3. Univariate fMRI results. Displayed are statistical maps of the go and no-go activations and the contrast between them projected onto the inflated surface of the FreeSurfer average brain. Color coding represents thresholding at $p < 0.005$ uncorrected; cluster $p < 0.05$ corrected. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
No-go vs. go stimulus effects observed using univariate analyses.

Lobe/region	Hemi	Size (mm^2)	MNI *X*	MNI *Y*	MNI *Z*	Cluster-wise *p*-value
Go activation						
Frontal						
preSMA	Left	391.3	−9.0	5.6	49.6	0.0004
Precentral	Left	371.0	−45.5	−2.7	13.5	0.0007
Occipital						
Lateral	Right	4282.8	30.0	−92.0	−6.8	0.0001
Lateral	Left	3721.2	−27.5	−87.4	−15.4	0.0001
No-go activation						
Frontal						
Lateral orbitofrontal	Right	1298.4	29.5	27.4	−1.0	0.0001
Rostral middle	Right	1081.0	22.7	50.7	23.2	0.0001
Pars opercularis	Left	433.2	−40.0	11.0	9.3	0.0001
Precentral	Right	376.8	45.7	0.5	45.6	0.0001
preSMA	Left	364.0	−9.3	8.4	44.9	0.0002
Rostral middle	Right	316.9	34.8	50.4	7.6	0.0004
Superior	Right	221.8	15.5	7.7	60.1	0.0073
preSMA	Right	202.6	10.3	13.0	44.3	0.0127
Temporal						
Fusiform	Left	4661.8	−39.6	−63.8	−9.5	0.0001
Middle	Right	286.9	60.3	−30.5	−10.2	0.0011
Parietal						
Supra marginal	Right	2461.3	59.5	−40.7	26.3	0.0001
Posterior cingulate	Right	410.9	4.3	−23.7	34.1	0.0001
Precuneus	Right	296.9	16.6	−68.8	37.2	0.0011
Superior	Left	178.6	−30.7	−48.2	34.8	0.0247
Occipital						
Lateral	Right	4638.4	30.0	−92.0	−6.8	0.0001
No-go vs. go activation						
Frontal						
Insula	Right	343.6	28.0	17.8	−10.1	0.0001
Pars triangularis	Right	416.3	39.9	23.1	9.9	0.0001
Postcentral	Left	400.5	−35.5	−30.3	55.1	0.0001
Caudal middle	Right	135.7	39.7	4.1	45.9	0.0474
Caudal middle	Right	155.1	35.9	3.7	34.3	0.025
Rostral middle	Right	175.7	44.0	30.6	30.0	0.0136
Temporal						
Middle	Right	234.0	61.8	−29.7	−10.4	0.0019
Parietal						
Inferior	Right	173.4	53.9	−48.7	27.0	0.014
Occipital						
Fusiform	Left	205.2	−40.0	−70.7	−11.8	0.013

occipital ROI showed no significant above-chance class prediction in either the left (mean accuracy 53.16%, $t(15)=0.73$, $p=0.476$, $d=0.376$) or right (mean accuracy=49.98%, $t(15)=1.38$, $p=0.198$, $d=0.713$) hemispheres (Fig. 6).

4. Discussion

The present study employed multi-voxel pattern analysis to characterize the differences in preSMA activation between executed

and inhibited motor responses in a go/no-go task. A univariate analysis illustrated typical activation of the right hemisphere inhibition network previously described (Aron, 2007; Blasi et al., 2006) when participants successfully withheld a motor response. Additionally, preSMA showed significant activation for both go and no-go stimuli based on a univariate analysis, but direct contrast of no-go and go stimuli failed to reveal a significant difference in the observed BOLD signal between stimulus conditions. However, when the voxels of an anatomically-defined preSMA ROI were subjected to MVPA, a significant difference in the activation pattern encoded by go as compared to no-go stimuli was observed. A control analysis employing an occipital ROI failed to illustrate a similar differentiation in early visual processing areas.

