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Testing the model of caudo-rostral organization of cognitive control in the human with frontal lesions

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ABSTRACT

The *cascade model* of cognitive control, mostly relying on functional neuroimaging studies, stipulates that the lateral frontal cortex (LFC) is organized as a cascade of executive processes involving three levels of cognitive control, implemented in distinct LFC areas from the premotor to the anterior prefrontal regions. The present experiment tested this model in patients with LFC lesions and studied the hierarchy of executive functions along the caudo-rostral axis, i.e. the respective roles of the different LFC areas in the control of behavior. Voxel-based lesion-symptom mapping and region of interest group analyses were conducted in 32 patients with focal LFC lesions who performed cognitive tasks assessing the cascade model. We first showed that three different LFC areas along the caudo-rostral axis subserved three distinct control levels, whose integrity is necessary for adaptive behavior. Second, we found that prefrontal cognitive control has an asymmetric organization: higher control processes involving more anterior prefrontal regions rely on the integrity of lower control processes in more posterior regions, while lower control processes can operate irrespective of the integrity of higher control processes. Altogether, these findings support a caudo-rostral cascade of executive processes from premotor to anterior prefrontal regions.

Introduction

The lateral frontal cortex (LFC) is a pivotal structure in the neural network involved in the inhibition of reflex or automatic actions and the elaboration or control of goal-directed behaviors. The question of its functional architecture is central, as it holds the key to understanding the functional architecture of cognition in general. Several models of the anatomical and functional organization of the LFC have been proposed and debated. There is a general agreement on two key ideas underlying these models. First, that the LFC is essential for temporal control: it serves as a temporal buffer between past events and future actions, allowing behaviors that follow internal goals to occur (Fuster, 2001; Goldman-Rakic, 1987; Petrides, 2005). Second, that the LFC exerts "top-down" cognitive control that modulates processes associated with the posterior regions on the basis of internal plans and goals (Miller and Cohen, 2001; Passingham, 1993; Shallice, 1988). Koechlin et al. (2003) have proposed a functional model combining these two critical dimensions of cognitive control, based on Shannon's theory of information (Berlyne, 1957). The novelty of this model lies in the fractioning of cognitive control itself: executive functions can be subdivided into hierarchical control levels depending on the amount of information required for action selection and on the temporal frame in which the stimulus occurs. This modular model involves three nested levels of processing, implemented in three different areas organized along the caudo-rostral axis of the LFC. The posterior LFC (the lateral premotor cortex/BA 6) subserves *sensory* control, i.e., it is involved in selecting appropriate behavioral response to stimuli based on stored sensorimotor associations. A caudal portion of the lateral prefrontal cortex (BA 9/44/45) is the neural substrate for *contextual* control, involved in selecting appropriate sensorimotor representations in the premotor cortex according to the immediate context; a more rostral portion of the lateral prefrontal cortex (BA 46) subserves *episodic* control, involved in selecting relevant caudal prefrontal representations according to the temporal episode in

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which the person is acting, i.e. according to temporally remote events. The implementation of this cognitive architecture within the LFC is supported by evidence from functional magnetic resonance imaging (fMRI) studies in healthy human subjects (Braver et al., 2003; Koechlin et al., 2003). It is interesting to note that after Koechlin's model, Badre and colleagues have also proposed a caudo-rostral model of functional organization of the LFC, based on fMRI and lesion studies (Badre and D'Esposito, 2007; Badre et al., 2009). This model matched Koechlin's one in terms of anatomical segregation along the caudo-rostral axis of the LFC, but it differed in the functions associated with each of the defined subregions (see Discussion).

This cascade model of cognitive control may modify our view of the functional organization of prefrontal cortex and may also modify our interpretation of the clinical signs observed in patients with prefrontal damages. However, to which extent this model may predict the behavioral deficits in patients with frontal lesions remains unknown. Indeed, functional neuroimaging and physiological measurements in intact systems only confirm the engagement of a brain region by a cognitive process but not its necessity for this process. This raises the issue regarding the causal hierarchy and the integration processes within this network. In particular, can higher control levels implemented in more anterior prefrontal regions operate irrespective of the integrity of lower control levels and more posterior prefrontal regions? To address this question, we tested the cascade model of cognitive control in a large cohort of patients with stable focal frontal lesions. Indeed, lesion studies, i.e. the study of deficits associated with damage to a specific brain region, may provide convincing evidence for the critical role of a brain region in certain cognitive processes and/or the control of a specific behavior (Rorden and Karnath, 2004; Sarter et al., 1996).

Thirty-two patients with LFC lesions and twenty-eight matched healthy participants were included in the study. All performed cognitive tasks testing the three levels of cognitive control (*episodic*, *contextual* and *sensory* control, see Fig. 1) as described in Koechlin et al. (2003). The tasks consisted of the presentation of series of colored visual stimuli (disks or letters) organized into blocks. Subjects made manual responses on the basis of an instruction cue that initiated each block. Task accuracy (percentage of correct answers) and Reaction Times were recorded in each condition and for each participant. All patients also underwent an anatomical T1-weighted MRI to map brain lesions.

