Executive functions and their disorders

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The term executive function defines complex cognitive processing requiring the co-ordination of several subprocesses to achieve a particular goal. Neuropsychological evidence suggests that executive processing is intimately connected with the intact function of the frontal cortices. Executive dysfunction has been associated with a range of disorders, and is generally attributed to structural or functional frontal pathology. Neuroimaging, with PET and fMRI, has confirmed the relationship; however, attempts to link specific aspects of executive functioning to discrete prefrontal foci have been inconclusive. Instead, the emerging view suggests that executive function is mediated by dynamic and flexible networks, that can be characterised using functional integration and effective connectivity analyses. This view is compatible with the clinical presentation of executive dysfunction associated with a range of pathologies, and also with evidence that recovery of executive function can occur after traumatic brain injury, perhaps due to functional reorganisation within executive networks.

The term 'executive function' is used as an umbrella for various complex cognitive processes and sub-processes. Most attempts to define executive function resort to a list of examples (such as task-switching, planning, or that other useful umbrella term 'working memory'), which reflects the fact that executive function is by no means a unitary concept. The neuropsychological literature converges on the view that successful performance on tests of executive function is critically dependent on the frontal cortex; indeed the terms 'executive function' and 'frontal lobe function' are often used synonymously. However, recent theories have suggested that this view is simplistic and subcortical regions may also be critically involved. Neuropsychological deficits of patients with Parkinson's disease, for example, suggest that striatal structures play a role in the mediation of executive processes.

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Advances in neuroimaging have provided the tools for assessing directly the neuronal basis of executive functions. Perhaps unsurprisingly, it appears that these complex processes are subsumed by distributed circuitry rather than discrete structures. A key advantage of the neuroimaging approach is that it has allowed a degree of localisation of different executive components within prefrontal regions, and the simple 'equivalence' of

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frontal lobe function and executive processing has, therefore, undergone a much more sophisticated dissection. Executive functions are compromised in an array of clinical disorders; patients with various neurological and psychiatric complaints, as well as those with trauma to the frontal lobes, exhibit executive deficits. Neuroimaging provides a means for exploring these deficits, as well as developing an understanding of recovery of executive function frequently seen in patients suffering traumatic brain injury or stroke. This chapter considers the nature of executive functions and how neuroimaging techniques have advanced our understanding of these processes, as well as how they are compromised.

Defining 'executive function'

Unlike other cognitive domains (such as memory or attention), there is no intuitive lay concept that incorporates the essence of executive function; therefore, any account of these processes must begin with definitions. Executive functions are those involved in complex cognitions, such as solving novel problems, modifying behaviour in the light of new information, generating strategies or sequencing complex actions. In a recent review, Funahashi[1] summarised executive function as 'a product of the co-ordinated operation of various processes to accomplish a particular goal in a flexible manner'. This flexible co-ordination of sub-processes to achieve a specific goal is the responsibility of executive control systems. When these systems break down, behaviour becomes poorly controlled, disjointed and disinhibited. Co-ordination, control and goal-orientation are, therefore, at the heart of the concept of executive function.

Executive functions and the prefrontal cortex

Patients with damage to the prefrontal cortex show impaired judgement, organisation, planning and decision-making[2], as well as behavioural disinhibition and impaired intellectual abilities[3]. In a laboratory setting, patients are impaired on tests such as set-shifting[4], planning[5], and various fluency tasks[6]. These impairments all point to a breakdown of co-ordination processes. Patients are relatively unimpaired on tests focusing on a particular function, but when a number of different functions must be co-ordinated in the laboratory or real-life, deficits are clearly observed. These observations led to the influential conclusion that executive functions are the province of the prefrontal cortex, and indeed 'executive function' and 'frontal lobe function' became almost interchangeable terms.'

Beyond the prefrontal cortex

A seminal paper by Alexander *et al*[7] proposed that a crucial organising principle of the brain is corticostriatal circuitry, intimately linking regions of the frontal cortex to striatal structures, via the thalamus and globus pallidus. This model suggests a functional, as well as anatomical, connectivity between frontal cortex and striatum. Divac *et al*[8] showed that lesions to the caudate nucleus in animals resulted in deficits that resemble those following prefrontal ablation. Evidence that striatal structures are also important in human executive functions comes from neuropsychological studies of neurological disorders. Patients with multiple systems atrophy, progressive supranuclear palsy and Huntington's disease[9,10] show significant deficits in executive function, but by far the most widely studied basal ganglia disorder is Parkinson's disease. Numerous neuropsychological studies have shown that Parkinson's disease is characterised by executive impairments[11,12], which are evident early in the course of the disorder when pathology is confined to basal ganglia regions, and are seen in patients who are unmedicated. Executive function deficits, therefore, appear to be a genuine concomitant of basal ganglia damage. This has led to the suggestion that executive function depends not on the prefrontal cortex in isolation, but on the intact functioning of corticostriatal circuitry mediated by dopaminergic neurotransmission.

