

Working memory and executive function: evidence from neuroimaging

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Traditional theories of working memory and executive function, when mapped in straightforward ways into the neural domain, yield predictions that are only partly supported by the recent neuroimaging studies. Neuroimaging studies suggest that some constituent functions, such as maintaining information in active form and manipulating it, are not discretely localized in prefrontal regions. Some hypothesized executive processes, such as goal management, have effects in several cortical regions, including posterior regions. Such results suggest a more dynamic and distributed view of the cortical organization of working memory and executive functions.

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Abbreviations

BA	Brodman's area
DLPFC	dorsolateral PFC
fMRI	functional magnetic resonance imaging
PET	positron emission tomography
PFC	prefrontal cortex
SPECT	single photon emission computed tomography

Introduction

Executive processes and working memory have proven to be a fruitful test bed for neuroimaging studies of cognition. Executive processes are implicated in complex cognition, such as novel problem solving, which entails identifying and coordinating the steps to a new goal, evaluating the intermediate outcome, and modifying the plan as needed. Executive processes are also associated with task-set control, modifying behavior as appropriate in light of changes in the environment, such as inhibiting prepotent or previous responses. Executive processes are also associated with the functions that are impaired as a consequence of frontal lesions, particularly those related to the implementation of schemas that organize behavior over time [1,2]. Working memory has been operationalized primarily as the processes and structures that keep information available over a relatively short time, such as postulated verbal and spatial peripheral buffers [3,4]. In this standard perspective, executive processes manipulate the contents of the working memory buffers.

In the first part of this article, we describe how recent advances in functional neuroimaging have been framed in light of some classic questions about the organization of working memory and executive processes. In the second part, we examine how these same neuroimaging results

suggest that the classic questions might be reconstrued, and then suggest some possible implications of these alternative hypotheses.

Classic issues

Perhaps the major theoretical issue concerning executive processes is whether discrete regions (modules) of the prefrontal cortex (PFC) are dedicated to particular operations and, if so, the characterization of those processes, including their domain specificity [5]. For example, Owen, Petrides and their colleagues [6,7] proposed that the mid-ventrolateral region (Brodman's area [BA] 45/47) supports the organization of response sequences based on information retrieved from posterior areas, whereas the mid-dorsolateral region (BA 9/46) supports the active manipulation or monitoring of information within working memory. Another proposal by Goldman-Rakic [8] is that PFC is organized by processing domain into object, spatial position, and verbal PFC regions.

Another issue concerns the relation between the computations of the prefrontal regions and those of more posterior regions in working-memory functions. For example, Goldman-Rakic [8] proposed that, in working memory tasks, the PFC regions operate conjointly with posterior regions as multi-modal domain-specific networks. The hypothesis that working-memory functions are accomplished by large-scale networks overlaps with other theoretical proposals, including Mesulam's framework [9]. Although the temporal relations among these various components may be critically important [10], they are only beginning to be addressed by neuroimaging studies [11].

A third issue is how to conceptualize the capacity constraints of working memory — a topic that was framed by Miller's classic chunking hypothesis [12]. When working memory is equated with information maintenance, constraints can be conceptualized as temporal. When the task is more complex, such as problem solving, these constraints may be conceptualized as limits in the complexity of the computations or representations [13,14]. For example, one proposal is that immediate thought varies in the amount of concurrent processing demand relative to a system's resources, and that constraints emerge from system throughput [15].

Neuroimaging results

The localization of working memory versus executive processing [6,7] was addressed in a meta-analysis of several positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies of verbal and spatial n-back tasks [16,17]. In an n-back task, sequentially presented items (letters, spatial positions, or

