Regional homogeneity of resting state fMRI signals predicts Stop signal task performance

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A B S T R A C T

It has been suggested that resting-state functional magnetic resonance imaging (RS-fMRI) is a promising tool to study the relation between spontaneous brain activity and behavioral performance. However, little is known about whether the local synchronization of spontaneous brain activity could predict response inhibition. In the current study, we used regional homogeneity (ReHo) to measure the local synchronization of RS-fMRI signals, and then investigated the relationship between ReHo and individual differences in response inhibition, as evaluated by the stop signal reaction time (SSRT) in a Stop signal task. The results showed that ReHo of RS-fMRI signals could successfully predict SSRT. Specifically, positive ReHo-SSRT correlations were observed in the bilateral inferior frontal cortex (IFC) and three critical components of the default mode network (DMN), and negative ReHo-SSRT correlations were observed in the rolandic area/posterior insula and the bilateral middle occipital cortex. The present results indicate the possible influence of the IFC and rolandic area/posterior insula on the efficiency of response inhibition, and demonstrate the importance of the DMN for the efficiency of cognitive task performance.

Introduction

Response inhibition refers to the ability to suppress responses that are no longer required or appropriate. This ability thus supports flexible behavior in ever-changing environments, and is a key component of executive control. Numerous studies have been carried out to examine the underlying neural basis of response inhibition (for reviews, see Chambers et al., 2009; Stinear et al., 2009; Verbruggen and Logan, 2009). In conjunction with other regions, such as the pre-supplementary motor area (Pre-SMA) and the subthalamic nucleus, these studies show that the right inferior frontal cortex (IFC) has been observed to play an essential role in response inhibition (Aron et al., 2003; Aron and Poldrack, 2006; Aron et al., 2007; Eagle et al., 2008; for reviews, see Chambers et al., 2009; Verbruggen and Logan, 2009). For example, the extent of damage to the right IFC has been reported to be directly correlated with subjects’ response inhibition performance (Aron et al., 2003). Deterioration of response inhibition has been linked to certain disorders such as attention deficit hyperactivity disorder (ADHD) (Nigg, 2001; Oosterlaan et al., 1998; Schachar and Logan, 1990), obsessive-compulsive disorder (Chamberlain et al., 2006; Menzies et al., 2007; Penades et al., 2007) and substance abuse (Monterosso et al., 2005; Nigg et al., 2006). Understanding the functional substrates of inter-individual differences in response inhibition has been suggested to be helpful for discovering “risk factors” for these disorders (Chambers et al., 2009).

Resting state functional magnetic resonance imaging (RS-fMRI) may be a valuable tool for analyzing the functional basis of inter-individual variation in response inhibition. RS-fMRI signals have been suggested to be functionally meaningful and reflect the “intrinsic” functional organization of human brain (Biswal et al., 1995; Fox et al., 2005; for reviews, see Raichle and Gusnard, 2005; Fox and Raichle, 2007; Raichle, 2010). Disturbances in resting state functional connectivity (RSFC) between brain regions have been reported in a number of pathological states (for a review, see Zhang and Raichle, 2010) including Alzheimer’s disease (Wang et al., 2006; Wang et al., 2007), multiple sclerosis (Low et al., 2002), depression (Anand et al., 2005; Greicius et al., 2007), schizophrenia (Liang et al., 2006; Zhou et al., 2007) and ADHD (Castellanos et al., 2008; Tian et al., 2006). Furthermore, several recent studies observed significant RSFC-behavior correlations across normal subjects (Hampson et al., 2006; Kelly et al., 2008; Seeley et al., 2007; Song et al., 2008). For instance, Hampson et al. (2006) observed significant correlations between working memory performance and RSFC within the default mode network (DMN), which has been suggested to fulfill a variety of “task irrelevant” functions such as stimulus-independent thought (McKiernan et al., 2006); for a review, see Buckner et al., 2008) and momentary lapses in attention (Li et al., 2007; Weissman et al., 2006).
2006). Kelly et al. (2008) reported that the strength of the negative correlation between the “task-positive” attentional network and the DMN was significantly correlated with individual differences in response time variability in the task not only during an Eriksen flanker task, but also during the resting state. These two studies not only demonstrated that the RSFC-behavior correlations could be a valuable method of examining individual differences, but also indicated that the DMN might be important for individual performances in cognitive tasks (Hampson et al., 2006; Kelly et al., 2008).

