Putting the brakes on inhibitory models of frontal lobe function

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ABSTRACT

There has been much recent debate regarding the neural basis of motor response inhibition. An influential hypothesis from the last decade proposes that a module within the right inferior frontal cortex (RIFC) of the human brain is dedicated to supporting response inhibition. However, there is growing evidence to support the alternative view that response inhibition is just one prominent example of the many cognitive control processes that are supported by the same set of 'domain general' functional networks. Here, I test directly between the modular and network accounts of motor response inhibition by applying a combination of data-driven, event-related and functional connectivity analyses to fMRI data from a variety of attention and inhibition tasks. The results demonstrate that there is no inhibitory module within the RIFC. Instead, response inhibition recruits a functionally heterogeneous ensemble of RIFC networks, which can be dissociated from each other in the context of other task demands.

Classic approaches to functional neuroimaging have produced a plethora of models ascribing highly specific cognitive processes to dedicated modules within the frontal lobes. However, there is growing evidence to support the view that the human frontal lobes house sub-regions of 'domain general' networks, each of which makes a broader contribution to cognition. Consequently, many models from the neuroimaging literature are likely to be both functionally and anatomically over-specified because they do not account for the general involvement in cognition of the brain regions that they pertain to or for the co-recruitment of those brain regions with distributed functional networks. A prominent example of this issue is the controversy regarding whether there is a module within the right inferior frontal cortices (RIFC) that is uniquely and specifically dedicated to the process of motor response inhibition.

Motor response inhibition refers to the process by which routine, initialised or otherwise, pre-potent motor responses are effortfully withheld or cancelled. This particular aspect of top-down control has been a major focus of research because a lack of inhibitory control is characteristic of a range of important clinical populations. Consequently, paradigms that are designed to measure motor response inhibition are becoming increasingly popular in clinical research and assessment. Most prominent amongst these is the Stop Signal Task (SST), in which the participant makes button presses in response to a frequent go

stimuli (Logan and Cowan, 1984) but must cancel the previously initiated response when an infrequent stop signal is presented at a brief offset after the go stimulus. Another prominent inhibition paradigm is the go/no go (GNG) task, in which the participant executes a button press in response to a frequent 'go' stimuli but must try to withhold that response when an infrequent 'no go' stimulus is displayed. Although the value of these paradigms as markers of cognitive impairment is well established, the neural mechanisms that support response inhibition remain the topic of much debate.

One prominent hypothesis states that a dedicated neural module within the RIFC is dedicated to supporting motor response inhibition (Aron, 2011; Aron et al., 2004). When environmental cues signal the requirement for inhibition, the RIFC module is proposed to down-regulate processes within the motor control areas of the brain via interactions with subcortical areas (Aron and Poldrack, 2006); in this manner, the RIFC module is proposed to work as a top-down braking system that rapidly halts all ongoing motor responses.

In support of the modular view, RIFC sub-regions reliably activate during GNG and SST tasks in healthy controls (Rubia et al., 2001a) but to a lesser extent in patients who suffer from impulsivity disorders, for example, attentional deficit hyperactivity disorder (Rubia et al., 1999, 2001b). Moreover, drugs that are used to treat patients with impulsivity disorders improve performance of and increase RIFC activation during the SST (Aron et al., 2003a; Chamberlain et al., 2008; Rubia et al., 2011). Finally, lesions to the RIFC are associated with impulsive behaviour and poor SST performance (Aron et al., 2003b), completing the

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active during and necessary for relationship that is a central tenet of cognitive neuroscience. Therefore, there is strong evidence to support the view that the RIFC is critically involved in motor response inhibition.

Nonetheless, it does not logically follow that the RIFC houses a dedicated response inhibition module, nor is it necessarily the case that an RIFC–subcortical pathway exists with the sole purpose of down regulating motor responses. Indeed, sub-regions of the human RIFC have been reported to be involved in a particularly broad range of cognitive tasks that require the top-down control of thoughts and actions (Duncan, 2001; Duncan and Owen, 2000). Representative examples include working memory maintenance (Hampshire et al., 2012; Owen, 1997; Owen and Hampshire, 2009), updating (Levy and Wagner, 2011; Verbruggen et al., 2010), attentional switching (Cools et al., 2002; Hampshire and Owen, 2006; Shallice et al., 2008), context monitoring (Chatham et al., 2012) and target detection (Hampshire et al., 2007, 2008; Linden et al., 1999). The latter example, target detection, is perhaps the most relevant because this paradigm requires motor responses to be initiated as opposed to inhibited when infrequent target cues are presented amongst sequences of more frequent distractor stimuli. Therefore, the design is similar to that of SST and GNG tasks with respect to the stimulus processing demands but differs in terms of the requirement for motor response inhibition (Erika-Florence et al., 2014; Hampshire et al., 2010). Given the results of the broader literature, it is likely that the RIFC regions observed during response inhibition are involved in a wider range of cognitive processes.