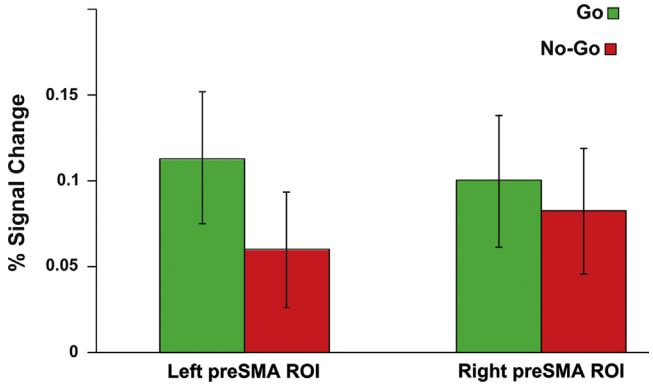

Fig. 4. Percent signal change within the anatomically defined preSMA ROIs for left and right hemisphere. Error bars represent within-subjects error.

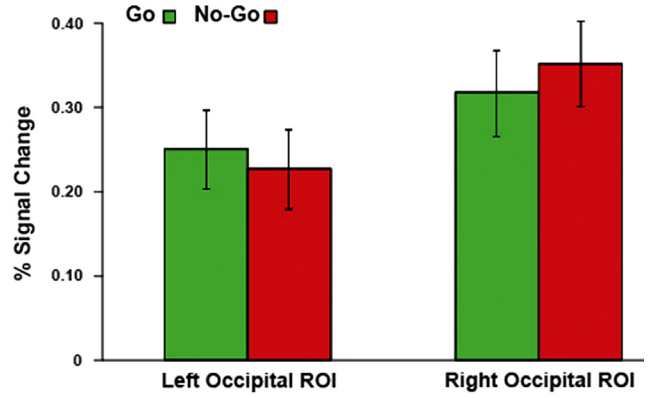

Fig. 5. Percent signal change with the occipital ROI for left and right hemisphere. Error bars represent within-subjects error.

These findings provide evidence for spatially-segregated populations of go and no-go neurons within preSMA, and support a direct role for the preSMA in response selection.

The reported results are consistent with those typical of a go/no-go task; the reduction in behavioral accuracy as well as the observed activation of the rIFG and reduced activity in left primary motor cortex elicited by no-go stimulus presentation suggest that the univariate event-related analysis methods described above did not obscure differences in preSMA activation during task performance. The absence of an observable difference in preSMA activation in the direct contrast of no-go and go stimuli is surprising given previous reports of such a finding (Braver, Barch, Gray, Molfese, & Snyder, 2001; Nee et al., 2007; Wager et al., 2005). However, the overlap in univariate go and no-go stimulus activation in preSMA is consistent with overlapping activations reported in prior imaging studies (Humberstone et al., 1997; Kiehl et al., 2000; Liddle et al., 2001; Mostofsky et al., 2003; Schulz et al., 2011; Swann et al., 2012), as well as recent reports ascribing separable response differentiation and inhibition functions to preSMA (Rae, Hughes, Weaver, Anderson, & Rowe, 2014).

The activation of preSMA in response to both go and no-go stimuli may be a signature of proactive as opposed to reactive cognitive control (Braver, 2012). That is, instead of an observable preSMA response solely to conflict-inducing stimuli, preSMA may be activated in anticipation of the requirement to select among possible response alternatives. Increased activity across the established response inhibition network (including preSMA) has been observed in a conditional stop signal task (Jahfari, Stinear, Claffey, Verbruggen, & Aron, 2009), as well as a cued go/no-go task (Schulz et al., 2011) which provide cues for subsequent response inhibition. This finding of preSMA and rIFG activation prior to the actual suppression of a motor response is consistent with a proactive recruitment of inhibition-related cognitive control, or "active breaking". In a related study, when successfully inhibited trials were compared to go trials where the potential requirement to inhibit some but not all responses was previously cued, no difference in preSMA activation was observed (Swann et al., 2012). Taken together, these results point to a proactive role in situations where an inhibitory response may be required, as opposed to a reactive role where inhibition is a necessary consequence of stimulus presentation. Such a proactive activation of preSMA across both go and no-go stimuli requires a tonic activation in anticipation of the possibility of activating the other nodes of the response inhibition network as task performance demands.

