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PARTLY SEGREGATED CORTICO-SUBCORTICAL PATHWAYS SUPPORT PHONOLOGIC AND SEMANTIC VERBAL FLUENCY: A LESION STUDY

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Abstract—Verbal fluency refers to the ability to generate as many words as possible in a limited time interval, without repetition and according to either a phonologic (each word begins with a given letter) or a semantic rule (each word belongs to a given semantic category). While current literature suggests the involvement of left fronto-temporal structures in fluency tasks, whether the same or distinct brain areas are necessary for each type of fluency remains unclear. We tested the hypothesis for an involvement of partly segregated cortico-subcortical structures between phonologic and semantic fluency by examining with a voxel-based lesion symptom mapping approach the effects of brain lesions on fluency scores corrected for age and education level in a group of 191 unselected brain-damaged patients with a first left or right hemispheric lesion. There was a positive correlation between the scores to the two types of fluency, suggesting that common mechanisms underlie the word generation independent of the production rule. The lesion-symptom mapping revealed that lesions to left basal ganglia impaired both types of fluency and that left superior temporal, supramarginal and rolandic operculum lesions selectively impaired phonologic fluency and left middle temporal lesions impaired semantic fluency. Our results corroborate current neurocognitive models of word retrieval and production, and refine the role of cortical-subcortical interaction in lexical search by highlighting the common executive role of basal ganglia in both types of verbal fluency and the preferential involvement of the ventral and dorsal language pathway in semantic and phonologic fluency, respectively.

Key words: language, executive functions, verbal fluency, brain lesion, basal ganglia.

INTRODUCTION

Verbal fluency – or word generation – tasks are classically used for the neuropsychological assessment of language and executive functions (Moscovitch, 1994). Fluency tasks consist in generating as many words as possible over a given time interval, without repetition and according to either a phonologic (each word begins with a given letter) or a semantic rule (each word belongs to a given semantic category, as e.g. animal or fruit (Bechtoldt et al., 1962; Hodges et al., 1992; Tombaugh et al., 1999).

Verbal fluency not only requires accessing and retrieving specific words within lexical memory, but also monitoring responses to avoid repetitions and suppressing task-irrelevant words to stick to the task rules. These tasks thus involve language processing and the three components of the Miyake's model of executive functions ('Shifting', 'Updating' and 'Inhibiting'; (Miyake et al., 2000). Importantly, while both semantic and phonologic fluency involve a mnesic-associative and an executive component, their relative contribution differs between the two types of fluency. Retrieving words belonging to a given semantic category can indeed be achieved based on the default semantic organization of conceptual knowledge (Shapira-Lichter et al., 2013): participants might rely on association chains between items in a given category based on the fact that the brain activity associated with finding a first item could spread to other items of the same category (Gruenewald and Lockhead, 1980). In contrast, phonologic fluency requires inhibiting the default semantic associations to search words according to the unusual 'first letter' association between them. Phonologic fluency has thus been advanced to load more strongly on the executive component than semantic fluency (Perret, 1974; Thompson-Schill et al., 1997; Thompson-Schill et al., 1998; Katzev et al., 2013), although control processes are also likely necessary in semantic fluency to shift between subcategories of items and resist the interferences from competing alternatives when a given semantic network is activated (Mummery et al., 1996; Reverberi et al., 2006).

Since current neurocognitive models of verbal fluency assume that different processes and strategies are involved in semantic and phonologic fluency, these two

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Abbreviations: DLPFC, dorsolateral prefrontal regions; FDR, False Discovery Rate; MNI, Montreal Neurological Institute; VLSM, Voxel-based Lesion Symptom Mapping.

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tasks should rely on partly segregated brain networks. These models are supported by functional neuroimaging evidence for a prominent role of left frontal executive regions in phonologic fluency (Mummery et al., 1996; Pujol et al., 1996; Phelps et al., 1997), and of temporal associative areas during semantic fluency (Martin et al., 1996; Gourovitch et al., 2000). However, neuropsychological literature reports a slightly different pattern of difference between the neural correlates of the two types of fluency. A meta-analysis of 30 neuropsychological studies including tests of verbal fluency in patients with brain damage indeed reports that while temporal structures are more important for semantic fluency, frontal damages impact similarly on phonologic and semantic fluency (Henry and Crawford, 2004). Of note, dorsal/ventral dissociations for phonologic and semantic processing have also been found related to other types of language impairments; deficits in oral expression can for example occur at the lexical–semantic or lexical–phonological levels (Henseler et al., 2014; Parker Jones et al., 2014).