patterns) are evaluated for their identity to an element that was presented n items previously. So, the task requires encoding, temporary maintenance and rehearsal, tracking of serial order, updating, and comparison and response processes. Smith and Jonides [16•] found that baseline, verbal identification tasks activated a left-lateralized network that included posterior parietal (BA 40), Broca's (BA 44), and supplementary motor and premotor areas (BA 6), the latter three of which were interpreted as supporting verbal rehearsal, and the network as supporting verbal storage. Also, the two- and three-back verbal tasks showed clusters of activation in the dorsolateral PFC (DLPFC), which were interpreted as reflecting the additional executive processes. When Smith and Jonides [16•] compared the results of n -back tasks of spatial position versus visual pattern, the pattern of results supported previous single cell research by indicating more parietal activation for spatial position versus more inferior temporal activation for patterns [18]. Smith and Jonides suggested a reconciliation of the Petrides/Owen and Goldman-Rakic views: domain specificity is reflected in the lateralization of activation (language is left- and spatial position is right-lateralized), and the manipulation of verbal information, as compared to simple storage, results in additional DLPFC activation. Although the data generally support the main point of their proposal, some aspects of the data complicate the model in which the addition of executive processes simply adds to activation in the DLPFC. First, as the authors recognize, the left-lateralized network for language versus spatial processing is only one of degree; there are right hemisphere foci for language and vice versa [17•]. Also, the two- and three-back tasks yield additional activation not only in prefrontal areas but also in other, more posterior cortical sites. The complexity that cautions against any simple mapping of function to location arises not just in these meta-analyses [16•,17•], but also in recent neuroimaging studies that directly address the localization question.

A recent event-related fMRI experiment contrasted the prefrontal regions hypothesized to be differentially associated with working-memory maintenance versus manipulation, using a letter-span task [19•]. After five letters were presented, the participant was either to remember them in the presented order or alphabetize them (manipulation) during an 8 s interval. As predicted, DLPFC was activated during letter manipulation; however, both the DLPFC and ventrolateral PFC were activated (but to different degrees) during both maintenance and manipulation, showing that there was no simple mapping between process and region.

Executive processing also has been studied in problem-solving tasks, such as the Tower of London task, in which performance is particularly impaired following frontal-lobe lesions. Recent PET and single photon emission computed tomography (SPECT) studies found activation in the prefrontal cortices [20–22] that increased with the number of subgoals needed to solve the problem, along with

activation in the right [20] or bilateral [21] parietal regions. These findings were replicated in a fMRI experiment conducted in our laboratory, with an important addition: the number of subgoals during the problem solving affected activation not only in the prefrontal regions but also in the parietal regions. Such data call into question the implicit hypothesis that executive processes are localized in the prefrontal regions and control lower-level processes in more posterior regions.

Reconstruals suggested by the neuroimaging data

Collaboration and redundancy

The prevailing account is still that each identifiable function is localized to a single cortical area. However, an alternative framework is emerging. One postulate of this new view is that each association cortical region has more than one function, and that the functions of distinct areas might overlap each other. The nondiscreteness of specialization is consistent with results of the various meta-analyses of neuroimaging studies of executive processes described above; moreover, this alternative hypothesis may not be restricted to executive and working-memory processes but may be a general principle of cortical organization. The same conclusion emerges from a recent fMRI study of object recognition [23•]. Although three distinct areas (in ventral temporal cortex) were activated preferentially in response to three different types of stimuli (faces, buildings, and letters), each area also responded to its two nonpreferred categories, at a lower level of intensity. This finding indicates that the representation of each of the categories is distributed over several areas, and each area contributes to the representation of several categories. One possible interpretation of the result is that the multiple activated areas perform different functions but closely collaborate in a distributed processing system, and their co-activation (albeit to different degrees) reflects processes unique to each area. Alternatively, there also may be some redundancy of function across the activated areas. In either case, the emerging view suggests that cognitive processes emerge from networks that span multiple cortical sites with closely collaborative and overlapping functions [8,9].

The concept of distributed large-scale networks is also consistent with single cell recording studies that find cells in multiple regions (such as prefrontal and parietal regions) with similar response profiles [24,25]. An important additional claim from the neuroimaging research is that there can be differential participation of component regions as a function of the computational load [26,27•].

The concept of cognitive processes as emerging from large-scale distributed networks is also engendering new research approaches. One new technique is the search for fine-scale temporal co-variation in the functional activation across cortical and subcortical regions, an analysis that is interpreted in terms of functional connectivity [28,29].

Another new approach is the use of computational modeling to account for the characteristics of large-scale, distributed networks as revealed by neuroimaging [30,31].