Despite its advantages in evaluating the “intrinsic” functional organization of human brain, RSFC analysis has several limitations. First, RSFC evaluates brain functions from the perspective of functional integration and thus can only provide information about the functional interactions between brain regions. Second, the most frequently used RSFC evaluation technique, namely, the seed-based correlation analysis, usually requires a priori definition of a region of interest (ROI), and thus the results could be strongly dependent upon how the ROI is chosen (Smith et al., 2011). The analyses of the local features of the RS-fMRI signals, for instance, the amplitude of low frequency fluctuations (ALFF) (Zang et al., 2007; Zou et al., 2008) and regional homogeneity (ReHo) (Zang et al., 2004), could be valuable complimentary methods for investigating spontaneous brain activity. ALFF evaluates the amplitude of spontaneous fluctuations of certain voxels, and ReHo measures the temporal synchronization of the time series of nearest neighbors. In contrast to RSFC, ALFF and ReHo require no a priori definition of ROIs, and can provide information about the local activity of separate brain regions. Therefore, ALFF and ReHo-behavior correlation analyses could also be profitable tools for investigating the neural basis of individual differences in behavior. In a pioneering study, Mennes et al. (2011) evaluated the correlations between ALFF of RS-fMRI signals and task-evoked activation, as well as performance in an Eriksen flanker task. They reported that resting state ALFFs could successfully predict task-evoked activations and behavioral performance.

In the current study, we employed ReHo of RS-fMRI signals to investigate the functional basis of individual differences in response inhibition. Subjects’ response inhibition ability was evaluated by their performance in a stop-signal task, namely, the stop signal reaction time (SSRT) based on the horse-race model (Logan and Cowan, 1984; Verbruggen and Logan, 2009). The stop-signal task has been shown to be a valuable tool for the study of response inhibition, and the SSRT in particular has been shown to be a critical measure of the cognitive control processes involved in stopping (Verbruggen and Logan, 2008, 2009). To predict inter-individual variation in response inhibition, we analyzed ReHo-SSRT correlations across 34 normal male subjects. Only males were included in this study, because it was conducted as part of a project aiming at the pathology analysis and preclinical diagnosis of ADHD, and this project includes only male subjects. The right IFC has been reported to play a critical role in the DMN during task performance (Aron et al., 2004; Verbruggen and Logan, 2008) and damage to this area has been found to be correlated with SSRT (Aron et al., 2003). Therefore, we predict that ReHo in the right IFC may be significantly correlated with SSRT. Furthermore, activity in the DMN during task performance has been observed to contribute to individual differences in lapses of attention (Weissman et al., 2006) and Stop signal errors (Li et al., 2007). We hypothesize that the DMN regions would also exhibit significant ReHo-SSRT correlations.

Materials and methods

Subjects

Thirty-four healthy male subjects (23.7 ± 3.8 years) participated in the present study. All were right-handed and had no history of neurological or psychiatric disorders. Written informed consent was obtained from each participant, and the study was approved by the Institutional Review Board of the State Key Laboratory for Cognitive Neuroscience and Learning, Beijing Normal University. Each subject performed a stop-signal task outside the scanner immediately after scanning. The subjects were required to perform the stop-signal task after RS-fMRI data acquisition for the consideration that RS-fMRI signals could possibly be modulated by preceding events (Albert et al., 2009; Tambini et al., 2010; Yan et al., 2009).

Behavioral data acquisition

The stop-signal task was programmed in Presentation (http://www.neurobs.com/) (Fig. 1). Each subject completed three blocks of stop-signal tasks. The blocks were separated by instructions for the subjects, and the subjects could begin each block by clicking the mouse to terminate the instruction screen. There were 80 Go and 20 Stop trials per block.

For the Go trials, subjects were instructed to respond as quickly as possible without sacrificing accuracy by clicking the left or right button of a mouse according to the direction of an arrow that appeared on the center of the computer screen. The arrow pointed to the left or the right in a pseudorandom order. The arrow was presented for 600 ms, and then a small “+” appeared to engage attention. The “+” remained on the screen for a randomly selected interval of 1400, 1800 or 2200 ms. For the Stop trials, subjects were instructed to stop their response on seeing a Stop signal (an additional upward arrow), which appeared shortly after the Go signal onset. It has been well established that the time interval between the Stop and the Go signals (stop-signal delay, SSD) directly influences the difficulty of a stop-signal task. For instance, the rate of successful response inhibition decreases with the increase of the SSD (Verbruggen and Logan, 2009). To yield approximately 50% successful response inhibition for the estimation of stop-signal reaction time (SSRT), the SSD of each Stop trial was dynamically adjusted (Band et al., 2003). Specifically, the SSD started at 250 ms and, if the subject successfully inhibited in a Stop trial, the next Stop trial would be made more difficult by increasing the SSD by 50 ms until the SSD reached a length of 550 ms. If the subject failed to inhibit, the subsequent Stop trial would be made easier by decreasing the SSD by 50 ms until the SSD attained a length of 50 ms.

