CORTEX XXX (2012) I–II

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Research report

Are core component processes of executive function dissociable within the frontal lobes? Evidence from humans with focal prefrontal damage

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ARTICLE INFO

Article history:
Received 29 May 2012
Reviewed 18 July 2012
Revised 21 September 2012
Accepted 26 October 2012
Action editor Angela Sirigu
Published online xxx

Keywords:
Prefrontal cortex
Executive function
Cognitive control
Working memory

ABSTRACT

Executive function encompasses a range of control processes supporting flexible, goal-directed behaviour. Attentional set-shifting, updating of information in working memory, and inhibitory control have been proposed as key components of executive function, but debate continues as to the validity of this conceptual framework, and the neural substrates of these putative components. Here we examined prefrontal structure–function relationships for each of these component processes in a large cohort of patients with focal prefrontal damage. Forty-five patients with focal damage to various sectors of prefrontal cortex (PFC), and 50 demographically matched healthy control subjects performed an attention shifting task, the Stroop colour naming task, and a spatial search task. Voxel-based lesion–symptom mapping revealed that damage to left ventrolateral PFC led to impaired performance on both the Stroop and attention shifting tasks. In contrast, performance of the spatial search task depended on several regions within PFC, but notably not left ventrolateral PFC. These observations were confirmed with direct comparison of performance between patients grouped according to lesion location. This dissociation partly supports the component process view of executive function, distinguishing the goal-directed regulation of attention (perhaps specifically in the verbal domain) from the requirements of the spatial search task, including the updating of information in spatial working memory. These findings are easier to reconcile with modular, material-specific accounts than with more unitary models of executive function.

1. Introduction

Executive function refers to a range of control mechanisms that modulate and organize more basic cognitive operations to allow goal-directed behaviour. Prefrontal cortex (PFC) is thought to make important contributions to executive function, but the precise nature of those contributions remains a matter of debate. Many current theories argue that component processes of executive function rely on specific regions within PFC (e.g, Petrides, 2005; Stuss et al., 1995). This is supported by functional imaging results showing differential haemodynamic responses of specific regions within PFC to

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http://dx.doi.org/10.1016/j.cortex.2012.10.014

different executive tasks. On the other hand, unitary accounts propose that at least some regions within PFC carry out general control processes, independent of the type of information being processed and adaptable to changing task demands (Duncan, 2001; Miller and Cohen, 2001). This view accommodates the observation that a large number of seemingly different tasks activate a limited set of regions, consistent with a general-purpose supervisory mechanism central to many cognitive operations (Duncan, 2010; Duncan and Owen, 2000). These regions, which Duncan has termed the 'multiple demand' network, include bilateral ventrolateral PFC (including anterior insula – AI – with its surrounding frontal operculum – FO), dorsolateral PFC, and the pre-supplementary motor area (pSMA) and adjacent dorsal anterior cingulate cortex (dACC) (Duncan, 2006, 2010).

These theoretical issues have important clinical implications for the diagnosis, measurement, and treatment of frontal-executive disorders: is it sufficient to capture executive function as a single construct, or are there key components that must be distinguished? Can we explain the effect of focal prefrontal damage as the disruption of a single, general-purpose control system, or does damage to specific prefrontal sub-regions have distinct effects?

Part of the difficulty in resolving this debate is conceptual ambiguity in the definition of executive function and its putative component processes. The level of explanation in the study of executive function tends to be more abstract than in many other cognitive domains (Burgess et al., 2006). Furthermore, many conventional tests of executive function are complex, plausibly relying on multiple cognitive processes (Jurado and Rosselli, 2007), making it difficult to determine what the basic components of executive function are and how they might be organized within PFC. Nonetheless, certain components recur across a variety of literatures. One reasonable starting point is the work of Miyake and colleagues, which demonstrated the validity of three widely-accepted putative components of executive functioning: mental set-shifting ("Shifting"), inhibition of pre-potent responses ("Inhibition"), and information updating and monitoring ("Updating") using a latent-variable approach in a large sample of young healthy subjects (Miyake et al., 2000).

Whether these component processes rely on distinct neural substrates within PFC remains to be answered definitively. Functional imaging data both support and refute this possibility: meta-analyses using broadly similar conceptual frameworks report both shared and distinct patterns of prefrontal and parietal activations across a range of specific executive tasks (Collette et al., 2005; Wager et al., 2004; Wager and Smith, 2003). In any case, functional imaging findings indicate correlation between brain activity and tasks, and are alone relatively weak tests of functional specialization within PFC.

Studies in patients with focal frontal damage can more directly address whether a given prefrontal region is necessary for performance of a particular task, and the pattern of impairment across tasks can provide evidence regarding the dissociability of these hypothesized component processes. While existing work with this method supports a key role for PFC in all three component processes, the regional specificity of these claims varies, and there has been no strong test of the dissociability of these processes. Here, we used a voxel-based lesion–symptom mapping (VLSM) method as well as region-of-interest group comparisons to test the necessity of specific prefrontal regions for three putative component processes of executive function, and to determine whether these processes can be dissociated.

We focused on three tasks, versions of which are widely used in both research and clinical contexts: an attention shifting task requiring set-shifting, the Stroop colour naming task requiring inhibition of a pre-potent response, and a spatial search task requiring updating. Previous neuropsychological studies have shown all three of these tasks, tested individually, to be sensitive to frontal lobe damage. However, evidence for regional specialization within PFC is either conflicting (Stuss et al., 2001; Vendrell et al., 1995 for Stroop task) or limited, with most studies focussing on the overall effect of frontal damage in patients with relatively large lesions (Owen et al., 1996; Rogers et al., 1998). Further, these studies did not examine the pattern of performance across executive tasks.

Despite the coarse grain of the structure–function evidence base, these tasks are widely used clinically and experimentally to assess the integrity of specific prefrontal sub-regions in various neurological and psychiatric populations. Anatomically specific claims are generally justified by the localized patterns of prefrontal activation observed in functional imaging studies using these tasks (e.g., Stroop task as an index of anterior cingulate cortex; Blair et al., 2006; Orem and Bedwell, 2010).

The aim of this study was to directly test whether distinct prefrontal regions are differentially and critically involved in performance of these tasks, and by extension critical to the three processes proposed as amongst the core elements of executive function. All three tasks were administered to a group of patients with focal lesions affecting various sectors of PFC. If prefrontal sub-regions make distinct contributions to these putative component processes, the effects of lesions to different prefrontal regions should be different for each task, i.e., it should be possible to dissociate performance. On the other hand, if prefrontal regions collectively contribute to a shared underlying mechanism critical for executive function more generally, or if the proposed component processes are not, in fact, distinct, there should be common patterns of widely distributed lesion–symptom associations across all three tasks.

2. Methods

2.1. Participants

Subjects with chronic, focal lesions affecting the frontal lobes (n = 45) were recruited from research databases at the University of Pennsylvania and McGill University. The group consisted of 21 patients with ischaemic or hemorrhagic stroke, 16 with resection of low-grade tumours, and eight with damage resulting from rupture of cerebral aneurysms. Of these, 16 were taking psychoactive medications, most commonly anticonvulsants or antidepressants. The tests were administered at least 6 months after the brain injury (mean 4.5 years, range = 10 months to 16 years). Demographically matched healthy control subjects (n = 50) were

Please cite this article in press as: Tsuchida A, Fellows LK, Are core component processes of executive function dissociable within the frontal lobes? Evidence from humans with focal prefrontal damage, Cortex (2012), http://dx.doi.org/10.1016/j.cortex.2012.10.014