The frontal lobes and the regulation of mental activity

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Results of neuroimaging and neuropsychological studies of frontal lobe function have been interpreted by some as evidence for specialized modules that are localized to distinct regions of frontal cortex, and that differ in both content and process from those in neighboring regions. These descriptions stand in stark contrast to the many domain-general theoretical accounts of the regulatory role of the frontal lobes in cognition. Recent attempts to understand how general regulatory mechanisms might operate across multiple domains (e.g. working memory, sentence comprehension) have been increasingly important in our understanding of the frontal lobes.

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Introduction

Nearly three decades ago, Aleksandr Luria proposed that regions of the prefrontal cortex (PFC) ''are in fact a superstructure above all other parts of the cerebral cortex, so that they perform a far more universal function of general regulation of behavior than that performed by the posterior associative centre'' [1]. In recent years, driven in many cases by neuroimaging data unavailable in Luria's day, some investigators have assigned vastly more specific functions to regions of the PFC. Here, we take up this debate, with a focus on the role of the left, ventrolateral prefrontal cortex (VLPFC) in working memory and language processing. We review some of the domain-specific hypotheses of the functions of the VLPFC, and we suggest an alternative interpretation that enables some unification of function across these different content areas.

In contrast to domain-specific accounts, the ascription of a general, regulatory function to the PFC necessitates an answer to the question: when is such regulation necessary? Certainly, many behaviors can be accomplished without the support of the PFC. A classic example is the ability of patients with PFC damage to learn the first card-sorting rule when sorting a multidimensional deck of cards (Wisconsin Card Sorting Task [2]), despite their inability to switch to a new rule. Botvinick and colleagues [3,4••] argued that regulation will be necessary when one must choose a weakly activated representation over a stronger one (i.e. prepotent response override) or when one must select among several weakly activated representations (i.e. underdetermined responding). In these situations, the PFC might function to regulate behavior by resolving competition among incompatible representations. For example, Desimone and Duncan [5] described top-down signals that bias competitive interactions between mutually inhibitory neurons; we recently extended their model of visual attention to competitive interactions among conceptual representations [6]. Miller and Cohen [7] suggested that, to ''deal with the multitude of possibilities and to curtail confusion'', the PFC sends biasing signals throughout the brain, in the service of a host of processes (e.g. memory retrieval, emotional evaluation, etc.).

Following Miller and Cohen [7], the goal here is to demonstrate how a common language can be applied to several distinct domains. We are not arguing against any form of organization by content; such an organization could emerge from the distinct corticocortical connectivity patterns that are associated with different regions of frontal cortex [8]. Rather, we are arguing that the use of content-specific terminology might obscure similarities between different domains. For example, why should one consider the process of elaborative semantic encoding when studying phonology? How does one relate morphosyntactic processes to the study of working memory? The sociology of science has the tendency to yield overly compartmentalized theories: one only gets the answers to the questions that one asks. Our goal is to highlight potential commonalities in information processing demands across seemingly distinct tasks or domains, in the hopes of informing our understanding not only of frontal cortex but also of the cognitive systems that it supports.

Regulation and working memory

We begin by considering a topic that has garnered more attention than perhaps any other in the study of PFC function: working memory. Even before the introduction of this term, animal models of the role of the PFC in memory over brief delays indicated that ''destruction of the frontal lobes leads, not so much to a disturbance of memory as to a disturbance of the ability to inhibit orienting reflexes to distracting stimuli'' [1]. This so-called 'interference hypothesis' explained why PFC-lesioned monkeys who failed to remember information over a brief delay in some circumstances improved when irrelevant and distracting stimuli were removed [9].

With the advent of functional neuroimaging, hypotheses for the role of the PFC in working memory proliferated along with the number of imaging studies [10]. For example, Cohen and colleagues [11] argued that a region of the ventrolateral prefrontal cortex (VLPFC) subserves explicit verbal rehearsal, based on interacting effects of memory load and delay duration on functional magnetic resonance imaging activity. A central debate in this area has concerned the extent to which regions of the PFC are specialized for certain content domains (e.g. objects versus locations [12,13]) or certain working memory processes (e.g. maintenance versus manipulation [14,15]). However, despite this controversy, most investigators have agreed on the importance of the PFC in working memory.

By contrast, a recent meta-analysis of neuropsychological studies of working memory showed that, unlike lesions in the temporoparietal cortex [16], lesions to the PFC did not reliably lead to impairments in working memory [17]. This seeming discrepancy of neuropsychological and neuroimaging studies has led to the re-emergence of the interference hypothesis, supported by several sources of evidence in humans. First, activation in the PFC, especially the VLPFC, is affected by the presence of interfering information [18,19,20••]. Second, in patients with PFC lesions, working memory deficits are pronounced on tasks with distractor-filled delay intervals [17]. We reported data from a patient with a VLPFC lesion who had a selective impairment in his ability to inhibit proactive interference in working memory [21,22••]. Third, oft-reported age-related declines in working memory can be eliminated by manipulations that reduce interference [23]. Fourth, individual variability in working memory can be explained by both resistance to interference [24,25] and inhibitory control (e.g. of eye movements [26]). All of these findings are better explained by a regulatory account of PFC function than by domain-specific alternatives (e.g. verbal rehearsal).