![Fig. 1. Schematic display of the stop-signal paradigm. The paradigm consisted of three blocks of stop-signal tasks, with 80 Go and 20 Stop trials in each block. For the Go trials, subjects were instructed to respond as quickly as possible by clicking the left or right button of a mouse according to the direction of an arrow that appeared on the center of the computer screen. The arrow was presented for 600 ms, then a small “+” was presented to engage attention. For the Stop trials, subjects were instructed to stop their response on seeing a Stop signal (an additional upward arrow) that appeared shortly after the Go signal onset. The time interval between the Stop and the Go signals (stop-signal delay, SSD) was changed dynamically to obtain a 50% inhibition rate (see Materials and methods).](image-url)
The subjects were instructed to respond to the Go signal as quickly as possible, but to withhold their response if a Stop signal appeared. Furthermore, it was emphasized that subjects should try to avoid the tendency to delay their responses in anticipation of a Stop signal. Directly before the collection of the behavioral data, each subject performed a training session of 20 trials (16 Go and four Stop trials).

Behavioral data, including both reaction time (RT) and accuracy, were collected with Presentation software (http://www.neurobs.com/). The SSRT provides an index of inhibitory function, and here it is estimated based on the horse-race model (Logan and Cowan, 1984), specifically, by subtracting SSD from the mean value of RT (Band et al., 2003).

MRI data acquisition

MRI data were obtained using a 3.0 Tesla Siemens Trio scanner at the Imaging Center for Brain Research, Beijing Normal University. Each subject underwent an 8-min fMRI scan during a conscious resting state immediately after the acquisition of the localizer images. Functional images were collected axially using an echo-planar imaging sequence sensitive to blood oxygen level dependent (BOLD) contrast. The acquisition parameters were: 33 slices, 2000/30 ms (TR/TE), 3.5/0.7 mm (thickness/gap), 220×220 mm (FOV), 7° (flip angle). During the resting state, the subjects were instructed to remain still, awake with their eyes closed, as motionless as possible and to think of nothing in particular (note: none of the subjects fell asleep during scanning, according to a simple questionnaire administered immediately after the scan). T1-weighted images covering the whole brain were then obtained sagittally with the following parameters: 128 slices, 2530/3.39 ms (TR/TE), 1.33/0 mm (thickness/gap), 256×256 (resolution), 240×240 mm (FOV), 7° (flip angle). Other scanning sessions not used in the present study are not described here.

Data preprocessing

The first 10 volumes of RS-fMRI data were discarded to ameliorate the possible effects of scanner instability and subjects’ adaptation to the environment. The remaining functional scans were corrected for within-scan acquisition time differences between slices, and then realigned to the first volume to correct for within-run head motions. This realigning step provided a record of head motions within each fMRI run. The functional scans were then spatially normalized to the East Asian brain template provided by SPMSM (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/), and resampled to 3×3×3 mm³. Through linear regression, the influences of linear trends were subsequently removed from the data. Finally, the waveform of each voxel was temporally band-pass filtered (0.01–0.08 Hz) to reduce the influences of low-frequency drift and high-frequency noise. All of these processes were conducted using DPARSF software (Yan and Zang, 2010; http://www.restfmri.net/forum/DPARSF).

ReHo analysis

ReHo was performed on a voxel-by-voxel basis by calculating Kendall’s coefficient of concordance (Kendall and Gibbons, 1990) of time series of a given cluster of neighboring voxels (see Zang et al., 2004 for details). Here, cubic clusters of 27 voxels were used and the ReHo value of every cubic cluster was assigned to the central voxel (Zang et al., 2004). A larger ReHo value for a given voxel indicates a higher local synchronization of RS-fMRI signals among neighboring voxels. To minimize the whole brain effect, voxel ReHo values were scaled by dividing each subject’s value by the mean value of their whole-brain ReHo. All of these procedures were performed using DPARSF software (Yan and Zang, 2010; http://www.restfmri.net/forum/DPARSF).

ReHo-SSRT correlation analysis

Pearson’s correlation analysis between the ReHo values and the SSRT was performed in a voxel-wise manner. To control for Type I error, Monte Carlo simulations were performed (parameters were: individual voxel p-value = 0.05, 10,000 simulations, 2 sided, FWHM estimated by 3dFWHMx, with a whole brain mask including 84,234 resampled voxels) using 3dClustSim in AFNI software (http://afni.nimh.nih.gov/afni). According to the simulations, a corrected significance level of p<0.05 could be obtained with cluster size > 1188 mm³ and individual voxel height threshold of p<0.05. The ReHo-SSRT correlation map was finally superimposed on a template provided in MIRCRO software (http://www.cabiatl.com/mricro/) for display, and all significant correlations were presented in MNI coordinates.

