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A dual but asymmetric role of the dorsal anterior cingulate cortex in response inhibition and switching from a non-salient to salient action

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ABSTRACT

Response inhibition and salience detection are among the most studied psychological constructs of cognitive control. Despite a growing body of work, how inhibition and salience processing interact and engage regional brain activations remains unclear. Here, we examined this issue in a stop signal task (SST), where a prepotent response needs to be inhibited to allow an alternative, less dominant response. Sixteen adult individuals performed two versions of the SST each with 25% (SST25) and 75% (SST75) of stop trials. We posited that greater regional activations to the infrequent trial type in each condition (i.e., to stop as compared to go trials in SST25 and to go as compared to stop trials in SST75) support salience detection. Further, successful inhibition in stop trials requires attention to the stop signal to trigger motor inhibition, and the stop signal reaction time (SSRT) has been used to index the efficiency of motor response inhibition. Therefore, greater regional activations to stop as compared to go success trials in association with the stop signal reaction time (SSRT) serve to expedite response inhibition. In support of an interactive role, the dorsal anterior cingulate cortex (dACC) increases activation to salience detection in both SST25 and SST75, but only mediates response inhibition in SST75. Thus, infrequency response in the dACC supports motor inhibition only when stopping has become a routine. In contrast, although the evidence is less robust, the pre-supplementary motor area (pre-SMA) increases activity to the infrequent stimulus and supports inhibition in both SST25 and SST75. These findings clarify a unique role of the dACC and add to the literature that distinguishes dACC and pre-SMA functions in cognitive control.

1. Introduction

Response inhibition, the ability to rapidly cancel an action, is a critical executive function. The stop-signal task (SST) is widely used to study response inhibition, where individuals respond to the same stimulus repeatedly and on a minority of trials must cancel this prepotent response (Logan et al., 1984). Previous functional magnetic resonance imaging (fMRI) studies using the SST have identified a network of brain regions that include the inferior frontal gyrus, insula, dorsomedial prefrontal cortex, and the basal ganglia, in response to stop versus go trials (see Li, 2014 for a review). However, whether these regions are specifically involved in motor inhibition, rather than saliency response, as in switching from a frequent to an infrequent action, remains unclear (Kenner et al., 2010; Obeso et al., 2013).

Previous studies have attempted to dissociate response-switching, or the ability to adapt to changing task demands, (Badre and Wagner, 2006; Jurado and Rosselli, 2007; Leber et al., 2008) and response inhibition, by altering the SST to include trials where subjects switch from one type of response to another, in addition to trials that require the dominant response to be stopped. However, these attempts yielded varied results. Kenner et al. (2010) reported that many cortical regions activated to both stop and switch trials, suggesting a general role in switching as opposed to inhibition. On the other hand, transcranial magnetic stimulation (TMS) of the pre-supplementary motor area (pre-SMA) disrupted stopping, but not switching (Obeso et al., 2013). Further, Roberts and Husain (2015) recently reported that an individual with a lesion to the caudal pre-SMA showed impairment in switching but not stopping. While these discrepancies may reflect differences in methodology (e.g., TMS vs. lesion; variation in brain locations examined), a common limitation is that both stop and switch trials are

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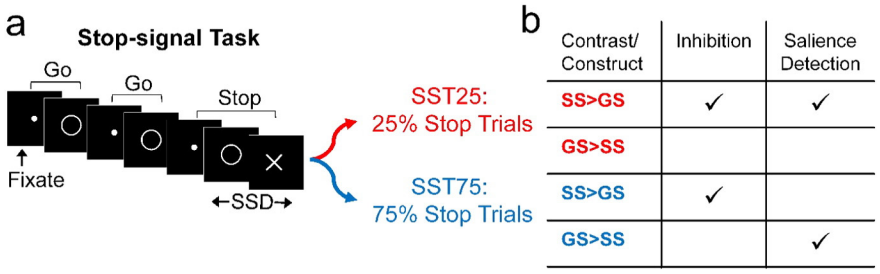

Fig. 1. a) Stop-signal task (SST) design. All participants performed two versions of the task: SST25 (25% stop trials) and SST75 (75% stop trials). b) The contrast SS > GS measures both response inhibition and salience detection in SST25, but only inhibition in SST75, where stop trials predominate. SS = stop success, GS = go success, SSD = stop-signal delay. A conjunction of SS > GS between SST25 and SST75 identifies correlates of "stopping," whereas a conjunction of SS > GS in SST25 and GS > SS in SST75 identifies correlates of saliency detection.

presented infrequently. Therefore, both trial types confound salient stimulus detection (responses to infrequent, arousing events; Horvitz, 2000) with the behavior of interest and require a form of "switching" from a dominant to a non-dominant action plan.

