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Engagement of large-scale networks is related to individual differences in inhibitory control

Eliza Congdon [a,b,*], Jeanette A. Mumford [c], Jessica R. Cohen [d], Adriana Galvan [a], Adam R. Aron [e], Gui Xue [f], Eric Miller [a], Russell A. Poldrack [a,c,g]

[a] Department of Psychology, University of California Los Angeles, Los Angeles, CA, USA
[b] Center for Neurobehavioral Genetics, University of California Los Angeles, Los Angeles, CA, USA
[c] Department of Psychology, University of Texas at Austin, Austin, TX, USA
[d] Department of Psychology, University of California Berkeley, Berkeley, CA, USA
[e] Department of Psychology, University of California San Diego, San Diego, CA, USA
[f] Department of Psychology, University of Southern California, Los Angeles, CA, USA
[g] Department of Neurobiology, University of Texas at Austin, Austin, TX, USA

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ABSTRACT

Understanding which brain regions regulate the execution, and suppression, of goal-directed behavior has implications for a number of areas of research. In particular, understanding which brain regions engaged during tasks requiring the execution and inhibition of a motor response provides insight into the mechanisms underlying individual differences in response inhibition ability. However, neuroimaging studies examining the relation between activation and stopping have been inconsistent regarding the direction of the relationship, and also regarding the anatomical location of regions that correlate with behavior. These limitations likely arise from the relatively low power of voxelwise correlations with small sample sizes. Here, we pooled data over five separate fMRI studies of the Stop-signal task in order to obtain a sufficiently large sample size to robustly detect brain/behavior correlations. In addition, rather than performing mass univariate correlation analysis across all voxels, we increased statistical power by reducing the dimensionality of the data set using independent component analysis and then examined correlations between behavior and the resulting component scores. We found that components reflecting activity in regions thought to be involved in stopping were associated with better stopping ability, while activity in a default-mode network was associated with poorer stopping ability across individuals. These results clearly show a relationship between individual differences in stopping ability in specific activated networks, including regions known to be critical for the behavior. The results also highlight the usefulness of using dimensionality reduction to increase the power to detect brain/behavior correlations in individual differences research.

Introduction

Understanding the relationship between trait or performance measures and task-induced neural activation represents a line of research that offers great potential for elucidating mechanisms of individual differences in cognitive function, as well as cognitive dysfunction. The role of individual differences in response inhibition is a particularly attractive area as it has widespread implications for executive control. However, this line of research is limited by the need to include a sufficiently large sample size in order to capture variability and to have adequate power for analysis. This is amplified in fMRI studies of individual differences that have used mass univariate (voxelwise) analyses, which are plagued by multiple comparisons problems.

In order to achieve sufficient power, and to fully characterize the pattern of individual differences in neural activation underlying response inhibition, we combined data from five separate fMRI studies that included scanning during performance of the Stop-signal task, a widely used measure of response inhibition. Although we conducted whole-brain correlation analyses for comparison, we also conducted probabilistic independent component analysis (ICA) as a form of data dimensionality reduction. This approach allowed us to correlate behavior with loading coefficients for each subject on components resulting from ICA, which reflect spatially independent

* Corresponding author. Department of Psychology and Center for Neurobehavioral Genetics, Franz Hall, Box 951563, Los Angeles, CA 90095-1563, USA. Fax: +1 310 206 5895.
E-mail address: econgdon@ucla.edu (E. Congdon).

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networks of activation. Our results demonstrate that this approach to dimensionality reduction 1) greatly reduces the multiple comparison issues common to this line of research; 2) substantially improves power for individual differences research; and 3) teases apart the role of functionally integrated networks underlying individual differences in response inhibition.

Response inhibition is the ability to suppress a prepotent or habitual response, including both motor actions and higher-order responses (such as thoughts, memories, or emotions) and is therefore critical to the ability to stop or suppress rapid, automatic behaviors in response to goals or environmental contingencies (Cools, 2008; Jentsch and Taylor, 1999; Nigg et al., 2005). The clinical significance of response inhibition is supported by a wide range of studies demonstrating impaired inhibition associated with disorders including Attention Deficit/Hyperactivity Disorder (ADHD) (Lijffijt et al., 2005; Oosterlaan et al., 1998; Schachar et al., 2005; Schachar and Logan, 1990), substance abuse (Ersche et al., 2008; Fillmore and Rush, 2002, 2006; Monterosso et al., 2005), Conduct disorder (CD) and comorbid CD/ADHD (Oosterlaan et al., 1998). For example, as compared to healthy controls, substance abusers show poorer ability to inhibit behavioral responses on a Stop-signal task, but unimpaired ability to execute responses on Go trials (Fillmore and Rush, 2002; Monterosso et al., 2005). Evidence that the impairment of drug abusing samples in performance of these tasks is specific to the inhibition, and not the execution, of a response underscores the clinical significance of mechanisms underlying response inhibition. In addition, there is evidence that response inhibition is correlated with measures of self-reported impulsivity in the healthy population (Avila and Parcet, 2001; Logan et al., 1997) (but see Enticott et al., 2006).

