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ORGANIZATION OF EXECUTIVE FUNCTIONS:
HEMISPHERIC ASYMMETRIES

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Abstract

This address provides a review of evidence for a deconstruction of executive functions, the set of cognitive operations which allow goal-directed behavior. The underlying working hypothesis is that some complementary and computationally diverse executive functions are dissociable not only functionally but also temporally and anatomically, along the left-right axis of prefrontal cortex and related neural networks. In particular, criterion-setting – the capacity to flexibly set up and select task rules – is more left-lateralized; monitoring – the process of continuously evaluating the internal or external contingencies to optimize behavior – is more right-lateralized; finally, superior medial prefrontal regions, including dorsal anterior cingulate cortex, have a role in energizing weakly activated but relevant processes. Several lines of empirical evidence, including neuroimaging and neuropsychological findings, are presented to support this tripartite model of executive functions. Evidence which is difficult to explain with this model and some future directions are also discussed.

Keywords: Criterion-Setting; Energization; Monitoring; Executive Functions; Prefrontal Cortex Fractionation.

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Executive functions are a set of goal-directed processes which hierarchically modulate and coordinate other lower-level operations. There is a scientific consensus that the prefrontal cortex (PFC) plays a key role for executive functions (e.g., Baddeley, 1986; Dehaene & Changeux, 1997; Duncan & Owen, 2000; Fuster, 1989; Luria, 1966; Miller & Cohen, 2001; Norman & Shallice, 1986). However, the nature of PFC is difficult to capture, due to its extraordinary complexity and flexibility. Thus, characterizing its functional organization and, in particular, how executive functions are distributed and implemented within and outside PFC, has traditionally been a fascinating but challenging enterprise.

Models of executive functions: unitary vs. fractionation views

Some of the models put forward to explain how these high-level functions are organized in the brain stress integration (Duncan & Owen, 2000; Fuster, Bauer, & Jervey, 1982; Miller & Cohen, 2001), whereas others focus on fractionation (Aron, Monsell, Sahakian, & Robbins, 2004; Godefroy, Cabaret, Petit-Chenal, Pruvo, & Rousseaux, 1999; Shallice, 2004; Stuss, 2011). Among the integrative views, the adaptive coding model (Duncan, 2001; Duncan & Owen, 2000) proposes that neurons in a distributed network of prefrontal regions show high flexibility in coding task-relevant information under different task demands. Electrophysiological findings support this model by showing that the activity in several prefrontal neurons flexibly adapts to different tasks and domains (Freedman, Riesenhuber, Poggio, & Miller, 2001; Rainer, Asaad, & Miller, 1998). Neuroimaging and neuropsychological evidence also supports the existence of a ‘multiple demand system’, including bilateral and superior medial PFC and mid-parietal cortex, especially involved in performing complex tasks (Duncan, 2010; Woolgar et al., 2010). This model emphasizes the interactivity of these fronto-parietal regions when facing demanding situations. On the other hand, some comprehensive reviews show clear tendencies of differential functional specialization of distinct prefrontal regions under various task contexts (Cabeza & Nyberg, 2000; Faw, 2003; Fuster, 1999; Shallice, 2004; Stuss, 2011).

While initial models of the executive functions were relatively agnostic about their precise organization within PFC (Baddeley, 1986; Norman & Shallice, 1986; Shallice, 1982; Umiltá, 1988), novel views have been proposed more recently to highlight functional fractionation in the frontal lobes along the three different axes: rostro-caudal, ventral-dorsal and right-left (e.g., Badre & D'Esposito, 2009; Grafman, Spector, & Rattermann, 2005; Koechlin, Corrado, Pietrini, & Grafman, 2000; Petrides, 2005; Stuss & Alexander, 2007). For instance, it has been shown that the level of representation varies along a rostro-caudal hierarchical gradient, going from simple S-R associations in motor and premotor regions to the episodic memory representations of entire task-sets towards the frontal pole (Badre & D'Esposito, 2009; Kim, Johnson, Cilles, & Gold, 2011; Koechlin & Summerfield, 2007; Tsujimoto, Genovesio, & Wise, 2011). Other authors have proposed similar gradients in social cognition, with increasing abstractness and complexity from posterior to anterior medial prefrontal regions (Amodio & Frith, 2006). More anteriorly, a gradient has been described which varies according to the external-internal nature of the information being processed (Christoff & Gabrieli, 2000; Gilbert et al., 2006). Moreover, it has been shown that different working memory processes (storage vs. manipulation/monitoring) are distributed along the ventral-dorsal axis (Owen, 1997; Petrides, 2005; Rowe, Toni, Josephs, Frackowiak, & Passingham, 2000). However, given that nature has provided the brain with an anatomo-functional organization into two hemispheres (e.g., Corballis, 2009; Gazzaniga, 2000; Hellige, 1993; Zatorre, Belin, & Penhune, 2002), it seems also critical to embark in a deconstruction of prefrontally-based processes along the left-right axis.

Although the study of hemispheric asymmetries in the frontal lobes has a long tradition in the emotional domain (e.g., Davidson, Schwartz, Saron, Bennett, & Goleman, 1979; Harmon-Jones & Sigelman, 2001; Schmidt & Fox, 1994; Tucker, 1987), this issue has more recently started to be extensively studied in cognition as well. In the 1990's, the most heavily investigated hypothesis of a prefrontal organization along the left-right axis was in terms of domain, with left and right prefrontal regions being more recruited in working memory tasks involving verbal/non-spatial and spatial processing, respectively (Baker, Frith, Frackowiak, & Dolan, 1996; Courtney, Petit, Maisog, Ungerleider, & Haxby, 1998; Fiez et al., 1996; McCarthy et al., 1996; Prabhakaran, Narayanan, Zhao, & Gabrieli, 2000; Smith, Jonides, & Koeppe, 1996; Sandrini, Rossini, & Miniussi, 2008). However, the issue of a clear-cut domain-based dichotomy in PFC remains unsettled (D'Esposito et al., 1998; Owen, 1998; Postle, Stern, Rosen, & Corkin, 2000). More recently, the working hypothesis that left-right prefrontal fractionation may not only depend on the domain but also on the type of processing, has received empirical credit, for instance as a result of neuropsychological dissociations (e.g., Shallice, 2004; Stuss et al., 2005; Stuss & Alexander, 2007; Stuss, Binns, Murphy, & Alexander, 2002; also see Aron et al., 2004; Vallesi et al., 2007a).

