

White matter structural connectivity underlying semantic processing: evidence from brain damaged patients

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Widely distributed brain regions in temporal, parietal and frontal cortex have been found to be involved in semantic processing, but the anatomical connections supporting the semantic system are not well understood. In a group of 76 right-handed brain-damaged patients, we tested the relationship between the integrity of major white matter tracts and the presence of semantic deficits. The integrity of white matter tracts was measured by percentage of lesion voxels obtained in structural imaging and mean fractional anisotropy values obtained in diffusion tensor imaging. Semantic deficits were assessed by jointly considering the performance on three semantic tasks that vary in the modalities of input (visual and auditory stimuli) and output (oral naming and associative judgement). We found that the lesion volume and fractional anisotropy value of the left inferior fronto-occipital fasciculus, left anterior thalamic radiation, and left uncinate fasciculus significantly correlated with severity of impairment in all three semantic tasks. These associations remained significant even when we controlled for a wide range of potential confounding variables, including overall cognitive state, whole lesion volume, or type of brain damage. The effects of these three white matter tracts could not be explained by potential involvement of relevant grey matter, and were (relatively) specific to object semantic processing, as no correlation with performance on non-object semantic control tasks (oral repetition and number processing tasks) was observed. These results underscore the causal role of left inferior fronto-occipital fasciculus, left anterior thalamic radiation, and left uncinate fasciculus in semantic processing, providing direct evidence for (part of) the anatomical skeleton of the semantic radiation tetwork.

Keywords: semantic network; DTI; connectome; brain-damaged patient

Abbreviations: ATR = anterior thalamic radiation; IFOF = inferior fronto-occipital fasciculus; MMSE = Mini-Mental State Examination; UF = uncinate fasciculus

Introduction

The semantic system supports a large range of human cognitive processes including language, object recognition, object use and

reasoning. Decades of neuroimaging and neuropsychological research on the neural basis of semantic processing has led to the consensus view that widely distributed brain regions are involved, including the middle temporal lobe, ventral temporal cortex,

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inferior parietal lobe, middle and inferior frontal gyri, medial prefrontal cortex and posterior cingulate (Dronkers et al., 2004; Martin, 2007; Patterson et al., 2007; Binder et al., 2009; Mahon and Caramazza, 2009; Wei et al. presentation order was randomized and was identical across subjects. There was a 60s response deadline. Participants were tested individually in a quiet room. Each session lasted no more than 2h; pauses for rest were included upon request.

Oral picture naming

One hundred photographs of objects were used, 20 items from each of five categories: animals, tools, common artefacts, fruits and vegetables, and large non-manipulable objects. Participants were instructed to name each object. The first complete response was scored for each item.

Oral sound naming

The test included 36 items: 10 animal sounds (e.g. barking of a dog), six tool sounds (pounding of a hammer), 10 sounds of common arte-facts (ringing of a telephone), and 10 other types of sounds (sound of thunder). Participants heard the target sound through earphones and were required to speak out the name of the objects that produced the sound (dog, hammer, telephone, thunder). The first complete response was scored for each item.

Picture associative matching

This task had the same format as the Pyramids and Palm Trees Test (Howard and Patterson, 1992), with each trial containing three photographed objects on a touch screen. Participants judged which of the two bottom photographs (e.g. orange, onion) was semantically closer to the top photograph (e.g. banana) by pressing the corresponding photograph on the touch screen. There were 50 trials in total, with 10 from each of the five categories in the oral picture-naming test. The three pictures in each trial were always from the same semantic category.

Control tasks

To assess the (relative) specificity of potential semantics-related fibres, we included two control tasks: a language task that requires minimal semantic processing, oral repetition; and a set of number tasks that do not involve object semantics. The oral repetition task included eight words and four sentences and the participants were asked to repeat the words/sentences they heard over earphones. The number task set included seven exact calculation questions (two addition, two subtraction, two multiplication, and one division) and five number questions (e.g. how many months are there in a year?).

