Investigating the Role of the Right Inferior Frontal Gyrus in Response Inhibition

An fMRI Approach

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Abstract

Numerous fMRI studies have demonstrated activation patterns during proactive inhibition similar to activations during reactive response inhibition, and prominent theories propose that frontal cortical regions, such as the right inferior frontal cortex (rIFG) of the human brain houses a dedicated region for proactive and reactive response inhibition. However, there is growing evidence to support the view that this 'inhibitory control hypothesis' is incorrect. In particular, it is still unclear whether the rIFG is specifically involved in inhibitory control or more generally in the detection of salient or task-relevant cues. The paradigms on which the former theories are based have often failed to distinguish between inhibitory and non-inhibitory cognitive demands. The fMRI study reported here sought to clarify the role of the rIFG in response inhibition by dividing the stimulus-response period of the Stop signal task (SST) into two temporally separated events – task initiation and successful response inhibition. This strategy enabled the disentangling of processes related to salience detection preparation-related from pure inhibition-related effects. We found rIFG activity during successful stopping, but not during a non-inhibitory related cue period. A subsequent PPI analysis revealed that the rIFG in fact became more decoupled with the supplementary motor area (SMA) as the Stop signal probability increased, while at the same time connectivity with the left inferior parietal cortex increased. Our findings suggest that rIFG and its related regions are not functionally unique in their sensitivities to inhibitory cognitive demands. Rather, they appear to be more linked to salience detection as a part of a ventral attention reorienting network.

Table of contents

1 Introduction

1.1 Theoretical background

Executive function refers to the ability to plan and execute behavior whilst constantly updating representations and goals in an ever-changing environment. One of the key elements of cognitive control is response inhibition, the ability to withhold dominant motor responses that are either inappropriate in a given behavioral context or unwanted because they interfere with completion of motor and/or cognitive goals (Aron, 2011). Inhibitory control is typically subdivided into two components: reactive and proactive inhibition. The former acts to cancel the execution of a planned response, while the latter is involved in adjusting response selection and preparation in anticipation of upcoming task demands. Inhibitory control has been found to be predictive of both cognitive abilities and academic achievement (Harnishfeger & Björklund, 1994). Conversely, impairments in response inhibition have been associated with various psychiatric disorders, such as obsessive compulsive disorder (OCD; Bannon, Gonsalvez, Croft, & Boyce, 2002), and posttraumatic stress disorder (PTSD; van Rooij, Geuze, Kennis, Rademaker, & Vink, 2014). Especially notable is attention-deficit/hyperactivity disorder (ADHD; McLoughlin et al., 2010; Simmonds, Pekar, & Mostofsky, 2008), in which a leading hypothesis proposes that failure to inhibit impulsive/off-task behavior is a core deficit of the disorder (Barkley, 1997).

Two popular paradigms used to study response inhibition in a laboratory setting are the Go/No-Go task (GNT) and the Stop-signal task (SST). In the typical GNT, participants are presented with frequent Go trials and less frequent No Go trials. Here, the task is to press a designated key when a Go signal is presented, and to inhibit this response when an infrequent No-Go signal is presented. The number of omission errors (Go errors), and number of commission errors (No-Go errors) are dependent variables that are used as a measure of inhibition in the Go/No-Go paradigm. According to Schachar et al. (2007), there are two types of motor response inhibition: action restraint (putting a not-yet initiated action on hold) and action cancellation (stopping an already initiated action). GNTs are usually employed to examine the former (Cohen & Lieberman, 2010), while the latter is mostly studied using SSTs. Similarly to GNTs, the SST is comprised of frequent Go trials and less frequent Stop

trials. In the standard SST, participants are presented with a binary stimulus, such as a left- or right-pointing arrow, and are required to respond as fast and as accurately as possible by pressing the corresponding button. If the trial is a Stop trial, a Stop signal, such as an auditory tone, is presented either simultaneously or immediately after the Go stimulus, indicating that the response must be cancelled (Cohen & Lieberman, 2010). Typically, participants are able to stop their response if the Stop signal is presented close to presentation of the go stimulus. However, response inhibition is not possible when the Stop signal is presented too close to the moment of execution (Cohen & Lieberman, 2010). Vince (1948) demonstrated that participants managed to withhold their responses only when the delay between the Go stimulus and the Stop signal (Stop signal delay; SSD) was short (i.e., 50 ms). At longer SSDs (i.e., 100 ms and longer) however, successful response inhibition was very rare, suggesting that the stop process started too late in order to cancel the response. A substantial amount of research has replicated these findings (e.g., Aron, 2011).

Accounting for these observations, Logan and Cowan (1984) proposed a so-called horse race model, arguing that response inhibition is determined by a race between two distinct neural processes – a go process and a stop process. The behavioral outcome (stopping or going) is determined by whichever process that first reaches a critical threshold. The race idea was implicitly present already in the work of Vince (1948), and Lappin and Eriksen (1966). Ollman (1973) later formalized the idea of a race between the go process and the stop process, and used the SST to test the hypothesis that subjects perform these tasks by setting a subjective deadline and then making either a stimulus controlled, or a 'guess' response, depending on whether stimulus controlled processing finished before the deadline. Hence, in SSTs, subjects would set the deadline so that the Stop signal could be detected before the deadline. Detecting the Stop signal before the deadline should result in successful stopping, while detecting the signal after the deadline should result in commission errors.

The early race models mainly focused on qualitative descriptions of go and stop performance, and were therefore limited and lacked a precise description of the main variable of interest, namely the latency of the stop process, commonly referred to as Stop signal reaction time (SSRT). Unlike the latency of overt choice responses, the SSRT cannot be directly measured, but must be estimated indirectly. There are a number of possible approaches to SSRT estimation (Logan & Cowan, 1984; Logan, 1994). The mean method, for example, involves subtracting the mean of the inhibition function on correct Stop trials

(estimated from the probability of responding at each SSD) from the mean value of the correct Go trials. Using variable SSDs, as is the case when applying so-called staircasing to dynamically adjust the difficulty of inhibition as a function of trial-by-trial performance, may complicate SSRT estimation. However, both simulations and reliability tests have demonstrated that if the staircasing procedure results in accuracy scores not significantly different from 50%, mean method SSRT estimates are most reliable (Band, van der Molen, & Logan, 2003; Logan et al., 1997; Williams, Ponesse, Schachar, Logan & Tannock, 1999). There is general consensus that SSRTs constitute reliable estimates of response inhibition efficiency (Leotti & Wager, 2014). In healthy adults SSRTs have been shown to range around 200 ms, whereas in individuals suffering from neuropsychiatric disorders the SSRTs were found to exceed 400 ms. Moreover, longer SSRTs were also reported in young children and elderly (Smittenaar et al., 2015). Due to the quantifiability and validity of the SSRT as an index of inhibition efficiency, the SST has become one of the most widely used paradigms to study response inhibition (Logan, 1994; Logan, Cowan & Davis, 1984).

