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

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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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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

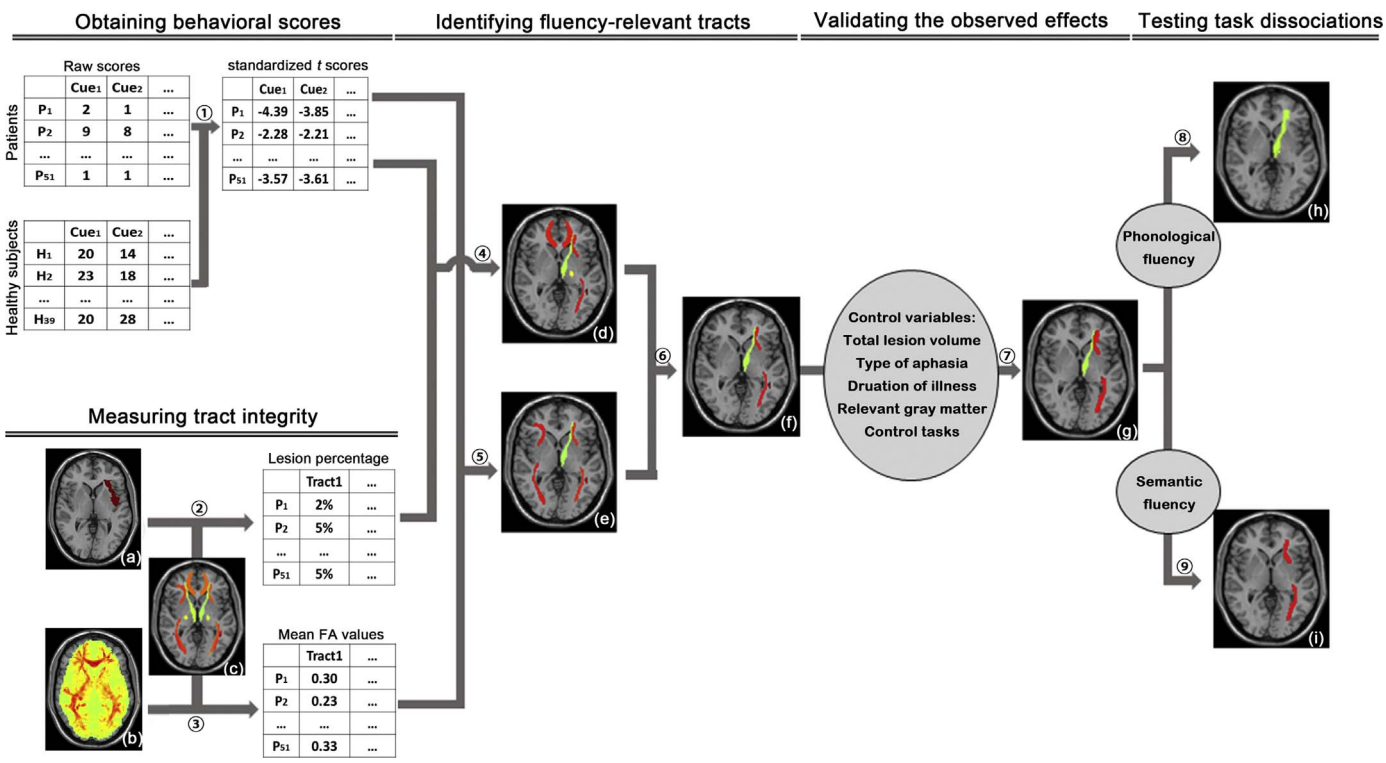

Fig. 1. Flowchart for the analyses in this study. (1) To exclude the influence of demographic factors on the patients' behavioral performance, the raw score of each verbal fluency clue per patient was corrected into a standardized *t* score through considering the distribution of raw scores of normal subjects. (2–3) Inputting the tract mask (c, JHU white-matter tractography atlas, Hua et al., 2008) into the lesion map (a) or the FA map (b) of each patient to calculate the percentage of voxels with lesion or mean FA value, respectively. (4–5) Obtaining the verbal fluency-relevant tracts (d, e) in separate analyses through correlating the behavioral t scores with the lesion percentages or the mean FA values across patients. (6) Extracting the common tracts of the lesion analysis and the mean FA analysis (f). (7) Validating the observed verbal fluency-related effects of each tract by additionally controlling for a wide range of potential confounding factors. (8–9) For the tracts that were found to be important for both semantic and phonological fluency tasks, each of them was investigated for relative importance between the two tasks (h, i) by additionally partialling out the t scores of one of the two tasks.

Table 1
Behavioral performance of subjects.

Task	Healthy subjects ($n=39$)	Patients ($n=51$)	
	Raw score	Raw score	Corrected *t* score
Verbal fluency task			
Semantic fluency			
Animal cue	19.26 (4.88)	9.76 (7.23)***	−2.15 (1.52)
Fruit/vegetable cue	20.14 (4.95)	9.31 (6.75)***	−2.04 (1.25)
Tool cue	12.38 (4.51)	6.12 (4.99)***	−1.29 (1.00)
Phonological fluency			
/Da4/ cue	12.31 (5.13)	5.55 (5.35)***	−1.35 (1.00)
/Bu4/ cue	11.44 (5.54)	5.78 (5.35)***	−1.06 (0.97)
Control task			
Number calculation	0.96 (0.08)	0.77 (0.28)***	−1.46 (2.35)
object perception	0.92 (0.06)	0.83 (0.11)***	−1.31 (1.67)

The numbers in parentheses are standard deviations.
*** Raw scores of patients were significantly lower than those of healthy subjects ($p < 0.001$).

the actual impairments. To rule out the confounding of these demographic variables, we used a single-case-to-controls method developed by Crawford and Garthwaite (2006). Each raw score of patients was corrected into a standardized '*t*' score by comparing the actual performance distribution in the healthy population (see details in Crawford and Garthwaite, 2006; Han et al., 2013). Note that our analyses got similar results using raw and standardized behavioral scores. For the sake of convenience, we report the results of standardized behavioral scores in the following text and those of raw scores in Supplementary Materials.