Imaging data

Patients were scanned at the China Rehabilitation Research Centre with a 1.5 T GE SIGNA EXCITE scanner. We collected three types of images: (i) high resolution 3D T₁-weighted images; (ii) FLAIR T₂-weighted images; and (iii) diffusion-weighted images. The 3D images were T1weighted 3D MPRAGE images on the sagittal plane with parameters: matrix size = 512×512 , voxel size = $0.49 \times 0.49 \times 0.70$ mm³, repetition time = 12.26 ms, echo time = 4.2 ms, inversion time = 400 ms, field of view = $250 \times 250 \text{ mm}^2$, flip angle = 15° , slice number = 248 slices. The FLAIR T₂ images were FLAIR T₂-weighted images on the axial plane with parameters: matrix size = 512×512 , voxel size = $0.49 \times$ $0.49 \times 5 \text{ mm}^3$, repetition time = 8002 ms, echo time = 127.57 ms, inversion = 2 s, field of view = $250 \times 250 \text{ mm}^2$, flip angle = 90° , slice number = 28 slices. Diffusion-weighted imaging had two separate sequences with different diffusion weighting direction sets so that 32 directions were covered in total. The first acquisition had the following parameters: 15 diffusion weighting directions, matrix size = 128×128 ,

voxel size = $1.95 \times 1.95 \times 2.6 \text{ mm}^3$, repetition time = $13\,000 \text{ ms}$, echo time = 69.3 ms, inversion time = 0 s, field of view = $250 \times 250 \text{ mm}^2$, flip angle = 90° , slice number = 53 slices. The other acquisition had the same parameters except that it included 17 different directions. The first two volumes were b0 volumes and the b-value of other volumes was 1000 s/mm^2 in each sequence. All the sequences except for FLAIR T₂ images were scanned twice to improve the quality of images.

Behavioural data preprocessing

As the patient group showed considerable variation in demographic properties (e.g. age, gender, education; Supplementary Table 1), 'raw' accuracy scores on the behavioural tasks might not meaningfully



Figure 1 Lesion overlap map of the 76 patients (the n value of each voxel denotes the number of patients with lesion).

integrity of white matter tracts in a given voxel for patients and healthy populations (Rolheiser et al., 2011; Wilson et al., 2011), reflecting fibre density, axonal diameter, and myelination in white matter (Basser and Pierpaoli, 1996). In our data set, each voxel in each patient had a lesion value (categorical variable) from the lesion map (Fig. 1) and a fractional anisotropy value (continuous variable) from the normalized fractional anisotropy map. It has been shown that lesioned brain regions have lower fractional anisotropy values than intact ones (Kim et al., 2005), thus these two variables are correlated to a certain degree. Nonetheless, fractional anisotropy analyses may provide additional information about the effects of the intact voxels in a given tract, which may in turn be affected by lesions in that tract. In our analyses we considered lesion percentage and fractional anisotropy variables separately to check for convergence and then their relative contributions were specifically examined by means of partial correlation. The lesion and fractional anisotropy maps were derived using the following procedures.

Structural magnetic resonance imaging data

For the 3D imaging data, we first co-registered each of the two sequences on the same native space using tri-linear interpolation method implemented in SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/ spm5) and then averaged them. The FLAIR T₂ images were co-registered and resliced to the native space of the averaged 3D images with tri-linear interpolation method in SPM5. Two trained personnel manually drew each patient's lesion contour on averaged 3D images slice by slice, visually referring to FLAIR T₂ images. This lesion-drawing procedure was supervised by an experienced radiologist. Each patient's structural images were resliced into $1 \times 1 \times 1 \text{ mm}^3$ voxel size, and then manually registered into Talairach space via the '3D Volume Tools' in BrainVoyager QX v2.0 (www.brainvoyager.com). We used the ANTs software package (Advanced Normalization Tools, http://www.picsl.upenn.edu/ANTS/) to extract the affine transformation matrix between native and Talairach spaces, which was employed to register and transform the lesion description into Talairach space using the 'WarpImageMultiTransform' program. The lesion description was transformed into the MNI space.

Diffusion magnetic resonance imaging data

For the diffusion-weighted imaging data, for each patient we first merged each of the 15 directions and 17 directions paired sequences into one single 4D nifti-1 format file and merged diffusion-weighted gradient tables of the two sequences. We then executed the following steps using a pipeline tool, PANDA (Cui et al., 2013) (http://www.

nitrc.org/projects/panda/), BET: skull removal; Eddycorrect: correction of eddy current distortion; DTIFIT, build diffusion tensor models. After obtaining the fractional anisotropy maps of each patient, we registered them with the FMRIB fractional anisotropy template in MNI space using ANTs (version 1.9). The normalization included two steps: linear rigid affine and non-linear transform registration. In linear affine transform, one affine transform.txt file for each participant was obtained using 'ANTs' program, and then the 'WarpImageMultiTransform' program was executed to produce the fractional anisotropy map in MNI space. In non-linear transform, a shell script 'buildtemplate' was used to obtain more fine-grained normalized fractional anisotropy map of each patient in MNI space.

