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Inhibition processes are dissociable and lateralized in human prefrontal cortex

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ABSTRACT

The prefrontal cortex (PFC) is known to make fundamental contributions to executive functions. However, the precise nature of these contributions is incompletely understood. We focused on a specific executive function, *inhibition*, the ability to suppress a pre-potent response. Functional imaging and animal studies have studied inhibition. However, there are only few lesion studies, typically reporting discrepant findings. For the first time, we conducted cognitive and neuroimaging investigations on patients with focal unilateral PFC lesions across two widely used inhibitory tasks requiring a verbal response: The Hayling Part 2 and Stroop Colour-Word Tests. We systematically explored the relationship between inhibition, fluid intelligence and lesion location using voxel-based lesion symptom mapping (VLSM). We found that PFC patients were significantly impaired compared with healthy comparison group (HC) on both suppression measures of the Hayling and on the Stroop, even when performance on a fluid intelligence test was covaried. No significant relationship was found between patients' performance on each Hayling suppression measure and the Stroop, once fluid intelligence was partialled out, suggesting that the two tests may involve different kinds of inhibition. After accounting for fluid intelligence, we found a significant interaction between tests, Hayling or Stroop, and site, left or right, of PFC damage. This finding suggesting lateralized functional organization was complemented and extended by our VLSM results. We found that performance on both Hayling suppression measures significantly relied on the integrity of a similar and relatively circumscribed region within the right lateral PFC, in the right lateral superior and middle frontal gyri. In stark contrast, performance on the Stroop relies on the integrity of left lateral superior and middle frontal gyri. Thus, lesion location, right or left PFC, is critical in producing impairments on two inhibitory tasks loading similarly on verbal control. This suggests that the two suppression measures of the Hayling and the Stroop are likely to assess dissociable components of executive functions, related to anatomically defined and lateralized PFC circuits. Our findings also suggest that inhibition may actually comprise qualitatively different forms with different neural substrates. This has clinical implications for the diagnosis and treatment of disinhibition impairments, a common behavioural problem caused by PFC lesions. Our results highlight the need to assess inhibition using a variety of tasks and to develop different types of treatments.

1. Introduction

Executive functions refer to a variety of general purpose control mechanisms thought to modulate and organize more basic cognitive sub-processes to achieve effective behaviour (e.g. Stuss and Levine, 2002). The prefrontal cortex (PFC) is widely acknowledged to make a

Abbreviations: ACC, anterior cingulate cortex; BA, Brodmann Area; CVA, cerebrovascular accident; GNT, Graded Naming Test; HC, healthy comparisons; IQ, intelligence quotient; LF, left frontal; MNI, Montreal Neurological Institute; NART, National Adult Reading Test; No, Number; PFC, prefrontal cortex; RAPM, Raven's Advanced Progressive Matrices; RF, right frontal; RIFG, right inferior frontal gyrus; ROI, region of interest; RT, reaction time; SD, standard deviation; TMT-A, Trail Making Test, Part A; VSLM, voxel-based lesion mapping; WAIS-R, Wechsler Adult Intelligence Scale-Revised

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fundamental contribution to executive functions. However, the precise nature of this contribution is incompletely understood (e.g. Hornberger and Bertoux, 2015). It is likely that a prefrontally located executive system critical for non-routine behaviour may be divided into anatomically separable subsystems (e.g. Stuss and Alexander, 2007; Shallice et al., 2008). Models have been proposed suggesting a functional organization of the PFC along the dorsal-ventral (Petrides, 2005) or rostro-caudal (Badre, 2008; Badre and D'Esposito, 2009) axis of the PFC. Lesion data also suggested that the functional organization of the PFC may be lateralized (Stuss and Alexander, 2007; Shallice and Gillingham, 2012). One prime example of this is that executive functions linked to verbal or non-verbal generation have been associated with left or right PFC respectively (e.g. Robinson et al., 2012).

Despite the likelihood of some anatomical separation, some theories suggest that the PFC carries out general control processes to match the requirements of the task being undertaken, independently of the type of information being processed (e.g. Duncan, 2001; Miller and Cohen, 2001). A large PFC-parietal network, named the *multiple-demand network*, has been shown to be associated with a wide range of cognitive operations in functional imaging work. This putative network has been proposed to be the seat of general fluid intelligence (*g*; e.g. Woolgar et al., 2010). It is well known that fluid intelligence is positively correlated with tests of executive functions and is impaired following frontal lesions (Duncan et al., 1995). However, very few studies that assume executive functions are separable and associated with different sub-regions of the PFC have actually investigated whether executive impairments in frontal patients can be explained by a fluid intelligence loss. A notable exception is represented by the study of Roca et al. (2010). The authors reported that, for several executive tests, such as the Wisconsin Card Sorting Test, Verbal fluency and the Iowa Gambling Task, when performance on a fluid intelligence test was taken into account, no significant difference was found in the performance of frontal patients and HC. Therefore, it remains important to establish the extent to which a loss of fluid intelligence can account for executive impairments in frontal patients.

