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Subdivision of frontal cortex mechanisms for language production in aphasia

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ABSTRACT

Ventrolateral prefrontal cortex (VLPFC) has long been linked to language production, but the precise mechanisms are still being elucidated. Using neuropsychological case studies, we explored possible sub-specialization within this region for different linguistic and executive functions. Frontal patients with different lesion profiles completed two sequencing tasks, which were hypothesized to engage partially overlapping components. The multi-word priming task tested the sequencing of co-activated representations and the overriding of primed word orders. The sequence reproduction task tested the sequencing of co-activated representations, but did not employ a priming manipulation. We compared patients' performance on the two tasks to that of healthy, age-matched controls. Results are partially consistent with an anterior–posterior gradient of cognitive control within lateral prefrontal cortex (Koechlin & Summerfield, 2007). However, we also found a stimulus-specific pattern, which suggests that sub-specialization might be contingent on type of representation as well as type of control signal. Isolating such components functionally and anatomically might lead to a better understanding of language production deficits in aphasia.

1. Introduction

Language production involves the conversion of a message or thought into a string of words. This process may include several component processes, including the selection of appropriate words, the sequencing of those words in a grammatical order, and the programming of articulatory motor movements. The ventrolateral prefrontal cortex (VLPFC), which includes Broca's area, has long been associated with language production. While the original hypothesis, traced back to Broca, tied this region to speech per se, more recent accounts have hypothesized that VLPFC is involved in higher-level cognitive and linguistic functions (see e.g., Cabeza & Nyberg, 2000). It is possible that different sub-regions within VLPFC support different sub-components that are involved in producing language. In this article, we explore the issue of sub-specialization from a neuropsychological perspective.

Previous neuroimaging and neuropsychological studies have suggested some possible subdivisions of prefrontal mechanisms for language. One dominant idea is that the posterior and dorsal part of VLPFC (Brodmann areas (BA) 44/6) might be responsible for processing phonological information and the anterior and ventral part (BA 47) for processing semantic information, with the intermediate region (BA 44/45) being responsible for processing syntax (Bookheimer, 2002). This is consistent with known connectivity patterns between posterior and frontal brain regions in the macaque monkey: a dorsal pathway from posterior temporal and inferior parietal regions – thought to be involved in phonological processing in humans – primarily targets posterior VLPFC while a ventral pathway from more anterior temporal regions – thought to be involved in semantic processing in humans – primarily targets anterior VLPFC (Hickok & Poeppel, 2004; Petrides & Pandya, 2009). Thus, it seems plausible that different parts of frontal cortex support higher-level cognitive processing of different kinds of linguistic representations that reside in temporal and parietal areas.

Direct evidence for the anterior–posterior semantic-phonological distinction in the frontal cortex of humans comes from a number of studies (Fiez, 1997; Hamilton, Martin, & Burton, 2010; McDermott, Petersen, Watson, & Ojemann, 2003; Poldrack et al., 1999). For example, McDermott et al. (2003) presented participants with 16-word lists and asked them to attend either to the meaning or the rhyme relations between words. Results showed preferential activation for the semantic condition in BA 47 and BA 44/45 and preferential activation for the phonological condition in frontal regions posterior to those found for the semantic condition (BA 44/6). Based on evidence from patients with brain damage, Martin and colleagues have suggested that semantic and phonological short-term memory (STM) components are separable both functionally and anatomically (Martin & He, 2004; Martin & Romani, 1994).

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A recent fMRI study from the same group showed increased activation in parts of VLPFC anterior to BA 44/6 when comparing high and low semantic STM load conditions (Hamilton et al., 2010). Analysis within a posterior BA 44 region of interest detected no such effect of semantic STM load, consistent with the hypothesis that this sub-region is not associated with semantic processing.

There is also evidence for anterior versus posterior semantics versus syntax parcellation within VLPFC. Dapretto and Bookheimer (1999) examined activation during a semantic condition where a same/different judgment between two sentences relied on the processing of word substitutions and that during a syntactic condition where the same/different judgment relied on the processing of syntactic alternations. The findings implicated BA 44 in syntactic processing and BA 47 in semantic processing (Dapretto & Bookheimer, 1999). Other fMRI studies have reported increased frontal activation for some syntactic structures over others, particularly in BA 44 (Caplan, Alpert, & Waters, 1998; Newman, Ikuta, & Burns, 2010). Such evidence is broadly consistent with specialization of posterior VLPFC for some sub-component of syntax, although the interpretation of the data with respect to the domain specificity or generality of the underlying mechanisms is still controversial (Novick, Trueswell, & Thompson-Schill, 2005).