However, the question remains as to the nature of the observed preSMA activation to go stimuli. Is the observed activation a partial engagement of the inhibition process more strongly associated with no-go stimuli, or does the go stimulus elicit a differentiated

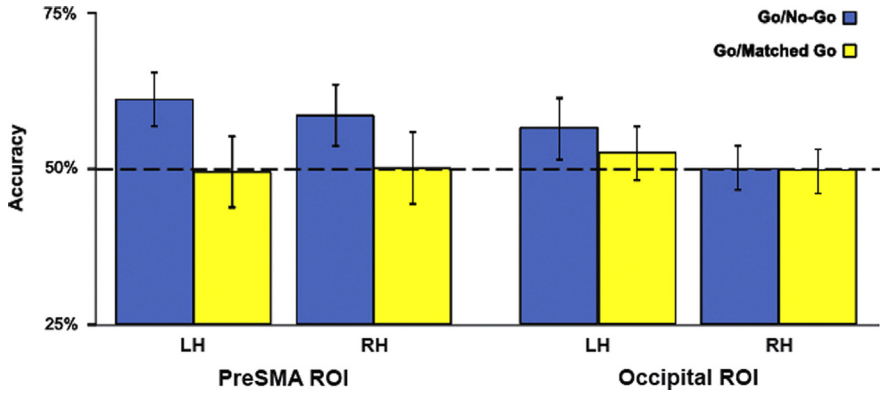

Fig. 6. MVPA classification accuracy for go/no-go comparison and control analysis (go/matched go) in preSMA and occipital ROIs. Dashed line indicates chance classification accuracy. LH = left hemisphere ROI, RH = right hemisphere ROI.

response within the established response inhibition network? The current data illustrate a differentiated signal encoded within the preSMA ROI depending on the required response (motor execution or response inhibition) associated with a given stimulus. Furthermore, this differentiated response to go and no-go stimuli is not seen in an occipital ROI. Since the occipital cortex is a site of overlapping univariate activation in the present task, the absence of a differentiated multivariate signal illustrates a degree of specificity in the encoding of response alternatives in the preSMA.

Single unit recordings in nonhuman primates (Isoda & Hikosaka, 2007) suggest that go and no-go stimuli are processed by separate neuronal populations within primate preSMA. Indeed, MVPA of the current data illustrates a differentiation between activation elicited by go and no-go stimuli within preSMA. These findings are consistent with non-human primate work (Isoda & Hikosaka, 2007) demonstrating heterogeneous neuronal populations within preSMA. In humans, similar heterogeneity is likely to be obscured by the presence of both go- and no-go-sensitive neurons when using a univariate analysis; here the increased resolution afforded by MVPA allows for the differences between go and no-go activity related to these clustered neurons to be more accurately characterized. Also consistent with single unit recording evidence, human neuroimaging (Brown, 2009; Milham & Banich, 2005) has described a region including preSMA that responds to competing response information, and does so independently from conflict (Rae et al., 2014). These previous results are inconsistent with a conflict monitoring explanation, but indicate that response representations are coded directly in preSMA.

In addition, the observed preSMA activation in response to no-go stimulus presentation is consistent with recent evidence that has linked negative motor areas (NMAs) directly with inhibitory control (for a review, see Filevich, Kühn, & Haggard, 2012). Direct stimulation of NMAs leads to the inhibition of motor responses late in information processing. Thus, the presence of NMAs in human preSMA provides a mechanism for inhibition based on activation of NMAs as opposed to a mechanism for inhibition based solely on the absence of activation associated with a go response. Therefore, NMAs provide a plausible mechanism for the differentiable activation patterns seen in response to both go and no-go stimulus presentation. Furthermore, these NMAs occur in distributed neuronal patterns within the preSMA as well as the lateral frontal cortex (Filevich et al., 2012). Motor programs or response representations associated with go responses and no-go inhibitions may exist across heterogeneous neuronal populations within the broader preSMA.

The current results further articulate the content of this previously described activation in the presence of multiple potential response representations. Both Milham and Banich (2005) and Brown (2009) interpret their results as evidence of direct motor signal processing in preSMA. In the current study, the differentiated patterns of activation within preSMA during the successful implementation of alternative stimulus–response associations during task performance—i.e., executed go responses and inhibited no-go responses—provide further evidence of the presence of these motor-related signals.

In addition, the differentiated response to go and no-go stimuli in areas of overlapping univariate activation appears to be specific to the preSMA, as a similar classification accuracy was not observed in an occipital ROI, which also showed overlapping univariate activation to go and no-go stimuli. The absence of an effect in the occipital ROI also argues against a purely sensory explanation for the differences seen in the preSMA. Physical differences between go and no-go stimuli are likely to be greatest during early visual processing. Thus, any differences in activation related to these physical differences would likely be found in the occipital cortex in addition to other brain areas. The data reported do not show this pattern of activation.