In this paper we are concerned with a specific executive process, *inhibition*, generally referred to as the ability to suppress inappropriate responses, a definition that we will adopt throughout our paper. *Inhibition* is widely accepted as one of the key components of executive functions (e.g. Miyake et al., 2000). Patients with PFC lesions may present impairments in tasks requiring inhibitory control and may manifest problems resulting from deficits in inhibition, such as inappropriate and/or perseverative behaviour. Functional imaging and animal studies have long been used to investigate inhibition (e.g. Aron et al., 2004a,b, 2014). However, there is a paucity of lesion studies on inhibition. So far, none has systematically investigated the relationship between fluid intelligence, inhibitory tasks and lesion location, despite the fact that some of the inhibitory tasks used are known to be related to fluid intelligence. Moreover, these few studies have used different tasks varying on important dimensions such as the response modality and have reported inconsistent results. Therefore, it remains unclear which PFC areas contribute to inhibition and how.

For example, Miyake et al. (2000) suggested that *inhibition* is related to performance on the Tower of Hanoi test, known to be significantly related to fluid intelligence (e.g. Zook et al., 2004). Aron et al. (2003) used a stop-signal task to investigate inhibition in patients with right PFC damage and HC and reported a significant correlation between right inferior frontal gyrus (RIFG) lesions and stop-signal reaction time (RT). They suggested that the RIFG was critical for inhibitory control in general. Unfortunately, it remains unclear whether the RIFG does indeed harbour an inhibitory system (e.g. see Parvizi, 2012, for a contrasting view). In a subsequent study, using essentially the same set of patients as previously reported, Aron et al. (2004a,b) adopted a test of task-set switching. They found that right frontal patients made more errors than left frontal patients, at a short response stimulus interval, supporting the idea that inhibition was mediated by the RIFG. However, Picton et al. (2007), using a go-no-go task, found that the incidence of false alarms was nearly three times higher, and significantly so, in patients with lesions in left superior medial frontal cortex than in patients with right inferior frontal lesions, who in turn were not very different from HC. A medial frontal involvement also seemed to be critical in a much earlier study (Drewe, 1975). These findings raise the possibility that other areas of the PFC may be involved in inhibition.

The Stroop is one of the most widely used tests in neuropsychology and it is considered a classic 'inhibitory' task (Stroop, 1935). The Stroop Colour-Word part of this test requires participants to name the ink colour in which a colour name is printed when the written name is incongruent (e.g. the word 'yellow' printed in red and the participant has to name the colour instead of reading the word). Thus, successful performance has long been thought to measure the ability to inhibit pre-potent verbal responses (e.g. Cohen and Servan-Schreiber, 1992; Logan, 1994; Friedman and Miyake, 2004). It has also been suggested that this task requires other abilities such as conflict monitoring (e.g. Botvinick et al., 2001; De Pisapia and Braver, 2006), modulation of strategic control (Kerns et al., 2004), working memory (e.g. Kimberg and Farah, 1993) and general goal maintenance (e.g. Cohen and Servan-Schreiber, 1992; West and Baylis, 1998). Similarly to the Tower of Hanoi Test, the Stroop has also been linked to fluid intelligence. It has been reported that in HC, performance on the Stroop is associated with performance on the Wechsler Adult Intelligence Scales-Revised (WAIS-R), suggesting that both are measures of *g* (e.g. Obonsawin et al., 2002).

For a long time, evidence for functional specialization within the PFC was conflicting for Stroop. In the first neuropsychological study of Stroop, which examined performance in 118 patients with focal lesions, Perret (1974) reported an impairment in patients with lesions in left dorsolateral PFC. Stuss et al. (2001) also reported poor Stroop performance after left dorsolateral and superior medial lesions, particularly involving the right supplementary motor area. In contrast, Vendrell et al. (1995) reported impairments on the Stroop in patients with lesions in right lateral PFC. The latter two studies included a sizeable number of patients with traumatic brain injury, patients with bilateral lesions, and patients with lesions extending beyond the PFC, raising the possibility that the findings may partially reflect damage beyond the identified area. Several small patient series with more or less selective lesions of anterior cingulate cortex (ACC) have also reported inconsistent results (e.g. Swick and Turken, 2002; Fellows and Farah, 2005; Baird et al., 2006). A number of recent studies have used Voxel-based Lesion Symptom Mapping (VLSM) to investigate the structure-function relationship in the Stroop. This is a method of image analysis allowing an operator-independent measurement of association between anatomical localization of brain tissue damage and patients' performance in a specific cognitive task (Bates et al., 2003). These studies have suggested that the left PFC is involved in the Stroop Colour-Word test. Thus, Tsuchida and Fellows (2013) investigated the performance of patients with PFC lesions on several executive tasks, including the Stroop and found that the left lateral PFC substantially contributed to performance on the Stroop (for additional findings suggesting a left PFC involvement, see Demakis (2004), Derrfuss et al. (2005)). In a subsequent study, Geddes et al. (2014) documented impairment in the Stroop task on a small number of patients with left ventral lateral PFC damage but not in patients with right ventral lateral PFC damage. Interestingly, the authors reported that patients with right ventral lateral PFC damage were impaired on the Eriksen Flanker tests (Eriksen and Eriksen, 1974), also requiring suppression of pre-potent responses. A further study using VLSM in a large sample of patients with PFC lesions (n=165) reported that the left dorsolateral frontal cortex was associated with poor performance on the Stroop (Glascher et al., 2012). Altogether, these findings have been taken to challenge the notion that the right lateral PFC is critical for inhibitory control in general (Tsuchida and Fellows, 2013) and to support a role