Brain-behaviour mapping analysis

To identify the major brain pathways responsible for object semantics processing, we examined the relationship between the integrity of the major tracts (measured by lesion percentage and fractional anisoptropy values) and degree of object semantics impairment. Specifically, we (i) correlated the lesion volume (percentage of voxels with lesion) and the mean fractional anisotropy value of each tract and object semantics performance; (ii) examined the relationship between lesion and fractional anisotropy measures in accounting for semantic behaviour; and (iii) entered the properties of the tracts observed in the correlation analyses into regression models to predict semantics-related tract effects by considering other potential contributing factors including overall lesion volume, cognitive state (MMSE score), types of brain damage, relevant grey matter lesions, and control tasks performance.

Tract-semantic mapping

To identify major white matter tracts, we adopted a widely used human brain white-matter template, the 'JHU white-matter tractography atlas' from FSL (http://www.fmrib.ox.ac.uk/fsl/data/atlas-descrip tions.html#wm), which contains 20 main white matter bundles and has three individual sets of sub-templates with different probability levels in the probability tractography map: 0%, 25% and 50%, reflecting the minimal percentage of subjects having a tract identified on each voxel on the basis of 28 normal subjects (mean age 29 years; 17 males, 11 females). The 0% map contains a relatively large proportion of grey matter or peripheric white matter; the 50% map contains only 12 tracts without bilateral uncinate fasciculus, cingulum gyrus, cingulum (hippocampus) (cingulum hippocampus), and superior longitudinal fasciculus (temporal part). We chose to use the 25%-threshold subtemplate, which contains 20 major tracts (Table 1). In order to rule out the possibility that any potential effects observed with the tracts in the 25% maps were driven by the relatively high grey matter or peripheric white matter inclusion, analyses were also carried out on the 50% map. The results of this additional analysis were highly convergent with those for the 25% maps (data not shown). Each analysis was also carried out only on the stroke patients (n = 66) in order to rule out potential confounding effects of lesion type (Table 2 and Supplementary Table 5).

Lesion-behaviour correlation

Three tracts (left cingulum gyrus, left cingulum hippocampus and right cingulum hippocampus) had lesions in fewer than five patients (Table 1) and were excluded from our lesion analysis. For each of the remaining 17 tracts, the lesion percentage (number of voxels with lesion divided by total number of voxels in the tract) was correlated with patients' scores in each of the three semantic tasks, as well as the semantic composite score. The results were adjusted for the 17

tracts with the Bonferroni correction method (P < 0.00294, corrected P < 0.05). Tracts showing significant correlation with all three semantic tasks were considered to be semantic-relevant fibres. Those associated with only one or two tasks are also reported.

Fractional anisotropy-behaviour correlation

For each of the 20 tracts in the template the mean fractional anisotropy value was obtained by averaging the fractional anisotropy values of all voxels in the tract. The mean fractional anisotropy value was then correlated with the scores on each semantic task and also the semantic composite scores across patients. The Bonferroni correction method (P < 0.0025, corrected P < 0.05) was implemented (on 20 white matter tracts).

We further evaluated whether fractional anisotropy values reveal information in addition to extent of lesion. In other words, we wanted to know whether the effects of a particular tract in semantic processing are fully captured by lesion extent or are also attributable to the 'efficiency' of the intact voxels in that tract. One may also imagine that a lesion affects a voxel's function in a continuous manner, which would not be reflected by the discrete lesion variable but by the fractional anisotropy variable. We thus: (i) calculated partial correlations between semantic composite scores and the mean fractional anisotropy values, with lesion percentage values as covariates; and (2) calculated the correlation between fractional anisotropy values of intact voxels (i.e. excluding the voxels with lesion) and semantic composite scores.

