

Right lateral prefrontal cortex – Specificity for inhibition or strategy use?

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The specific functions of prefrontal cortex (PFC) subregions remain a matter of controversy. There is an urgent need to resolve this debate, in particular to improve outcomes for patients with behavioural problems caused by PFC dysfunction. One of the most prevalent behavioural symptoms is disinhibition, *i.e.*, the inability to suppress a response to a prepotent stimulus, which can cause great distress to patients and their families. Functional imaging and animal lesion models have been long been used to study disinhibition but there is still no consensus as to how different PFC subregions contribute to this deficit. At the same time, there are few human lesion studies on disinhibition and few attempts have been made to translate imaging and animal findings back to patients.

In the current issue of *Brain*, Robinson and colleagues address this issue by investigating the specificity of PFC subregions for verbal initiation, suppression and strategy use in a large cohort (n=90) of lesion patients (Robinson *et al.* 2015). More specifically, the authors contrasted the performance of frontal (n=60) and posterior (n=30) patients on the Hayling Sentence Completion Test (Burgess & Shallice, 1996). The Hayling test consists of two parts, with the first part of the test asking participants to complete sentences with appropriate words (for example: “He posted the letter without a ...” could be completed by saying ‘stamp’) – measuring initiation. By contrast, the second part of the test requires participants to complete a similar set of sentences by providing words that are unrelated to the sentence frame (for example: “The captain wanted to stay with the sinking...” should be completed by a word that has no nautical reference, such as ‘banana’ or ‘desk’) – measuring inhibition/suppression. The second part of the test also allows establishment of strategy use, as most participants adopt strategies to complete the sentences with unrelated words. For example, participants complete the sentences by naming objects that are present in the testing environment, such as a desk or a shelf. Robinson and colleagues show that initiation deficits and failure of suppression of prepotent word completion are specific to patients with frontal

lesions. More importantly, there is a specific right frontal lesion effect for strategy use, whereby patients with lesions in this region fail to suppress words because they can not adopt an appropriate strategy to successfully complete the task.

Previous studies investigating the inhibition lesion correlates of the Hayling test have obtained similar findings in smaller lesion samples. For example, Roca and colleagues (2010) reported that right rostral prefrontal cortex lesions are directly linked to suppression deficits. More recently, Volle and colleagues (2012) reported that suppression deficits are related to frontal lesions, with right inferior frontal lesions associated with significantly longer reaction times. This nicely dovetails with the current findings, which also show significant slowness for the suppression condition in the case of right lateralised lesions. However, the current study is the first to link those deficits to the failure of strategy use instead of inhibition/suppression effects per se.

The inferior frontal cortex has been known for a long time to be related to response inhibition. In particular, the right inferior frontal gyrus (IFG) has been implicated in action cancellation tasks, such as stop-signal or go/no-go tasks (*e.g.*, Aron *et al.* 2003), which usually require participants to respond to one stimulus while inhibiting a response to another. However, a clear discrepancy emerges when contrasting the IFG findings for action cancellation with the current Hayling findings, as little strategy use is needed to perform a stop signal or go/no-go task since the response options are extremely limited and no generation of alternative responses is needed. Does this mean that the strategy use findings of Robinson and colleagues are not in line with previous lateralised frontal and particularly IFG findings? Not necessarily, as previous studies have also highlighted that right prefrontal lesions can be related to creativity and problem-solving deficits and not only inhibitory function per se. For example, using a non-verbal problem-solving task, Miller and Tippett (1996) reported that patients with right frontal lesions are impaired on measures of strategy shift and

strategy use compared to controls, while patients with left-frontal or non-frontal lesions are not impaired. Similarly, the failure to develop an efficient strategy and to execute a predetermined plan, as measured by the Hotel task, has also been related to right inferior frontal cortex (Roca *et al.*, 2010). Taken together, these deficits of strategy application associated with right frontal lesions support the results of Robinson *et al.*

How can the inhibitory and strategy use findings for the right lateralised PFC and IFG be reconciled? One potential commonality between tasks as different as action cancellation (e.g., the stop-signal task) and strategy use (e.g., Hayling, real-life problem solving) might be the maintenance of task goals. Such a supervisory attentional system would be engaged by all tasks that entail monitoring of whether or not an adaption of behaviour is required. Indeed, failure to maintain the task goal in the Hayling would lead to inhibition/suppression deficits as a result of erratic responses, i.e., the failure to implement and maintain the appropriate strategy across trials. Similarly, failure to maintain the task goal would lead to deficits in stop-signal or go/no-go tasks, as patients might respond erratically even with limited responses available. Thus, sustaining task goals across trials might well be required for tasks as varied as action cancellation and strategy use in verbal suppression. A recent meta-analysis across functional neuroimaging executive tasks (though without the Hayling) appears to corroborate this notion (Cieslik *et al.* 2015). The study by Cieslik and colleagues shows that right IFG, as well as right anterior insula, are activated across many types of executive tasks requiring maintenance of task goals.

Does this mean that the right lateralised PFC might not be as critical for inhibition as previously thought? The findings of Robinson and colleagues raise the question as to whether the right lateral PFC might be part of an inhibition network requiring the concerted interaction of various brain regions for inhibition/suppression to occur. This notion is supported by previous findings from Volle *et al.* (2012) and from

our lab (Hornberger *et al*, 2011) highlighting the fact that orbitofrontal cortex lesions/atrophy are also strongly related to inhibition/suppression deficits on the Hayling. These orbitofrontal changes might be related more to the prediction and evaluation of specific behavioural outcomes (Rudebeck & Murray, 2014), with patients unable to resist the prepotent response due to a failure to re-evaluate their responses. Unfortunately, the study by Robinson *et al*. did not include any patients with orbitofrontal lesions, which would have been an interesting contrast to the right lateralised lesions and might have allowed the dissociation of strategy use versus re-evaluation of responses during Hayling performance. Clearly, future lesion studies addressing this gap could be of great value for delineating PFC subregion functionality further.

Taken together, the novel findings of Robinson and colleagues highlight the specific role of the right prefrontal cortex in adopting appropriate strategies in a verbal suppression task. The findings further challenge the current notion of the right frontal cortex being related to inhibitory deficits per se. Instead, a more general task maintenance deficit resulting in a failure to adapt behaviour might reconcile existing inhibition findings. Finally, the current study highlights again the value of human lesion studies to corroborate and challenge functional neuroimaging and animal lesion findings.

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