Earlier versions of the SST were generally used to elicit reactive (outright) stopping in response to an unanticipated Stop signal. This has received some criticism, and it has been argued that, in order to understand how response inhibition is achieved in the context of everyday behavior, research must shift focus to proactive inhibitory control as it has more ecological validity (Smittenaar, Rutledge, Zeidman, Adams, Brown, Lewis, & Dolan, 2015). Instead of being triggered exogenously by external stimuli, proactive inhibition is endogenously activated by internal goals, and is implemented beforehand, restraining action initiation in preparation for a potential Stop signal (Braver, 2012). Proactive inhibition is thus studied by examining the effect of uncertainty on Go trial RTs. Recent work has demonstrated that presenting subjects with informative cues indicating the probability of a Stop signal in the upcoming trial enables the investigation of proactive, in addition to reactive inhibition (Aron, 2011). The measure of proactive inhibition is indexed by the stop-signal probability slope, or preparatory cost (PC) function, which is the change in go-trial RT per unit increase in stop-signal probability (Verbruggen, Aron, Stevens & Chambers, 2010; Vink, Kahn, Raemaekers, van den Heuvel, Boersma, & Ramsey, 2005). Previous research on proactive inhibition has consistently demonstrated that participants exhibit response slowing on Go trials (increased PC) when the probability of stopping is increased (Verbruggen & Logan, 2009). A study conducted by Zandbelt and Vink (2010) manipulated the probability of Stop signal occurrence by presenting visual cues of different colors corresponding to percent Stop signal probability.

Both Go trial RTs and Stop trial accuracy scores increased linearly as a function of Stop signal probability, displaying a clear effect of proactive inhibitory control.

Several independent lines of research have reported a negative correlation between SSRT and PC. As higher PCs indicate better proactive inhibitory control and higher SSRTs indicate poorer reactive inhibitory control, the negative correlation between the two implicates a positive relationship between proactive and reactive inhibition (Chikazoe et al., 2009; Verbruggen & Logan, 2009; Vink et al., 2005). This is interpreted to mean that proactive inhibitory control in Go trials facilitates reactive inhibitory control in Stop trials. In other words, response slowing that is triggered either in response to informative cues or strategically (when accuracy is favored over speed), increases the likelihood of an action being stopped (Aron, 2011). These findings suggest that the ability to inhibit a pre-planned motor action relies on the degree of Stop trial anticipation, representing a link between proactive and reactive inhibitory mechanisms.

1.2 Neural correlates of response inhibition

The SST has been used in combination with various techniques, such as functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). A recent review reported a neural network that is assumed to be critical for response inhibition (Aron, 2011), consisting of the right inferior frontal gyrus (rIFG), particularly the pars opecularis, the supplementary motor area (SMA), and basal ganglia, particularly the subthalamic nucleus (STN). Specifically, these regions were shown to exhibit strong activity when contrasting successful Stop trials with successful Go trials. From this, it was proposed that both the rIFG and SMA implement reactive stopping by transmitting impulses to the STN, which exerts inhibitory effects on the primary motor cortex, thus interrupting implementation of the Go response. Other areas relevant to response inhibition include the anterior insula (aINS) and the striatum, particularly the putamen (Swick, Ashley, & Turken, 2011; Zandbelt & Vink, 2010). The importance of rIFG in reactive response inhibition has been supported by brain stimulation studies. Results from a TMS study conducted by Chambers et al. (2006) demonstrated that temporary disrupting the rIFG's pars opercularis selectively worsened the individual's ability to inhibit a dominant response, as indexed by increased SSRTs. Conversely, Jacobson, Javitt and Lavidor (2011) used tDCS to investigate the effect of

electrical stimulation of the rIFG, and found that the ability to inhibit prepotent responses was significantly improved in participants who received tDCS before the SST. Anodal rDCS was reported to increase the likelihood of spontaneous neuronal firing by subthreshold depolarization, while cathodal tDCS was shown to inhibit spontaneous neuronal firing by subthreshold hyperpolarization (Stagg & Nitsche, 2011).

Numerous fMRI studies have demonstrated activation patterns during proactive inhibition similar to activations during reactive response inhibition (Aron, 2011; Cai et al., 2016; Jahfari, Stinear, Claffey, Verbruggen, & Aron, 2010; van Belle et al., 2014; Vink et al., 2015; White et al., 2014). The two inhibitory control modes seem to both rely on a right lateralized network with the rIFG as its main region (Aron, 2011). While weak activations within this network are proposed to act as a brake on motor responses, great activations will enable outright stopping of motor responses. This is in line with the proposed link between proactive and reactive inhibition, and thus in turn supports the claim put forward by the inhibition control hypothesis: that rIFG is the brain's reactive as well as proactive inhibition module.

A substantial amount of research has provided empirical evidence for an inhibition-related connectivity between the rIFG and the SMA. Anatomical connectivity has been observed through DTI (Aron et al., 2007), and the strength of this connection has been shown to predict performance on response inhibition tasks (Buch, Mars, Boorman, & Rushworth, 2010). Increased functional connectivity between these areas has also been observed during SST performance (Duann et al., 2009), and firing TMS pulses to the rIFG has been associated with both attenuated behavioral performance and SMA activity (Zandbelt, Bloemendaal, Hoogendam, Kahn, & Vink, 2012). A recent study further demonstrated that functional connectivity between the rIFG and SMA could predict impulsive actions, indexed by SST performance, but not impulsive choices, indexed by performance on a delay discounting task (*in press*, Wang et al., 2016). It is now known that the SMA is involved cognitive functions, such as temporal processing, in addition to direct motor functions (Strick et al., 2009), providing a plausible explanation for earlier findings linking it to the performance of precisely timed action responses (Halsband, Ito, Tanji, & Freund, 1993). Moreover, studies on non-human primates have pointed out the SMA as the source of the proactive inhibitory control signal that modulates the baseline motor activity (Chen, Scangos, & Stuphorn, 2010).

1.3 Modular and Network Perspectives of Inhibitory Control

On the basis of the abovementioned results, an inhibitory control hypothesis has been proposed, stating that 'a specific executive function, response inhibition, can be localized to a discrete region of the inferior prefrontal cortex' (Aron et al., 2003; 2004), and that 'inhibition is localized to the rIFG alone' (Aron et al., 2004). Similarly, it has been proposed that both proactive and reactive inhibition is accomplished by a single, central mechanism of inhibitory control, located in the inferior frontal cortex, while the cite of inhibition is the motor cortex of the brain (van Boxtel, van der Molen, Jennings & Brunia, 2001). Although a recently revised version of this hypothesis emphasizes that brain regions such as the STN, SMA, aINS, and rIFG form a network, the rIFG is still considered a major hub specialized for the implementation of inhibitory control (Aron, 2011; 2014). As it proposes one specific brain area and its connection pathways to support a discrete cognitive function, this theory represents a modular view.