To complicate matters further, data-driven analyses have demonstrated that the RIFC contains multiple functionally distinct sub-regions and moreover, each sub-region activates in close association with an intrinsic network, the other components of which are distributed throughout the brain (Beckmann and Smith, 2004; Damoiseaux et al., 2006; Dosenbach et al., 2008; Erika-Florence et al., 2014; Rosazza and Minati, 2011; Smith et al., 2009a; Zhang and Li, 2012). In a recent series of studies, it has been demonstrated that components throughout RIFC–whole brain networks activate to a similar level during the SST and across a broad range of other task conditions that do not involve the effortful cancellation of motor responses (Erika-Florence et al., 2014; Hampshire et al., 2010; Sharp et al., 2010; Swick and Chatham, 2014). Of particular relevance to the current study, it has recently been reported that RIFC sub-regions show an increase in functional connectivity during motor response inhibition and other attentionally demanding task conditions, that is, they co-activate in a synchronous manner as an ensemble (Erika-Florence et al., 2014). The strength of this change in network connectivity correlates with individual differences in Stop Signal Reaction Times (SSRT), the most commonly applied measure of response inhibition ability. Based on this observation it has been proposed that motor response inhibition is just one specific example of a broader class of top-down control processes that are supported by dynamic interactions that occur throughout 'domain general' networks.

However, the original proponents of the modular hypothesis have questioned this alternative network perspective. More specifically, it has been suggested that the studies providing evidence counter to the modular hypothesis or RIFC function did not examine the precise location of the RI module and moreover, that some of the attentional control conditions that were applied may have had hidden inhibitory demands (Aron et al., 2014a,b). Here, I address these arguments with further analyses of two previously published SST studies and a new target detection/GNG task, which are designed to differentiate between the cognitive processes that are typically confounded in SST and GNG paradigms.

First, independent components analyses (ICA) are applied separately to data from each of the three studies to test whether there is a consistent data-driven functional parcellation of the RIFC across task contexts and whether there is any evidence within that parcellation of a distinct functional sub-region at the proposed coordinates of the response inhibition module. Then further analyses are undertaken of previously reported data to determine whether the exact proposed coordinates of

the inhibition module, or any other sub-regions of the RIFC, activate either specifically or particularly strongly during motor response inhibition relative to a wide range of other task conditions. Data from the new study are then examined in greater depth in order to probe the conditions under which RIFC sub-regions can be dissociated from each other. Finally, functional connectivity analyses are conducted on data from the new study to determine whether the widespread increases in network functional connectivities that were previously reported during the SST may be replicated in the context of target detection and GNG paradigms.

Materials and methods

Participants

Fourteen participants undertook study 1, 16 participants undertook study 2 and 15 participants undertook study 3. All participants were right handed, aged between 18 and 40, had normal hearing and normal or corrected to normal vision. Exclusion criteria included a history of neurological or psychiatric illness and the taking of psychoactive medications. Participants gave informed consent prior to commencing the studies.

Task designs

The design of study 1 has been reported in detail in a previous article in this journal (Hampshire et al., 2010); in brief, there were three blocks of scanning acquisition during which participants undertook a classic SST paradigm and two attentional control variants of the task. In all three of the acquisition blocks, participants viewed a series of left and right arrows that appeared on the screen in rapid succession. Less frequently, an up arrow appeared a short variable delay after the onset of the left or right arrow (Fig. 1a), and this formed the cue for an additional behaviour that varied across the three blocks. During the first block, participants were instructed to silently count the total number of up-arrow cues that were presented without making any motor responses ('COUNT'). At the end of the block, participants were asked to report the total number of up arrows that they had counted. In the second block (RESPOND), participants responded to the up-arrow cue with a left or right button press the direction of which was defined by the immediately preceding lateral arrow. In the third block, participants were instructed to make left or right button presses as soon as possible after the appearance of the left and right arrows, but to try and cancel that response whenever an up arrow was presented ('INHIBIT'). This latter condition was equivalent to the response inhibition manipulation employed in classical SST tasks. Participants viewed a total of 131 left and 131 right arrows per 9-min acquisition block, 68 of which were followed by up arrows. Left and right arrows were displayed on the screen for 300 ms with a predefined pseudo-randomised ISI such that arrows occurred at either 1600, 1700, 1800, 1900 or 2000 ms intervals. Up arrows were displayed unpredictably after the left and right arrows with a predefined and pseudo-randomised offset from the start of the left or right signal of between 300 and 900 ms.

The design of study 2 was similar to that of study 1 and has been reported in detail elsewhere (Erika-Florence et al., 2014); in brief, there were four blocks of scanning acquisition during which participants undertook either a variant of the classic SST or one of three attentional control variants of the task. In all four blocks, frequent left and right arrows were displayed with a variable inter-stimulus interval (1600, 1700, 1800, 1900 or 2000 ms). In 91 trials per block an infrequent stimulus interrupted a frequent stimulus at an unpredictable offset (mean = 323 ms, SD = 122 ms). Unlike study 1, the infrequent stimulus could be either an up or a down arrow presented randomly and with equal frequency. Furthermore, each task consisted of 4×180 s periods of task interleaved with 5×40 second periods of rest. This design allowed sustained task vs. rest activations and transient activations