2.3. Imaging data collection and preprocessing

Imaging data were collected at the China Rehabilitation Research Center with a 1.5T GE SIGNA EXCITE scanner. The parameter of scanning and preprocessing for obtaining the lesion map and the FA map were identical to Han et al. (2013). There were three types of images: high-resolution 3D T1-weighted images by MPRAGE images on sagittal plane (repetition time (TR) = 12.26 ms; echo time (TE) = 4.2 ms; flip angle = 15°; field of view (FOV) = 250 × 250 mm^2; voxel size = 0.49 × 0.49 × 0.70 mm^3; inversion time = 400 ms; slice number = 248 slices), FLAIR T2-weighted images on the axial plane (TR = 8002 ms; TE = 127.57 ms; flip angle = 90°; FOV = 250 × 250 mm^2; voxel size = 0.49 × 0.49 × 5 mm^3; inversion time = 2 s; slice number = 28 slices), and diffusion-weighted images (DWI), which had two separate sequence with different diffusion weighting direction (first acquisition had 15 diffusion weighting direction and the second had 17 with same parameters: TR = 13000 ms; TE = 69.3 ms; flip angle = 90°; FOV = 250 × 250 mm^2; voxel size = 1.95 × 1.95 × 2.6 mm^3; inversion time = 0 s; slice number = 53 slices; b-value = 1000 s/mm^2). All the sequences were scanned twice to improve the quality except for FLAIR T2-weighted images.

2.3.1. Structural magnetic resonance imaging data

We first co-registered the two sequence of the 3D imaging data on the same native space using tri-linear interpolation method applied in SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5); we then co-registered and resliced the FLAIR T2 images to the native space of the averaged 3D images using tri-linear interpolation method in SPM5. Each patients' lesion contour was draw on 3D images by two trained person slice by slice, visually referring to FLAIR T2 images, and this procedure was supervised by a superior radiologist. Patients' structural

images were resliced into $1 \times 1 \times 1$ mm^3 voxel size. In the preprocessing, some studies adopt automatic normalization method in which the local detailed information of brain images are automatically evaluated and matched (e.g. Price et al., 1998), but this method couldn't excluded the effect of lesion in the brain, which might cause extra distortions on the images. To resolve the problem, one method usually first masks the lesions, and then inputs the remaining intact issues into the normalization processing (Brett et al., 2001). By contrast, manual registration method might more or less overcome such a limitation. Thus, it was adopted by the present study. Specially, each patient's structural images were registered into Talairach space via the '3D Volume Tools' in BrainVoyager QX v2.0 (www.brainvoyager.com), in which we manually marked the anterior commissure to posterior commissure plane and the borders of the Cerebrum. The affine transformation matrix between native and Talairach spaces was extracted with ANTs software package (Advanced Normalization Tools, www.picsl.upenn.edu/ANTS/). The lesion images were transformed into Talairach space using this matrix with 'WarpImageMultiTransform' program. Given that the registration procedure was based on anatomical landmarks without evaluating local detailed information of brain, it was not affected by the lesions. The lesion image was finally transformed into the MNI space using the affine transformation matrix between MNI and Talairach spaces using a similar method.

2.3.2. Diffusion magnetic resonance imaging data

We first merged the two paired sequences into one single 4D nifty-1 format file and their diffusion-weighted gradient tables. Then we executed BET: skull removal; Eddycorrect (correction of eddy current distortion) and DTIFIT (build diffusion tensor models) with a pipeline tool, PANDA (Cui et al., 2013) (www.nitrc.org/projects/panda/), then we registered those fractional anisotropy maps with the FMRIB fractional anisotropy template in MNI space with ANTs (version 1.9). The normalization had two parts: 1) linear rigid affine transform, which first obtain an affine transform.txt file for each participant, and then produce the fractional anisotropy map in MNI space with 'WarpImageMultiTransform' program. 2) non-linear transform registration, which obtained more fine-grained normalized fractional anisotropy map of each patient in MNI space with shell script 'buildtemplate'.

2.4. Identifying verbal fluency tracts

To find white-matter pathways that support semantic and phonological fluency processing, we separately correlated the integrity of each of the major tracts and the performances of semantic and phonological fluency. Twenty tracts were extracted from the "JHU white-matter tractography atlas" (Hua et al., 2008) in the FMRIB Software Library (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases). We used the 25%-threshold sub-template. Furthermore, two additional tracts (the left and right FAT tracts) were also included because they have been found to be associated with verbal fluency processing (Catani et al., 2013). They were obtained from the "NeuroVault" webpage (Gorgolewski et al., 2015) and masked with 60% threshold (see details in Table 2).

Given that the following analyses were highly similar for semantic and phonological fluency, for simplicity, we used the term "semantic (and phonological)" to denote the analyses separately parallel to them.

2.4.1. Lesion-behavior correlation

Three tracts (left cingulate gyrus, left cingulum hippocampus, right cingulum hippocampus) had lesions in less than five patients (see Table 1) and were excluded from our lesion analysis. For each of the remaining 19 tracts, the lesion percentage (number of voxels with lesion divided by total number of voxels on the tract) was correlated with the corrected t scores of each cue of semantic (and phonological) fluency tasks across 51 patients. There were 3 semantic cues and 2 phonological cues. The results for each cue were adjusted for the 19 tracts with the Bonferroni correction method ($p < 0.0026$, corrected $p < 0.05$).

2.4.2. FA-behavior correlation

For each of the 22 tracts, the mean FA value (averaging the FA values of all voxels in the tract) was correlated with the scores of each fluency cues across 51 patients. The Bonferroni correction method ($p < 0.0023$, corrected $p < 0.05$) was implemented on the 22 white-matter tracts.

A tract was considered to be related with semantic (and phonological) fluency processing only if it showed significant correlation effects in both the lesion and FA analyses for each of semantic (and phonological) cues.

2.5. Validating the effects of verbal fluency tracts

To examine whether the observed verbal fluency-related white-matter tract results were driven by various potentially confounding variables, we again correlated the semantic (and phonological) fluency composite scores with lesion percentages or mean FA values of each observed tract, additionally partialling out the following variables respectively. To simplify, the behavioral indexes of these analyses implemented semantic (and phonological) fluency composite scores, which were computed by averaging the z-transformed "t" scores of semantic (and phonological) cues.

2.5.1. Total lesion volume

This variable was calculated as the total number of lesion voxels in the whole brain.

2.5.2. Type of aphasia

The patients were distributed into seven types of aphasia (motor, sensory, anomia, conduction, global/mixed, subcortical aphasia, and non-aphasia) and one for others. It was scored as a categorical variable.

2.5.3. Duration of illness

We treat the duration variable (the months of duration of brain damage) as covariate. Because of the unreliability of white-matter measures early after stroke, and the functional/structural reorganization of white-matter tracts later after this disease, we further calculated the correlations only in the patients whose stroke duration were between 3 and 10 months ($n = 22$).