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Table 1 Correlation coefficients between white matter tract integrity (lesion percentages and mean fractional anistropy values) and performance on the three semantic tasks across 76 patients

	Tract	Total volume	Number of		esion-behavic	or correlation		Fractio	nal anisotropy	-behaviour co	rrelation
		(mm³)	patients with lesion	NAO	OSN	PAM	Composite	NGO	NSO	PAM	Composite
~	L anterior thalamic radiation	8128	44	-0.59***	-0.48***	-0.41**	-0.57***	0.51***	0.52***	0.44***	0.57***
2	R anterior thalamic radiation	7576	33	0.32	0.32	0.2	0.32	-0.39**	-0.40^{**}	-0.15	-0.36*
e	L corticospinal tract	5464	44	-0.3	-0.3	-0.07	-0.26	0.57***	0.63***	0.29	0.58***
4	R corticospinal tract	4760	28	0.38*	0.41 **	0.24	0.40**	-0.43**	-0.48***	-0.23	-0.45^{**}
2	L cingulum gyrus	1552	4	Ι	I	I	I	0.03	0.12	0.25	0.15
9	R cingulum gyrus	608	7	0.17	0.13	0	0.12	-0.17	-0.07	0.11	-0.05
~	L cingulum hippocampus	248	0	I	I	I	I	0.02	0.02	0.07	0.04
00	R cingulum hippocampus	544	2	I	I	I	I	-0.2	-0.15	0.02	-0.13
6	Forceps major	5744	18	0.07	0.07	0.12	0.1	-0.13	-0.14	-0.06	-0.13
10	Forceps minor	19712	46	0.01	-0.04	-0.11	-0.06	-0.03	-0.04	0.19	0.04
1	L inferior fronto-occipital fasciculus	5048	44	-0.54^{***}	-0.52^{***}	-0.37*	-0.56***	0.62***	0.57***	0.44**	0.63***
12	R inferior fronto-occipital fasciculus	6304	35	0.33	0.33	0.21	0.34**	-0.36*	-0.39*	-0.16	-0.35
13	L Inferior longitudinal fasciculus	5400	25	-0.24	-0.13	-0.04	-0.16	0.40***	0.34	0.27	0.39**
4	R Inferior longitudinal fasciculus	3152	6	0.23	0.21	0.12	0.22	-0.28	-0.25	-0.06	-0.23
15	L superior longitudinal fasciculus	9472	45	-0.49***	-0.44***	-0.07	-0.39**	0.52***	0.51***	0.07	0.43**
16	R superior longitudinal fasciculus	7456	19	0.23	0.23	0.03	0.19	-0.37*	-0.35*	-0.14	-0.33
17	L uncinate fasciculus	744	23	-0.49***	-0.41 **	-0.35*	-0.49***	0.55***	0.51***	0.37*	0.55***
18	R uncinate fasciculus	448	15	0.26	0.29	0.14	0.27	-0.34	-0.36	-0.17	-0.34
19	L superior longitudinal fasciculus (temporal part)	96	7	-0.12	-0.08	60.0	-0.04	0.22	0.13	0.05	0.16
20	R superior longitudinal fasciculus (temporal part)	72	9	0.17	0.16	0.08	0.16	-0.26	- 0.3	-0.1	-0.26
-					:	:					

L = left; R = right; OPN = oral picture naming; OSN = oral sound naming; PAM = picture associative matching; composite = composite score. Bonferroni corrected: *P < 0.05; **P < 0.01; ***P < 0.001; -could not carry out this analysis due to few patients.

total lesion volume values (total number of lesioned voxels across the whole brain) as covariates.

Types of brain damage

The patients included in the study presented with various types of brain damage. To ensure that the semantic-tract association effect we observed was not secondary to the influence of disease type, we carried out partial correlations between patients' semantic composite scores and lesion percentages or the tracts' mean fractional anisotropy values, with lesion type, MMSE scores and total lesion volume values as covariates. Lesion type was coded as 1 for stroke, 2 for trauma and 3 for others. Additionally, we also obtained the correlation between semantic scores and lesion percentages and mean fractional anisotropy values in each tract only for the 66 patients with stroke, and, in a separate analysis, only for the 25 patients with stroke in the left hemisphere, with MMSE scores and total lesion volume values as covariates.