In sum, evidence from language studies has suggested a gradient between semantic processing in anterior VLPFC and phonological processing in posterior VLPFC with syntactic processing somewhere in between. However, the functions of lateral PFC (LPFC), or subdivisions among them, are clearly not limited to the domain of language. There is general consensus that this region is involved in cognitive control or the coordination of thoughts and actions in accordance with goals. Koechlin and colleagues have proposed an influential "cascade model" with respect to the organization of cognitive control processes for selecting actions (Koechlin, Ody, & Kouneiher, 2003; Koechlin & Summerfield, 2007). Under this model, cognitive control involves at least three nested levels of processing whose anatomical loci are hypothesized to lie on a posterior-to-anterior axis within LPFC: lateral premotor areas support sensory control or the selection of motor actions in response to stimuli; posterior LPFC supports contextual control or the selection of motor actions that takes into account (immediate) contextual signals; and anterior LPFC supports episodic control or the selection of motor actions that takes into account the broader temporal episode. Put another way, the integration of more and more temporally distant events is thought to require the operation of more and more anterior portions of LPFC. Further, the processes are supposed to be hierarchically organized such that increased activation of more anterior regions modulates the activation of less anterior regions but not vice versa (Koechlin et al., 2003; Koechlin & Summerfield, 2007. See Badre and D'Esposito (2007) for a different hierarchical proposal).

It might be worth exploring whether these broad organizing principles that have been proposed for dorsolateral PFC and action selection can explain the observed sub-specialization within ventrolateral PFC for different linguistic processes. For example, the processing of semantic and discourse information might require the integration of current input into a broader context ("episodic control" in the cascade model) while the processing of phonological or local syntactic information might require lower-level cognitive control ("sensory control" or "contextual control" in the cascade model). This could explain the localization of semantic processing to anterior PFC and phonological and syntactic processing to more posterior regions (Bornkessel-Schlesewsky, Grewe, & Schlesewsky, 2012).

Our motivation in exploring the sub-specialization issue was to better understand the language impairments in aphasia that follow damage to the frontal cortex. Although the relation between frontal damage and production impairments in aphasia is often taken for granted, the two do not always go together (Dick et al., 2001; Dronkers, Wilkins, Van Valin, Redfern, & Jaeger, 1994). It is possible that different sub-components of language production rely on different neural substrates, leading to the inconclusive findings. Thus, our approach has been to isolate particular cognitive components in patients with focal frontal lesions.

In a preliminary study with aphasic patients, we reported that some frontal patients had difficulty in flexibly sequencing words (Thothathiri, Schwartz, & Thompson-Schill, 2010). We used a simple two-word picture-naming task that isolated sequencing from other sentence processing components such as verb retrieval and syntactic–semantic mappings. Post-hoc anatomical analysis tied a sub-region within LPFC, namely BA 44/6, to exaggerated interference when participants were primed with a noun in one phrasal position and then had to produce that same noun in the other phrasal position. Frontal patients who had BA 44/6 damage showed this pattern while others, whose lesions spared this sub-region, did not. We interpreted these data within a larger framework wherein lateral PFC supports cognitive control, particularly the biasing of competing representations during the selection of a single representation. Invoking this framework, Robinson and colleagues have suggested that the inability to select amongst verbal responses under conditions of high competition is central to what Luria termed "dynamic aphasia" (Luria, 1970; Robinson, Blair, & Cipolotti, 1998; Robinson, Shallice, & Cipolotti, 2005). Our more specific suggestion was that the BA 44/6 sub-region within PFC might be associated with sequencing or "selection for position" (Thothathiri et al., 2010). When multiple words or items are co-activated, selecting the right word or item at the right time might require an intact BA 44/6.

Other studies have also tied sequencing operations to the posterior-most region of VLPFC, adjoining and including the premotor cortex (Gelfand & Bookheimer, 2003; Grewe et al., 2006). For example, Gelfand and Bookheimer (2003) reported that the posterior part of Broca's area was activated during sequence manipulation irrespective of whether the stimuli were phonemes or hummed notes. Within the domain of language, Bornkessel-Schlesewsky and colleagues have suggested a functional gradient within VLPFC for sequencing, wherein activation in posterior sub-portions correlates with sentence-internal or local aspects of sequencing and activation in anterior sub-portions is sensitive to the relation between the current sentence and the broader discourse (Bornkessel-Schlesewsky et al., 2012). This interpretation seems consistent with the cascade model described above. Sequencing or ordering different items with respect to one another (e.g., say *X* after *Y*) is a contextual process, which might be supported by posterior LPFC. Additionally, the modulation of sequencing by semantic or discourse constraints might require the recruitment of episodic control supported by anterior LPFC.

In the current study, we sought to establish the *causal* links between different sub-regions within LPFC and the different components that might be involved in producing a sequence of words. We chose patients with different lesion profiles primarily affecting the premotor cortex, posterior VLPFC or anterior VLPFC, and examined the impact of such lesions on two different sequencing tasks. In the multi-word priming task, participants were required to sequence two nouns during spoken production. On critical trials, we manipulated whether a primed noun was produced in the same position or a different position from the previous trials. In the sequence reproduction task, we manipulated sequencing demands not by a priming manipulation but by presenting the entire sequence all at once or item by item. Patients with different lesion profiles showed different patterns of deficits on the two tasks. Our results speak to the architecture of cognitive control in LPFC and the implications of this