The neuroimaging evidence for a dedicated inhibition module has been accused of being unconvincing (Hampshire & Sharp, 2015). One such criticism is that studies trying to localize the inhibition module typically assume that brain activation during the cancellation of a routine action must reflect a neural inhibition process. The frequently reported heightened activation in the rIFG during successful versus unsuccessful Stop trials, that been interpreted as evidence for a specific inhibition process, could also be a consequence of for instance transient lapses in attention causing slowed intentional processing of Stop cues. Importantly, several other studies using similar designs have reported the opposite pattern of results (Chamberlain et al., 2009; Erika-Florence et al., 2014; Hampshire et al., 2010; Menon et al., 2010). Arguably, a more reasonable contrast is the contrast of event-related activations during Stop minus Go trials, which in general generates very reliable activations in the rIFG. However, studies employing this contrast may have failed to take into account the potentially confounding cognitive demands involved in it, and thus ignored to control for potentially spurious effects. As a consequence, the observation of regional activation may be interpreted in different ways. Furthermore, several studies have reported rIFG activity during tasks that have no overt response inhibition demands (Shallice et al., 2008). For instance, recent studies have used novel variants of the SST to vary motor inhibition demands while controlling for

attention (Erika-Florence et al., 2014; Hampshire et al., 2010; 2011; 2015). Results from these studies show that although the rIFG was activated on Stop trials, similar levels of activation were evident during blocks in which the same Stop stimuli were simply monitored, cued the execution of a planned motor response, or cued the incrementing of an internal count. Additionally, a parallel study controlled the attentional demands on Stop trials by using a Continue condition, in which an additional infrequent stimulus signaled that there would be no need to cancel the initiated response (Sharp et al., 2010). However, the Stop and Continue stimuli generated similar activations throughout the rIFG region.

Taken together, these findings indicate that functional activations during the SST do not relate to response inhibition *per se*. Rather, this suggests that the rIFG has a more general task-oriented role in cognition (Hampshire et al., 2010, Chatham et al., 2012; Duncan, 2001). Accordingly, rIFG has been identified as a brain region in the ventral attention network. According to the neuroanatomical model of attention networks put forward by Corbetta and colleagues (Corbetta & Shulman, 2002; Corbetta et al., 2008), two cortico-cortical neural systems are involved in the ongoing monitoring and attending to environmental stimuli. A dorsal frontoparietal network, whose core regions include dorsal parietal cortex, and dorsal frontal cortex, embodies the top-down control mechanisms proposed by theories such as biased competition model (Desimone & Duncan, 1995). The dorsal system both generates and maintains endogenous signals based on current goals an preexisting information about likely contingencies and sends out top-down signals that bias the processing of appropriate stimulus features and locations in sensory cortex. The ventral system is not activated by expectations or task preparations, but responds along with the dorsal network when behaviorally relevant objects are detected. Core regions of the ventral network include the temporoparietal junction (TPJ) cortex (defined as the cortex at the intersection of the inferior parietal cortex, and the lateral occipital cortex), and ventral frontal cortex, including parts of the middle frontal gyrus (MFG), aINS, and rIFG. The two attention systems dynamically interact to determine where and what we attend to. That is, during focused attention, the ventral network is suppressed to prevent reorienting of attention to distracting events. However, whenever behaviorally relevant objects appear outside our current focus of attention, output from the ventral network interrupts (or brakes) the ongoing process in the dorsal network, which in turn shifts attention toward the novel object of interest (Corbetta et al., 2008).

The present study

The present study addresses the question of whether frontal activation in response inhibition tasks is specifically associated with the suppression of a motor response, or whether the rIFG plays a more general role in attentional control, in terms of detecting behaviorally relevant or salient events. Here, we directly test whether sub-components of the rIFG can reasonably be described as inhibitory modules, or whether these are better understood in terms of general cognitive control mechanisms. For this purpose, we used fMRI and a modified SST, including a Stop signal probability cue which was temporally separated from the stimulus-response display, so as to prevent crossover confounds between the various processes occurring during a trial. The cue could indicate either a high (50%), low (25%), or zero (0%) probability of Stop signal occurrence, so as to identify possible probability context modulations of both neural activity and behavioral responses related to different degrees of proactive preparation. The effect of stop-signal probability on brain activation was investigated for both models in predefined regions of interest (ROIs). In addition to most frequently reported regions, such as rIFG, rIPC, SMA, PMd, aINS and striatum, we also included lIFG and lIPC. The inclusion of left regions was based on recent evidence demonstrating significant lIFG and lIPC activations during reactive inhibition (Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010). Patient data reporting inhibition deficits following lIFG damage provides further evidence for its role inhibitory control. The ROIs were built from local maxima coordinates provided in two relevant previous studies (Zandbelt et al., 2013; Hampshire et al.,2010). Carefully controlled contrasts were performed to identify the neural contributions in reactive and proactive inhibitory control. Furthermore, psychophysiological interaction (PPI) analysis was utilized to test multiple opposing predictions from the inhibition control hypothesis and the attentional network hypothesis. For this purpose, we isolated the time point in at trial where the participant performs the task while at the same time preparing for a potential Stop signal, but before an actual response cancelling is involved. That is, we modeled the brain activations related to simply starting the task by pressing the button.

Neuroimaging predictions

The inhibitory control hypothesis assumes that this recruitment is the neural signal that is responsible for outright stopping. Thus, it predicts that the rIFG should be recruited during successful reactive inhibition, i.e., when motor responses are withheld, due to increased activations when the chance for a Stop signal is high. Thus, it predicts that the rIFG should be recruited after presentation of an important cue, regardless of the subsequent response, in order to increase the chance of successful action cancellation. The network perspective on the other hand, hypothesizes that rIFG contributions to response inhibition should be explained in terms of increased activations as a prerequisite for successful stops. Rather, the role of rIFG in inhibition is better understood in terms of interacting dorsal and ventral networks supporting a broader class of cognitive demands, such as attentional control and reorienting. Thus, derived from the theory put forward by Corbetta and Shulman (2002), the rIFG should – as a part of the ventral network – be modulated by the degree of proactive or top-down requirements, in terms of suppression during high proactive control states, and vice versa.

Behavioral predictions

Primarily, we predicted Go trial RTs to increase as a function of Stop signal probability. We thus expected RTs to be fastest in zero probability (ZP, 0%) Go trials, slower for low probability (LP, 25%) Go trials, and slowest in high probability (HP, 50%) Go trials, reflecting an increasing proactive preparation to stop. As a result of being more prepared, stopping in the 50% condition should in theory be more effective than in the 25% condition, something we hypothesized would manifest as a decrease in SSRT with increasing Stop signal probability.

2 Methods

2.1 Participants

Using opportunity sampling, we collected data from 24 subjects (males = 10; age range = 18-30, M = 23.25 years, SD = 2.69), mostly students from the University of Oslo. All participants were physically and mentally healthy, had normal or corrected-to-normal vision and no metal implants or medical conditions that could put them at risk during scanning. After receiving information about the study, each participant gave their written informed consent. All procedures conformed to the WMA Helsinki declaration of 2013. Due to various imaging-related (head movement) and task-related issues (e.g., response strategy implementation and task misinterpretation), data from five participants were excluded from the study, leaving a total of 19 data sets for further analyses (males = 8).

2.2 Design

A 2 (*trial type*: Go, Stop) x 3 (*Stop signal probability*: 0%, 25%, 50%) within-subject factorial design was implemented for our study. Dependent variables included Go trial RTs, Stop trial SSRTs, and accuracy scores, and BOLD signals.

2.3 Materials

Setup

During the practice session, stimuli were presented on a BenQ screen with resolution of 1280x720 pixels and 60 Hz refresh rate. Each participant was situated approximately 50 cm away from the screen. During the scanning session, stimuli were presented on a MR-compatible LCD screen (NNL LCD Monitor®, NordicNeuroLab, Bergen, Norway) with resolution of 1920x1080 pixels and 60 Hz refresh rate. The screen was located behind the scanner tube, and participants viewed the screen through a mirror installed on the top of the head coil. The viewing distance was approximately 1.2 meters and a field of view measuring 32°. For the practice session, responses were made using a standard QWERTY keyboard. For the scanning session, responses were delivered using a fiber-optic response grip (ResponseGrip®, NordicNeuroLab, Bergen, Norway) with two response buttons.