Fractionation of prefrontal cortex along the left-to-right dimension

The present address provides a selective review, including up to date multimodal evidence, for the hypothesis of prefrontal functional deconstruction along the x-axis (i.e., left, middle, right). However, it should be clear upfront that this approach cannot give an exhaustive description of the complex distribution of executive functions in the brain. Rather, it would be fruitful to consider this view in combination with other above-mentioned models, which were proposed to account for the organization of executive functions along other orthogonal axes, in order to obtain a more complete picture.

Moreover, it is important to point out that 'fractionation' or 'deconstruction' refer to the investigative process that, through carefully designed experimental paradigms, lead to statistical findings of a relatively higher engagement of right and left PFC in different functions, and by no means I will imply that the fractionation concerns an all-or-none modularity in this complex and richly connected region of the brain. Virtually all the prefrontal regions have the necessary flexibility for an overlap of the processes they are engaged in (e.g., Duncan & Owen, 2001), but empirical evidence strongly suggests that they are relatively more specialized for different, complementary operations. Finally, PFC should not be seen as a monolithic structure, but rather as a set of nodes which are functionally connected with extensive networks, especially involving several fronto-posterior (e.g., Bunge, 2004; Gazzaley et al., 2007; Vallesi & Crescentini, 2011), fronto-striatal (e.g., Alexander, DeLong, & Strick, 1986; Haber, Fudge, & McFarland, 2000; Robbins, 2007) and chemical neuromodulatory (e.g., Colzato, Waszak, Nieuwenhuis, Posthuma, & Hommel, 2010; Robbins & Arnsten, 2009) circuits. As an example, a recent functional Magnetic Resonance Imaging (fMRI) study (Gazzaley et al., 2007) revealed that activity in the left dorsolateral prefrontal cortex (DLPFC) enhanced its functional connectivity with a scene-selective visual associative area when the task was to encode scenes and forget faces with respect to the opposite condition (also see Sandrini et al., 2008, for related evidence with Transcranial Magnetic Stimulation, TMS). The control of connectivity between DLPFC and the task-relevant regions could be even more complex. For instance, in another fMRI study (Sakai, Rowe, & Passingham, 2002), although the activity in DLPFC (Brodmann Area, BA, 46) was not significantly coupled with activity in either frontal eye fields (area 8) or the intra-parietal sulcus on their own, it was associated with tighter correlation between these two areas. This higher-order correlation strongly suggests a modulatory role of DLPFC (see Miller & Cohen, 2001).

For the sake of clarity, however, this address will mainly focus on three prefrontal regions which represent key nodes of the neural underpinning of corresponding executive functions. The starting point is the ROtman-Baycrest Battery for Investigating Attention (ROBBIA) model proposed by Stuss and colleagues (Stuss, 2011; Stuss et al., 2002; Stuss, Shallice, Alexander, & Picton, 1995). Three processes have been identified on the basis of vast neuropsychological evidence (e.g., Stuss & Alexander, 2007; Stuss, 2011): criterion-setting, energization and monitoring. I will first define each of these processes according to their computational, anatomical and temporal characteristics. I will then review empirical evidence supporting the model, also pointing out exceptions which the model encounters difficulty to account for. Although I will mainly focus on neuroimaging studies of healthy brains, I will also review evidence from other neuroscientific methods, since a multi-modal approach is better suited to gather converging information and to surpass the drawbacks of each single methodology.

A first executive function this review focuses on is criterion-setting (or task-setting), which can be defined as the capacity to form or select task-relevant rules (Stuss & Alexander, 2007). At a more general level, it has been defined as strategy production (Cabeza, Locantore, & Anderson, 2003; Shallice, 2004). In many cases, it consists of forming new associations between different items. Once these associations have been set up, they can then be flexibly selected and integrated according to the task-relevant criteria. Criterion-setting is implemented in left prefrontal regions, mainly including ventro- and dorso-lateral PFC. This process is important not only to set up task-relevant associations but also, as a flip side, to suppress the task-irrelevant criteria and operations, especially if those are part of one’s repertoire of prepotent routine action schemata and, as such, inappropriately compete for the control of behavior. In the memory encoding domain, Fletcher and colleagues (Fletcher, Shallice, & Dolan, 2000) summarized this dual functional nature of left lateral PFC (selecting and suppressing) as ‘sculpting the response space’. From a temporal point of view, given its nature, it can be viewed as a proactive and phasic process, mostly required during early phases of task acquisition (learning, encoding, instruction periods).

The second function covered in this review is energization, although some authors (e.g., Stuss, 2011) do not consider it as an executive process in a strict sense. This is a process that provides energetic resources to other task-relevant operations, when those are in a weak state of activation. Temporally, energization may be required during early stages of task acquisition, for instance because of conflict with well-established rules, difficulty and time-pressure, or later on, because of fatigue, tiredness and boredom. The superior medial PFC, including dorsal portions of the anterior cingulate cortex (ACC), has been proposed to underlie energization (Paus, 2001; Stuss et al., 2005) and resource allocation under difficult task contexts (Barch et al., 1997).