2.5.4. Effects of verbal fluency-related grey-matter

This variable was the lesion percentages of each of semantic (and phonological) fluency-related grey-matter region. To obtain these regions, we conducted a voxel-based lesion-symptom mapping (VLSM) analysis (Bates et al., 2003; Rorden et al., 2007), in which semantic (and phonological) fluency composite scores of between patients with lesion and without lesion on each voxel were compared using nonparametric Brunner-Munzel test (Brunner and Munzel, 2000) [false discovery rate (*FDR*) corrected, $q < 0.05$]. Voxels in which fewer than five patients had lesions were excluded from the analysis. The resulting whole brain VLSM map was then overlaid on a grey-matter mask (SPM5 template, probability higher than 0.40).

2.5.5. Performance of nonverbal control tasks

They were the corrected t scores of number calculation and object perception tasks.

2.6. Testing the dissociation of fluency tasks for verbal fluency tracts

For the tracts that were attributable to both semantic and phonological fluency processing in the above analyses, we further examined whether they had the significant effects of semantic fluency over and above phonological fluency, or vice versa. The semantic and phonological fluency tasks involve in task-specific processing (e.g., semantic

Table 2
Correlation coefficients between the integrity of 22 tracts and performance on verbal fluency tasks in patients.

Tract	Total volume (mm^3)	Patients with lesion	Semantic fluency						Phonological fluency			
			Lesion-behavior correlation			FA-behavior correlation			Lesion-behavior correlation		FA-behavior correlation	
			Animal cue	Fruit/ Vegetable cue	Tool cue	Animal cue	Fruit/ Vegetable cue	Tool cue	*/Da4/* cue	*/Bu4/* cue	*/Da4/* cue	*/Bu4/* cue
ATR_L	8128	28	−0.39#	−0.47**	−0.47**	0.56***	0.49**	0.63***	−0.49**	−0.50**	0.48**	0.53**
ATR_R	7576	22	0.33	0.38	0.28	−0.27	−0.33	−0.14	0.33	0.24	−0.28	−0.23
CT_L	5464	24	−0.19	−0.26	−0.28	0.38#	0.30	0.45*	−0.29	−0.25	0.40	0.36#
CT_R	4760	20	0.47**	0.52**	0.43*	−0.40#	−0.44*	−0.31	0.44*	0.40#	−0.41	−0.33#
CG_L	1552	1	/	/	/	0.21	0.13	0.28	/	/	0.08	0.24
CG_R	608	6	0.06	0.09	−0.09	0.09	0.04	0.25	0.02	0.05	0.06	0.16
CH_L	248	0	/	/	/	0.18	0.08	0.18	/	/	0.17	0.06
CH_R	544	1	/	/	/	−0.07	−0.12	0.06	/	/	−0.08	−0.15
FMA	5744	9	0.11	0.07	0.13	0.11	0.02	0.16	0.07	0.13	0.03	0.06
FMI	19712	18	−0.00	−0.10	−0.05	0.18	0.09	0.27	−0.10	−0.14	0.16	0.25
IFOF_L	5048	28	−0.49**	−0.46*	−0.55***	0.64***	0.57***	0.71***	−0.50**	−0.50**	0.55***	0.54***
IFOF_R	6304	22	0.25	0.34	0.23	−0.23	−0.32	−0.14	0.30	0.32	−0.20	−0.18
ILF_L	5400	16	−0.35	−0.37	−0.38#	0.45*	0.35	0.51**	−0.34	−0.29	0.31	0.30
ILF_R	3125	7	0.13	0.07	0.05	−0.13	−0.16	−0.02	0.13	0.14	−0.12	−0.08
SLF_L	9472	29	−0.53**	−0.55***	−0.59***	0.56***	0.51**	0.62***	−0.52**	−0.48**	0.53**	0.53***
SLF_R	7456	16	0.25	0.32	0.16	−0.24	−0.36	−0.17	0.27	0.21	−0.25	−0.22
UF_L	744	17	−0.45*	−0.41*	−0.52**	0.64***	0.51**	0.71***	−0.43*	−0.40#	0.53**	0.50**
UF_R	448	11	0.22	0.29	0.21	−0.27	−0.40#	−0.18	0.30	0.29	−0.28	−0.25
SLF_L(T)	96	6	−0.26	−0.27	−0.14	0.35	0.38	0.43*	−0.22	−0.13#	0.37	0.39
SLF_R(T)	72	8	0.12	0.08	0.02	−0.08	−0.17	−0.1	0.12	0.15	−0.16	−0.16
FAT_L	5272	31	−0.49**	−0.50**	−0.50**	0.44*	0.35	0.52**	−0.54***	−0.51**	0.40#	0.40#
FAT_R	4921	23	0.30	0.43*	0.25	−0.08	−0.20	0.01	0.32	0.29	−0.07	−0.04

L = left, R = right, ATR = anterior thalamic radiation; CT = corticospinal tract; CG = cingulum gyrus; CH = cingulum hippocampus; FMA = forceps major; FMI = forceps minor; IFOF = inferior fronto-occipital fasciculus; ILF = inferior longitudinal fasciculus; SLF = superior longitudinal fasciculus; UF = uncinated fasciculus; (T) =(temporal part); FAT = frontal aslant tract. Bonferroni corrected: # $p < 0.1$; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; "/" could not carry out the analysis because of few patients.

category retrieval, phonetic category encoding) and task-general processing (e.g., executive control). When a tract was found to be associated with these two fluency tasks, it might be dedicated to 1) only task-general processing, 2) only the two task-specific processing, 3) both task-general and the two task-specific processing), or 4) both task-general and one task-specific processing. In the last case, the tract could be found unique contributions to one fluency task compared to the other one. Therefore, the partial correlations were performed between semantic fluency composite scores and lesion percentages or mean FA values, regressing out phonological fluency composite scores. The same analysis procedure was also applied to the phonological fluency composite scores.

3. Results

3.1. Behavioral performance of participants

The raw scores indicate that brain-damaged patients generated less exemplars for semantic and phonological fluency cues than normal subjects (p-values $< 10^{-5}$, Table 1). Furthermore, the patients had low corrected "t" scores on the tasks (mean: −1.58; range: −2.15 to −1.06), indicating the impairments of their semantic and phonological fluency processing. The t scores were significantly correlated between the three semantic cues ($R_{\text{animal-fruit/vegetable}} = 0.85$, $p < 10^{-15}$; $R_{\text{animal-tool}} = 0.8$, $p < 10^{-12}$; $R_{\text{fruit/vegetable-tool}} = 0.77$, $p < 10^{-9}$), and between the two phonological cues ($r = 0.82$; $p < 10^{-13}$).

