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Addressing the selective role of distinct prefrontal areas in response suppression: A study with brain tumor patients

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ABSTRACT

The diverging evidence for functional localization of response inhibition within the prefrontal cortex might be justified by the still unclear involvement of other intrinsically related cognitive processes like response selection and sustained attention. In this study, the main aim was to understand whether inhibitory impairments, previously found in patients with both left and right frontal lesions, could be better accounted for by assessing these potentially related cognitive processes. We tested 37 brain tumor patients with left prefrontal, right prefrontal and non-prefrontal lesions and a healthy control group on Go/No-Go and Foreperiod tasks. In both types of tasks inhibitory impairments are likely to cause false alarms, although additionally the former task requires response selection and the latter target detection abilities. Irrespective of the task context, patients with right prefrontal damage showed frequent Go and target omissions, probably due to sustained attention lapses. Left prefrontal patients, on the other hand, showed both Go and target omissions and high false alarm rates to No-Go and warning stimuli, suggesting a decisional rather than an inhibitory impairment. An exploratory whole-brain voxel-based lesion-symptom mapping analysis confirmed the association of left ventrolateral and dorsolateral prefrontal lesions with target discrimination failure, and right ventrolateral and medial prefrontal lesions with target detection failure. Results from this study show how left and right prefrontal areas, which previous research has linked to response inhibition, underlie broader cognitive control processes, particularly involved in response selection and target detection. Based on these findings, we suggest that successful inhibitory control relies on more than one functionally distinct process which, if assessed appropriately, might help us to better understand inhibitory impairments across different pathologies.

1. Introduction

Everyday life activities require the ability to willingly refrain from unwanted actions and implement goal-directed ones. Without these abilities it would be difficult to imagine driving a car, playing sports or even crossing the street safely. The processes underlying these essential human abilities fall under the umbrella term of executive functions. Even though it is well acknowledged that executive functions depend on the integrity of the prefrontal cortex (PFC), it has been a difficult enterprise to causally map distinct cognitive processes to dedicated brain regions within the frontal lobes. Partly this is due to the difficulty in defining separable functions and their presumed underlying processes. Moreover, the majority of the tests aimed at investigating a certain executive function lack the specificity required to identify unequivocally the process of interest and its neural correlates. Inhibition is an important example of a widely accepted executive function for which there is still an ongoing debate regarding its discreteness as a cognitive construct and its underpinning neural mechanisms (Aron et al., 2014a; Hampshire and Sharp, 2015; Swick and Chatham, 2014).

A major problem in studying response inhibition is that it occurs alongside different related control processes like response selection, sustained attention and working memory (Chambers et al., 2009). The adequacy of classic inhibitory paradigms, such as Go/No-Go (GNG) and Stop Signal Task (SST), in assessing response inhibition without entangling other closely related processes has been controversial

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(Criaud and Boulinguez, 2013; Mostofsky and Simmonds, 2008). Although these paradigms have brought considerable evidence for a sub-set of frontal areas specialized in inhibiting behavior, results from lesion and functional imaging studies do not show consistent results regarding the localization of a putative inhibitory module (see Bari and Robbins, 2013, for a comprehensive review).

One of the most prominent models of inhibitory control highlights the critical role of the right inferior frontal cortex (rIFC), along with that of pre-SMA and the sub-thalamic nucleus, in response inhibition tasks (Aron et al., 2004b). According to this model, the rIFC is proposed to suppress a motor response in a top-down manner once a relevant environmental or internal signal has been captured. In support of this model, many neuroimaging studies show reliable activations of rIFC during both GNG and SST paradigms (Aron et al., 2004b; Buchsbaum et al., 2005; Nakata et al., 2008; Rubia et al., 2001, 2003). Evidence also comes both from virtual and real lesions studies that suggest a critical involvement of the rIFC in response inhibition (Aron et al., 2003; Chambers et al., 2006; Molenberghs et al., 2009).

Other studies have, however, challenged the rIFC exclusive role in response inhibition by providing evidence that the same areas are also being recruited when the environment needs to be monitored for infrequent stimuli that require response initiation, and not only response inhibition (Braver et al., 2001; Chatham et al., 2012; Dodds et al., 2011; Hampshire et al., 2009; Sharp et al., 2010; Walther et al., 2011). This raised the issue of whether the engagement of rIFC areas in GNG and SST tasks may be due to “oddball” effects (Mostofsky and Simmonds, 2008) and more generally to the recruitment of the ventral attentional network involved in detecting behaviorally relevant stimuli (Corbetta and Shulman, 2002). Two recent studies have explored the involvement of the rIFC in paradigms similar to GNG and SST tasks that require a response to be initiated as opposed to inhibited when an infrequent target is presented within a sequence of more frequent distractors (Erika-Florence et al., 2014; Hampshire, 2015). By varying systematically attentional and inhibitory demands of the tasks, both studies found that target detection and response inhibition activated to the same level the rIFC area and increased functional connectivity between sub-regions within that area. Based on these results the authors suggested that the rIFC regions are unlikely to host a specific inhibitory module but instead support a broader set of cognitive control functions through dynamic interactions within distributed functional networks.