Once a new rule has been acquired, one needs to monitor whether it is being applied correctly and whether it matches the current goals. Thus, the last executive process this review focuses on is monitoring, a quality-check process which continuously evaluates whether other ongoing processes are fine-tuned with the probability structure of critical events. The final goal of monitoring is the optimization of behavior. A monitoring function has been attributed to the right lateral PFC in the literature (Cabeza et al., 2003; Champod & Petrides, 2007; Shallice, 2004; Stuss & Alexander, 2007). Being it a reactive, evaluative process, its time-course is expected to be tonic and long-lasting. This process has received many definitions that speak to the importance and ubiquity of it, but also to the need for experiments that are carefully designed to capture the multifaceted nature of this function and its neural underpinning. Petrides (2005, p. 789) defines monitoring as “the capacity to hold abstract coded representations of events that are expected to occur, so as to mark their occurrence or non-occurrence (i.e. monitor their relative status in relation to each other and the intended plan)”. In a similar vein, Stuss and Alexander (Stuss & Alexander, 2007, p. 909) define monitoring as “checking the task over time for ‘quality control’ and the adjustment of behavior” (also see Shallice, 2004). The same authors state that monitoring may occur at many levels: the task-specific ongoing activity; the timing of activity; temporal anticipation of the stimulus onset; detecting errors and divergence between behavior and external reality.

There are clearly other processes carried out by the same and other frontal regions (e.g., emotional regulation in inferior medial PFC and insula) but this review will not focus on those. The ROBBIA model (e.g., Stuss & Alexander, 2007), with its proposed deconstruction of executive functions into criterion-setting, monitoring and energization, closely resembles the Montesquieu’s tripartite system theory (de Secondat, 1748), according to which a separation of legislative, judicial, and executive powers is important for the efficient guidance of a democratic state. This similitude is certainly suggestive, but it is also a useful heuristic to understand how complementary functions in PFC may flexibly guide other neural processes in the rest of the brain. I shall now review empirical evidence in favor of the tripartite ROBBIA model of executive functions.

Executive functions: empirical evidence for the tripartite ROBBIA model

Criterion-setting

Tasks typically entailing criterion-setting are those which require activation of weak and novel rules with the concomitant suppression of prepotent but inappropriate ones. Those tasks usually engage left lateral prefrontal regions. In the famous Stroop task, the more automatic word reading operation has to be suppressed in favor of a less prepotent one (naming the color of a color word), especially when interference between the two sources of information (color and meaning) has to be solved. Patients with left frontal lesions show impaired performance in the Stroop task (Perret, 1974; Stuss, Floden, Alexander, Levine, & Katz, 2001). Converging neuroimaging evidence also shows a left-lateralization in the PFC during the performance of this task (see Derrfuss, Brass, Neumann, & von Cramon, 2005, for a meta-analysis). Zysset and associates (Zysset, Muller, Lohmann, & von Cramon, 2001) found a key role of left inferior frontal cortex (vs. ACC) in solving the Stroop interference. Another recent fMRI study of ours (Floden, Vallesi, & Stuss, 2011) also shows that greater activation of the left dorsolateral prefrontal cortex (DLPFC) is related to a reduced Stroop interference, specifically in an unblocked and uncued context, which maximally taxes criterion-setting.

Another example is the verbal fluency test, in which the more customary strategy of searching words through semantic associations should be suppressed in order to activate the weaker but task-relevant strategy of searching words by first letter. Left frontal patients are impaired in this task (Baldo, Schwartz, Wilkins, & Dronkers, 2006; Perret, 1974; Stuss et al., 1998; see Schlosser et al., 1998, for converging fMRI evidence).

Evidence for a criterion-setting role of the left PFC under non-routine conditions also comes from a random number generation task, which is known to require controlled processes (e.g., Towse & Cheshire, 2007). The performance in this task is disrupted by TMS over the left DLPFC, but not over the right homologous region (Jahanshahi et al., 1998): the inappropriate but more habitual strategy of counting by ones increases while the more appropriate but unusual strategy of counting by two decreases. The direction of this effect depends on the TMS frequency applied (Knoch, Brugger, & Regard, 2005). Moreover, activation of the left DLPFC is inversely related to the use of the more habitual strategy of counting by ones under time-pressure, as revealed with Position Emission Tomography (PET; Jahanshahi, Dirnberger, Fuller, & Frith, 2000b). Not only left PFC but more complex frontostriatal circuits are involved in random number generation since, in Parkinson's disease patients, deep brain stimulation of the subthalamic nucleus and the internal segment of the globus pallidus lead to performance improvement and decline in this task, respectively (Jahanshahi et al., 2000a). It should also be noted that the left-lateralization in the PFC for the inhibitory aspect of criterion-setting may partially depend on the specific task requirements. In the motor domain, for instance, other studies show that reactive response suppression recruits right inferior prefrontal gyrus and superior medial frontal regions (e.g., Aron et al., 2004; Kenner et al., 2010; Ridderinkhof, Forstmann, Wylie, Burle, & van den Wildenberg, 2010).

Another test which requires criterion-setting is the task-switching paradigm, in which the phasic activation of an appropriate rule has to be accompanied by the suppression of another one, which was recently activated but no longer applicable. Neuroimaging evidence shows that switching task-sets in a context-dependent manner recruits the left DLPFC (Garavan, Ross, Murphy, Roche, & Stein, 2002; MacDonald, Cohen, Stenger, & Carter, 2000) and the left inferior frontal junction (Brass & von Cramon, 2004), especially to resolve switching-related conceptual interference (Badre & Wagner, 2006). In an elegant fMRI study, Kim and co-workers (Kim et al., 2011; also see Kim, Cilles, Johnson, & Gold, 2011) found that stimulus-, response- and set-switch commonly activate two regions in the left hemisphere: inferior frontal junction and posterior parietal cortex, although each type of switching also activated distinct clusters within and outside these regions. On the other hand, task-switching per se is not necessarily associated with right prefrontal activations (Brass et al., 2004; Hedden & Gabrieli, 2010).

The left PFC involvement in task-switching is causal in nature, as demonstrated by the fact that patients with lesions involving this region are impaired in this paradigm (Mecklinger, von Cramon, Springer, & Matthes-von Cramon, 1999; Rogers et al., 1998; Stablum, Leonardi, Mazzoldi, Umiltá, & Morra, 1994; but see Aron et al., 2004; Kenner et al., 2010; for evidence of a role of the right inferior frontal gyrus). Using a task-switching paradigm, Shallice and colleagues (Shallice, Stuss, Alexander, Picton, & Derkzen, 2008) showed that left lateral prefrontal patients made more errors than both controls and other prefrontal patients in the first phase of a condition with a short (200 ms) interval between cue and target (cf. Aron, et al., 2004).