Image acquisition

Acquisition of structural and functional data was performed on a 3 Tesla Philips Achieva whole body MR scanner, equipped with an 8-channel Philips SENSE head coil (Philips Medical Systems, Best, The Netherlands). A BOLD-sensitive T2* weighted echo-planar imaging sequence was set to the following parameters: repetition time [TR] = 2208 ms; echo time [TE] = 30 ms; flip-angle = 80˚; voxel size = 3 × 3 × 3 mm; acquisition matrix = 64 × 64; field of view [FoV] = 192 mm; number of axial slices: 42, no gap. The slices were oriented to cover the brain from the cranial vertex to the upper brainstem. In order to avoid saturation effects, five dummy scans were collected at the beginning of each run. Initial structural images were acquired through a high-resolution T1 weighted sequence (180 sagittal slices, TR = 6.7 ms; TE = 3.1 ms; flip angle = 8˚; FoV = 256 × 256 × 180; voxel size = 1 × 1 × 1 mm). The whole MRI run, including a 7.5 minute structural scan, had a total duration of about one hour.

Stop signal task

Our SST was developed in the E-Prime 2.02 software (Psychology Software Tools, Pittsburgh, PA). The task was similar to that used in the delayed-response stop-signal anticipation task as used by Zandbelt et al. (2013) and Vink et al. (2015). Basically, this task consists of a vertical bar with a designated goal area near the top. When initiated, the bar starts filling up at a constant speed. When this rapid accumulation has reached the goal area, the participant responds to make it stop, typically by the push of a button. Stopping within the goal area results in a successful trial, while stopping above or below the goal area results in a failed trial. In some of the trials, however, the bar will stop on its own at some point between the bottom of the bar and the lower threshold of the goal area. In this task, that event represents the Stop signal, and when it occurs, the participant must respond by inhibiting his or her planned response. A Stop trial is successful when the participant manages to react to the Stop signal by inhibiting the response, and when the inhibition fails, the Stop trial is unsuccessful. Stop signal probability (high/low/zero) for each trial is indicated by a visual cue which is presented right before the onset of the task. For maximal engagement of the neural inhibition systems, a common way of ensuring that the subject is always kept at the limit of his or her own capacity is to dynamically adjust the SSD so that the next Stop trial after a successful Stop trial will have slightly more delayed Stop signal, and the next Stop trial after an unsuccessful Stop trial will have a slightly less delayed Stop signal, resulting in a more or

less even distribution of correct and incorrect Stop trials. This is often referred to as a *staircasing procedure*. Since there were two Stop trial types in our experiment (HP and LP) and they were unequal in terms of difficulty, we implemented staircasing for each of them separately.

The trial events of our SST is presented in figure 1. Here, instead of pressing a button to stop the bar from moving, the participant both initiates and completes the task in an on-off-manner. By pressing and holding a button the bar starts filling up, and by releasing it, it stops. We also modified the task so that there was a fairly large gap between the HP and the LP condition (50% versus 25%). Since too high a proportion of stop-trials may give rise to undesirable response strategies, we adjusted the distribution so that the ratio of stop to Go trials was approximately one to three (23% stop and 77% go).

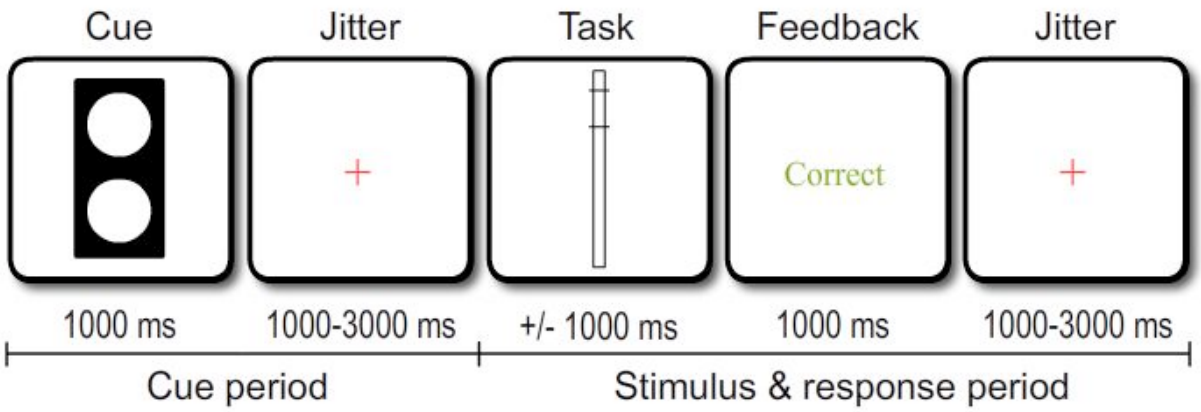

Fig. 1. Trial events. At the onset of every trial a cue was presented for 1000 ms informing the participant about Stop signal probability (0%, 25% or 50%). During the stimulus-response period, which started after a variable delay, a stimulus was presented requiring participant to make a response (Go trial) or to inhibit a response (Stop trial). A feedback screen was then presented for 1000 ms, followed by a second variable delay.

2.4 Procedure

Before the experiment, all participants were provided with an information sheet that informed them about the study and their participation rights. After reading the information sheet and signing the consent form, each participant went through a practice session in order to familiarize themselves with the task. The practice session consisted of three parts, each introducing a new element of the task. The first part consisted of only Go trials, the second consisted of both Go and Stop trials, and probability cues were introduced in the third part. There were 20 Go only trials in first part, 20 trials including Stop trials in the second part, and 40 trials including Stop signal probability cues in the third part. After the practice session, each participant was informed about MRI safety and afterwards positioned inside the scanner. In order to minimize undesirable head motion the participants were instructed to refrain from moving their head and limbs during the scanning.

Before presenting participants with the task we first acquired T1-weighted anatomical images. After that, the participant was presented with a SST that consisted of a total of 400 trials: 80 HP Go trials, 80 HP Stop trials, 120 LP Go trials, 40 LP Stop trials, and 160 ZP Go trials. The trials were pseudo randomized and presented to participants in a counterbalanced fashion. In order to reduce fatigue effects, three breaks lasting for 2 minutes each were implemented into the fMRI run. The duration of the experiment was 50 minutes and participants were informed that they could withdraw from the study at any time. After the experiment the participant was extracted from the scanner room and debriefed about the experiment.

2.5 Analyses

2.5.1 Behavioral data

All behavioral analyses were conducted in version 22 of the IBM SPSS software. The dependent variables of interest were go-trial RT and SSRT, with Stop signal probability as the independent variable. In line with previous research (Zandbelt et al., 2013), the effect of Stop signal probability on go-trial RT was taken to reflect proactive inhibition. SSRTs were taken as a representation of reactive inhibition. SSRT values were estimated for each subject using the mean method (Logan & Cowan, 1984). This was done separately for HP and LP, enabling

the investigation of probability effects on SSRT. The following steps were taken to prepare behavioral data for analysis: RT values for the Go trials were organized into three probability categories (HP, LP, and ZP); SSRT values for the Stop trials were organized into two (HP and LP). For each participant, Go trial RT and Stop trial SSRT means were calculated for each Stop signal probability (Go trials: HP, LP, ZP; Stop trials: HP, LP). The mean values for Go trials were entered into a repeated-measures ANOVA to investigate the effect of Stop signal probability. Thereafter, a paired samples t-test was performed on Stop trial averages to test the difference between HP and LP SSRTs.

