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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