Neuropsychologia 101 (2017) 85–96

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Structural connectivity subserving verbal fluency revealed by lesion-behavior mapping in stroke patients

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ARTICLE INFO

Keywords:
Semantic fluency
Phonological fluency
White-matter connectivity
DTI
Stroke patients

ABSTRACT

Tests of verbal fluency have been widely used to assess the cognitive functioning of persons, and are typically classified into two categories (semantic and phonological fluency). While widely-distributed divergent and convergent brain regions have been found to be involved in semantic and phonological fluency, the anatomical connectivity underlying the fluency is not well understood. The present study aims to construct a comprehensive white-matter network associated with semantic and phonological fluency by investigating the relationship between the integrity of 22 major tracts in the whole brain and semantic fluency (measured by 3 cues) and phonological fluency (measured by 2 cues) in a group of 51 stroke patients. We found five left-lateralized tracts including the anterior thalamic radiation (ATR), inferior fronto-occipital fasciculus (IFOF), uncinate fasciculus (UF), superior longitudinal fasciculus (SLF) and frontal aslant tract (FAT) were significantly correlated with the scores of both semantic and phonological fluencies. These effects persisted even when we ruled out the influence of potential confounding factors (e.g., total lesion volume). Moreover, the damage to the first three tracts caused additional impairments in the semantic compared to the phonological fluency. These findings reveal the white-matter neuroanatomical connectivity underlying semantic and phonological fluency, and deepen the understanding of the neural network of verbal fluency.

1. Introduction

Verbal fluency is the process of producing as many words as possible according to a given cue. Tests of verbal fluency have been widely used to assess verbal and executive control abilities for brain-injured patients (Lezak, 1995; Ruff et al., 1997; Stuss et al., 1998; Troyer et al., 1998), psychopathic subjects (Rosser and Hodges, 1994; Phillips, 2004; Lencz et al., 2006; Juhasz et al., 2012; Hatton et al., 2014; Bauer et al., 2015), and healthy individuals (Mayr and Kliegl, 2000; Kavé and Knafo-Noam, 2015). The verbal fluency test is typically classified into two tasks: semantic and phonological ones (Baldo et al., 2006; Robinson et al., 2012). The former requires the subject to generate words belonging to a given semantic category (e.g., animal) within a time limit; the latter requires generating words starting with a given letter (Mummery et al., 1996), mora (Dan et al., 2013), or syllable (Glikmann-Johnston et al., 2015). These two tasks partially depend on shared cognitive processes (e.g., executive function, energization, self-monitoring, attention, processing speed, language) and distinct ones (e.g., semantic versus phonological memory) (Ruff et al., 1997; Unsworth et al., 2011; Biesbroek et al., 2015). Recent neuroimaging and neuropsychological research has reached a consensus that widely-distributed, separate and shared brain regions are involved in semantic and phonological fluency. The cortical regions responsible for semantic fluency include the left temporal cortices (Frith et al., 1995; Troyer et al., 1998; Henry and Crawford, 2004; Baldo et al., 2006; Libon et al., 2009; Birn et al., 2010) and the right inferior frontal gyrus (Buckner et al., 1995; Watanabe et al., 1998; Dan et al., 2013; Biesbroek et al., 2015). Those responsible for phonological fluency include the posterior and dorsal portions of the left inferior frontal gyrus (Bookheimer, 2002; Costafreda et al., 2006; Fiez, 1997; Gabrieli et al., 1998; Heim et al., 2009; Robinson et al.,

Abbreviations: ATR, anterior thalamic radiation; FA, fractional anisotropy; IFOF, inferior fronto-occipital fasciculus; MMSE, Mini-Mental State Examination; SLF, superior longitudinal fasciculus; UF, uncinate fasciculus; FAT, frontal aslant tract

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http://dx.doi.org/10.1016/j.neuropsychologia.2017.05.008
Received 22 January 2017; Received in revised form 4 May 2017; Accepted 6 May 2017
Available online 08 May 2017
0028-3932/

2012; but see Biesbroek et al., 2015) and the supplementary motor area (Schlösser et al., 1998; Grogan et al., 2009; Cook et al., 2014). Regions shared by semantic and phonological fluency are localized in the left frontal lobe (Baldo and Shimamura, 1998; Baldo et al., 2001; Robinson et al., 2012), parietal lobe and thalamus (Birn et al. 2010, Frith et al., 1995; Stuss et al., 1998; Wagner et al., 2014; Whitney et al., 2009).

Although researchers have identified multiple grey-matter regions of verbal fluency, less is known about the white-matter networks contributing to this processing. Recent methodological advances enable the direct in vivo examination of the relationship between specific white-matter tracts and verbal fluency. Relevant studies mainly focus on examining the correlations between the pathology of individual white-matter pathways and the deficits of semantic and/or phonological fluency in patients. Semantic fluency was found to be supported by the left inferior fronto-occipital fasciculus (IFOF) in patients harboring left diffuse low-grade glimo (Almairac et al., 2014). Phonological fluency was supported by the left superior longitudinal fasciculus (SLF) in patients with penetrating traumatic brain injury in the whole brain (Cristofori et al., 2015) and the left frontal aslant tract (FAT) in patients with primary progressive aphasia (Catani et al., 2013) or intraoperatively electrostimulation (Kinoshita et al., 2014; Kemerdere et al., 2016). However, the left uncinate fasciculus (UF) was associated with both semantic and phonological fluencies in patients with the left UF removal (Papagno et al., 2011). Our prior studies also found that left ATR, IFOF and UF are involved in semantic processing while left SLF is related to phonological processing (Han et al., 2013, 2014).