Thus, the performance deficits shown by patients with left lateral prefrontal damage are mostly evident during early phases of task acquisition (Alexander, Stuss, Shallice, Picton, & Gillingham, 2005; Shallice et al., 2008). Mirroring the neuropsychological literature, neuroimaging evidence also shows that activation in this region, sometimes together with that in ACC, diminishes with practice in a variety of tasks (Bunge, 2004; Fletcher et al., 2000; Jueptner et al., 1997; Raichle et al., 1994; Toni, Ramnani, Josephs, Ashburner, & Passingham, 2001; Vallesi, McIntosh, Alexander, & Stuss, 2009b; Wolfensteller & von Cramon, 2010).

Focusing more on the temporal aspect, some neuroimaging studies demonstrate that phasically switching between different tasks (local switching) is accompanied by activation in left prefrontal and parietal regions, while right prefrontal and ACC regions show sustained activation during mixed vs. pure blocks, but are not specifically associated with local switching (Braver, Reynolds, & Donaldson, 2003; Wang, Kuhl, Chen, & Dong, 2009). This evidence is compatible with the view that the left prefrontal criterion-setting process acts in a phasic manner, while right prefrontal monitoring has a long-lasting time-course.

Most of the criterion-setting tasks reviewed so far strongly rely on verbal processing. For instance, the left-lateralized areas most critically involved in task-switching are those which are also related to language processing (Mecklinger et al., 1999). Moreover, there is some indication that learning-related activation of the left PFC may depend on the verbal components of a task (Petersen, van Mier, Fiez, & Raichle, 1998). Additionally, there are domain-dependent exceptions in the literature to the rule that criterion-setting is left-lateralized in PFC. For instance, although suppressing prepotent but task-irrelevant operations is left-lateralized with the verbal Stroop task (e.g., Floden et al., 2011; MacDonald et al., 2000), a right prefrontal lateralization has been often observed for suppressing non-target items in spatial Stroop-like tasks such as the Eriksen's flanker task (e.g., Hazeltine, Poldrack, & Gabrieli, 2000). However, the issue concerning which factor, domain or process, is critical in driving PFC lateralization is still not settled. A neuropsychological study (Alexander et al., 2005), for instance, showed an impaired learning specific to left lateral frontal lesions (BA 44, 45, 47/12) in a purely visuo-motor 5-choice RT task, demonstrating that left-prefrontal criterion-setting is, in certain instances, independent of the verbal requirements of the task.

Similar evidence of left-lateralization of criterion-setting in prefrontal cortex independently of verbal-requirement was found in another recent fMRI study of ours (Vallesi, McIntosh, Crescentini, & Stuss, in press). In that study, participants were required to flexibly stress either speed or accuracy during perceptual decision-making. The task was to decide whether the predominant color of a dichromatic box was green or orange. An initial cue instructed participants to make either a fast or an accurate decision on the subsequent colored box. Initial cue-related fMRI activations included the right cerebellum and the left middle frontal gyrus selectively when switching from speed to accuracy. Consistent with its role in criterion-setting, activation in the latter region during early phases (cue-related) of switch-to-accuracy trials was positively correlated with the adoption of stricter response criteria as computed with a diffusion model analysis (e.g., Spaniol, Voss, Bowen, & Grady, 2011).

A similar role for left PFC has emerged in reasoning. A neuropsychological study (Langdon & Warrington, 2000) demonstrated that left hemisphere lesions, including frontal but also posterior regions, are associated with deficit in both verbal and spatial abstract reasoning, while right hemisphere lesions only affected the latter. More specifically, neuroimaging evidence shows that left inferior (BA 44) and middle (BA 8/9) frontal gyri are more involved in deduction and induction, respectively (Goel & Dolan, 2004), although in that study also right dorsolateral prefrontal regions were involved. More recent neuropsychological studies, however, show that left lateral prefrontal regions, but not right ones, have a key role in deduction (Reverberi, Shallice, D'Agostini, Skrap, & Bonatti, 2009) and induction (Reverberi, Lavaroni, Gigli, Skrap, & Shallice, 2005). In the related domain of problem solving, the ability to integrate complex relationships among stimuli involves left anterior PFC (Kroger et al., 2002).

The evidence reviewed so far suggests a left prefrontal lateralization in the capacity to momentarily gather novel or weakly associated Stimulus-Response (S-R) representations to fulfill the task demands, and to suppress other potential representations that are not task-relevant (e.g., Buckner, 2003; Nolde, Johnson, & D'Esposito, 1998; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997). However, the left PFC is relevant to form associations not only between stimuli and responses but also between stimuli with each other. In an event-related potential (ERP) study with paired associates memory paradigm (Kim, Vallesi, Picton, & Tulving, 2009), during an encoding phase participants were exposed to pairs of words subsequently presented one after the other that had to be remembered in a later test. A sustained late positivity, which occurred between 1 and 1.6 sec after the presentation of the second word, when conceivably the two words had already been semantically processed (N400) and separately encoded (P500), was associated with later successfully recalled paired associates (also see Kounios, Smith, Yang, Bachman, & D'Esposito, 2001). A likely source of this ERP late wave, as shown by a minimum norm source analysis, was spread in the left PFC (Kim et al., 2009). A putative evolutionary function of encoding in episodic memory is to build up a database of associations to be checked when facing novel situations, a function which has been closely linked to criterion-setting (Burgess & Shallice, 1996; Shallice, 2004).

Another critical question is whether setting the criteria for suppressing the inappropriate responses without selecting an alternative response is a necessary and sufficient condition to engage the left PFC. In a recent study (Vallesi et al., 2009b), we tested this hypothesis by using a go/nogo version of a paradigm sensitive to left prefrontal lesions (Alexander, Stuss, Picton, Shallice, & Gillingham, 2007). In our task (Vallesi et al., 2009b), combinations of letters and colors defined go stimuli (e.g., ‘red O’ and ‘blue X’; 50%) and two categories of nogo stimuli, matched for frequency of occurrence (25% each). The high-conflict nogo stimuli were given by feature combinations that were complementary to those defining go stimuli (e.g., ‘blue O’ and ‘red X’), while the low-conflict nogo stimuli were defined as colored numbers. The task was divided into early and late phases. A multivariate Partial Least Square analysis of the neuroimaging data showed, among other results, a cohesive network, mainly left-lateralized, which was functionally connected to a seed in the left ventrolateral PFC. This network was maximally activated in the condition in which task-setting was mostly required: the high-conflict nogo trials administered in early phases.