We then analyzed the data following two different approaches. We first tested the hypothesis that *sensory*, *contextual* and *episodic* control levels involve segregated regions on a caudo-rostral axis in the LFC. For that purpose, we performed an analysis based on a cluster-by-cluster lesion–behavior mapping technique (Kinkingnehun et al., 2007). According to previous fMRI studies (Koechlin et al., 2003; Kouneiher et al., 2009), we expected that *sensory*, *contextual* and *episodic* deficits would be associated with focal damage to BA 6, BA 45 and BA 46, respectively.

Secondly, we addressed the question of the hierarchy of control between the different areas involved in this caudo-rostral organization by performing a group analysis that compares the performance of patients with lesions of the lateral premotor cortex (n = 11), caudal prefrontal cortex (n = 9) and rostral prefrontal cortex (n = 6) to the performance of 28 healthy controls. In this second study, we excluded patients with frontal lesions that did not involve the described regions of interest (i.e. BA 6, BA 44/45, or BA 46/47). In accordance with the hierarchical organization predicted by the cascade model described above, we expected that higher control processes involving more anterior prefrontal regions rely on the integrity of lower control processes in more posterior regions, whereas lower control processes can operate irrespective of the integrity of higher control processes.

Methods

This study was approved by institutional ethics committees for biomedical research (CCPPRB of the Pitié-Salpêtrière Hospital, Paris, France and Ethics Committee of the Salvador Hospital, Santiago, Chile). Subjects provided written informed consent before their inclusion in the study.

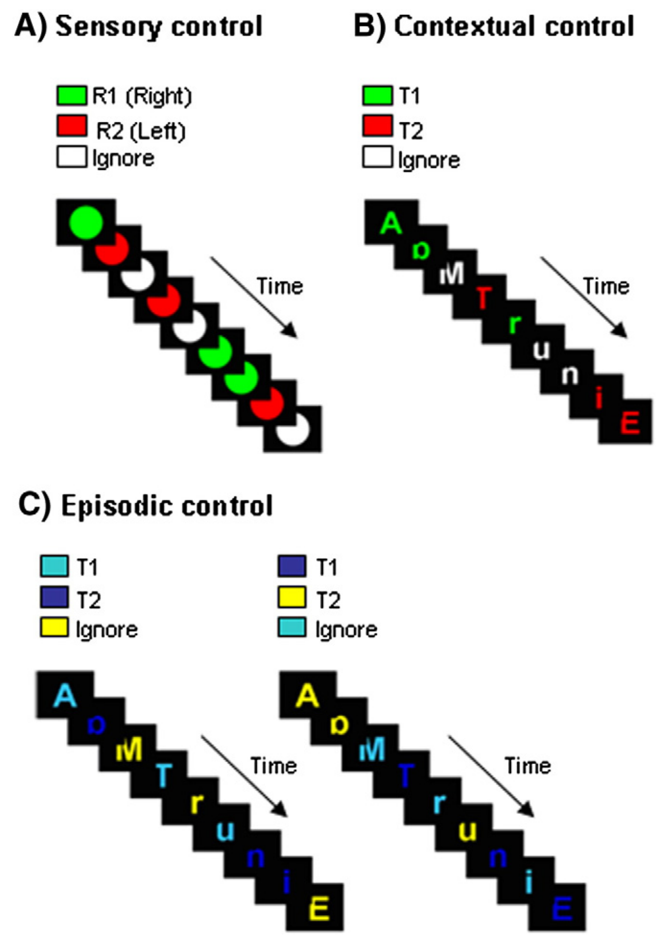

Fig. 1. Behavioral tasks. Participants performed the three tasks described in Koechlin et al. (2003) to assess the different levels of cognitive control. They had to provide a manual response to colored visual stimuli (disks or letters), on the basis of an instruction cue that initiated each block. (A) *Sensory* condition: participants had to press the right button when a green disk was presented on the screen (R1) and the left button when a red disk was presented (R2). They had to ignore white disks. (B) *Contextual* condition: participants had to make a letter discrimination using the right and left response buttons, the task being determined by the color of the letter ("*contextual* signal"). For green letters, participants had to perform a lower/upper case discrimination task (T1). For red letters, they had to perform a consonant/vowel discrimination task (T2). They had to ignore white letters. (C) *Episodic* condition: subjects performed the task as in the *contextual* condition except that association between the color and task varied according to the instruction cue. In one block, cyan letters were associated with T1, blue ones with T2 and yellow ones were ignored. In another block (initiated by another instruction cue) blue letters were associated with T1, yellow ones with T2 and cyan ones were ignored.

Participants

Thirty-two patients with focal frontal lesions were included in the study (mean age: 49.38 years [SD: 11.9]; years of formal education: 12.41 [SD: 3.58]; patients with right frontal lesions, n = 18, patients with left frontal lesions, n = 14). They were recruited from the Neurovascular and Neurosurgical Departments of La Pitié-Salpêtrière Hospital (Paris, France) and the Neurology Department of the Salvador Hospital (Santiago, Chile). They were selected based on the following criteria: (1) the presence of a single frontal focal lesion, excluding lesions extending to other lobes, and confirmed by an anatomical T1-weighted 3D MRI; (2) the absence of a prior history of neurological disease, psychiatric disorder or substance abuse; (3) the ability to understand and perform the tasks (in particular, patients did not exhibit