While the above studies have determined four left anatomical fiber bundles that are responsible for verbal fluency processing, they might not be conclusive for the following reasons: 1) For the studies with tumor patients, many years of long-standing glioma may give rise to a functional/structural reorganization of the brain (Desmurget et al., 2006; Rosenberg et al., 2008; Briganti et al., 2012). Therefore, the observed tracts might not meaningfully reflect the structural networks of verbal fluency in a healthy population; 2) The lesions of the studies only covered limited tracts without the opportunity to reveal the effects of the remaining tracts of entire brain; and 3) Most of the studies only adopted a cue for a given fluency task. Abundant evidence has demonstrated cognitive and neural dissociations across semantic categories (Martin et al., 1994; Caramazza and Shelton, 1998; Martin, 2007) and phonological cues (Abrahams et al., 2003; Heim et al., 2008; Sheldon and Moscovitch, 2012; Katzev et al., 2013). Thus, a single cue might only identify partial neuroanatomical connectivity of verbal fluency.

The current study is designed to reconstruct a comprehensive white-matter network underlying semantic and phonological fluency by investigating the relationship between the integrity of 22 major tracts in the whole brain and performances of semantic fluency (measured by 3 cues) and phonological fluency (measured by 2 cues) in a group of 51 stroke patients (see Fig. 1 for the flowchart of this study).

2. Materials and methods

2.1. Participants

Healthy subjects and patients with brain damage took part in the present study. Behavioral and neuroimaging data for both subject groups were collected using identical procedures. All were native Chinese speakers and provided informed written consent. This study was approved by the Institutional Review Board of the National Key Laboratory of Cognitive Neuroscience and Leaning, Beijing Normal University.

2.1.1. Healthy subjects

Thirty-nine healthy subjects (20 males) were recruited. All were right-handed (Edinburgh Handedness Inventory criterion; Oldfield, 1971). Their average age was 48.87 years [*standard deviation* (*SD*) = 11.17; range: 26–73 years], and the mean years of formal education was 13.49 (SD = 3.9; range: 9–22). They had normal or corrected-normal vision and hearing, and had no history of psychiatric or neurological diseases. The Chinese version of the Mini-Mental State Examination (MMSE; Folstein et al., 1975; maximum score: 30) was applied to measure general cognitive state (mean = 28.8; SD = 0.87; range: 27–30) (see Supplementary Table 1 for details).

2.1.2. Patients

Fifty-one right-handed stroke patients (40 males) were chosen from the China Rehabilitation Research Center. They all suffered from their first brain injury, which was at least 1-month post-onset (mean = 11.9 months; *SD* = 34.4; range: 1–184 months). They could follow task instructions and had no other neurological or psychiatric diseases. The patients' mean age was 46.8 years (*SD* = 11.0; range: 20–70 years), and the mean years of formal education was 13.1 (*SD* = 3.3; range: 2–19). Neuropsychological tests of Chinese aphasia (Gao et al., 1993) revealed that 6 patients did not present symptoms of aphasia and 1 patients suffered from dysgraphia, while the remaining patients suffered from motor ($n = 8$), sensory ($n = 8$), conduction ($n = 3$), anomia ($n = 7$), global/mixed ($n = 14$), and subcortical aphasia ($n = 4$). The mean score on the MMSE was 22.1 (*SD* = 7.7; range: 3–30) (see Supplementary Table 2 for details).

The two subject groups were comparable in years of education ($t = -0.45$, $p > 0.66$), and different in age ($t = -0.88$, $p > 0.38$) and gender distributions ($x^2 = 7.33$, $p < 0.07$). Most of participants in the present study (42 healthy subjects, 45 patients) were identical to those of our recent studies (Han et al., 2013, 2014). The difference in subject cohorts for the studies was simply due to the difference of available behavioral data.

2.2. Behavioral data collection and scoring

2.2.1. Data collection

Each subject was administered two verbal fluency tasks (semantic and phonological fluency) and two nonverbal control tasks (number calculation and object perception) (see Table 1). Each fluency task required subjects to orally generate as many words as they could in one minute for a given cue. The cues in *semantic fluency task* consisted of three categories (animals, fruits and vegetables, tools), and subjects generated words belonging to each category. Those in *phonological fluency task* were two Chinese syllables (*/bu4/* and */da4/*, the number of the syllable represents the tone of the syllable preceding it in the Chinese language), and generated words beginning with each syllable. The two syllables as initial syllables correspond to the maximum number of words in the Chinese corpus (202 words, 227 words, respectively; Sun et al., 1997). *The number task* included seven exact calculation questions (two additions, two subtractions, two multiplications, and one division). *The object perception task* was adopted from the size match test (Test 7) in the Birmingham Object Recognition Battery (Riddoch and Humphreys, 1993). Participants were tested individually in a noise-attenuated room. Each session lasted no more than 2 h, and pauses were allowed upon request. Testing serial order of the tasks was identical across subjects.

2.2.2. Data scoring

The subjects' responses on the verbal fluency tasks were taped using two digital recorders and were transcribed for scoring. The words that they produced were scored as correct if they belonged to the given cue and were not repetitions. Thus, each subject had five "raw" verbal fluency scores (i.e., total numbers of correct words within a minute) corresponding to three semantic cues and two phonological cues. Correct rates were used as the "raw" scores of two control tasks (number calculation, object perception). Given that our patient sample had large variations in demographic attributes (age, sex, education level), their "raw" scores might not meaningfully reflect the degree of