Energization

Evaluating the energy- and effort-related demands during task performance involves ACC (Boksem & Tops, 2008; Walton, Bannerman, Alterescu, & Rushworth, 2003). Given its rich connections with dorsal sensorimotor striatum (Kunishio & Haber, 1994), motor circuitry (Devinsky, Morrell, & Vogt, 1995; Dum & Strick, 1991) and arousal-related midline thalamic nuclei (Van der Werf, Witter, & Groenewegen, 2002), as revealed in animal work, this region is well-located to play the role of an interface between cognition and motor output by distributing energetic resources to other brain regions involved in the task at hand (Paus, 2001; Shackman et al., 2011).

Superior medial prefrontal areas, including ACC, are engaged not only during novel and difficult conditions (e.g., Raichle et al., 1994), but also during over-learned tasks (Koechlin et al., 2000) and sustained attention (Cohen et al., 1988; see Rushworth, Hadland, Gaffan, & Passingham, 2003, for evidence in monkeys). Moreover, activation in this brain region is often sensitive to time on task (Paus et al., 1997; Vallesi, McIntosh, Shallice, & Stuss, 2009c), above and beyond response conflict or error likelihood (Grinband et al., 2011; cf. Yeung, Cohen, & Botvinick, 2011). This is consistent with the role of ACC in energization of task-relevant processes that may lack resources due to fatigue, tiredness or boredom. Accordingly, task-related activity of the ACC increases following sleep deprivation (Drummond, Brown, Salamat, & Gillin, 2004; Habeck et al., 2004).

In our fMRI study on Speed-Accuracy trade off regulations reviewed above (Vallesi et al., in press), increased time-pressure given by the necessity to maintain speed from one trial to the next recruited the ACC during target-related periods. Another study using oscillatory brain activity confirmed a role of ACC in decision-making under speed instructions, especially in conflicting conditions (Pastotter, Berchtold, & Bauml, in press), compatible with a role in action energization.

A relationship between speed and activation in the ACC has been described with fMRI (Fleck, Daselaar, Dobbins, & Cabeza, 2006), PET (Naito et al., 2000) and ERP (Mulert, Gallinat, Dorn, Herrmann, & Winterer, 2003) studies. Reduced pre-stimulus activity in ACC and right prefrontal regions predicts attentional lapses and response slowing (Weissman, Roberts, Visscher, & Woldorff, 2006). Moreover, patients with damage in this region are selectively impaired in terms of absolute speed, when compared to both controls and other prefrontal patients (Alexander et al., 2005; Shallice et al., 2008; Stuss et al., 1998; 2002; 2005). Lesions of ACC and supplementary motor area, or interruptions of fronto-striatal circuits including these nodes, cause impaired motor initiation, motor neglect, reduced responses to pain and, as a more dramatic example, akinetic mutism, a clinical syndrome characterized by abulia and loss of spontaneous speech and motor activity (Alexander, 2001; Devinsky et al., 1995; Mega & Cohenour, 1997; Nagaratnam, Nagaratnam, Ng, & Diu, 2004; Plum & Posner, 1980; Tengvar, Johansson, & Sorensen, 2004).

In time preparation, patients with superior medial prefrontal lesions, including ACC, when required to prepare a response to a target appearing after fixed time intervals (foreperiods), showed three patterns of abnormal behavior, all compatible with a role of this region in energization: they were generally slower, they showed a disproportional slowing after longer preparatory intervals (6-7 vs. 3-4 sec) and their RTs did not benefit from an alerting warning signal (Stuss et al., 2005).

The energization account is at least partially incompatible with another influential model of cognitive control, mainly inspired by neuroimaging studies, which attributes a key role to the ACC in conflict monitoring and error detection (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Kerns et al., 2004; Milham et al., 2001). On this model, ACC evaluates cognitive conflict and potential errors, and sends signals to lateral PFC for its resolution. Consistent with this view, an electrophysiological marker of these processes (Error-related Negativity, ERN) has a plausible cortical generator in ACC (Dehaene, Posner, & Tucker, 1994). However, this region cannot distinguish between errors and correct responses (i.e., no ERN difference between these two conditions) or implementing online behavioral adjustments according to experienced conflict if lateral PFC is damaged (Gehring & Knight, 2000), suggesting that the latter critically modulates the functionality of ACC (Morishima, Okuda, & Sakai, 2010). Work with monkeys has shown that conflict-induced behavioral adjustments persist after ACC lesions but vanish after DLPFC lesions (Mansouri, Buckley, & Tanaka, 2007). Moreover, while ACC is recruited in children and adults during high-risk (vs. low-risk) decision making, the right ventrolateral PFC, but not ACC, is involved in processing negative feedback, inconsistent with a role of ACC in error monitoring (van Leijenhorst, Crone, & Bunge, 2006).

Replicating many previous neuroimaging studies, we also found an involvement of ACC in the Stroop task (Floden et al., 2011). This region was involved in the same condition as the left DLPFC: incongruent trials presented in an uncued, unblocked context, which did not permit adequate advance preparation to forthcoming conflict. However, activation in ACC was positively correlated with the Stroop interference (but see Melcher, Born, & Gruber, 2011). That is, poorer performers during Stroop interference conditions in our task were those who activated ACC more. Conversely, as reviewed above, the activation in left PFC was negatively correlated with Stroop interference, consistent with its role in criterion-setting. The two regions were anti-correlated across participants, suggesting that ACC was unlikely to directly trigger successful conflict resolution in left DLPFC (cf. Botvinick et al., 2001; Kerns et al., 2004). Similarly, using the Tower of London planning test (Shallice, 1982), it has been shown that the best performers (>70% correct) activated left DLPFC more than the standard performers (<70% correct), while standard performers tended to activate more the ACC (Cazalis et al., 2003). Thus, further studies are required to directly disentangle the energization and conflict monitoring accounts of ACC.