Regulation and language processing

Luria described aphasic patients who, typically following PFC lesions, had trouble switching from one word to another, made frequent intrusions from previously named items or were unable to produce spontaneous speech in unconstrained settings (i.e. dynamic aphasia). In contrast to other types of aphasia, Luria's account of frontal lobe aphasia emphasized the general regulatory function of the PFC instead of any language-specific process. Here, again, Luria's work was prescient of a current debate about the role of the PFC in language processing. Based primarily on neuroimaging studies, some have proposed regional VLPFC specificity for language processes such us phonology, syntax and semantics [27]. By contrast, we have argued that regions of the VLPFC subserve more general regulatory mechanisms that support these linguistic functions [28].

It is clear that the processing of linguistic stimuli will, at least in some circumstances, activate the PFC, and specifically the VLPFC. However, given that language-specific processing does not uniquely [29,30•] or necessarily [31] activate these regions, the question then becomes, under what circumstances will the VLPFC be recruited during language processing? For example, VLPFC involvement during picture naming is modulated by variables such as picture-name agreement [32] and semantic context [33], and the effects of VLPFC damage on language fluency vary with contextual constraints [34] and cues [35]. Cognitive control mechanisms subserved by the PFC might be demanded by linguistic tasks requiring sustained access to content in temporal regions [36] and suppression of irrelevant contextual information [37]. We turn now to three examples drawn from areas of psycholinguistic inquiry — verb processing, semantic processing and sentence processing — in which we assert that domain-specific patterns might be equally well explained by more general regulatory functions.

Verb processing

Some of the first neuroimaging investigations of cognition [38,39] found VLPFC activity when subjects generated a verb to a target noun, in contrast to when nouns were simply repeated. Yet, the difficulty in determining exactly how these two tasks differ illustrates the problem of identifying the factors that engage prefrontal mechanisms. One hypothesis, supported by the observation that patients with damage to the VLPFC are often worse at producing verbs than nouns [40], is that the VLPFC represents and processes verb-specific information. However, further research has demonstrated that verb-processing deficits can arise as a result of damage to posterior brain regions, and that anterior lesions can lead to language-processing deficits that selectively spare verbs [41,42]. Subsequent neuroimaging studies using tasks other than verb generation have yielded mixed results on the specific involvement of the VLPFC in verb processing [43]. These findings could be interpreted in a broader framework of the VLPFC as a cognitive control mechanism that regulates interactions between competing representations.

The necessity of the VLPFC for verb processing seems to be influenced by specific lexical properties. First, the VLPFC might be necessary to select a single meaning of a verb with multiple competing meanings; some patients with PFC damage are worse at retrieving verbs with several context-dependent meanings (e.g. 'go') than verbs with fewer possible meanings (e.g. 'crawl') [44]. Second, multiple possible verb conjugations might require a cognitive control mechanism to settle on one context-appropriate ending; activity in the VLPFC is greater during verb processing than during noun processing when morphosyntactic information is present [45•] but not when morphosyntactic information is absent [46], possibly because there are more morphosyntactic markers for verbs than for nouns in the English language. Consistent with this account, a recent neuroimaging study comparing verb processing with noun processing in Mandarin Chinese (a language with no morphological markers on verbs or nouns) reported no differences between the two grammatical classes in the VLPFC [47].

In the verb-generation task, demands for cognitive control might occur when choosing one associated verb for a given noun from among competing alternatives. For example, some nouns (e.g. 'cat') have many weakly associated verbs (and strongly associated non-verbs), whereas others (e.g. 'scissors') have a strongly associated verb. We found that competition among responses (as in the case of 'cat') was associated with increased VLPFC activity in the verb-generation task [31]. In addition, priming non-verb knowledge (e.g. color) increased VLPFC activation during retrieval of an associated verb for a repeated item [48]. Furthermore, patients with VLPFC damage were impaired at retrieving verbs only under conditions of increased competition [49]. These findings support the hypothesis that the verb-generation task — and verb processing more generally — requires VLPFC involvement only in the context of high conflict.

Semantic processing

Numerous investigators have proposed that the VLPFC specifically supports controlled semantic retrieval or semantic working memory, primarily on the basis of neuroimaging studies requiring classification or retrieval of words based on semantic relationships [38,39,50–52]. The effect on VLPFC activation of reducing semantic processing demands by stimulus repetition supports this interpretation [53,54]. Furthermore, contrasts between phonological and semantic tasks have revealed an apparent content-specific delineation of anterior and posterior VLPFC regions [52,53,55]. Finally, VLPFC damage can lead to short-term memory impairments that are specific to semantic (but not phonological) information [56].