Laboratory measures of response inhibition, such as the Go/No-Go and Stop-signal paradigms, require participants to respond on a set of relatively frequent trials (Go trials), but to inhibit responding to a separate set of infrequent (Stop trials) (Chambers et al., 2009; Verbruggen and Logan, 2009). In addition, response inhibition is thought to be involved across a number of other paradigms, including response interference, switching, and reversal learning tasks, and the common factor linking these tasks appears to be the need to maintain a goal in the face of strongly activated, but inappropriate, representations or distracting stimuli (Friedman and Miyake, 2004). An advantage of the Stop-signal task is the use of an adaptive procedure to determine the delay at which the stop signal must be presented in order to result in successful stopping on 50% of trials, which makes greater demands on a participant's inhibitory control. The Stop-signal task is based on a horse-race model, which assumes that independent go and stop processes race against one another to determine whether a response is executed or inhibited (Logan and Cowan, 1984; Logan, 1994) (though the independence assumption can be relaxed (Boucher et al., 2007)). This model allows for the estimation of a measure called the stop signal reaction time (SSRT), an individualized measure of a participant's inhibitory ability that controls for difficulty level. It has been shown to distinguish individuals with impaired inhibitory control from healthy controls (Lijffijt et al., 2005; Rucklidge and Tannock, 2002). For these reasons, the Stop-signal task has broad external and translational validity (Verbruggen and Logan, 2008).

There is considerable evidence suggesting that the inhibition or suppression of a motor response relies upon a right-lateralized fronto-basal-ganglia circuit. Multiple neuroimaging studies of response inhibition using Go/No–Go and Stop-signal tasks have implicated a set of regions, including the right inferior frontal cortex (IFC), pre-supplementary association area (pre-SMA) and superior frontal gyrus, and structures of the basal ganglia, including the subthalamic nucleus (STN) (Aron and Poldrack, 2006; Aron et al., 2007; Chamberlain et al., 2009; Garavan et al., 1999; Rubia et al., 2001), and these results are supported by lesion (Floden and Stuss, 2006; Aron et al., 2003), TMS (Chambers et al., 2006; Chen et al., 2009; van den Wildenberg et al., 2009), and DBS studies (Ray et al., 2009). Beyond stopping, there is evidence supporting the role that these regions play in regulating inhibitory control, such that the same regions responsible for stopping a response also modulate the speed–accuracy trade off in decision making. For example, activity in the right IFC, pre-SMA, and STN is correlated with conflict-related slowing in a selective Stop-signal task (Aron et al., 2007) and activity in STN neurons has been shown to control the switch from automatic to volitional saccades in macaque monkeys (Isoda and Hikosaka, 2008). In addition, in Parkinson's patients, STN disruption leads to impaired decision making in high conflict conditions, suggesting that the STN acts to raise the response threshold in the face of conflict (Frank et al., 2007).

Some previous studies have reported relationships between individual differences in stopping ability and fMRI signals. Negative correlations between activation during inhibition and SSRT (reflecting a positive relation between activation and stopping ability) have been observed in a number of regions including the right IFC and right STN (Aron and Poldrack, 2006), the left superior frontal gyrus (SFG) and left precentral gyrus (Li et al., 2006), as well as the pre-SMA and caudate (Li et al., 2008). However, other studies have reported greater activation in the bilateral STN, right globus pallidus, and bilateral putamen in individuals with longer SSRT during successful stopping (Li et al., 2008). Although there is some support for a relationship between neural activation and individual differences in go trial performance (Garavan et al., 2006), the relationship between activation and individual differences in response execution has received less attention.

As previously stated, one potential problem with previous studies is that they have used mass univariate (voxelwise) analyses (which require correction for multiple comparisons) along with relatively small sample sizes, which together result in very low power to detect correlations (Yarkoni, 2009). An alternative to this approach, which we utilize here, is to reduce the dimensionality of the dataset and then perform correlational analyses on the reduced data. A common method for dimensionality reduction with fMRI data is ICA (Calhoun et al., 2009; McKeown and Sejnowski, 1998; Beckmann and Smith, 2004). This method decomposes an fMRI dataset into a set of (temporally or spatially) independent components that are combined to produce an approximation to the observed data.

In the present study, we used the probabilistic ICA approach (Beckmann and Smith, 2004) as implemented in the MELODIC toolbox within the FSL software suite (Smith et al., 2004). Although ICA is usually applied to fMRI time series, here we apply it to a set of individual activation maps; thus, it identifies spatially independent components along with the loading on each of those components for each individual (see (Smith et al., 2009) for a similar approach) while also allowing for condition-specific analyses. These loading coefficients, rather than raw voxel values, thus serve as the data to be related to behavior. In particular, rather than correlating behavior and raw voxel values for each person, repeated across all voxels in the brain, we correlated behavior with the loading coefficient for each subject (the subset of voxels that make up a given component). By greatly reducing the number of comparisons to be performed, this approach reduces multiple comparison issues and allows more powerful detection of brain/behavior correlations.

Methods

Samples

Raw data were included from five separate fMRI studies conducted on two scanners at the University of California, Los Angeles, each of which included two Stop-signal scan sessions administered in rapid event-related designs. While each study had its own additional inclusion and exclusion criteria (see below), all samples included right-handed healthy English-speaking subjects, free of neurological or psychiatric history, not currently taking psychoactive medication, with normal or corrected-to-normal vision and with no counter-