Monitoring

To develop a predictive model of the outside world, one needs to monitor the environmental contingencies, extract prognostic regularities and take care of exceptions (Vallesi, Mapelli, & Cherubini, 2009a). Using another version of the temporal preparation task reviewed above, with foreperiods varying randomly and equiprobably across trials, a different deficit emerged in patients with lesions to the right lateral PFC (Stuss et al., 2005). This group was selectively impaired in the so-called variable foreperiod effect: shorter RTs for longer foreperiods (Bertelson & Boons, 1960; Steinborn & Langner, 2011; Woodrow, 1914). A strategic account has historically been proposed to explain the variable foreperiod effect (see Niemi & Näätänen, 1981; Vallesi, 2010, for reviews). On this account, the conditional probability of stimulus occurrence which increases towards longer FPs is monitored and used to optimize response preparation (e.g., Elithorn & Lawrence, 1955; Näätänen, 1970; but see Los & van den Heuvel, 2001). A critical link between this monitoring process underlying the variable foreperiod effect and the right lateral PFC has more recently been confirmed by converging neuropsychological (Vallesi et al., 2007a; also see Triviño, Correa, Arnedo, & Lupiañez, 2010) and TMS (Vallesi, Shallice, & Walsh, 2007c) evidence. This effect is not present in 4-year old children (Vallesi & Shallice, 2007b), probably because the prefrontal region responsible for it is not yet mature at that age (e.g., Delalle, Evers, Kostovic, & Uylings, 1997; Huttenlocher & Dabholkar, 1997). Moreover, we found in an fMRI study (Vallesi et al., 2009c) that activation in the right, but not left, DLPFC was positively correlated with the size of the FP effect, at least in young adults (see Vallesi, McIntosh, & Stuss, 2009d). The right lateral prefrontal cortex has also been involved in tasks which require explicit monitoring of temporal information, such as time discrimination and reproduction tasks (Basso, Nichelli, Wharton, Peterson, & Grafman, 2003; Coull, Cheng, & Meck, 2011; Coull, Vidal, Nazarian, & Macar, 2004; Jones, Rosenkranz, Rothwell, & Jahanshahi, 2004; Koch, Oliveri, Torriero, & Caltagirone, 2003; Lewis & Miall, 2003; Picton, Stuss, Shallice, Alexander, & Gillingham, 2006).

Monitoring recruits right lateral PFC not only in temporal preparation, as shown in the variable FP task, but also in other domains, such as space. Making predictions in the temporal and spatial domain, indeed, preferentially engages right fronto-parietal regions (Beudel, Renken, Leenders, & de Jong, 2009). We recently conducted an fMRI study (Vallesi & Crescentini, 2011) to further understand what type of spatial contingencies require the monitoring function of right lateral PFC. Participants were required to play the role of ‘traffic agents’ that had to constantly track the behavior of an inattentive driver circling a roundabout. Their task was to press a button when a car hit the crash-barrier. Specifically, the car could follow different types of trajectories with different degrees of regularity and predictability before hitting the crash-barrier. In a regular predictable condition, for instance, the car gradually approached one crash barrier. In another, it followed a zig-zag trajectory. In the latter case, monitoring would be useless, since approaching a crash-barrier was often misleading. Despite matched performance in these two conditions, the right inferior prefrontal and parietal cortices were maximally activated (and functionally connected) during regular predictable trajectories and minimally during random and zig-zag ones. This finding suggests that a right fronto-parietal network is involved in monitoring environmental contingencies that can meaningfully inform expectancy not only in the temporal domain but also in the spatial domain (also see Boulinguez, Ferrois, & Graumer, 2003).

There are many other fields in which a monitoring account may explain the recruitment of right prefrontal regions:

(i) In problem solving, while the left PFC is involved in finding novel solutions, as reviewed above, the right PFC is critically involved in monitoring whether a given rule still holds, since lesions in this region increase the rate of capture errors (Reverberi et al., 2005). Neuroimaging evidence is also consistent with this model (e.g., Turner et al., 2004; Corlett et al., 2004).

(ii) In classical conditioning, recruitment of a right lateralized network, including dorsolateral PFC, has been observed in the extinction phase, as revealed by PET (Hugdahl, 1998). On the tripartite (ROBBIA) model of PFC reviewed here, the recruitment of right dorsolateral PFC in this condition could be interpreted as relevant for monitoring the changes in external contingencies and stimulus-reward associations to control extinction.

(iii) Evaluation of goal values also involves the right DLPFC, as shown with food values (Camus et al., 2009), risk-taking (Knoch et al., 2006), and unfair offers in the ultimatum game (Knoch, Pascual-Leone, Meyer, Treyer, & Fehr, 2006; Sanfey, Rilling, Aronson, Nystrom, & Cohen, 2003).

(iv) Monitoring the idiomatic meaning of a sentence, clearly a linguistic task, critically involves not only the left dorsolateral PFC but also the right homologous region, as revealed with TMS (Rizzo, Sandrini, & Papagno, 2007).

(v) In the neuropsychiatric literature, delusional beliefs have been proposed to emerge as a deficit of two components, one being responsible for the content of the belief and the other for failing to reject this belief. This reality-check component, which is very similar to the monitoring process reviewed here, is associated with pathology of the right lateral PFC (Coltheart, Langdon, & McKay, 2011; also see Signer, 1994). Future research should check whether a right PFC deficit in monitoring could also underlie other productive symptoms in psychiatry, including hallucinations (cf. Hugdahl, 2009).