Frontal and temporal areas have also been advanced to be involved in both types of fluency by studies focusing on cluster-switch behaviors; this concept refers to a word-retrieval strategy generally at play during verbal fluency tasks, which consists in generating words belonging to a given subcategory and then shifting between subcategories. According to this framework, frontal areas are suggested to be involved in switching and temporal areas in sweeping within a semantic or phonological field (e.g. Troyer et al., 1998).

Because of their connections to the cortical structures supporting verbal fluency, basal ganglia have also been involved in word production tasks (Fu et al., 2002). In the ganglia-thalamo-cortical loops, the DLPFC is connected to the dorsolateral caudate nucleus and the internal globus pallidus. Fluency impairments following basal ganglia disruption have notably been demonstrated in clinical studies on HIV (Thames et al., 2012), as well as in Huntington and Parkinson patients (Lawrence et al., 1998; Benke et al., 2003), and might follow from a disruption of the maintenance, monitoring and selection of goal-relevant representations by prefrontal cortices (Wagner et al., 2001).

Critically, current lesion data are undermined by a high degree of inconsistency in the effects of lesions on verbal fluency performance. These discrepancies most likely follow from the fact that the lesion studies having tested the two types of fluency in the same patients included small sample sizes (e.g. 32 in Martin et al., 1990, 32 in Vilkki and Holst, 1994, 12 in Baldo and Shimamura, 1998). In addition to limiting the statistical power of the analyses, small sample sizes tend to reduce the portion of the brain in which the effects of lesions are tested, leaving unresolved the role of many brain areas (e.g. Baldo et al. (2006), which included only left-hemispheric patients). Moreover, in most of previous lesion studies on verbal fluency, patients were selected based on a priori hypotheses on the role of specific brain regions or on the association between verbal fluency and specific neuropsychological syndromes (e.g. studies with aphasic patients in Grossman (1981), frontal or temporal patients in Troyer et al. (1998), or cortical lesions in Henry and Crawford (2004)).

With the aim of identifying the brain structures whose integrity is necessary for phonologic and/or semantic fluency, we analyzed statistically the relationship between verbal fluency performance and focal lesion locations using Voxel-based Lesion Symptom Mapping (VLSM; Bates et al., 2003). In contrast to functional neuroimaging approach, the analysis of the effects of lesion allows to establish causal relationships between brain and behavior and not only correlational associations between activity in a given brain area and performance at a given task.

To prevent selection biases, we opted for the most data-driven approach as possible by focusing on an unselected group of hemispheric brain damaged patients without any exclusion criteria at the level of lesion site or clinical profile. Most notably, we included both left and right hemispheric patients; while the prominent involvement of left hemispheric structure in fluency is clinically obvious, there is indeed lack of direct empirical evidence for this question. Moreover, we included a very large sample of 191 patients to optimize the statistical sensitivity and brain coverage of our analyses. Because age and education level have been shown to influence fluency performance (Tombaugh et al., 1999; Katzev et al., 2013; Marsolais et al., 2015), we used the continuous fluency scores corrected for these factors as behavioral inputs in the analyses. We further analyzed the correlation between the score at each of the fluency task.

EXPERIMENTAL PROCEDURES

Population

Hundred and ninety-one in-patients from the Neuropsychology departments of the *Hôpital Fribourgeois* and the *Centre Hospitalier Universitaire Vaudois* were included retrospectively in the study. All the patients were hospitalized between 2007 and 2015 for a first unilateral hemispheric lesion. The patients were aged 62.2 ± 14.9 years (mean ± SD) and the group included a total of 71 women (see Table 1 for detailed demographic information). The routine neuropsychological assessment including the fluency

Table 1. Detailed demographic information.

	Group size	Sex		Damaged hemisphere		Education level (/3)
		Male	Female	Left	Right	
Stroke	134	91	43	77	57	1.7
Tumor	57	29	28	31	26	1.9