3.2. Verbal fluency-relevant tracts

Table 2 displays the results of correlation analyses between tract integrity and the impairments of verbal fluency cues. The lesions of patients were distributed widely, covering mostly white-matter and grey-matter areas, with most patients having lesions in the insula and its surrounding white-matter tissues. Although the mean FA map of the patients showed the basic white-matter connectivity skeleton, the FA values were significantly reduced compared with those of the healthy adults (Fig. 2).

3.2.1. Lesion-behavior correlation

Performance on each of the three cues in semantic fluency task was significantly correlated with the lesion percentages of four tracts: the left IFOF ($r = -0.55$ to -0.46, corrected p-values < 0.05), left SLF ($r = -0.59$ to -0.53, corrected p-values < 0.01), left UF ($r = -0.52$ to -0.41, corrected p-values < 0.05) and left FAT ($r = -0.50$ to -0.49, corrected p-values < 0.01), however, the left ATR was significantly correlated with two cues of semantic fluency ($r = -0.47$ and -0.47, corrected p-values < 0.01) and marginally significantly correlated with one semantic cue ($r = -0.39$ corrected p-values < 0.06). Four tracts were significantly negatively correlated with the t scores of both cues of the phonological fluency task: the left ATR ($r = -0.50$ and -0.49, corrected p-values < 0.01), left IFOF (r=-0.50 for both cues, corrected p-values < 0.01), left SLF ($r = -0.52$ and -0.48, corrected p-values < 0.01) and left FAT ($r = -0.54$ and -0.52, corrected p-values < 0.01) while the left UF was significantly negatively correlated with */da4/* cue ($r = -0.43$, corrected p-values < 0.01) but marginally significantly correlated with the */bu4/* cue ($r = -0.40$, corrected p-values < 0.06) (Fig. 3). Additionally, we also observed that the lesion volume of the right corticospinal tract was significantly positively correlated with performance of semantic cues ($r = 0.43$ to 0.52, corrected $p < 0.01$), and */da4/* cue ($r = 0.44$, corrected $p < 0.05$); the lesion volume of the right FAT was significantly positively correlated with one semantic cue ($r = 0.43$, corrected $p < 0.05$).

3.2.2. FA-behavior correlation

The mean FA values of four tracts were significantly positively correlated with the performance on each semantic fluency cue: the left ATR ($r = 0.49$ to 0.63, corrected p-values < 0.01), left IFOF ($r = 0.57$ to 0.71, corrected p-values < 0.001), left SLF ($r = 0.51$ to 0.62, corrected

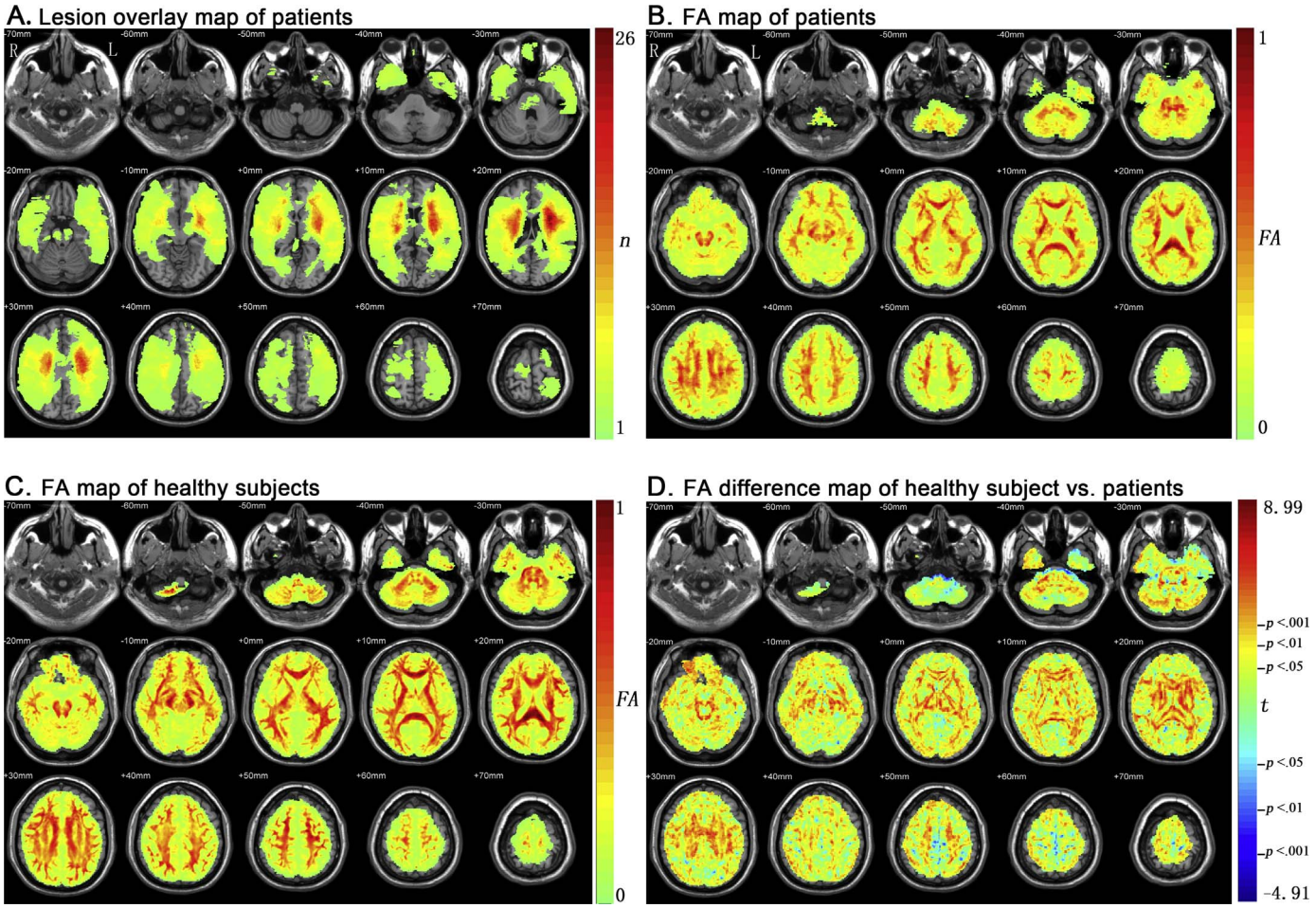

Fig. 2. Raw neuroimaging maps of subjects. (A) The number of patients with lesion; (B-C) The mean FA value of subjects; (D) The *t* values of FA values between subject groups (two-sample *t*-test), $t > 1.99$, $p < 0.05$; $t > 2.64$, $p < 0.01$; $t > 3.41$, $p < 0.001$.