In support of this idea, multiple neuropsychological studies failed to find SST or GNG impairments in patients with brain damage including rIFC (Dimitrov et al., 2003; Floden and Stuss, 2006; Krämer et al., 2013; Picton et al., 2007). While the study by Krämer and colleagues (2013) did not find unilateral PFC areas to be critically involved in response inhibition, they reported more frequent Go omissions in right versus left prefrontal patients in a condition with infrequent No-Go trials. This result goes in line with a more general target detection function of right lateral PFC areas (Shallice et al., 2008a; Stuss et al., 2005; Vallesi, 2012). In other studies, however, the authors observed different areas to be involved in inhibitory impairments. In particular, Picton and colleagues (2007) have found that patients with left superior medial PFC damage made significantly more false alarms in a GNG task with respect to right inferior frontal patients and healthy controls. Conversely, Floden and Stuss (2006) demonstrated that damage to right superior medial frontal regions impaired inhibitory control in the SST. Finally, the study by Swick and colleagues (2008) examined the performance of patients with left IFC damage on a GNG task in comparison with a group of orbitofrontal patients and healthy controls. The authors found that left IFC patients responded more often to No-Go stimuli than controls and interpreted this result as evidence against the dependence of inhibitory control exclusively on rIFC or superior medial areas. Based also on the results from their meta-analysis, these authors suggested that the left IFC role is also critical in suppressing prepotent responses. However, this finding was recently rebutted by Aron and colleagues (2014b) argument that left frontal patients might have been impaired because of the task's No-Go frequency (50% and 10%), which required more decision-making processes, and because of its verbal WM demands (not responding to one letter of the alphabet).

As discussed earlier, a possible explanation of these contrasting results could reside in the weakness of the currently used inhibitory tasks to disentangle other intrinsically related cognitive processes (Criaud and Boulinguez, 2013). While the typically found right prefrontal lateralization of inhibitory processes could be accounted for by a more general role of right prefrontal areas in detecting critical events (Langner and Eickhoff, 2013; Shulman et al., 2009; Vallesi, 2014), the finding of an engagement of left prefrontal areas in the same tasks (Meffert et al., 2016; Swick et al., 2008; Zhang and Li, 2012) may have risen from more left lateralized co-occurring processes like task setting and response selection, or verbal WM requirements (Fletcher et al., 2000; Mostofsky and Simmonds, 2008; Smith et al., 1996; Vallesi et al., 2012). Moreover, given the correlational nature of the evidence from neuroimaging studies, the hypothesis of a specialized inhibitory module localized in the rIFC can unlikely be ruled out solely based on this methodological approach. Therefore additional lesion studies covering appropriately left and right prefrontal areas and investigating both inhibitory and other potentially related processes are critical for determining whether successful response inhibition depends critically on one specific lateralized prefrontal area.

To test this hypothesis, in the present neuropsychological study we adopted a simple GNG task design in which there was a single Go stimulus and a single No-Go stimulus and their presentation was equiprobable. We chose to use a 50% GNG probability design for two reasons. First, we wanted to avoid “oddball” effects so that failure in inhibiting responses to infrequent No-Go stimuli would not be confounded with a No-Go detection problem. The second reason was to separate eventual response selection deficits from inhibitory ones, since the former should be observed as both frequent false alarm and target omission errors, while the latter only as a higher false alarm rate. Even though the majority of the task designs requiring inhibitory control build a prepotent response tendency by reducing the frequency of No-Go trials, this has been shown as an unnecessary manipulation in simple GNG task designs since different studies observed a strong motor activation related to No-Go events regardless of their frequency (Boulinguez et al., 2008, 2009; Jaffard et al., 2007; see Criaud and Boulinguez, 2013 for a discussion). Furthermore, in order to assess a possible target detection deficit, and to be able to dissociate it from an inhibitory impairment, we administered a simple RT task in which a target stimulus, requiring a fast response, was preceded by a warning stimulus, which did not require a response. The rationale for the selection of this task, also known as the Foreperiod (FP) task, was twofold. First, it is a simple target detection task in which sustained attention is crucial for fast and accurate responses, and during which sustained attention lapses should be seen as failures in target detection. Second, it has been observed that warning stimuli, even if completely predictable, induce motor activation and can cause false alarms (Boulinguez et al., 2008). Therefore possible inhibitory difficulties could be observed also as responses to warning stimuli and/or anticipations of the target stimuli. Moreover, different neuropsychological studies have shown a specific target occurrence monitoring impairment in right prefrontal patients in terms of RTs (Stuss et al., 2005; Vallesi et al., 2007). In particular, when the time interval between the warning and the target stimuli varies randomly and equiprobably (as in the typical variable FP paradigm), RTs get faster as the FP increases, given that the probability of target occurrence increases (i.e., FP effect). Right prefrontal patients do not show this typically found FP effect, probably because they do not keep track efficiently of the increasing probability of target occurrence. However, when the FP duration is kept constant (i.e., fixed FP paradigm), this FP effect is not observed and thus right prefrontal patients’ RT performance is in the normal range, while superior medial frontal regions