2.5.2 fMRI data

Preprocessing and analysis of fMRI data was performed in the SPM12 software (http://www.fil.ion.ucl.ac.uk/spm/). Raw fMRI data went through standard preprocessing steps: Functional images were corrected for differences in acquisition times across all slices, using the central slice as a reference. To adjust for head motion, functional images were registered to the mean image using 4^{th}-degree B-spline interpolation. Estimated motion parameters were inspected to ensure that absolute motion over the course of the experiment did not exceed 3 mm. The anatomical image was co-registered to the mean functional image using the mutual information criteria method, and segmented and normalized to the Montreal Neurological Institute template brain using linear and non-linear deformations. The normalization parameters were applied to the functional and anatomical images. Functional images were spatially smoothed using an 8-mm full-width at half-maximum Gaussian kernel. The T1-weighted images were skull-stripped using an automated brain extraction method.

First level statistical analysis was performed within the framework of the general linear model (GLM; Friston, 1995). Functional images were first submitted to two separate GLMs: (1) cue period, and (2) successful inhibition. Brain activations time-locked to the (1) presentation of the cue period (epochs starting at cue presentation onset, duration = 1 second) were modeled based on stop-signal probability. Brain activations time-locked to (2) Successful Stop trials and Successful Go trials were modeled as zero-duration events based on ‘probability uncertain’ (25% and 50%) trials and ‘no probability certain’ (0%) trials, respectively. We accounted for residual head motion effects by including the 6 motion parameters from the realignment procedure as regressors of no interest into the statistical model. Low frequency drifts were controlled using a discrete cosine transform with a cutoff

of 128 s. For the cue analysis, contrast images were generated for each subject for the comparisons (1) High versus Zero, (2) Low versus Zero, and (3) High versus Zero > Low versus Zero. For the successful inhibition analysis, one contrast image was generated from the Successful Stop versus Successful Go trials contrast. Model parameters were finally estimated using classical restricted maximum likelihood algorithms.

Thereafter, mean activation levels (i.e., parameter estimates) were extracted from predefined regions of interest (ROIs) for all contrasts. The effect of stop-signal probability on brain activation was investigated for both models in predefined regions of interest (ROIs). The ROIs were built from local maxima coordinates provided in two relevant previous studies (Zandbelt et al., 2013; Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010) using the MarsBar ROI toolbox (Brett, Anton, Valabregue, & Poline, 2002). All ROIs are presented in figure 2. Each ROI was analyzed at an α threshold of .05 (FWE corrected) in the SPM GUI, using the ROI analysis option provided by the WFU Pickatlas software (Maldjian, Laurienti, Burdette, & Kraft, 2003). The resulting p-values were further corrected for multiple comparisons using Bonferroni correction; 11 ROIs resulting in an α threshold of .0045. Following the ROI analysis procedure, corresponding whole brain analyses were carried out, so as to indicate the validity of our ROIs. The significance threshold was set to $p<0.05$, FWE corrected.

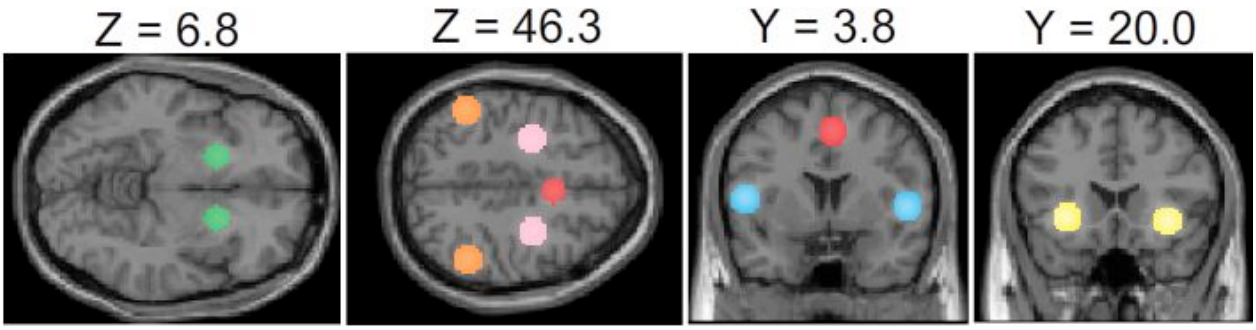

Fig. 2. Our predefined ROIs included the following regions: bilateral striatum (green), bilateral IPC (orange), bilateral PMd (pink), bilateral IFG (blue), bilateral insula (yellow) and SMA (red).

Finally, a PPI analysis was performed to investigate context-specific (HP versus LP) changes in coupling between the SMA and the rest of the brain during task initiation. An additional GLM was used to model task-related brain activations occurring before the actual execution or cancelling of a go response. This GLM was identical to the previously described for the cue period analysis, with one exception: brain activations time-locked to the onset of the task initiation (duration = 0) were modeled across stop-signal probability 50%, 25% and 0%. A significant PPI entails a change in the slope of the regression of activity in a 'response' region onto activity in a 'seed' region from one condition to another. The PPI term used to test the opposing predictions regarding the role of rIFG in response inhibition can be expressed as [Seed Region x (HP > LP)]. Thus, a positive PPI indicates that the slope of the regression line is more positive in the HP condition as opposed to the LP condition, whereas a negative PPI indicates that the slope is more negative in the HP condition compared to the LP condition. A seed region (SMA) was isolated, based on the local maximum from the one-sample t-test for the HP + LP > Z contrast from the cue period analysis. For each subject, we extracted the first eigenvariate of the fMRI-signal (adjusted for head motion) from a sphere with 8-mm radius centered around the local maximum. We obtained estimates of neural activity in this region by hemodynamic deconvolution using parametric empirical Bayes (physiological vector). The psychological vector was a delta function coding for onset times of HP (1) and LP (-1) trials. The PPI was computed by taking the product of the physiological and psychological vectors at each point in time. The physiological and psychological PPI vectors were then convolved with the canonical hemodynamic response function, and entered as regressors in a first-level general linear model. A contrast image was created for the PPI. The contrast images of all participants were tested at the second level in a one-sample t-test to identify regions showing a positive or negative PPI, using cluster-level inference.

3 Results

3.1 Behavioral data

SSRTs

The paired samples t-test was significant [t_{18} = - 6.48, p < .0001], demonstrating that, SSRT in the 25% condition was higher compared to the 50% condition. The eta squared statistic (.65) indicated a large effect size. The accuracy scores in both Stop signal probability contexts were close to 50% (LP context = 47.1%, HP context = 53.7%), which is indicative of successful staircase procedure.