p-values < 0.01) and left UF ($r = 0.51$ to 0.71, corrected *p*-values < 0.01). This was also true for both cues of phonological fluency tasks: the left ATR ($r = 0.48$ and 0.53, corrected *p*-values < 0.01), left IFOF ($r = 0.54$ to 0.55, corrected *p*-values < 0.001), left SLF ($r = 0.53$ to 0.53, corrected *p*-values < 0.001) and left UF ($r = 0.50$ to 0.53, corrected *p*-values < 0.01) (Fig. 3). In addition, the scores on one semantic fluency cues was significantly correlated with the mean FA value of the left corticospinal tract ($r = 0.45$, corrected *p*-values < 0.05) as well as the temporal part of the left SLF ($r = 0.43$, corrected *p*-values < 0.05), and significantly negatively correlated with the right corticospinal ($r = 0.44$, corrected $p < 0.05$) while two cues of semantic fluency were positively correlated with the left ILF ($r = 0.45$ and 0.51, corrected $p < 0.05$) and left FAT ($r = 0.44$ and 0.52, corrected $p < 0.01$).

The five tracts (left ATR, IFOF, SLF, UF and FAT) showing convergence across lesion and FA analyses might be dedicated to verbal fluency processing. They were considered further in the following analyses.

3.3. Validation of the effects of verbal fluency tracts

Table 3 shows the results of the effects of the verbal fluency-related tracts after controlling for the following potentially confounding factors.

3.3.1. Total lesion volume

The total lesion volume values were not significantly correlated with semantic or phonological fluency composite scores ($r = -0.14$ to -0.11, *p*-values > 0.34). When the values were treated as covariate, the lesion percentages of the above five tracts were significantly correlated with semantic or phonological fluency composite scores (partial $r = -0.59$ to -0.43, *p*-values < 0.003). Similarly, the mean FA values of the five tracts also remained significantly correlated with both composite scores (partial $r = 0.44$ to 0.68, *p*-values < 0.002).

3.3.2. Type of aphasia

The type of aphasia was significantly correlated with the scores of semantic fluency and phonological fluency ($r = 0.61$ to 0.63, *p*-values < 10^{-5}). When we controlled for aphasia type, the lesion percentages of the above five tracts remained significantly correlated with semantic or phonological fluency composite scores (partial $r = -0.52$ to -0.36, *p*-values < 0.02) except for the correlation between left UF and phonological fluency ($r = -0.27$, *p*-values < 0.06). Similarly, the mean FA values of above five tracts were also remained significant (partial $r = 0.37$ to 0.66, *p*-values < 0.009).

3.3.3. Duration of illness

The duration of the disease was not correlated with the composite scores of semantic fluency or phonological fluency ($r = -0.08$ to 0.05, *p*-values > 0.58). When regressing out this confounding factor, both lesion percentages and mean FA values of the above five tracts were still significantly correlated with the both fluency composite scores (lesion percentage: partial $r = -0.60$ to -0.43, *p*-values < 0.002; FA value: partial *r*: 0.43–0.69, *p*-values < 0.003). Furthermore, when our analysis was conducted only in the patients having stroke duration time between 3 and 10 months ($n = 22$), the above five tracts still significantly correlated with the composite scores of both fluency tasks