Effects of grey matter lesion

To elucidate whether effects of white matter tracts could be accounted for by structural grey matter lesions (or preservation) we further performed the following analyses. We first checked whether the lesion percentage in the semantics-relevant regions correlated with semantic deficits; then examined whether the white matter tracts of interest had effects on semantic processing above and beyond these grey matter lesioned regions by performing partial correlations between semantic composite scores and lesion percentages or mean fractional anisotropy values on these tracts, covarying the lesion percentages of each semantics-relevant grey matter region, the MMSE scores and total lesion volume values. The reverse partial correlation was also conducted, i.e. examined the effects of grey matter regions while covarying the white matter tract values. The semantics-relevant grey matter regions were derived from our previous results in Wei et al. (2012, Fig. 3 and Table 2), including significant clusters in dorsomedial prefrontal cortex, left inferior frontal gyrus, left middle temporal gyrus, left

Non-semantic control tasks

To explore whether the semantics-related tracts were (relatively) specific to object semantic processing, we examined the association between these tracts (lesion percentage and fractional anisotropy) and two non-semantic control tasks. For each tract, oral repetition and number task scores were each correlated with the lesion percentages or mean fractional anisotropy values in all patients, with MMSE scores and total lesion volume values as covariates. We further examined whether the semantic effect was significant over and above any potential effects of these control tasks by a partial correlation analysis between semantic composite scores and lesion percentages or fractional anisotropy values, with the control task scores, MMSE scores and total lesion volume values as covariates.

Results

Behavioural and imaging analyses

The raw behaviour mean accuracies of the 76 patients in the three semantic tasks were: oral picture naming, $71 \pm 28\%$ (mean \pm SD); oral sound naming, $52 \pm 29\%$; and picture associative matching, $86 \pm 11\%$. Those of healthy control subjects were $97 \pm 3\%$, $82 \pm 11\%$ and $94 \pm$



Figure 2 Relationships between white matter tract integrity and semantic composite score: Reduced fractional anisotropy (FA) and greater lesion percentage in left IFOF, left ATR and left uncinate fasciculus (UF) were associated with deficits in semantic composite score.

IFOF: r = 0.49, P < 0.00001; left ATR: r = 0.54, P < 0.00001; left uncinate fasciculus: r = 0.46, P < 0.0001).

Assessment of unique contribution of the relevant white matter tracts with regression analyses

We used multiple regression to specifically test whether each of the three tracts shown to be associated with semantic processing in the above correlation analyses made unique contributions beyond the other tracts by entering two tracts first and considering the effects of the third tract in a second step. When lesion percentage was considered, the left ATR showed a significant unique effect as indicated by the fact that it had significant predictive power for semantic composite scores (r^2 change = 0.06, P < 0.02) after controlling for the contribution of left IFOF and left uncinate fasciculus. Left IFOF did not show significantly additional contribution beyond the effects of left ATR and left uncinate fasciculus, and neither did left uncinate fasciculus relative to left IFOF and left ATR. When mean fractional anisotropy was considered, the left IFOF showed a marginally significant unique effect for semantic composite scores (r² change = 0.03, P < 0.07) after controlling for the contribution of left ATR and left uncinate fasciculus. Left ATR did not show a significantly additional contribution beyond the effects of left IFOF and left uncinate fasciculus, and neither did left uncinate fasciculus relative to left IFOF and left ATR.

Summary

The integrity of left IFOF, left ATR, and left uncinate fasciculus were found to correlate significantly with performance across all semantic tasks in our patient group. The fractional anisotropy measure showed additional effects beyond the lesion measure. In the regression model, left ATR showed significant unique effects in predicting semantic performance beyond the other two tracts in the lesion analyses, and left IFOF showed marginally unique effects in the fractional anisotropy analyses. No unique contributions of uncinate fasciculus above the other two tracts were observed in either analysis. The overall regression results indicate that the effects of these tracts may be correlated and our data set does not show strong distinctions among them. We therefore included all three tracts in further analyses.

Validating the semantics: relevance of the observed tracts

The above analyses revealed that the integrity of left IFOF, left ATR, and left uncinate fasciculus significantly predicts semantic processing ability in our patients. To further verify that the three white matter fibres are relevant for semantic processing, we carried out the control analyses below, in which normalized semantic composite t-scores were used for simplicity. The results are shown in Table 2. A highly similar pattern of results was obtained when raw accuracy of patients' performance was used with demographic variables partialled out (Supplementary Table 4).