The present findings are also consistent with theoretical models suggesting that preSMA plays an active role in executing responses associated with task goals (Rushworth, Walton, Kennerley, & Bannerman, 2004). This direct influence on task performance is in line with recent characterizations of preSMA as an "action-selection director" (Ridderinkhof et al., 2011) that adjudicates between available action affordances. Taylor, Nobre, and Rushworth (2007) suggest that direct conflict resolution by preSMA requires a selective enhancement of the signal associated with the appropriate motor response; this enhanced signal then exerts a modulatory influence on downstream motor areas.

If preSMA participates directly in conflict resolution, differentiated representations of potential responses must be locally instantiated. One proposed mechanism for this is the maintenance of active task sets, which keep appropriate stimulus–action responses in a sustained cognitive state (Rogers & Monsell, 1995). Such maintenance requires a tonic, endogenous signal that facilitates goal-directed behavior (Sakai, 2008). Dosenbach, Fair, Cohen, Schlaggar, and Petersen (2008) argue that preSMA is part of a wide network of frontal and parietal regions responsible for the top-down control of attention. This cingulo-opercular control network, including preSMA, provides the necessary stable maintenance signal. Within this control network, preSMA is theorized to implement the appropriate task sets as performance demands evolve (Dosenbach et al., 2006). As the response set is accessed, the differentiated response representations encoded in preSMA are activated as part of a direct conflict resolution mechanism (Petersen & Posner, 2012). When response conflict is resolved, preSMA participates in the selection among the active response sets.

The association between preSMA and task set has recently been articulated in a number of theoretical models of cognitive control (Banich, 2009; Brown, 2009; Dosenbach et al., 2008; Mostofsky & Simmonds, 2008; Petersen & Posner, 2012). Across these models, preSMA has been implicated in processing available response alternatives and serving as a maintenance signal of task set rules (Dosenbach et al., 2008; Petersen & Posner, 2012), or as the final processing step before motor response execution (Banich, 2009) or inhibition (Mostofsky & Simmonds, 2008).

The involvement of preSMA in direct response representation encoding is further supported by recent evidence of dynamic classification of stimulus features in preSMA (Woolgar, Hampshire, Thompson, & Duncan, 2011). Increases in the level of discrimination between response alternatives have been observed when BOLD response in preSMA is subjected to MVPA, similar to the results of the current study. If preSMA serves only as a general conflict monitor, this level of dynamism in coding stimulus properties is beyond that necessary for accurate task performance. Conversely, if preSMA participates in task set maintenance, the flexible encoding of different task set parameters is required for accurate performance in a variety of tasks.

However, alternative explanations for the observed results in the present study do remain. The differentiated response present in preSMA but absent in the occipital cortex may be related to differences in the frequency of go and no-go stimuli across the current task. Recent evidence has demonstrated a common neural substrate for both novelty and error processing within the broader medial frontal cortex (Wessel, Danielmeier, Morton, & Ullsperger, 2012) and the exact role of the medial frontal cortex, including preSMA, in processing novel as opposed to control-inducing stimuli (like the no-go stimulus in the current task) remains to be characterized. Alternatively, the absence of a differentiated response in the occipital ROI may be due to a lack of statistical power, as the current analysis included only 16 healthy participants. Nonetheless,

the present results are consistent with both the extant single unit data and theoretical accounts of a direct role for preSMA in conflict resolution and response representation.

The use of MVPA in the current study allows for the characterization of preSMA activation at a higher level of resolution than traditional univariate analyses; this is especially important given single unit recordings showing heterogeneous neuronal populations within preSMA in non-human primates. If neurons sensitive to alternative responses are located in close proximity, differentiation among them may be difficult to characterize. The results shown here provide a compelling link between non-human primate and human investigations of cognitive control. Taken together, the present results support the theoretical mechanism described by Petersen and Posner (2012) and Dosenbach et al. (2008). Specifically, the differences in preSMA activation characterized by MVPA are consistent with the ongoing maintenance and manipulation of stimulus–action representations, or task set activations associated with the appropriate response to a given stimulus. Furthermore, these findings are in agreement with prior evidence of a direct role for preSMA in response selection (Coxon, Stinear, & Byblow, 2008; Taylor et al., 2007), of which inhibition is one such selection (Mostofsky & Simmonds, 2008; Rae et al., 2014), and inform the ongoing debate as to the function of preSMA and medial frontal cortex in decision making.

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