A monitoring role of right mid-DLPFC has emerged regardless of the task context (e.g., Henson, Shallice, & Dolan, 1999; Petrides, 2000; Stuss et al., 2005; Vallesi et al., 2007c). However, there are rare attempts to test whether, within a single experimental session, the same area within right PFC is involved in monitoring different materials. One is a recent fMRI study on long-term memory retrieval, which showed the same level of activation in the right DLPFC regardless of whether post-retrieval evaluation was applied to semantic or episodic information (Hayama & Rugg, 2009). As another example, an fMRI study by Fleck and colleagues (Fleck et al., 2006) showed an engagement of the right DLPFC (BA 46/10) in low-confidence decisions both in memory retrieval and in a visuo-perceptual discrimination task.

Complementarities between Left and right PFC

While the recruitment of ACC for a given task seems to be independent of the task requirements, such as the precise domain and response modality (Barch et al., 2001), there are some suggestions that the left and right PFC activations may at least partially depend on the domain (e.g., Baker, Frith, Frackowiak, & Dolan, 1996; Courtney et al., 1998). However, as reviewed above, many lines of evidence show that a purely domain-based explanation of the involvement of left and right prefrontal regions does not fully explain the available evidence. Many of the works reviewed so far engage either left or right PFC. I will now review selected studies, drawn from three different fields, in which both regions are engaged with the same test and material but in different aspects of the task. These studies are particularly relevant to determine whether prefrontal lateralization depends on the process or on the domain.

The first example comes from planning. Using the Tower of London task, a recent fMRI study demonstrated a double dissociation between left and right DLPFC (Kaller, Rahm, Spreer, Weiller, & Unterrainer, 2011). In that study, manipulations of goal hierarchy, which required the production of a successful strategy, entailed left PFC. On the other hand, search depth manipulations, which taxed monitoring of different internally generated interdependencies, recruited right PFC. In other studies (Crescentini, Seyed-Allae, Vallesi, & Shallice, in preparation; Newman, Greco, & Lee, 2009), initial planning activates more left anterior and dorsolateral PFC independently of difficulty and working memory demands, while the right DLPFC is activated during the most difficult planning conditions only. Moreover, while left PFC is important both for effortful, gradual search solutions and for abrupt insight solutions, the right PFC is recruited only with the latter (Aziz-Zadeh, Kaplan, & Iacoboni, 2009). Overall, these results suggest that left and right DLPFC are involved in the generation of strategies to solve problems, and in evaluating the appropriateness of more complex strategies or less transparent solutions, respectively (also see Grafman et al., 2005).

The second example concerns inductive reasoning. In a neuropsychological work on this cognitive capacity, Reverberi and colleagues (Reverberi, D'Agostini, Skrap, & Shallice, 2005) used the Brixton test, a spatial version of the Wisconsin Card Sorting Test. In that study, while left frontal patients were impaired in discovering the rules, right frontal ones showed increased capture errors. By using exactly the same material, this study corroborates the critical role of left lateral PFC in hypothesis generation (related to criterion-setting) and that of right DLPFC in monitoring changing contingencies. Importantly, this study, together with other ones (Crescentini et al., 2011; Langdon et al., 2000), shows that left PFC is involved in reasoning not only with verbal tasks but also with spatial ones, compatible with a process-specific and domain-independent role of this region in criterion-setting.

As a third example of studies in which a criterion-setting/monitoring distinction in the prefrontal cortex has emerged using the same material, I will use episodic memory. According to the Hemispheric Encoding/Retrieval Asymmetry (HERA) model (Tulving, Kapur, Craik, Moscovitch, & Houle, 1994), encoding and retrieval differentially involve more left and right prefrontal areas, respectively. Some authors (e.g., Cabeza et al., 2003) argue that this is due to the fact that left PFC is involved in tasks which require semantically-guided generation of information, while right PFC is engaged by tasks which tap monitoring and checking of retrieved information, even in studies using verbal material. This model has received extensive empirical support (e.g., Nyberg et al., 1996; Rossi et al., 2006; Sandrini, Cappa, Rossi, Rossini, & Miniussi, 2003).

However, there are exceptions to the HERA model, at least in its first formulation. First, while verbally-based encoding requires left prefrontal regions (Nyberg et al., 1996; Rugg, Fletcher, Frith, Frackowiak, & Dolan, 1997; Tulving et al., 1994), encoding of non-verbalizable material has produced a more heterogeneous set of results, with a few studies showing that the prefrontal recruitment is left-lateralized (Haxby et al., 1996; Nyberg et al., 1996) or bilateral (Roland & Gulyas, 1995; Schacter et al., 1995), and most works showing a right prefrontal involvement (Epstein, Sekino, Yamaguchi, Kamiya, & Ueno, 2002; Kelley et al., 1998; Klingberg & Roland, 1998; Opitz, Mecklinger, & Friederici, 2000). The latter set of findings is inconsistent with the view that the left PFC plays a completely domain-independent role in criterion-setting and encoding (cf. Habib, Nyberg, & Tulving, 2003). Most of the studies that found a right prefrontal involvement in encoding have used novel, unfamiliar and abstract material (e.g., Golby et al., 2001; Kelley et al., 1998; Sandrini et al., 2003). This raises the question, which further studies should address, whether left-prefrontal activations at encoding are driven by the use of verbal and verbalizable memoranda, or by the need to integrate novel items to pre-existing semantic knowledge. A possibility is that this integration is not achievable by the left DLPFC only with more abstract information which, to be encoded, needs additional or alternative right-lateralized processes.

A second exception to the HERA model is that left prefrontal activations, either alone or together with right frontal ones, have been observed in many studies during retrieval. This left PFC engagement often occurs when retrieval is based on high familiarity confidence (Yonelinas, Otten, Shaw, & Rugg, 2005) and on clear recollection (Cansino, Maquet, Dolan, & Rugg, 2002; Manenti, Cotelli, Calabria, Maioli, & Miniussi, 2010; Mitchell, Johnson, Raye, & Greene, 2004; Nolde et al., 1998; see Rugg, Otten, & Henson, 2002; Yonelinas, 2001, for reviews). However, a lack of involvement of the right lateral PFC under confident and recollection-based retrieval is perfectly consistent with the tripartite model of executive functions (i.e., the ROBBIA model), which would predict an engagement of this region only when evaluation is necessary to double-check the products of retrieval in the absence of confident recollection. Thus, the right DLPFC is more consistently recruited, also with verbal material, when the retrieval relies on familiarity monitoring and evaluation (Schacter, Buckner, Koutstaal, Dale, & Rosen, 1997)**.** A right DLPFC activation has for instance been observed in judgment of frequency tasks, in which contextual recollection probably based on left PFC does not sufficiently fulfill task demands (Dobbins, Simons, & Schacter, 2004), in 'Know' vs. 'Remember' decisions (Henson, Rugg, Shallice, Josephs, & Dolan, 1999), or in confidence judgments (Henson, Rugg, Shallice, & Dolan, 2000; also see Cruse & Wilding, 2011; Vallesi & Shallice, 2006, for ERP evidence).