In the response-switching literature, efforts have been made to understand the role of salience detection by manipulating whether a task shift requires alternation from a dominant to a non-dominant action. In these reports, shifts to an infrequent stimulus type, compared to a frequent stimulus type, engage a wide array of cortical and subcortical structures (Badre and Wagner, 2006; Braver et al., 2001; De Baene and Brass, 2013; Dove et al., 2000; Rushworth et al., 2001). On the other hand, the role of inhibition in these processes remains unclear, as response switching engages inhibition of the current, prevailing response (Koch et al., 2010; Wessel and Aron, 2013) and yet most studies do not provide a quantifiable measure of motor inhibition. Thus, it remains a challenge to distinguish activities related to rule switch (as in alternating between two equiprobable actions) or saliency (as in shifting from a frequent to less frequent response) from those related to motor inhibition.

Here, to address this issue, we used a within-subject design where 16 individuals performed two variants of the SST during fMRI: a conventional version with 25% stop and 75% go trials (SST25), and a modified version (SST75) where trial probabilities were reversed with 75% stop and 25% go trials. While in SST25 a successful stop, as compared to go trial, involves both response inhibition and detection of a salient (infrequent) stimulus, in SST75 the same contrast involves response inhibition but not salience detection as stop trials dominate the task. Using this design, we hoped to dissociate regional activations to response inhibition and saliency processing. In particular, in the SST, we can obtain a measure of stop signal reaction time (SSRT) to quantify the efficiency of response inhibition (Logan et al., 1984). A shorter SSRT indicates a more efficient process of response inhibition. Thus, greater regional activations to stop as compared to go success trials in association with the SSRT serve to expedite response inhibition (Chao et al., 2009; Zhang et al. 2015). Greater regional activations both to stop as compared to go trials in SST25 and to go as compared to stop trials in SST75 support salience detection. We examined neural processes both shared by and distinct to saliency processing and motor inhibition.

2. Methods and materials

The study was performed under protocols approved by the Yale Human Investigation and MRI Safety Committees. Sixteen adults (8 females, mean age of 29 ± 6 years) participated in the experiment. All participants were free from medical, neurological and psychiatric illnesses, denied use of illicit substances and tested negative in urine screen on the day of fMRI.

2.1. Behavioral task

During fMRI, participants performed the stop-signal task (SST; Logan et al., 1984; Fig. 1a) as in our previous work (Farr et al., 2012; Hu et al., 2014; Winkler et al., 2013). There were two trial types: go and stop, randomly intermixed. A small dot appeared on the screen to engage attention at the beginning of a go trial. After a randomized time interval (fore-period) between 1 and 5 s, the dot turned into a circle (the go signal), prompting the subject to quickly press a button. The circle vanished at a button press or after 1 s had elapsed, whichever came first, and the trial terminated. A premature button press prior to the appearance of the circle also terminated the trial. In a stop trial, an additional X, the stop signal, appeared after and replaced the go signal. The subjects were told to withhold their button press upon seeing the stop signal. The stop-signal delay (SSD) — the time interval between the go and stop signal — started at 200 ms and varied from one stop trial to the next according to a staircase procedure, increasing and decreasing by 67 ms each after a successful and failed stop trial (De Jong et al., 1990; Levitt, 1971). There was an intertrial interval of 2 s. Subjects were instructed to respond to the go signal quickly while keeping in mind that a stop signal could come up in a small number of trials. Depending on the actual stimulus timing (trials varied in fore-period duration) and speed of response, the total number of trials varied slightly across subjects in an experiment. With the staircase procedure, we anticipated that the subjects would succeed in withholding their response in approximately half of the stop trials. The stop-signal reaction time (SSRT) was computed by subtracting the critical stop-signal delay, or the estimated SSD required for a subject to get half of stop trials correct, from the median go RT (Li et al., 2008).

We computed post-error slowing (PES) as described in detail in our earlier studies (Ide and Li, 2011; Ide et al., 2015; Li et al., 2006; Liao et al., 2014). Briefly, four main types of trial outcome were first distinguished:

Table 1
Summary of behavioral performance. GoRT = Go trial reaction time, SERT = stop error reaction time, SSRT = stop signal reaction time, PES = post-error slowing, FP = fore-period; values are mean ± standard deviation; t and p values are based on a paired sample t test (n = 16).

	SST25	SST75	t	p
Median GoRT (ms)	597 ± 88	787 ± 137	−6.037	**0.000**
Median SERT (ms)	514 ± 75	696 ± 134	−6.570	**0.000**
GoRT − SERT	94 ± 32	109 ± 47	−0.964	0.350
% go success	98 ± 2	89 ± 11	3.263	**0.005**
% stop success	54 ± 3	55 ± 5	−1.312	0.209
SSRT (ms)	226 ± 41	204 ± 44	1.706	0.109
PES (effect size)	1.69 ± 1.83	1.07 ± 1.24	1.327	0.205
FP effect (effect size)	1.70 ± 1.23	0.59 ± 1.16	2.069	0.056