Go RTs

The one-way repeated measures ANOVA output revealed that the assumption of sphericity (Mauchly's test) had been violated $\chi 2$ (2) = 8.06, p = .018, therefore degrees of freedom were corrected using Huynh-Feldt estimates of sphericity (ε = .80).The main effect of Stop signal probability was significant, [$F_{1.61,\ 35.32}$ = 19.05, p < .0001, $\eta p2$ = .46]. Three paired samples t-tests were used to make post hoc comparisons between conditions. A first paired samples t-test indicated that there was a significant difference in Go RT scores for 0% Stop signal probability (M = 477.49, SD = 9.93) and 25% Stop signal probability (M = 481.60, SD = 8.29): t_{18} = -2.89, p = .008. A second paired samples t-test indicated that there was a significant difference in Go RT scores for 0% Stop signal probability (M = 477.49, SD = 9.93) and 50% Stop signal probability (M = 486.37, SD = 7.73): t_{18} = -5.03, p < .0001. A third paired samples t-test indicated that there was a significant difference in Go RT scores for 25% Stop signal probability (M = 481.60, SD = 8.29 and 50% Stop signal probability (M = 486.37, SD = 7.73) conditions: t_{18} = -4.56, p < .0001.These results imply that Stop signal probability context does have an effect on Go RT scores. Specifically, these results suggest that RTs were faster in the 0% Stop signal probability context and slower in the 25% and 50% Stop signal probability contexts. Moreover, these results also suggest that Go RTs were faster in the 25% Stop signal probability context than in 50% Stop signal probability context where RTs were slowest.

Table 1. Descriptive statistics

	ZP (0%)	LP (25%)	HP (50%)
Go trials			
Accuracy (%)	87.3 ± 11.6	76.4 ± 13.2	55 ± 15.8
RT (ms)	477.5 ± 9.9	481.6 ± 8.3	486.4 ± 7.7
Stop trials			
Accuracy (%)	-	47.1 ± 4.3	53.7 ± 7.5
SSRT (ms)	-	212.9 ± 14.6	183.9 ± 26.5

Numbers represent means and standard deviations for the behavioral data (accuracy, Go trial reaction times, and Stop signal reaction times)

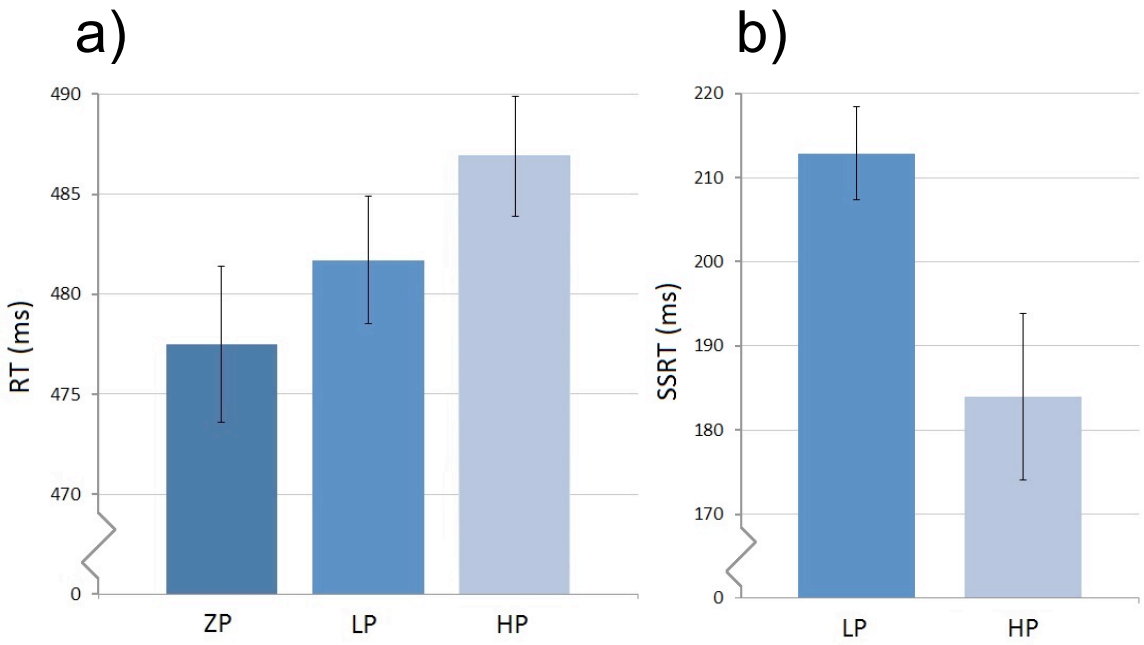

Fig. 3. *Panel a*: Mean Go trial RTs across the zero, low, and high probability conditions. *Panel b*: Mean SSRTs for Stop trials across low and high probability conditions. Error bars represent 95% CI.

3.2 fMRI data

Successful Inhibition. First, we identified brain regions showing significant activations during successful inhibition contrasted with Go trials, demonstrating significantly activated clusters in the left and right aINS [t_{18}= 9.35, p < .001; t_{18} = 11.11, p < .001, respectively], right PMd [t_{18} = 5.80, p = .001], SMA [t_{18}= 6.04, p < .001], left right IFG [t_{18}= 5.02, p = .003; t_{18} = 6.52, p < .001, respectively], and left and right IPC [t_{18} = 7.50, p < .001; t_{18} = 6.52, p < .001, respectively]. No activations were observed in the left or right striatum.

Cue Period. Next, we contrasted activation in trials with a > 0% minus 0% Stop signal probability, first from the cue period. Significantly activated clusters during the cue period were observed in the left aINS [*high>zero:* t_{18} = 8.44, p < .001; *low>zero*: t_{18} = 7.50, p < .001], right aINS [*high>zero:* t_{18} = 7.47, p < .001; *low>zero*: t_{18} = 7.16, p < .001], left PMd [*high>zero:* t_{18} = 6.55, p < .001; *low>zero*: t_{18} = 8.15, p < .000], right PMd [*high>zero:* t_{18} = 6.40, p < .001; *low>zero*: t_{18} = 8.91, p < .001], SMA [*high>zero:* t_{18} = 7.42, p < .001; *low>zero*: t_{18} = 8.55, p < .001], left striatum [*high>zero:* t_{18} = 8.71, p < .001] and right striatum [*high>zero:* t_{18} = 5.47, p = .001]. No striatal activations were revealed in the LZ contrast. Moreover, no significant rIFG and rIPC activity was found in the HZ and LZ contrasts. Next, contrasting activation in trials with 50% versus 25% Stop signal probability revealed significant activations in the right aINS [t_{18} = 6.37, p < .001] and right striatum [t_{18} = 5.44, p = .001] during the cue period.

PPI Analysis. The main PPI finding is presented in figure 4. The analysis shows significant differences in coupling between the SMA and the left inferior parietal cortex (lIPC) as a function of probability (50%>25%). Specifically, connectivity increased between the SMA and the lIPC when there was a high chance of stop, compared to when there was a small chance of stop [$t(18)$ = 5.56; p < .001]. Conversely, the same contrast was associated with decreased coupling between SMA and rIFG. This result indicates that stronger activations of the SMA during the cue period when the probability of a Stop signal is high was associated with corresponding activations in the lIPC, together with corresponding deactivations in the rIFG.