Other disorders of executive function

Frontal lobe lesions and basal ganglia disorders are not the only pathologies to be related to executive dysfunction. Patients with frontal dementia and with Alzheimer's disease also exhibit executive deficits, as do patients with the AIDS-dementia complex. There is also evidence that patients with subcortical ischaemic vascular disease[13] show selective deficits on tests of executive function. Furthermore, executive deficits are common in patients with various psychiatric disorders, including depression[14,15] and schizophrenia[16,17]; both disorders are characterised by a wide range of deficits, but there is a strong argument that executive function is particularly compromised. In all these disorders, the executive deficits are attributed to either frontal lobe damage or dysfunction, or to disruption in fronto-subcortical connectivity.

Neuroimaging of executive functions

The neuropsychological literature, reviewed (very) briefly above, clearly implicates the prefrontal cortex as a key determinant of executive function.

However, executive function is not a unitary concept and the prefrontal cortex is a heterogeneous neuro-anatomical region[18]. It, therefore, seems intuitively plausible that different regions of the prefrontal cortex may mediate different aspects of executive function. Other important questions are the extent to which prefrontal regions may recruit posterior cortical and subcortical regions during executive functioning, and how the essential flexibility of executive control is achieved at a neuronal level. Neither the animal nor the human neuropsychological literature have provided compelling evidence on these issues, (see Roberts *et al*[19] for discussion). Advances in functional neuroimaging have provided the tools to assess prefrontal mediation of executive functions in more detail.

Functional specialisation within the prefrontal cortex

The issues of whether different regions of the prefrontal cortex are specialised for different aspects of executive function, and, more controversially, how that specialisation may be characterised, are central to gaining a better understanding of executive processing through neuroimaging.

Lateral frontal cortex and working memory

An influential hypothesis distinguishing different prefrontal regions in functional terms is the theory that dorsolateral and ventrolateral prefrontal regions fulfil different functions[20,21]. This is a hierarchical 2-stage model of prefrontal contribution to working memory. The ventrolateral prefrontal region (VLPFC) is proposed to control the retrieval of representations from posterior cortex and, according to some[22], the on-line maintenance of these accessed representations. The dorsolateral region (DLPFC) is then proposed to mediate the monitoring and manipulation of the representations maintained in VLPFC. There are numerous studies lending support to this theory. For example, Rowe *et al*[23] found that maintenance of spatial representations was associated with very little activation of DLPFC, whereas selecting between different representations produced significant DLPFC activity. Similarly, Wagner *et al*[24] reported that rote rehearsal in working memory preferentially activated VLPFC, while elaborative rehearsal preferentially activated DLPFC. Furthermore, their event-related design allowed them to demonstrate a significant temporal difference between VLPFC and DLPFC responses. The DLPFC response systematically lagged behind the VLPFC response, consistent with a hierarchical model.

However, not all evidence supports the simple separation between DLPFC and VLPFC function. Several studies have reported similar patterns of response in DLPFC and VLPFC during maintenance rehearsal[25]. In a

neuropsychological study, Petrides[26] found that selective damage to DLPFC did not disrupt maintenance at a low load (relatively few items to be remembered), but as the load increased, impairments became apparent. It thus appears that DLPFC may play some role in maintenance in working memory, at least at high loads. The debate continues, with some authors arguing that the effects of increasing load in DLPFC actually reflect increased monitoring when stimuli are encoded[26], while others[24] are content to allow for a limited role of DLPFC in maintenance *per se*.

Clustering of frontal activations in executive function

Whether or not DLPFC and VLPFC play dissociable roles in working memory function, it is clear that these regions are also involved in other aspects of executive function. In a recent meta-analysis, Duncan and Owen[28] considered the pattern of activation observed in studies chosen to reflect a wide range of different tasks. Their initial analysis considered studies of auditory discrimination, divided visual attention, motor initiation, task-switching, planning and semantic processing. In spite of the diversity of task demands, there was a striking clustering of the activations observed in these studies. Specifically, three main clusters were distinguished; dorsal anterior cingulate, a region dubbed 'mid-dorsolateral' and a 'mid-ventrolateral' region.

