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BRIEF COMMUNICATIONS

Role of frontal *versus* temporal cortex in verbal fluency as revealed by voxel-based lesion symptom mapping

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Abstract

Category and letter fluency tasks have been used to demonstrate psychological and neurological dissociations between semantic and phonological aspects of word retrieval. Some previous neuroimaging and lesion studies have suggested that category fluency (semantic-based word retrieval) is mediated primarily by temporal cortex, while letter fluency (letter-based word retrieval) is mediated primarily by frontal cortex. Other studies have suggested that both letter and category fluency are mediated by frontal cortex. We tested these hypotheses using voxel-based lesion symptom mapping (VLSM) in a group of 48 left-hemisphere stroke patients. VLSM maps revealed that category and letter fluency deficits correlate with lesions in temporal and frontal cortices, respectively. Other regions, including parietal cortex, were significantly implicated in both tasks. Our findings are therefore consistent with the hypothesis that temporal cortex subserves word retrieval constrained by semantics, whereas frontal regions are more critical for strategic word retrieval constrained by phonology. (*JINS*, 2006, *12*, 896–900.)

Keywords: Fluency, Lexical retrieval, Letter fluency, Category fluency, Temporal cortex, Frontal cortex, Semantic retrieval

INTRODUCTION

Verbal fluency tasks require participants to generate words belonging to a given semantic category (e.g., animals) or starting with a given letter (e.g., words beginning with the letter *F*). Participants are generally given one minute to retrieve as many words as they can, and they are also instructed to avoid repetitions. Given these demands, verbal fluency tasks engage several cognitive processes, such as working memory, self-monitoring, and cognitive flexibility (Rosen & Engle, 1997; Schwartz et al., 2003; Troyer et al., 1998). Letter fluency additionally requires a strategic search through lexical or phonologic memory, while category fluency involves a search through conceptual or semantic memory.

Several studies have attempted to delineate brain regions associated with letter and category fluency performance. These studies have included dual task paradigms with normal participants, functional neuroimaging, and lesion studies. For example, Martin et al. (1994) tested normal participants in dual task conditions and found that a concomitant finger-tapping task (putatively, a frontal task) disrupted letter fluency, while an object decision task (putatively, a temporal lobe task) disrupted category fluency. These findings led them to conclude that frontal cortex is crucial for phonemically driven word retrieval (i.e., letter fluency), while temporal cortex underlies semantically based word retrieval (i.e., category fluency).

Several functional neuroimaging studies have directly tested this model of letter and category fluency. Mummery et al. (1996) found greater left temporal activation (inferior and anteromedial) during category fluency performance and greater left frontal activity during letter fluency performance. These earlier results were replicated in a subsequent study by Gourovitch et al. (2000) who found relatively greater anterior activation during a letter fluency task and greater left temporal cortex activation during a category

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fluency task. However, there were additional activations, with letter fluency activating right anterior temporal regions and left inferior parietal cortex, and category fluency activating the left hippocampus and medial frontal cortex. Therefore, both letter and category fluency were associated to some degree with regions in both frontal and temporal cortex.

Findings from patient studies of verbal fluency also provide somewhat mixed results with respect to the dissociation between letter and category fluency performance. Some studies have indicated that letter fluency is relatively compromised in frontal/anterior patients, while category fluency is reduced in temporal lobe/posterior patients (e.g., Alzheimer's patients; Janowsky et al., 1989; Monsch et al., 1994). However, studies that have tested both types of fluency tasks in the same patients have reported that both letter and category fluency are similarly impaired in patients with frontal lesions (e.g., Baldo & Shimamura, 1998; Schwartz & Baldo, 2001). These findings have been attributed to frontal patients' reduced ability to make strategic and effective searches through memory, whether that search is phonemically or semantically driven (see also Troyer et al., 1998). A recent meta-analysis reached a similar conclusion, namely, that frontal patients are comparably impaired on letter and category fluency measures (Henry & Crawford, 2004). However, they did find a significant difference in focal temporal lobe patients such that temporal lesions were associated with a larger deficit in category fluency relative to letter fluency.

In the current study, we had the opportunity to apply a new, quantitative technique to the analysis of lesion data to explore the relative contribution of left frontal cortex and left temporal cortex to verbal fluency performance. Voxel-based lesion symptom mapping (VLSM) is a statistical technique for analyzing the relationship between lesion data and continuous behavioral measures (Bates et al., 2003). From lesion data, VLSM generates statistical maps of brain regions contributing to behavioral performance in specific tasks. VLSM does not compare groups (e.g., frontal *vs.* temporal) but rather uses all patients' lesions and performs t tests at every voxel. Using this method, we sought to resolve some inconsistencies from the previous lesion and neuroimaging studies of verbal fluency. Our findings provide important support for the hypothesis that letter fluency is primarily mediated by left frontal cortex and category fluency by left temporal cortex.