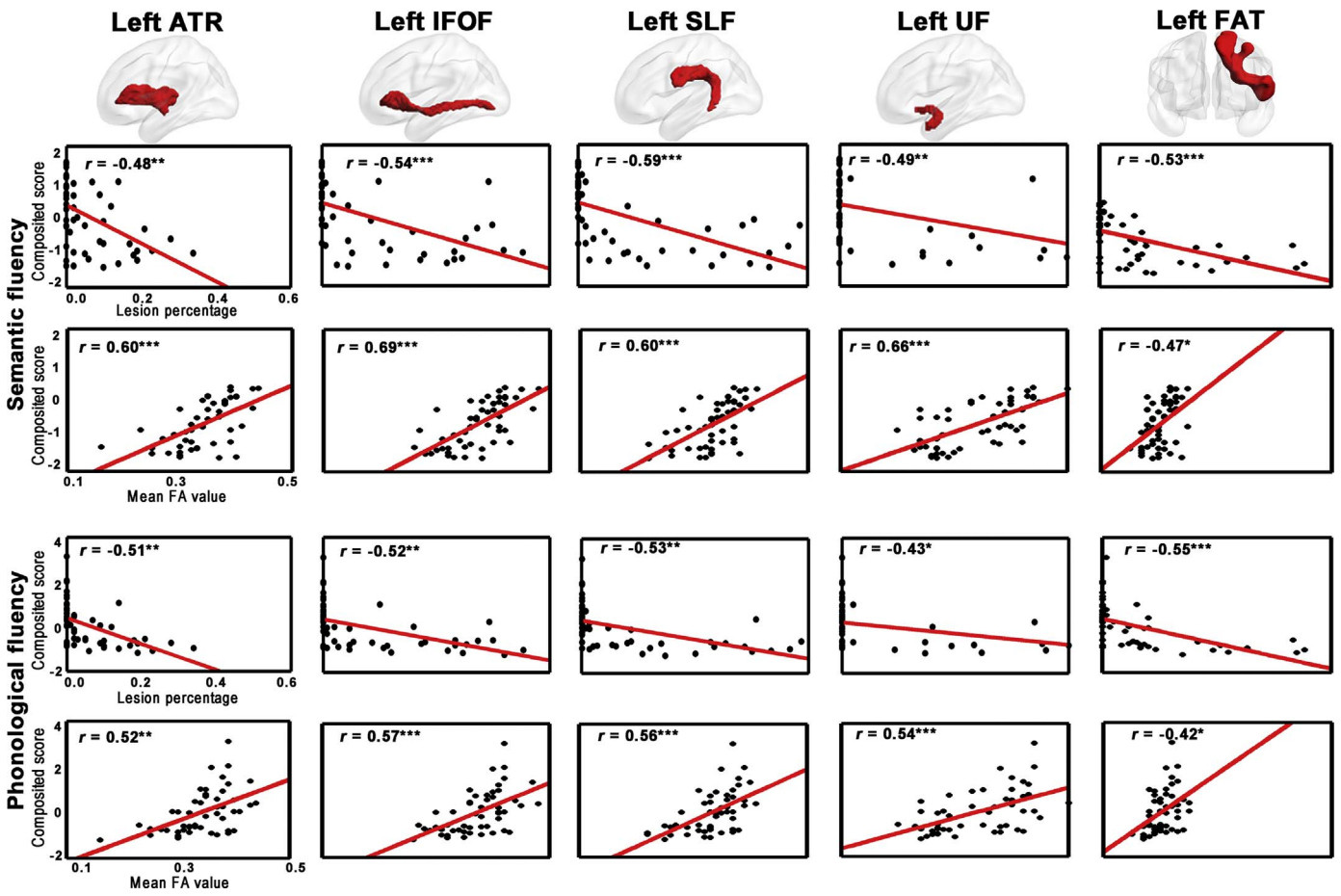

Fig. 3. Scatter diagram of tract integrity (lesion volume percentage and mean FA value) of the five tracts and the behavioral performance of semantic and phonological fluency across patients. The top row shows the shape of the tracts. ATR = anterior thalamic radiation; IFOF = inferior fronto-occipital fasciculus; SLF = superior longitudinal fasciculus; UF = uncinated fasciculus; FAT = frontal aslant tract.

respectively (lesion percentage: partial $r = -0.65$ to -0.47, p-values < 0.03; FA value: partial r: 0.52–0.80, p-values < 0.02).

3.3.4. Influence of verbal fluency-related grey-matter

As presented in Fig. 4, the VLSM analyses revealed that the regions involved in semantic and phonological fluency processing were similar, including the left insula, inferior/middle frontal gyrus, precentral and postcentral gyrus, putamen, and superior/middle temporal gyrus. This is highly consistent with previous findings (Gurd et al., 2002; Glikmann-Johnston et al., 2015). After covarying the lesion volumes of the semantic fluency-related cortical regions, the mean FA values of the four tracts (left ATR, IFOF, SLF and UF) were still significantly correlated with semantic fluency composite scores (partial $r = 0.42$ to 0.54, p-values < 0.003) and phonological composite scores (partial $r = 0.34$ to 0.44, p-values < 0.02). Moreover, the lesion percentages of the left ATR and left SLF also showed significant correlations with these scores (partial $r = -0.41$ to -0.41 to -0.31, p-values < 0.03). Similar patterns were also observed in the correlations with the phonological composite scores (lesion percentage: partial $r = -0.39$ to -0.34, p-values < 0.02).

3.3.5. Performance on control tasks

The corrected t scores of the nonverbal control tasks (number calculation, object visual perception) were significantly correlated with the composite scores of semantic and phonological fluency ($r = 0.30$ to 0.51, p-values < 0.05). When we treated the control task scores as covariates, the integrity values of the above five tracts remained significantly correlated with the composite scores of semantic and phonological fluency respectively (lesion percentage: partial $r = -0.49$ to -0.30, p-values < 0.05; FA value: partial $r = 0.30$ to 0.62, p-values < 0.04).

The above analyses demonstrated that the effects of the five left tracts (left ATR, IFOF, UF, SLF and FAT) could not be fully accounted for by the possible confounding variables. These results suggest that the tracts were critical for both semantic and phonological fluency processing, and their degeneration caused the disorders of the two types of verbal fluency.

3.4. Dissociation between the two verbal fluency tasks on verbal fluency tracts

To further elucidate the relative importance of the five observed verbal fluency-related tracts for the two verbal fluency tasks (semantic vs. phonological fluency), we calculated the correlation between the lesion percentages or mean FA values of each tract and the composite scores of one task of interest, with the composite scores of the other task and other five potential confounding factors as covariates. We observed that the FA values of left ATR, IFOF and UF were kept significant correlation with semantic fluency when the covariates included the phonological fluency scores and the potential confounding factors (partial $r = 0.36$ to 0.49, p-values < 0.02). Other correlations did not reach significance level (p-values > 0.05). These indicate that the left ATR, IFOF and UF had unique contributions to semantic fluency over and above phonological fluency.

4. Discussion

The primary objective of this study is to reveal the major white-

Table 3
Partial correlation coefficients between the integrity of five tracts and composite scores of verbal fluency, controlling for individual potential confounding factors.

Control variable	Type of verbal fluency	Type of correlation analysis	Left ATR	Left IFOF	Left SLF	Left UF	Left FAT
Total lesion volume							
	Semantic	Lesion-behavior correlation	−0.47***	−0.52***	−0.59***	−0.48***	−0.52***
		FA-behavior correlation	0.59***	0.68***	0.60***	0.66***	0.47***
	Phonological	Lesion-behavior correlation	−0.52***	−0.53***	−0.53***	−0.43**	−0.57***
		FA-behavior correlation	0.53***	0.57***	0.57***	0.55***	0.44*
Type of aphasia							
	Semantic	Lesion-behavior correlation	−0.45***	−0.44**	−0.47***	−0.36*	−0.39*
		FA-behavior correlation	0.60***	0.66***	0.53***	0.57***	0.43*
	Phonological	Lesion-behavior correlation	−0.52***	−0.43**	−0.36**	−0.27#	−0.40*
		FA-behavior correlation	0.51***	0.51***	0.46***	0.39**	0.37*
Duration of illness							
	All patients (n=51)						
	Semantic	Lesion-behavior correlation	−0.49***	−0.54***	−0.60***	−0.50***	−0.55***
		FA-behavior correlation	0.60***	0.69***	0.60***	0.67***	0.47***
	Phonological	Lesion-behavior correlation	−0.52***	−0.53***	−0.52***	−0.43**	−0.55***
		FA-behavior correlation	0.53***	0.58***	0.57***	0.54***	0.43*
	Patients with 3–10 month onset time (n=22)						
	Semantic	Lesion-behavior correlation	−0.47*	−0.60**	−0.60**	−0.57**	−0.65**
		FA-behavior correlation	0.80***	0.74***	0.52*	0.71***	0.64**
	Phonological	Lesion-behavior correlation	−0.52*	−0.60**	−0.57**	−0.48*	−0.64**
		FA-behavior correlation	0.74***	0.71***	0.62**	0.66***	0.66*
Relevant effect of grey matter							
	Semantic	Lesion-behavior correlation	−0.31*	−0.23	−0.41**	−0.14	−0.14
		FA-behavior correlation	0.42**	0.54***	0.49***	0.53***	0.28
	Phonological	Lesion-behavior correlation	−0.39**	−0.26	−0.34*	−0.09	−0.25
		FA-behavior correlation	0.34*	0.39**	0.44**	0.38**	0.23
Nonverbal control tasks performance							
	Semantic	Lesion-behavior correlation	−0.37**	−0.42**	−0.45**	−0.38**	−0.46***
		FA-behavior correlation	0.51***	0.60***	0.46***	0.62***	0.36*
	Phonological	Lesion-behavior correlation	−0.42**	−0.40**	−0.34*	−0.30*	−0.49***
		FA-behavior correlation	0.41**	0.43**	0.37**	0.45**	0.30*