Overall severity and total lesion volume

The semantic composite scores based on the three semantic tasks showed significant correlations with MMSE scores (r = 0.80, P < 0.0001) and total lesion volume values (r = -0.22, P < 0.05). When factoring out these two confounding variables, the semantic composite scores remained significantly correlated with lesion percentages (left IFOF: partial r = -0.37, P < 0.002; left ATR: partial r = -0.25, P < 0.03; left uncinate fasciculus: partial r = -0.34, P < 0.004) and with mean fractional anisotropy values of the three tracts of interest (left IFOF: partial r = 0.42, P < 0.0003; left ATR: partial r = 0.47; P < 0.0003).

Types of brain damage

Lesion type index was not correlated with semantic composite scores (r = 0.04, P = 0.73). When we included this index in addition to MMSE scores and total lesion volume values as covariates, the correlation between the semantic composite scores and the integrity measures of left IFOF, left ATR and left uncinate fasciculus were still all significant (lesion percentage: left IFOF, partial r = -0.39, P < 0.0007; left ATR, partial r = -0.28, P < 0.02; left uncinate fasciculus, partial r = -0.35, P < 0.003; mean fractional anisotropy, left IFOF: partial r = 0.43, P < 0.0002; left ATR, partial r = 0.36, P < 0.002; left uncinate fasciculus, partial r = 0.46, P < 0.00004). The pattern held up well for the correlation with MMSE scores and total lesion volume values as covariates when we considered only the 66 stroke patients (lesion percentage: left IFOF, partial r = -0.49, P < 0.00005; left ATR, partial r = -0.34, P < 0.007; left uncinate fasciculus, partial r = -0.43, P < 0.0004; mean fractional anisotropy: left IFOF, partial r = 0.42, P < 0.0006; left ATR, partial r = 0.39, P < 0.002; left uncinate fasciculus, partial r = 0.42, P < 0.0005); and when we considered only the 25 patients with left hemisphere strokes (lesion percentage: left IFOF, partial r = -0.57, P < 0.005; left ATR, partial r = -0.22, P = 0.32; left uncinate fasciculus, partial r = -0.41, P < 0.05; mean fractioOF,Pudr_{P40}(**Derecht ())**

Discussion

Using behavioural, structural and diffusion MRI data of 76 braindamaged patients, we observed that the lesion volume and fractional anisotropy value of left IFOF, left ATR and left uncinate fasciculus significantly correlated with semantic impairment severity on tasks across different modalities of inputs (visual or auditory stimuli) or outputs (oral production or associative judgement). These relationships remained even when we controlled for a wide range of potential confounding variables, including overall cognitive state, whole lesion volume and type of brain damage. Furthermore, these effects cannot be fully explained by relevant grey matter involvement, and were (relatively) specific to object semantic processing as no correlation with performance on nonobject-semantic control tasks (oral repetition and number tasks) were observed.

One can envision several ways in which a connection functions in semantic processing, including: (i) to bind different aspects of semantic knowledge (e.g. knowledge about sensory and motor properties); (ii) to connect semantic knowledge with various other cognitive functions for a given task context (e.g. verbal system, episodic memory, executive control); and (iii) to establish a larger network whose overall pattern/state underlies semantic processing. The functions that our observed tracts serve in semantic processing need to be understood in the context of the regions they connect, as discussed below.

Left inferior fronto-occipital fasciculus

Our results showing a causal role of left IFOF in semantic processing are in line with a series of previous studies (Duffau et al., 2002, 2005, 2009; Mandonnet et al., 2007; Duffau, 2008; Acosta-Cabronero et al., 2010, 2011; de Zubicaray et al., 2011; Schwindt et al., 2011) and add important evidence that clarifies the interpretation of those studies. Duffau and colleagues have shown that temporary dysfunction of the left IFOF induced by intraoperative electrical stimulation led patients to make semantic errors in oral picture naming (Duffau et al., 2002, 2005, 2009; Duffau, 2008; Mandonnet et al., 2007). Although semantic errors can originate from either the semantic system or the lexical retrieval process (Caramazza and Hillis, 1990; Cloutman et al., 2009), our finding that IFOF lesions are associated with deficits not only in verbal tasks (object picture naming and object sound naming) but also in a non-verbal task (picture associative matching) suggest that left IFOF is necessary for semantic processing (without excluding the possibility that it is also necessary for lexical retrieval).