Open questions for future research

The works reviewed above have already started to uncover which executive functions can be identified, where in the prefrontal cortex and when during task execution. In particular, they provide evidence for a dissociation of at least three key executive functions: criterion-setting, energization and monitoring. However, many looming questions originating from the ROBBIA model of executive functions still need to be answered, including those concerning its generalizability to different domains, as reviewed above. Rather than exhaustively describing all the other possible open issues, I will outline three of them below.

Bilateral prefrontal activations. The tripartite model reviewed here encounters some apparent difficulty in explaining patterns of co-activation among lateral prefrontal regions in both hemispheres and ACC rather than a clear-cut lateralization of functions, as shown in several neuroimaging studies. This bilateral fronto-parietal network is usually recruited during performance in complex and demanding task conditions (e.g., Duncan & Owen, 2000;

Klingberg, O'Sullivan, & Roland, 1997). This network, although extensive, seems to be specific, as revealed by an elegant neuropsychological study (Woolgar et al., 2010), which showed that the volume of lesions of any node within this multiple demand network negatively correlate with the degree of general intelligence, while such a relationship is not observed with lesions outside the network. An over-recruitment of such a bilateral network has been shown to have, in certain circumstances, a compensatory role in normal aging, especially under difficult and novel task-conditions (Cabeza, Anderson, Locantore, & McIntosh, 2002; Park & Reuter-Lorenz, 2009; Vallesi, McIntosh, & Stuss, 2011). A load-sensitive bilateral fronto-parietal network may be required whenever a single hemisphere has reached its capacity limits (Dumontheil, Thompson, & Duncan, 2011) such as when facing complex task demands (e.g., Newman et al., 2009; Crescentini et al., in preparation). Therefore, it is advisable that studies aimed at addressing the functional fractionation of PFC adopt simple experimental designs, to precisely tap a process which may require the engagement of a specific prefrontal region within its capacity-limits. Alternatively, if the task needs to be multi-componential, it should use a ‘scaffolding’ design and be accompanied by a good task analysis to allow that proper contrasts between conditions identify precise cognitive components based on distinct prefrontal nodes (e.g., Badre & D'Esposito, 2007; Stuss et al., 2005).

Advantages of prefrontal asymmetries. Many adaptive advantages may derive from a lateralized brain (Corballis, 2009): greater computational speed and efficiency; parallel processing of information; preventing interhemispheric conflict. Consistent with this view, performance advantages of hemispheric lateralization have been observed in both human species (Corballis, Hattie, & Fletcher, 2008; Crow, Crow, Done, & Leask, 1998; Peters, Reimers, &

Manning, 2006) and non-human ones (e.g., Rogers, Zucca, & Vallortigara, 2004; cf. Dadda, Zandoná, Agrillo, & Bisazza, 2009). These studies, however, have mostly focused on perceptual or motor asymmetries. Therefore, the precise advantages of preserving the left-middle-right prefrontal division among the three executive functions reviewed in this address still need to be discovered. Studies of individual differences, which correlate the magnitude and direction of prefrontal lateralization with performance on tasks tapping the three executive processes detailed here, would be very useful for that purpose.

Origins of prefrontal asymmetries. Another open question is how hemispheric asymmetries develop in general, and how these mechanisms may apply to the executive functions reviewed in the present address. The two hemispheres have different developmental trajectories not only in young infants (Chiron et al., 1997), but already during the course of fetal development (e.g., Domellof, Johansson, & Ronnqvist, 2011). This happens for a variety of genetic and circumstantial reasons which are not yet fully understood (Hellige, 1993; Previc, 1991). In particular, certain areas of the right hemisphere mature more quickly than the homologous areas of the left hemisphere (Geschwind & Miller, 2001), a pattern that is reversed in the peri-natal period (e.g., Gupta et al., 2005). Functional dissociations accompany these anatomical asymmetries (e.g., Mento, Suppiej, Altoe, & Bisiacchi, 2010). Thus, the right hemisphere is on average more developed than the left one at the time when the fetal brain is exposed to stimuli with a low spatial and temporal frequency, also due to the immaturity of the perceptual system. The left hemisphere consequently starts developing later on, when the capacity limits are less constrained, and therefore it takes control over faster processes and higher-frequency stimulus ranges, such as those typical of language (Hellige, 1993; Turkewitz G., 1988). This scenario, although clearly speculative, fits well with the executive function model detailed in this address, by assuming that right PFC becomes specialized for a monitoring process with long-lasting and continuous time-course, while left prefrontal regions occupy the niche left available by the right homologous regions and specializes in a more phasic and flexible criterion-setting process. Future developmental work should try to corroborate this scenario, also taking into consideration that hemispheric asymmetries in general, and prefrontal asymmetries in particular, may show high intra- and inter-individual variability, and may emerge from partially independent probabilistic biases (e.g., Whitehouse & Bishop, 2009).

Conclusion

In summary, in this address I marshaled empirical evidence which helps characterize three essential executive functions: (i) criterion-setting, a process required to set-up and flexibly select non-routine task rules; (ii) energization, which is necessary to boost their implementation, and (iii) monitoring, the ability to check that ongoing processes are consistent with the current goals. These functions, albeit interacting, can be distinguished based on their *modus operandi*, which entails different computational properties, distinct temporal profiles and dissociable anatomical substrates in the prefrontal cortex and related networks.

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