Table 2. ROI and whole brain findings

Analysis	Contrast	laINS	raINS	lPMd	rPMd	SMA	lIFG	rIFG	lIPC	rIPC	Left Striatum	Right Striatum
Cue Period ROI	*HZ*	*	*	*	*	*	*				*	*
	LZ	*	*	*	*	*			*			
	HL		*									*
Cue Period GLM	*HZ*	*	*	*	*	*					*	
	LZ	*	*	*	*	*						
	HL											
Successful stop ROI	*>0% vs 0%*	*	*		*	*	*	*	*	*		
Successful stop GLM	*>0% vs 0%*	*	*		*	*		*	*	*		

Asterisks indicate that the activation passed FWE correction (and Bonferroni correction for ROIs).

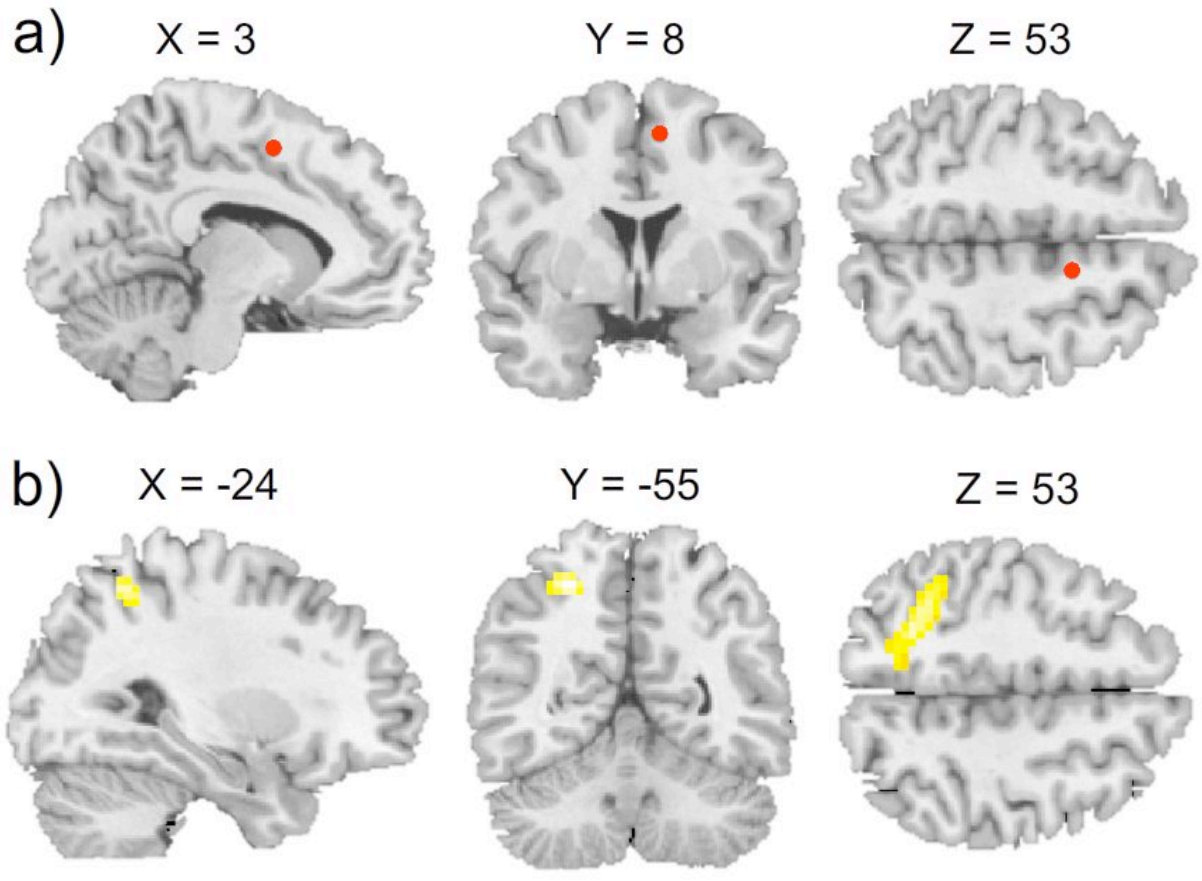

Fig. 4. Visualization of PPI seed and response regions across saggital, coronal, and transverse planes. *Panel a:* SMA seed based on the local maxima from the HZ contrast during cue period. *Panel b:* Area showing a positive PPI with the SMA from the HL contrast at task initiation.

4 Discussion

Here we investigated the underlying neural basis of inhibition and contextual cue processing in nineteen healthy participants performing the modified SST while undergoing fMRI. Firstly, our behavioral findings are consistent with previous research manipulating Stop signal probability. Responses were faster on Go trials with 0% Stop signal probability and became progressively slower as Stop signal probability increased. Moreover, response slowing was found to be significantly greater in trials with 50% Stop signal probability than in trials with 25 % Stop signal probability, indicating that participants were slowing down their responses in anticipation of a Stop signal. Next, in accordance with the horse race model (Logan & Cowan, 1984), it was shown that participants were poorer at inhibiting responses when SSD between the Go stimulus and Stop signal was increased. Furthermore, the SSRTs were found to be significantly shorter when participants performed the task in a 50% Stop signal probability context than in a 25% Stop signal probability context.

The primary aim of this study was to investigate whether frontal areas normally associated with response inhibition are specifically related to this construct, or whether they have a more general role in the detection of salient or unexpected events. Although the results presented here are somewhat consistent with those of previous studies insofar as they demonstrate that rIFG sub-regions are strongly activated during successful inhibition in an SST, they also highlight how the hypothesis of unique inhibitory control modules within the frontal lobes is inaccurate. Counter to the notion of a module for proactive inhibition, our results clearly demonstrated absence of sustained proactive activation in the rIFG during the SST: No significant activations were shown in neither the rIFG nor its sub-regions during presentation of the Stop signal probability cue. Rather, cue period activations were observed in brain regions that are known to support motor planning and action monitoring, as well as withholding arm movements (Duque, Labruna, Verset, Olivier, & Ivry, 2012). Although the activation in rIFG during successful inhibition of a go response is in line with the predictions derived from inhibition control theory, suggesting that this activity reflects the neural correlates of a cancellation of a planned response, the increased rIFG response during successful stops versus successful Go trials may also reflect a more general salience detection mechanism. Contrasting correct Stop trials with correct ZP trials could conceptually reflect

the neural activation related to outright stopping. Alternatively, it might reflect the mere detection of a rare, salient Stop signal. However, if the assumption that the rIFG contributes to action cancellation by sustained activations over the duration of a trial is correct, then rIFG activations should be observable also when the participant starts to actively engage in the task, and this activation should be increasing in parallel with increased probability for a Stop signal. Our PPI results did not confirm the inhibition control hypothesis. That is, we did not find that activation of the SMA, an area related to motor preparation, was proportional to the activation in rIFG. Rather, our results demonstrated a positive PPI between the SMA and lIPC, while at the same time a negative PPI between SMA and rIFG. That is, during non-inhibitory related task events, our results demonstrated a significant decoupling of the rIFG with the SMA, as well as a significantly increased coupling with the lIPC when the probability of a Stop signal was high compared to when it was low.