The initial analysis was followed by a more systematic assessment of studies which had manipulated a particular cognitive demand: response conflict, task novelty, working memory load, memory delay or perceptual difficulty. For each of these demands, five or more studies had assessed the effects of manipulating that demand. Once again, the clustering was striking, with the same three areas involved in all five types of manipulation. The authors concluded that a common network, involving these three regions, is recruited by diverse cognitive demands. However, they did not rule out the possibility that there may be finer specialisations within this network. One possibility is that there is fine specialisation within each region at a level that cannot be resolved by functional imaging, particularly in group studies where the necessary normalisation and smoothing of raw images reduce the anatomical resolution. An alternative, and not mutually exclusive, possibility is that specialisation within these regions is a matter of degree, such that although a broad network is activated by different tasks, the relative magnitude of activations within each region may be task-dependent. Finally, it is possible that the three regions **do** subserve different functions, but that these functions are sufficiently abstract to be involved in many different complex cognitive tasks. The evidence discussed above, that DLPFC and VLPFC may play differential roles in working memory, would support this final suggestion. Evidence from

studies using N-back (see below) and reverse span tasks[20,22] also point to a selective enhancement of DLPFC activity (but not VLPFC or dorsal cingulate activity) when subjects must undertake re-organisation of material in working memory. Again this supports the suggestion that there is at least some degree of functional segregation among these three prefrontal regions.

Specialisation for material rather than function

A different approach to the issue of prefrontal specialisation focuses on whether different regions are recruited depending on the nature of the material being processed in a particular task[29]. Specifically, it is argued that prefrontal cortex is organised into verbal, spatial and object-processing regions. This theory has been addressed in detail by two recent meta-analyses of N-back tasks. In these tasks, subjects are presented with a series of stimuli, one at a time, and are required to report whether the present stimulus is the same as one several stimuli before (2 stimuli before in a 2–back task, 3 before in a 3-back, and so on). The nature of the stimuli can be varied, as can the working memory load (the higher 'N', the harder the task). These tasks are classic executive function tests in that they require subjects to monitor stimulus input and flexibly up-date information in working memory to generate appropriate responses. In their meta-analysis, Smith and Jonides[30] reported that increasing the demands of N-back tasks was associated with increasing DLPFC activity, and that verbal compared to spatial N-back tasks recruited more left-sided compared to right-sided regions. The authors suggested that these data could be interpreted as supporting both domain specificity **and** functional specificity models, with domain specificity reflected by laterality of response and functional specificity reflected by the VLPFC/DLPFC dissociation, as proposed by the hierarchical Petrides/Owen theory. However, another meta-analysis of N-back tasks by D'Esposito *et al*[22] suggested that such distinctions may be too simplistic. They found that any domain-specificity was more a matter of degree than a complete dissociation. Also, they stressed that posterior cortical areas, as well as prefrontal regions, were selectively recruited by increasing cognitive demands. As with the functional specialisation debate, it appears that the concept of domain specificity is more complex than it first appeared.

Distributed networks and functional integration

The neuroimaging literature reviewed above is starting to suggest that a new approach may be needed to understand prefrontal mediation of executive function[31]. Various meta-analyses, including those discussed here, lead to an emerging view that executive processes are mediated by networks incorporating multiple cortical regions (posterior as well as

prefrontal regions) with collaborative and overlapping functions[29,32]. A key contribution of functional neuroimaging is the demonstration that the component regions may be differentially engaged depending on the cognitive load[33]. This view represents a major conceptual shift, and significantly increases the challenge to functional imaging. Instead of a relatively straightforward exercise in one-to-one mapping of structure to function, this view necessitates an understanding of how multiple brain regions may be flexibly combined with each other. These combinations may depend not only on task requirements but also on individual skills and experience.

Many early functional imaging studies of cognition focused on the functional segregation approach of mapping individual functions to discrete regions. If executive function is to be better understood by a flexible, collaborative and overlapping network model, this will involve a paradigm shift towards a functional integration approach. Structural equation modelling and effective connectivity analysis can be used to assess the dynamic changes in functional interactions between regions of a network depending on the cognitive demands[34]. McIntosh *et al*[35] used a working memory task with variable delays and showed that the strength of the top-down connection between prefrontal cortex and temporal and occipital areas increased as the delay, and therefore cognitive load, increased. Top-down, condition-specific modulation of visual processing by the prefrontal cortex has also been demonstrated[36], suggesting that flexible interactions between prefrontal and posterior regions may influence perception as well as cognition. Other studies have reported dynamic task-dependent changes in functional interaction between prefrontal regions dependent on task demands[37]. In a recent review, Funahashi[1] presents converging evidence from single unit recording studies in animals and functional imaging studies using the effective connectivity approach, and suggests that understanding the dynamic and flexible modulation of neuronal interactions is the key to understanding how the brain exerts executive control.