Results

Behavior

The mean RT for correct Go trials was 492±70 ms, and subjects made fewer than three discrimination errors (missed or incorrect clicks) on average, out of 240 Go trials. The Stop inhibition rate was 52.35±2.29%, which was close to 50% and thus would yield accurate estimates of SSRT (Band et al., 2003). The average SSRT was 229±27 ms. Both the RT for Go trials and the SSRT in the present study were in the previously established typical range for young adults of a similar age (e.g., 223.1±26.3 ms in the study by Zheng et al., 2008). Consistent with the race-model assumption of the independence of Go and Stop processes (Logan and Cowan, 1984), the correlation between the Go RT and SSRT was not significant (n=34, r=0.27, p=0.12), and the mean RT for unsuccessful Stop trials to which subjects responded was significantly faster than the mean RT on Go trials (437±59 ms vs. 492±70 ms, t=12.53, p=4.28×10⁻ⁱ⁴).

ReHo-SSRT correlations

At a threshold of p<0.05 (corrected), significant positive ReHo-SSRT correlations were observed in the bilateral IFC and three DMN regions, namely, the bilateral medial prefrontal cortex (MPFC), the bilateral precuneus and the left inferior parietal lobule (IPL) (Fig. 2, Table 1). Significant negative ReHo-SSRT correlations were observed in the bilateral rolandic area/posterior insula, the bilateral middle occipital cortex (MOC), the left inferior temporal cortex (ITC) and the right superior temporal cortex (STC) (p<0.05, corrected) (Fig. 2, Table 1).

Discussion

In the current study, we performed ReHo-SSRT correlations to investigate the basis of individual differences in response inhibition. Significant positive ReHo-SSRT correlations were observed in the bilateral IFC and the DMN, and significant negative ReHo-SSRT correlations were observed in the bilateral rolandic area/posterior insula, the bilateral MOC and the left ITC. The present findings support a critical role of the IFC in response inhibition, and indicate that the DMN might exert an important influence on individual performance in response inhibition.

Significant positive ReHo-SSRT correlations in the DMN

Raichle et al. (2001) first proposed the concept of the DMN based on the observations that certain regions, such as the precuneus/PCG, MPFC and bilateral IPL, consistently exhibited task-induced deactivations during a wide variety of goal-directed behaviors. Since that report, the DMN has been extensively investigated, and has been suggested to
underlie a variety of functions such as stimulus-independent thought (Buckner et al., 2008; McKiernan et al., 2006), momentary lapses in attention (Li et al., 2007; Weissman et al., 2006) and spontaneous cognition (Buckner et al., 2008). All of these processes tend to influence the effectiveness of task performance. Furthermore, based on the negative correlation between RS-fMRI signals of the DMN and those of the task-positive network, Fox et al. (2005) proposed the existence of intrinsic behavioral competition between task-focused attention and the processes subserving stimulus-independent thought.

These aforementioned findings indicated the importance of DMN activity in inter-individual variations in cognitive task performance. Consistent with these findings, Hampson et al. (2006) reported that working memory task performance was correlated with the strength of functional connectivity between two critical components of the DMN: the PCC and the MPFC. Li et al. (2007) observed that the greater activity of the DMN regions before “Stop” signals could predict performance errors in the coming “Stop” trials. In this study, resting state ReHo in three DMN regions, namely, the bilateral precuneus, bilateral MPFC and left IPL, was correlated with SSRT (Fig. 2, Table 1). The present findings are consistent with the suggestion that DMN activities may possibly influence goal directed behavior and/or mental effort during cognitive tasks (Li et al., 2007; Weissman et al., 2006).

**Significant positive ReHo-SSRT correlations in the IFC**

Converging evidence suggests that the right IFC is important for successful response inhibition (for reviews, see Aron et al., 2004; Chambers et al., 2009; Verbruggen and Logan, 2009). In a pivotal study by Aron et al. (2003), patients with damage to the right IFC were found to exhibit longer SSRT during stop-signal task performance compared to healthy controls. Moreover, the volume of the lesion damage to the right IFC was correlated with SSRT across subjects; the greater the damage, the longer the SSRT (Aron et al., 2003). In another study by Aron and Poldrack (2006), right IFC activation during a Stop signal task was negatively correlated with SSRT, that is, the subjects that were faster to inhibit responses exhibited stronger activation in the IFC. In the present study, the right IFC exhibited a significant ReHo-SSRT correlation (p < 0.05, corrected) (Fig. 2, Table 1). The present finding of a significant ReHo-SSRT correlation in the right IFC further supports the notion of a critical role of this area in individual subjects’ inhibition performance.