The increased coupling of the SMA and parietal regions during high Stop signal probabilities may be interpreted to reflect increased top-down signals from the dorsal network, reflecting a more proactive state in the 50% condition compared to in the 25% condition. Accordingly, studies have demonstrated that key nodes of the goal-driven network are increasingly engaged when one anticipates the need to inhibit and override planned actions. Moreover, a recent study demonstrated that advance preparation of action plans directly modulated the need for involvement of ventral network areas in order to withhold a planned motor action. Interestingly, the strength of ventral network projections were stronger when stopping had to be engaged reactively, compared to when it was proactively prepared in advance (Jahfari et al., 2012). The decoupling of the SMA to the rIFG, together with the increased coupling with the parietal cortex in our study, mimics this dynamic relationship between the top-down mechanisms. Thus, our PPI findings fit well with the proposed dorsal-ventral relationship in Corbetta and Shulman's (2002) theory of attentional control. In the HP condition, which was assumed to evoke a more proactive state, activations in the IPC may have exerted substantial top-down influence over rIFG, preventing this area from interfering or redirecting attention toward salient task-irrelevant stimuli, unless relevant to the task (i.e., deactivate unless a Stop signal). One plausible explanation to the rIFG activity during the successful Stop trials would thus be the result of salience detection, rather than pure response inhibition. From this we suggest that the role of the rIFG and its sub-regions may be seen as more linked to salience detection as a part of a ventral attention reorienting network than as a specific module for response inhibition. A meta-analysis reports significant overlap between

attentional/working memory functions and response inhibition in the rIFG and insula, supporting the claim that these regions support a more general range of cognitive functions, rather than being functionally unique in their sensitivities to inhibitory cognitive demands (Criaud & Boulinguez, 2013). The present study adds substantial evidence supporting the proposal that rIFG contributions in inhibition may play a more general role in the detection of rare and salient events (Walther et al., 2011).

Considering that the right parietal cortex has been most frequently related to visual attentional functions, it might be argued that an interpretation of the left parietal activations within the framework of attentional control network is somewhat speculative. However, several studies have reported results suggesting that other parietal regions may be important for directing attention in relation to response modalities other than eye-movement and visual attention orienting (Rushworth et al., 2001). Specifically, it has been hypothesized that a left parietal area is important for attention in relation to limb movements. Rushworth and colleagues (2001) have referred to this process as 'motor attention', and should thus be distinguished from visual attention orienting. Accordingly, the left parietal cortex has been found crucial for anticipatory motor control, presumably by subjective timing through sensorimotor feedback matching, and thus causally involved in right hand anticipatory motor control (Krause & Pollok 2014). The proposed role of the left parietal regions in motor anticipation was supported in a study demonstrating that a left superior parietal lobe (SPL) network consisting of the superior parietal gyrus (SPG), the left angular gyrus (AG), and the left and right superior occipital gyrus, displayed activation only during proactive inhibition (van Belle et al., 2014). Specifically, this activation pattern was stronger during Go trials with an > 0% Stop signal probability than during Go trials with Stop signal probability of 0%. Similarly, SST-evoked lIPC activity has been found to be predictive of the effectiveness of PTSD treatment, arguably due to its involvement in contextual cue processing and working memory updating (van Rooij et al., 2014).

The interpretations of our findings within Corbetta and Shulman's (2002) framework of attentional control networks correspond neatly to the dual mechanism of control (DMC) theory (Braver et al., 2012). According to this theory, general cognitive control varies along a continuum, from a proactive (goal-driven) mode in one end, to a reactive (stimulus-driven) mode in the other. Although the proactive and reactive control modes differ in various characteristics depending on task, most cognitive tasks depend upon the dynamic interplay

between the two modes. Under the proactive control mode, goal-related contextual information is actively sustained prior to the onset of a challenging task, in order to bias processes such as attention and interference prevention in a top-down manner. This control strategy is recruited to prepare appropriate responses ahead of upcoming events and effectively carry them out when needed. In contrast, control processes in the reactive control mode are recruited only at a later stage, triggered by detection of a critical or alerting event (Braver et al., 2012). This theoretical perspective also corroborate with Aston-Jones and Cohen's (2005) adaptive gain theory. According to this theory, adaptive behavior in a diverse and changing world requires a trade-off between exploiting known sources of reward and exploring the environment for other, potentially more behaviorally relevant objects or events. The neural substrate of this adaptive trade-off has been linked to the locus-coeruleus norepinephrine (LC-NE) system. LC neurons exhibit two modes of activity – phasic and tonic. While phasic LC activation is driven by the outcome of task-related decision processes and is proposed to facilitate ensuing behaviors that optimize task performance (exploitation), tonic LC mode is associated with disengagement from the current task and a search for alternative behaviors (exploitation). Historically, however, the LC-NE system was merely assumed to be implicated in general arousal, rather than in control of adaptive behavior. The arousal view was motivated largely by the consistent observation that highly salient and arousing stimuli elicit a phasic activation of LC neurons. However, traditional theories of LC-NE function tying this structure to basic arousal did not precisely describe the specific mechanisms by which this system produces these changes in arousal, and thus left important questions unanswered about the relationship between arousal and behavior (Aston-Jones & Cohen, 2005).

As exemplified above by the longstanding LC-NE arousal hypothesis, several researchers have argued that the attempt to map a discrete inhibitory ability to one specific brain module is misguided. Similarly, the controversy about how to map the neural correlates of response inhibition illustrates the more general issue of how to define the fundamental components of human cognition. The controversy about how to map the neural correlates of response inhibition illustrates the more general issue of how to define the fundamental components of human cognition. Terms such as inhibition, working memory, attention, and executive functions describe important aspects of cognition that appear to be qualitatively distinct, and as a consequence are often assumed to relate to different neural systems. Accordingly, separate lines of research have sought to map them onto the brain. Yet tasks that

are designed to probe these aspects of cognition tend to activate the same functional networks. Thus, the intuitive constructs that have historically constituted our taxonomy of human cognition appear largely orthogonal to the underlying functional organization of the brain. An alternative approach is to categorize cognitive processes based on their relationship with functional networks. Hence, a simpler explanation for the experimental findings is that there is no response inhibition module. Rather, the rIFG houses components of a more general processing resource. This globalist model proposes that some regions of cortex are domain-general (Duncan & Owen, 2000; Fedorenko et al., 2013). That is, they rapidly adapt to support a variety of novel or demanding tasks. Cortical regions showing this type of flexibility have been variously referred to as multiple-demand cortex (MDC; Duncan & Owen, 2000; Duncan, 2005), the cognitive control system (Cole & Schneider, 2007), or the task-activation ensemble (Seeley et al., 2007). Several studies have reported that the functional networks observed within MDC are very consistent across diverse cognitive tasks (Freedman et al., 2001). (Freedman et al., 2001). Furthermore, these neurons can switch from coding for one aspect of a multistage task to another in a fraction of a second, and have the capacity to maintain preparatory information in stable low-activity states (Stokes et al., 2013). The MDC includes the rIFG. Interestingly, however, the wider set of brain regions recruited during response inhibition tasks correspond closely to MDC (Erika-Florence et al., 2014). Taken together, the most parsimonious explanation of the SST is one example of the broad class of intentional processes that are supported by domain-general systems. The present findings support this global view, and argue that most of the activity elicited by the SST might actually be driven by the engagement of high attentional or working memory resources, not by inhibitory processes per se.

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