Neuroimaging of executive dysfunction

As discussed above, executive dysfunction is associated with a range of neurological and psychiatric disorders. The ubiquity of executive impairments, often in the absence of structural damage to the prefrontal cortex, is intuitively consistent with the network view of executive function. A dynamic and flexible neuronal network could be compromised in many different ways, and to different extents. It could also, potentially, prove more robust in the face of traumatic insult than a fixed one-to-one mapping between structure and function.

Executive dysfunction mediated by impaired connectivity?

The executive dysfunctions associated with basal ganglia disorders provide neuropsychological evidence that frontostriatal circuitry, rather than discrete prefrontal regions, may be important in mediating executive function. PET studies of patients with Parkinson's disease[38] have shown that two different tests of executive function (planning and spatial working memory) are associated with abnormal function in the globus pallidus. Regional cerebral blood flow in the prefrontal cortex, however, was not significantly different from that seen in controls. The authors argue that striatal dysfunction affects the expression of frontal lobe functions by disrupting transmission through frontostriatal circuitry. More recently, a structural equation modelling approach has been used to look directly at whether Parkinson's disease is associated with disrupted connectivity. Rowe *et al*[39] found that 'attention to action', where subjects had to focus on forthcoming motor responses, was associated with enhanced effective connectivity between prefrontal and premotor regions in normal subjects. This enhanced connectivity was not seen in patients with Parkinson's disease, suggesting a context-specific functional disconnection within cortical networks.

The disorder where executive dysfunction has been most extensively studied using functional imaging is probably schizophrenia. There have been many studies demonstrating hypofrontality associated with executive impairments in schizophrenia, although many of these studies are plagued by confounds[40]. In the absence of a clear focal pathology, theories of disordered connectivity in schizophrenia are particularly appealing[41,42]. Analyses of functional and effective connectivity have clearly demonstrated abnormalities in schizophrenic patients during performance of executive tasks. Fletcher *et al*[43] reported abnormal anterior cingulate modulation of fronto-temporal connectivity during list learning. Prefrontal disconnectivity has also been associated with verbal fluency[44] and working memory[45]. Neuroimaging evidence for impaired connectivity has provided the insights that underpin a new generation of neuropathological and neurodevelopmental theories of schizophrenia[46,47].

Implications for recovery

The dynamic network approach to understanding executive function also has implications for understanding how the brain recovers from trauma. Executive function is frequently compromised as a result of brain injury, but, like language and motor functions, executive functions may recover to at least some extent. Functional imaging provides an exciting tool to study recovery. Both PET and fMRI have been used to demonstrate that there is extensive functional re-organisation following a head injury or stroke[48,49]. Neighbouring or contralateral regions may

be recruited to subserve the original function; the extent to which this occurs is dependent on age, neurological status and exact task demands[50]. The processes of recovery and re-organisation are conceptually more plausible in a dynamic and flexible network model. However, these processes remain poorly understood and are an important challenge for future functional imaging research.

Conclusions and future directions

Executive function is, by definition, complex, and this review has only scratched the surface of the current debates concerning the neuronal basis of executive function and dysfunction. It is clear that although the prefrontal cortex is a vital component of the circuitry subserving executive function, posterior cortical regions and subcortical structures collaborate with prefrontal cortex to mediate successful executive processing.

The advent of functional neuroimaging techniques has provided the means to study the neuronal basis of human executive function directly. Early imaging experiments attempted to dissociate component processes of executive function and attribute them to discrete prefrontal foci. Although there is some evidence for both functional and material specificity in prefrontal cortices, it appears that this is more a matter of degree than reflecting fixed and fundamental dissociations. It is also clear that the same prefrontal regions mediate very different executive functions. An increasingly influential view is, therefore, that we should not be looking for one-to-one mappings between structure and function. Rather, we should be using more sophisticated analysis approaches to study flexible and dynamic changes in effective and functional connectivity between brain regions. This has dramatic implications for our understanding of normal and abnormal executive functions.

From a clinical perspective, a dynamic network approaches is synchronous with the rising trend for disconnection models of neurological and psychiatric disorders. Important challenges for the future will be to gain a more through understanding of these models, and to construct theoretical frameworks for understanding the mechanisms of both disconnection and functional re-organisation.

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