METHODS

Participants

A total of 48 patients (14 women and 34 men) who had suffered a single, left-hemisphere cerebrovascular accident (CVA) were tested in the current study. Patients were all native English speakers and were premorbidly right-handed, according to the Edinburgh Handedness Inventory (Oldfield, 1971). All patients were tested in the chronic phase of their CVA, at least 9 months post-onset (M = 62.8 months; *SD* = 59.7; range, 9–273 months). Patients ranged in age from 43 to 80 years (M = 62.9; *SD* = 9.6). Patients' education ranged from 8 to 20 years (M = 14.7; *SD* = 2.9). Based on clinical examinations, patients had no prior history of neurologic injury (other than the CVA), psychiatric illness, or alcohol/drug abuse. Although our patient database contained a larger patient sample, only those patients meeting the above criteria and who had received the letter and category fluency measures are reported here. Also, three patients with less than eight years of education and two patients under age 40 were initially tested but then excluded to maintain a more homogeneous sample and reduce the potential impact of these variables on the verbal fluency results.

Patients' overall language status was evaluated by the Western Aphasia Battery (mean aphasia severity score = 79.8 out of 100; *SD* = 20.6; Kertesz, 1982). Patients were excluded from the study if they could not comply with task instructions.

Participants read and signed consent forms before testing. The protocols under which these data were collected were approved by the Institutional Review Board of the VA Northern California Health Care System, Martinez, CA, and were in compliance with the Helsinki Declaration.

Materials and Procedures

Testing took place in a noise-attenuated room. Letter and category fluency tasks were administered to patients as part of a larger research battery that included both language and cognitive testing. In the letter fluency task, patients were first asked to name words that began with the letter *F*. The examiner recorded the patients' responses for 90 s. (The 90-s procedure was chosen rather than a 60-s procedure to be comparable to another study by our group.) Patients were subsequently asked to generate words beginning with the letters *A* and then *S*. Following letter fluency, patients were given 90 s to generate items belonging to the semantic categories *fruits*, *animals*, and *supermarket items*, in that order. The order of the fluency conditions was fixed and was consistent across all patients. In both letter and category fluency conditions, patients were told to avoid repetitions. Performance for both fluency tasks was computed as the number of correct items generated in response to all three cues. Items were scored as correct if they belonged to the category and were not repetitions.

Data were analyzed using VLSM (see Bates et al., 2003). Patients' lesions were first imaged by magnetic resonance imaging (MRI) or computed tomography (CT) at least three weeks post-onset of the CVA. A board-certified neurologist who was blind to the patients' clinical presentations reconstructed the lesions onto standardized brain templates, which consisted of 11 slices in the axial plane (according to the atlas of DeArmond et al., 1976). Lesion data files for each patient were then entered into a VLSM analysis along with the behavioral data from each patient. Separate analyses were performed for letter and category fluency performance. The VLSM analyses conducted *t* tests at every voxel to compare performance in patients with and without a lesion in that voxel. The *t* tests were confined to those voxels where there were at least eight patients in each group (i.e., with and without a lesion), to maintain a reasonable level of statistical power. Colorized maps were then generated based on the resultant *p* values at each voxel (where $\alpha = .05$), and subtraction maps were computed based on the *t* statistics.

RESULTS

Mean letter fluency performance (*FAS*) across all patients was 18.8 words ($SD = 17.6$) in 90 s, and mean category fluency performance (*fruits, animals*, and *supermarket items*) was 30.5 items ($SD = 22.1$) in 90 s. VLSM analyses revealed that letter fluency was significantly associated with lesions in frontal regions [Brodmann's Area (BA) 4, 6, and 44; see Figure 1]. There were also significant foci in parietal cortex (BA 1–3, 7, 39, 40, 43), the post-central gyrus, anterior temporal cortex (BA 22), as well as the insula and putamen. Category fluency was associated with lesions in more posterior cortex, including regions of the left temporal lobe (BA 22, 37, 41, 42) and the post-central gyrus. Similar to letter fluency, category fluency was also affected by damage to parietal cortex (BA 39, 40), as well as the insula and putamen.

To visualize those regions specific to letter versus category fluency performance, subtraction maps were computed for letter minus category fluency and for category minus letter fluency. As can be seen in Figure 2, letter fluency (minus category fluency) was associated with frontal cortex (BA 4, 6, 44), parietal cortex (BA 1–3, 39, 40), a small portion of anterior temporal cortex (BA 22), and the insula and putamen (see Figure 2). The right side of Figure 2 shows that category fluency (minus letter fluency) was associated with more posterior regions, including predominantly temporal regions (BA 22, 37, 38, 41, 42), as well as parietal cortex (BA 7, 39).