Rather than mediating semantic processing *per se*, these effects might reflect regulatory control functions of the VLPFC, such as the selection of task-relevant representations among competing sources of information [31]. Neuroimaging data indicating apparent content specificity in the VLPFC could reflect either regulation via dedicated connections to posterior domain-specific cortical regions [57] or confounded variations in processing demands [58]. For example, we varied regulatory demands by manipulating sources of competition in semantic classification, comparison and generation tasks, and found effects of competition in the VLPFC across all tasks [31]. Recently, Hamilton and Martin [22••] suggested that so-called 'semantic working memory deficits' are, in fact, the result of a failure to inhibit active, interfering representations (see also [59•]). They described patients whose errors consisted of intrusions from previously presented words [60]; interestingly, such patients also showed increased susceptibility to proactive interference on a nonsemantic item recognition test [22••].

Category and property decisions that require access to abstract semantic information specifically activate the VLPFC [61,62]. Similarly, during semantic comparisons, VLPFC activity increases as the strength of association between the words decreases [63]. Although Wagner and colleagues interpreted this finding as evidence for a domain-specific controlled retrieval process, the pattern of results is also easily explained by a regulatory response to conflict; control mechanisms in the VLPFC might become increasingly necessary as semantic relations between lexical items become weaker, as a result of conflict between underdetermined responses. Wagner *et al.*'s description of 'controlled semantic retrieval' might simply be an example of a regulatory control function; however, the use of this domain-specific terminology masks the similarity of this mechanism to other known functions of the PFC.

Sentence processing

Sentence processing historically has been described as the cardinal function of the left VLPFC, on the basis of the observation that anterior lesions can lead to a deficit in sentence production and comprehension [64]. However, damage to the VLPFC does not always lead to a sentence-processing deficit, and such deficits might result from damage to other brain regions [65]. Furthermore, patients with so-called agrammatic aphasia are able to make subtle grammaticality judgments [66], suggesting that the VLPFC is not always necessary for sentence processing. Some neuroimaging studies link the VLPFC specifically to syntactic processing [67] or to specific syntactic operations identified in current linguistic theories [68•,69]; however, recent reviews of neuroimaging studies have shown that the VLPFC is not consistently [65] or exclusively [70] activated by sentence processing.

Alternatively, the contribution of the VLPFC to syntactic processing could be viewed in the broader framework of the regulatory functions of the PFC. In line with this hypothesis, the comprehension of sentences with a non-canonical word order specifically leads to increased activity in the VLPFC [65]. These sentences might require inhibition of a prepotent interpretation of word order in building the correct syntactic structure. This might explain why patients with agrammatic aphasia have difficulty even with syntactically simple sentences, when semantic information contradicts the correct thematic role assignment [71]. Greater VLPFC activity has also been found during the comprehension of syntactically ambiguous, compared with syntactically unambiguous, sentences, even when these stimuli were matched on syntactic complexity [72]. In such sentences, the VLPFC might feed a biasing signal to posterior regions to settle on one syntactic interpretation. Children with as yet immature VLPFC function [73] rely to a greater extent on syntactic constraints imposed by the verb, and are less able to use contextual information from the referential scene in parsing temporarily ambiguous sentences [74]. These results indicate that the VLPFC might be important in overriding the more reliable mapping between a verb and its most common syntactic parse in favor of less reliable contextual information.

Conclusions

At first glance, it might appear somewhat contradictory to organize a discussion of 'current opinions' in neurobiology around ideas that were described over three decades ago. In the intervening years, new neuroimaging methods have changed the landscape of research on PFC function; however, the topography of this new landscape might be a better reflection of the organization of scientific communities than of the organization of the PFC. In this context, we believe that Luria's seminal observations about frontal lobe function are just as relevant today as they were when first published.

A century before Luria, neurologist John Hughlings Jackson described the frontal lobes as the least organized (i.e. least differentiated) structure in the brain. However, the variation across regions of the PFC, both in patterns of connectivity [75] and in cytoarchitecture [76] would appear to indicate some fractionation of this structure comprising over 30% of human cortical mass. The organization of this article in some ways is a metaphor for the possible organization of the PFC: despite the content-specific organization of topics herein, we have tried to interject a coherent theme into each discussion. Likewise, our comments above in no way rule out the hypothesis that different subregions of the PFC are preferentially recruited in different contexts (e.g. verbal or nonverbal). Where we depart from other domain-specific theorists is our assertion that common mechanisms are subserved by these regions, and that apparent content specificity is a result of connectivity with posterior, domain-specific processing regions. Thus, we suggest that the question for investigators studying cognitive processes within each of these domains should not be 'is there a specific PFC response?', but rather 'under what circumstances is the PFC recruited?'. By studying regulatory functions in multiple domains, we are likely to progress more quickly in our understanding of the role of the PFC in human cognition.

We end with a comment from Luria's chapter on frontal lobe function, from which we have borrowed not only several insightful ideas but also the title of this article: "...the functional organization of the human frontal lobes is one of the most complex problems in modern science, and so far only the first step has been taken in the analysis of the various syndromes which can arise in lesions of the corresponding parts of the brain. Nothing is more certain, therefore, than that the next decade will see a substantial increase in our knowledge of this complex region".

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