Full names of the tracts are given in Table 2.
# $p < 0.10$.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

matter fiber bundles supporting two main types of verbal fluency processing: semantic and phonological fluency. Using cognitive-behavioral and brain imaging measures in 51 stroke patients, we observed five left-hemispheric tracts in the whole brain (the left ATR, IFOF, SLF, UF and FAT) whose integrity degree were significantly correlated with the severity of deficits in semantic and phonological fluency. These effects were still significant after we regressed out the influence of individual potential confounding factors (e.g., total lesion volume). Further analysis revealed that the damage to the left ATR, IFOF and UF caused additional unique deficits for semantic fluency over phonological fluency.

Although the literature has uncovered that the left IFOF, SLF and UF engage in verbal fluency (Papagno et al., 2011; Almairac et al., 2014; Cristofori et al., 2015), our results further expanded those findings. First, we confirmed the findings of SLF and UF through using short-term brain damaged subjects to overcome the functional/structural reorganization of long-term brain damage, and adopting multiple fluency cues for each task to overcome the bias of single fluency cue (Almairac et al., 2014). Second, we considered all main tracts of the whole brain rather than only a limited number of tracts and identified other verbal fluency-related tracts (the left ATR). Third, we controlled for a wide range of potentially influential factors and further validated our result pattern.

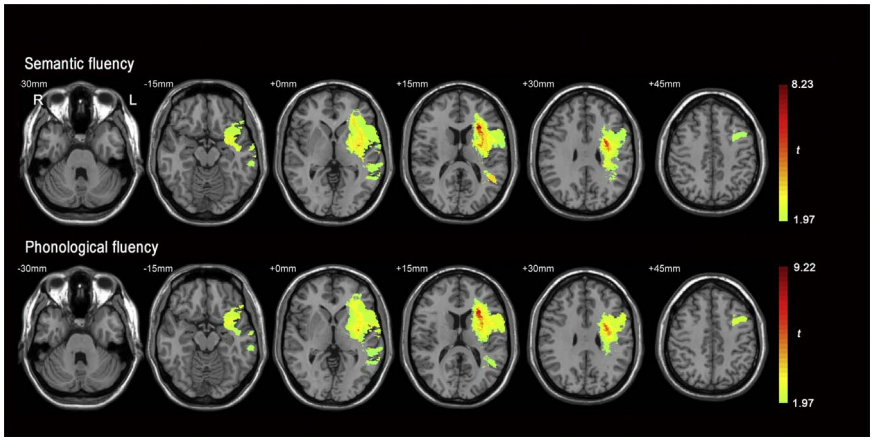

Fig. 4. Results of voxel-based lesion-symptom mapping (VLSM) analysis for semantic and phonological fluency in patients. Voxels in which fewer than five patients had lesions were excluded from the analysis.

Finally, we investigated the relative role of each tract for semantic and phonological fluency, and found that semantic fluency relied on these tracts more than did phonological fluency. Briefly, the current study identified a distributed convergent and divergent anatomical network between semantic and phonological fluency. The following sections will discuss the pivotal role of these tracts in verbal fluency.

4.1. Left anterior thalamic radiation

The left ATR is a major white-matter tract projection from the anterior and midline nuclear groups of the left thalamus to the left prefrontal cortex. The left prefrontal lobe has been widely reported to participate in verbal fluency processing in studies using neuropsychological methods (Miller, 1984; Rogers et al., 1998; Stuss et al., 1998), functional MRI (Birn et al., 2010; Whitney et al., 2009; see meta-analysis in Wagner et al., 2014), positron emission tomography (Mummery et al., 1996; Ravnkilde et al., 2002; Laisney et al., 2009), and functional near infrared spectroscopy (Dan et al., 2013). Meanwhile, the left thalamus is activated when subjects produce words with particular cues (Ravnkilde et al., 2002; Abrahams et al., 2003; Indefrey and Levelt, 2004; Birn et al., 2010).

Recent studies have identified that the left ATR tract plays a critical role in semantic information processing (Han et al., 2013; Mirman et al., 2015). Therefore, it is not surprising to find that this tract contributes to semantic fluency. However, it is unclear whether this tract damage also causes phonological fluency disruption. We speculate that this might relate to the role this tract plays in verbal memory (Mori et al., 1986; Wagner et al., 1998), executive function and planning complex behaviors (Floresco and Grace, 2003; Van der Werf et al., 2003; Zoppelt et al., 2003; Mamah et al., 2010). Take verbal memory, for example. The presence of lesions in the left ATR had a strict association with the severity of memory loss in patients with Alzheimer's disease (Niida et al., 2013; Torso et al., 2015). The left thalamic infarction caused a disturbance in verbal memory (Mori et al., 1986). The left prefrontal cortices were activated by verbal memory tasks (Wagner et al., 1998). Given that both semantic and phonological fluencies depend on verbal memory and executive control functions while this tract have extra function on semantic processing, the disconnection of the left ATR bundle led to the disruption of both fluency processes and more damage to semantic fluency.

4.2. Left inferior fronto-occipital fasciculus

The IFOF is historically described as the longest associative bundle in the human brain and it divides into two subcomponents: the superficial layer, which connects the inferior frontal gyrus with parietal lobule, occipital cortex, Wernicke's area and fusiform gyrus; and the deep layer, which connects the superior parietal lobule, occipital extrastriate cortex and fusiform gyrus to the dorsolateral prefrontal cortex, lateral orbito-frontal and middle frontal gyrus (Sarubbo et al., 2013). Some evidence has shown that the processing of verbal fluency involves the left frontal cortex (Billingsley et al., 2004; Henry and Crawford, 2004; Libon et al., 2009; Robinson et al., 2012), parietal lobule and fusiform gyrus (Indefrey and Levelt, 2004; Sheldon and Moscovitch, 2012).