To be sure that the 90-s fluency procedure was not anomalous (relative to the more conventional 60-s procedure), we generated new letter and category fluency VLSM maps for performance during the first 60 s only. The VLSM maps for 60 s *versus* 90 s were almost indistinguishable, which is likely due to the fact that the patients generated very few items in the last 30 s of all fluency conditions.

DISCUSSION

The current study used a new technique, voxel-based lesion symptom mapping (VLSM), to identify brain regions associated with letter versus category fluency performance in a large group of stroke patients with left-hemisphere lesions. Letter fluency was associated with damage to more anterior regions, including left frontal cortex, while category fluency was associated with lesions in more posterior regions, primarily left temporal cortex. These findings are consistent with the hypothesis that letter fluency engages frontal circuits, whereas category fluency relies predominantly on temporal cortex, as suggested by some previous neuroimaging and patient studies (e.g., Milner, 1964; Monsch et al., 1994; Mummery et al., 1996). This dissociation accords with models that place an emphasis on inferior frontal cortex for the construction of basic word forms and strategic word retrieval and temporal cortex for associating concepts with lexical labels.

At first pass, the current findings seem to stand in contrast to previous conclusions that frontal cortex plays a role in both letter and category fluency performance due to its

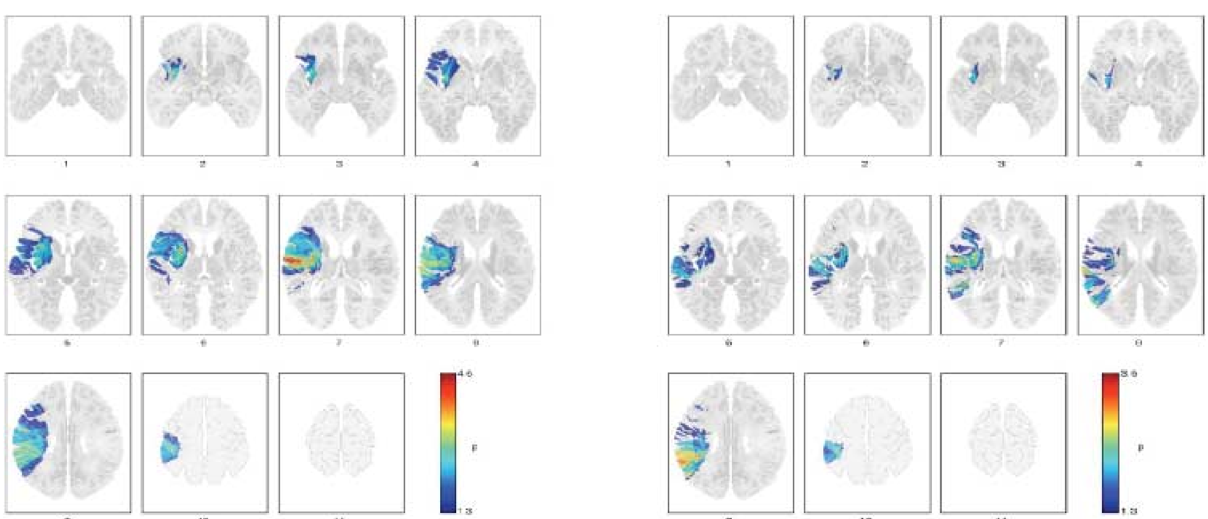

Fig. 1. Voxel-based lesion symptom mapping (VLSM) maps showing *p* values of all significant voxels for letter fluency (left) and category fluency (right). All *p* values are in $-\log 10$. Only voxels with significant *p* values ($\alpha = .05$) are shown.