What kind of mechanism underlies the functioning of left IFOF in semantic processing? The IFOF, the longest associative bundle, was recognized early, yet only recently has its precise anatomical structure been elucidated. Through dissection of post-mortem brains and diffusion tensor imaging methods with healthy 'in vivo' brains, Martino et al. (2010) and Sarubbo et al. (2013) observed that the IFOF includes two subcomponents. The superficial layer connects the superior parietal lobule, the occipital extrastriate cortex, Wernicke's territories and fusiform gyrus to the inferior frontal gyrus (pars triangularis and opercularis), through the extreme and external capsules. The deep layer has three portions: a posterior portion connecting the superior parietal lobule/ occipital extrastriate cortex/fusiform gyrus to the dorsolateral prefrontal cortex /middle frontal gyrus; a middle portion connecting the superior parietal lobule to the middle frontal gyrus/lateral orbito-frontal cortex; an anterior portion connecting the occipital extra-striate cortex/fusiform gyrus to the basal orbitofrontal cortex and partially overlapping with the uncinate fasciculus.

Turken and Dronkers (2011) reported that IFOF connects posterior middle temporal gyrus and anterior inferior frontal cortex [Brodmann area (BA)47]. They showed this by carrying out fibre-tracking analyses using seeds that have been shown to be relevant to semantic processing in voxel based lesion-symptom mapping analyses: middle temporal gyrus, anterior superior temporal gyrus/BA22, BA47, BA46 and superior temporal sulcus/ BA39. Left posterior middle temporal gyrus and inferior frontal cortex were also the two grey matter regions whose extent of damage correlated with semantic scores above and beyond the effects of three white matter tracts in our analyses, suggesting the particular significance of these two regions along IFOF. Given that posterior middle temporal cortex, adjacent Wernicke's areas, and inferior frontal regions are consistently shown to be involved in language comprehension and production tasks (Hillis et al., 2001; Vigneau et al., 2006; Binder et al., 2009), this section of the surface layer of the IFOF pathway may be specifically involved in bridging semantic memory with the verbal system.

Interestingly, fusiform gyrus and dorsolateral prefrontal cortex are activated by visual, auditory and tactile object information (Kassuba et al., 2011). Therefore, the deeper layer of IFOF may also be important for object semantic processing, serving a binding function of different modalities of object information. The exact functions of the subcomponents of IFOF that anatomically connect these different grey matter structures remain to be uncovered.

Left anterior thalamic radiation

Our results also revealed that left ATR is necessary for semantic processing. ATR is a major white matter tract projection from the thalamus that penetrates the anterior limb of the internal capsule, carrying reciprocal connections from the hypothalamus and limbic structures to the frontal cortex, including Broca's area (pars triangularis and pars opercularis). Its abnormality has been reported to be associated with autism (Cheng et al., 2010; Tan et al., 2010; Cheon et al., 2011), impaired episodic memory and executive function in late-life depression (Sexton et al., 2012), and schizo-phrenia (Mamah et al., 2010).

To our knowledge, our study provides the first direct empirical evidence for the ATR's crucial role in the semantic system, perhaps because previous studies tended not to include it as a tract of prior interest. Nonetheless, there is evidence that the two major regions it connects—inferior frontal gyrus and thalamus—might be involved in semantic processing. As reviewed above, the role of inferior frontal gyrus in semantic processing has been commonly accepted. The thalamus has been found to be relevant for a variety of cognitive functions such as episodic memory, executive function, as well as language (Vermeer et al., 2003; Sexton et al., 2012; for a review see Crosson, 2013). Neuropsychological studies have found that dominant thalamus infarct leads to thalamus aphasia, manifesting three main features: (i) fluent output with mainly semantic paraphasias (Crosson, 1984); (ii) auditory-verbal comprehension impairment; and (iii) preserved repetition (Crosson, 1992). This profile fits with deficits to the semantic system or the measured by the joint performance in three jo:9e1t p5(th9.3(tasks7(the)-3across)]TJ[(m-1.426 TDsurvisual)-539forand)-538.3(auditor.7(543)-3input)-537

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