Overlap in functions across cortical regions

If small cortical regions may participate in more than one function, then there may be some overlap between entire large-scale networks subserving different processes. This hypothesis is consistent with an fMRI study that contrasted visual versus linguistic strategies for representing concrete sentences; the patterns of activation suggested overlapping (rather than dissociated) networks, in which different regions made differential contributions to the two strategies [32••]. To the extent that cognitive strategies can be thought of as being executive functions, this study also supports the hypothesis that areas outside of the prefrontal cortex (e.g. left superior temporal gyrus) contribute to 'executive' functions. An overlap of large-scale networks that subserve different processes was also found in a neuroimaging study that contrasted the use of spatial cues versus temporal cues in visual detection [33]. The two types of cue activated overlapping networks in the prefrontal regions (including DLPFC and the ventrolateral PFC), but the parietal activation was lateralized depending on the cue type, with more left-lateralized activation for temporal cues and more right-lateralized activation for spatial cues.

Computational quantity and quality

Another finding is that the degree and location of the activation of a given brain area is dynamically determined by the precise quality and quantity of the computational load carried by the area. Graded studies quantitatively manipulate the computational load imposed during a task, to examine the dose–response relation of load to the activation volume and intensity. For example, in n-back tasks, the amount of activation in DLPFC increases with n [34]. In an event-related fMRI study of sentence comprehension, the time-locked activation increased more rapidly for the more difficult (negative) than easier (affirmative) sentences in a network of areas, precluding the possibility that the greater activation for more difficult computations reflects differential processing time [35]. Thus, the mapping of process to cortical location depends in part on the computational load, not only with executive and working memory processes, but also in sentence comprehension [26] and mental rotation [36].

Capacity limits

Another important result is that there is a limit to the workload that a system or its parts can bear. In an n-back task, the amount of activation in the left DLPFC increased with n up to two items, and then decreased, reflecting the behavioral and concomitant neural inflection point at the upper limit of performance [37]. Other cortical regions showed monotonic relations between n and activation volume, arguing against such effects being attributable to global effortful attention. Moreover, as Callicott *et al.* [37]

note, the behavioral constraint may arise not from the limit of a single key region (such as DLPFC) but may be a network phenomenon.

Conclusions

One implication of recent neuroimaging studies is that there is no one-to-one mapping of process to cortical region, which must modify the goal of determining the cortical mosaic. Considerable research progress has been made in cognitive neuroscience and cognitive science by considering systems, such as those constituting executive processes and working-memory processes, as nearly dissociable; but it increasingly appears to be time to examine their interaction. More importantly, the emerging view raises a new question: what mechanisms determine the relative allocation of functions to regions? We have already cited evidence that such a dynamic allocation occurs over the short-term in tasks that vary in demand. Over the longer term, neuroimaging studies of stroke recovery and rehabilitation suggest an increasing ability to recruit regions that are contralateral or adjacent to the lesioned area. An fMRI study of two adult patients (one with a left frontal and one with a left temporal lesion) performing a sentence comprehension task at intervals after their strokes ranging from days to several months, showed increasing recruitment of the region contralateral to the stroke-induced lesion that correlated with spontaneous language improvement [38•,39]. Developmental data also suggest a more dynamic view of cortical recruitment. For example, an fMRI study of the language processing of children who had suffered left hemisphere brain injuries found extensive right temporal activation [40]. Other data show that following brain damage, there is recruitment in contralateral and neighboring regions to different degrees depending on factors that include age and neurological status [41], as well as task properties. Although we have focussed on neuroimaging of high-level processes, a more dynamic and distributed view of cortical processing is also emerging from electrophysiological research on sensory and motor systems as well [42,43].

Finally, the emerging view suggests that we reconsider the implicit assumption that there is a fixed, relatively small number of cortical networks to be mapped. Instead, multiple brain regions might combine with each other in vast number of ways, depending on the task requirements and, more generally, on the types of cognitive skills that a person within a culture develops. Whether it be the more arbitrary demands of a n-back task or the less arbitrary demands of solving algebra equations, we can expect that an appropriate network has been configured, whose constituency may well be of interest. Also of interest are the general mechanisms and principles by which the networks come to be configured and refined. In this view, the variety and generativity of human cognition, like the variation observed in other complex adaptive systems, arises from the combinatorics of simpler elements. Thus, a challenge for future research will be to characterize not

only the simpler elements, but also the mechanisms underlying the combinatorics, and the nature of the resulting networks.

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