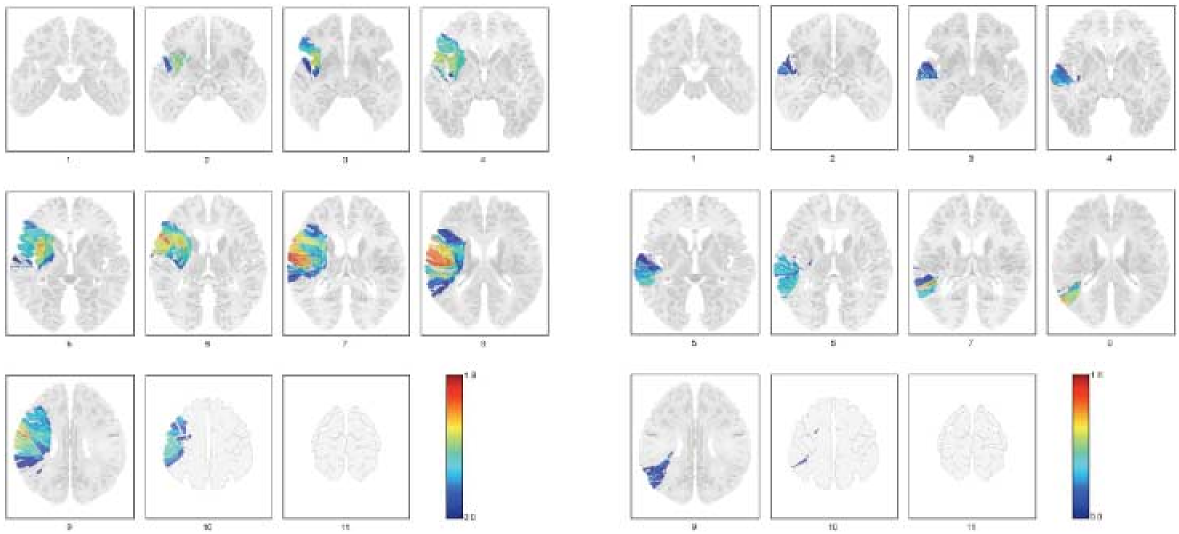

Fig. 2. Subtraction maps based on the *t* statistics for letter minus category fluency (left) and category minus letter fluency (right).

role in strategic retrieval (e.g., Baldo & Shimamura, 1998; Henry & Crawford, 2004). It is possible that the current methodology, VLSM, is more sensitive than traditional lesion studies to the relative role of discrete brain regions in a given behavior. Previous lesion studies of verbal fluency instead may have been more sensitive to the relative performance of patients versus controls and thus detected decrements in patients on both fluency tasks. Lastly, it is possible that the degree of frontal involvement in category fluency depends on the semantic category tested. That is, certain semantic categories may engage frontal/strategic search processes if they are broader and require frequent switching between subcategories (e.g., see Troyer et al., 1998). To assess this possibility, we generated three separate VLSM maps for *fruits*, *animals*, and *supermarket items*. The maps for *fruits* and *animals* showed significant foci primarily in posterior regions, confirming the results of our current study. However, the VLSM maps for *supermarket items* also showed some additional foci in frontal cortex. It is likely that this effect stems from the fact that the *supermarket* category requires more switching between subcategories (e.g., dairy products, fruits, meats, etc.), as well as a more dedicated search strategy, such as imagining oneself going down the different aisles at the grocery store.

Importantly, our new data suggest that fluency tasks also rely on regions outside frontal and temporal cortex. For example, both letter and category fluency tasks were also affected by lesions in inferior parietal cortex, a region often associated with verbal working memory (e.g., Jonides et al., 1998). It is possible that both fluency tasks engaged working memory mechanisms, for example, to hold in mind the task rules, maintain set, and avoid repetitions. Using functional MRI, Gourovitch et al. (2000) reported similar findings with inferior parietal cortex being activated in both letter and category fluency conditions.

Letter and category fluency tasks were also affected by lesions in the insula and putamen. Previous neuroimaging studies of verbal fluency have also reported activation in these subcortical regions (e.g., Fu et al., 2002). We have previously shown that the anterior insular region is critical for articulatory coordination (Dronkers, 1996). It is unclear, however, why this region remained in the letter fluency subtraction map, because both letter and category fluency tasks engage articulatory mechanisms similarly. Apparently, letter fluency relied on this region more, perhaps due to the additional phonological component of the task.

Previous lesion and neuroimaging studies have found more left-hemisphere involvement for verbal fluency tasks, whereas the right hemisphere is implicated in nonverbal fluency tasks such as design fluency (e.g., Jones-Gotman & Milner, 1977). However, a few studies have also detected significant activations in the right hemisphere (e.g., Gourovitch et al., 2000). Because the present study was restricted to patients with left-hemisphere lesions, our findings do not speak to the relative contribution of the right hemisphere to verbal fluency. A possible extension of the present study would thus be to include such a patient sample in future research.

In conclusion, a new lesion mapping method (VLSM) allowed us to assess the neural correlates of fluency deficits, simultaneously and parametrically for both category and letter fluency, looking at regions either commonly or differentially involved in both tasks. Our comparison maps revealed a strong association of letter and category fluency with frontal and temporal cortex, respectively, although additional regions were also observed. These findings are consistent with the hypothesis that letter-based word retrieval depends on frontal cortex due to its role in strategic retrieval of word forms, while category-based word retrieval depends more heavily on temporal cortex due to its role in accessing lexical–semantic networks. How these two systems interact and regulate each other in normal, healthy brains remains an important question for future research (Schwartz et al., 2003).

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