Recent evidence has shown that the left IFOF plays a causal role in semantic processing (Duffau et al., 2002, 2005, 2009; Mandonnet et al., 2007; Duffau, 2008; Acosta-Cabronero et al., 2010, 2011; Han et al., 2013; Mirman et al., 2015) and semantic fluency (Almairac et al., 2014). Furthermore, this tract has been found to be associated with executive function (Pérez-Iglesias et al., 2010; Kucukboyaci et al., 2012; Santiago et al., 2015). For instance, its FA values were associated with the scores of executive function in patients with coronary artery disease (Santiago et al., 2015). Executive function encompasses a broad range of functions, including attention, set-shifting, and response inhibition. These functions might be involved in both semantic and phonological fluency processing. Therefore, the pathology of this tract caused both impaired semantic and phonological fluency. Furthermore, this tract is also additionally correlated with semantic processing in semantic verbal fluency, leading to the added importance of semantic fluency relative to phonological fluency.

While Almairac and colleagues (2014) proposed that the left IFOF contributes to semantic fluency rather than phonological fluency (Almairac et al., 2014), we found that this tract is involved in both types of verbal fluency processing. There are at least four possibilities why this tract seemed to have effects on phonological fluency only appeared in our study and not in the prior study. First, the brain lesion of the patients in the prior study might be only localized in the tract's semantic branches, but in both semantic and executive function branches in our study. Second, the prior study only used one phonological cue in phonological fluency task (letter “P”) and might have the cue bias, leading to the null results of phonological fluency. However, we adopted two phonological cues to avoid the bias. Third, the performance of phonological verbal fluency was scored on the basis of the subject responses in 2 min in the prior study, but 1 min in our study. Because the number of generated words in verbal fluency obviously declined faster in the second minute compared to the first (Holtzer et al., 2009), it is possible that the patients' performance reached a ceiling effect by minute two. If that were so, then the effects of phonological fluency would only be found in responses within 1 min and not 2 min. Finally, patients with long-term brain tumors in the prior study may have reorganized phonological fluency functioning to other white-matter tracts.

4.3. Left uncinate fasciculus

The left UF is a hook-shaped bundle that links the left anterior temporal lobe with the left inferior frontal gyrus and the lower surfaces of the left frontal lobe (Catani et al., 2002; Schmahmann et al., 2007). Our recent study (Han et al., 2013) identified it as a semantic-related tract (but see Duffau et al., 2009). Diao et al. (2015) further found the correlation of this tract FA value with semantic verbal fluency in patients with temporal lobe epilepsy. Papagno et al. (2011) also observed that the removal of the tract affected abilities of verbal fluency. In addition, this tract may also be involved in verbal memory processing (Diehl et al., 2008; McDonald et al., 2008; Niogi et al., 2008), which was observed not only in adults but also in children and adolescents (Mabbott et al., 2009) and across clinical populations (e.g., individuals with temporal lobe epilepsy, schizophrenia, or mild cognitive impairment (McDonald et al., 2008)). By contrast, a significant correlation did not appear between the FA value of the tract and performance on visual memory task (McDonald et al., 2008).

Given that both semantic and phonological fluency tasks require the involvement of verbal memory, the left UF dysfunction caused the impairments of both types of tasks. Moreover, this tract is additionally responsible for semantic processing (Galantucci et al., 2011; Agosta et al., 2012; Han et al., 2013), indicating that it has a more predominant role on semantic fluency over phonological fluency.

4.4. Left superior longitudinal fasciculus

The SLF is an important dorsal long-range bundle with three distinct branches: SLF I (connecting the superior and medial parietal cortex to the dorsal and medial cortex of the frontal lobe and the supplementary motor cortex), SLF II (connecting caudal-inferior parietal cortex with the dorsolateral prefrontal cortex) and SLF III (connecting the supramarginal gyrus with the ventral premotor and prefrontal cortex) (Schmahmann et al., 2007).

The left SLF has been widely reported to be associative with language articulation (Breier et al., 2008; Han et al., 2014; Johnson et al., 2015), processing speed (Turken et al., 2008; Kerchner et al., 2012) and working memory (Vestergaard et al., 2011; Peters et al.,

2012). Both semantic and phonological fluency tasks are involved in phonological output. Hence, this tract disconnection causes the abnormality of these two tasks. Other studies also found a close relationship between verbal fluency and the left SLF (Shinoura et al., 2012; Cristofori et al., 2015). A meta-analysis conducted by Peters et al. (2012) showed that the FA value of the left SLF was a significant predictor of verbal fluency.

4.5. Left frontal aslant tract

The left FAT connects the pre-supplementary motor area to the posterior part of Broca's area (Lawes et al., 2008; Ford et al., 2010; Catani et al., 2012). It is always left-lateralized in right-handed subjects, suggesting a role in language processing (Catani et al., 2012). The FA measurements and radial diffusivity measurements of the tract were significantly correlated with the mean length of utterance and words per minute in patients with primary progressive aphasia (Catani et al., 2013). Moreover, the intraoperative electrostimulation on this tract would interrupt the fluent speech of patients during the surgery (Kinoshita et al., 2014; Kemerdere et al., 2016). This tract is also associated with speech production (Kronfeld-Duenias et al., 2016). Our results are consistent with these previous findings and further reveal that the tract also engages in semantic fluency processing.

4.6. Methodological considerations

While the present study reconstructs a neuroanatomical network of verbal fluency, it might have the following limitations. First, although we sought to recruit a variety of lesion distributions in our patients, the numbers of patients with different lesions were not equivalent across tracts (see Table 1). The effects of the tracts with only a few lesioned patients might not be determinable. Second, the structural network of verbal fluency was constructed on the basis of a Chinese population, and it is unknown whether such a network has consistency across ethnic groups. Finally, some studies have reported that cortical regions on the right hemisphere also participate in verbal fluency processing (Indefrey and Levelt, 2004; Sheldon and Moscovitch, 2012; Biesbroek et al., 2015; Leyden et al., 2015). However, our study only observed tracts of verbal fluency in the left hemisphere, this may because the high rate of aphasia in our samples (45/51). Indeed, although we recruited the stroke subjects regardless of their aphasia, most of the patients who voluntarily participated in our study were suffering from language deficits, and hoped to be evaluated for their language ability. Therefore, our patient sample included a high proportion of aphasic patients. Future research should examine how verbal fluency information is transferred in bilateral hemispheres.

4.7. Conclusion

The present study identified a left-lateralized white-matter network supporting verbal fluency processing composed of five major tracts (left ATR, IFOF, UF, SLF and FAT). The degree of damage to the tracts were significantly correlated with the severity of the deficits of semantic and phonological fluency. Moreover, the left IFOF, ATR and UF have unique contributions to semantic fluency compared to phonological fluency. These findings identified the same white-matter network for semantic and phonological fluency but apparently the contribution of several of these tracts to semantic fluency is independent of phonological fluency performance.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuropsychologia.2017.05.008.

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