Although several neuroimaging studies on response inhibition have reported bilateral IFC activation (Bunge et al., 2002; Konishi et al., 1999; Li et al., 2006; Menon et al., 2001), the role of the left IFC has been less rigorously examined. In the current study, the left IFC also exhibited a significant ReHo-SSRT correlation (Fig. 2, Table 1). This finding suggests that the left IFC may also play an important role in response inhibition. Further studies are needed to validate this suggestion.

**Significant negative ReHo-SSRT correlations**

In this study, we observed significant negative ReHo-SSRT correlations in the bilateral rolandic area/ posterior insula (Fig. 2, Table 1).

![Fig. 2. Brain regions exhibited significant ReHo-SSRT correlations.](image-url)
The rolandic area has been reported to play an important role in motor preparation (Tzagarakis et al., 2010). ADHD children with rolandic spikes have been reported to make significantly more commission errors in inhibition (Holtmann et al., 2006). The posterior insula is anatomically linked to the Pre-SMA, a critical component of the inhibition circuitry (Aron and Poldrack, 2006; Chambers et al., 2009), and has been suggested to be involved in environmental monitoring and response selection (Cauda et al., 2011; Kurth et al., 2010; Taylor et al., 2008). Therefore, the present finding of a significant ReHo-SSRT correlation in the rolandic area/posterior insula is consistent with their functions in motor preparation and response selection, which are closely related to response inhibition (Chambers et al., 2009). Moreover, the present finding indicates the importance of the rolandic area/posterior insula for the efficiency of response inhibition.

Significant negative ReHo-SSRT correlations in the bilateral MOC and the left ITC observed in this study might be explained by their roles in visual information processing. The MOC receives visual information from the primary visual cortex (V1), processes the information, and then relays the processed information to other regions for further processing. The ITC has traditionally been deemed as the terminal of the ventral visual stream, which is associated with form perception and has been regarded as a higher order visual region (Iacoboni et al., 2001; Vaina and Cross, 2004), but the underlying relationship between the right STC activities and subjects’ performances in the stop-signal task is still unclear.

Methodological issues and future directions

Some methodological issues need to be addressed in the present study. First, it is difficult to determine the physiological significance of the direction of the ReHo-SSRT correlations before the physiological significance of ReHo is further elucidated. Based on RS-fMRI, He et al. (2007) reported significant ReHo in the DMN regions, which have been suggested to be more active than other regions during resting state (Raichle et al., 2001). Zang et al. (2004) detected significantly higher ReHo in the primary motor cortex during a finger tapping task state than during resting state, similar to task activation detected by conventional general linear model. They also found significantly decreased ReHo in the DMN during task state than resting state, a similar pattern with DMN deactivation during goal-directed tasks (Zang et al., 2004). These studies indicated that ReHo might have some relevance to the level of brain activities, but further studies are needed to investigate its physiological significance.

Second, ReHo measures the local synchronization and hence may result in additional smoothness. We re-estimated the smoothness by 3dFWHMx on the ReHo maps. The estimated size of spatial smoothness was larger than before (originally 4.61, 4.49, and 5.52 mm, on the preprocessed RS-fMRI data; but 6.94, 7.03, and 6.98 mm now). With the new smooth size for multiple comparison correction (3dClustSim in AFNI software, http://afni.nimh.nih.gov/afni), only one cluster in the left MPFC (the largest one in Table 1) survived the new criteria (minimally 120 voxels). This more conservative result seems quite stringent. The smoothing effect by ReHo per se needs further statistical studies in the future. ADHD is more common in males than in females, and this is why the current study only tested male participants. It would be useful for future studies to investigate the effects of gender on ReHo-SSRT correlations.

Third, as mentioned above, the present study is part of a project aiming at the pathology analysis and preclinical diagnosis of ADHD.

Conclusions

In summary, we performed ReHo-SSRT correlations to investigate the basis of individual differences in response inhibition. Close ReHo-SSRT relations were observed in the bilateral IFC, bilateral rolandic area/posterior insula, bilateral MOC, left ITC and some DMN regions. The present findings have three implications: 1) providing further support for the critical role of the IFC in response inhibition, and indicating their possible influence on the efficiency of response inhibition; 2) demonstrating the importance of the DMN in goal-directed behavior and/or mental effort during cognitive tasks; 3) illustrating that resting-state brain activities could be used to predict subjects’ cognitive task performance.

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