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The Semantic Anatomical Network: Evidence From Healthy and Brain-Damaged Patient Populations

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Abstract: Semantic processing is central to cognition and is supported by idely distributed gray matter (GM) regions and hite matter (WM) tracts. The exact manner in hich GM regions are anatomically connected to process semantics remains unkno n. We mapped the semantic anatomical net ork (connectome) by conducting diffusion imaging tractography in 48 healthy participants across 90 GM "nodes," and correlating the integrity of each obtained WM edge and semantic performance across 80 brain-damaged patients. Fifty-three WM edges ere obtained hose lo er integrity associated ith semantic deficits and together ith their linked GM nodes constitute a semantic WM net ork. Graph analyses of this net ork revealed three structurally segregated modules that point to distinct semantic processing components and identified net ork hubs and connectors that are central in the communication across the subnet orks. Together, our results provide an anatomical frame ork of human semantic net ork, advancing the understanding of the structural substrates supporting semantic processing. *Hum Brain Mapp 36:3499–3515, 2015.* © 2015 Wiley Periodicals, Inc.

Key words: semantics; hite-matter net ork; module; connectomics; diffusion tensor imaging

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INTRODUCTION

Semantic processing entails the access to general kno l-edge of objects, people, and facts in various contexts and is central to a ide range of cognitive processes. Decades of studies have investigated the cortical regions and major hite matter (WM) tracts that support semantic processing. Functional neuroimaging studies during task and resting states and neuropsychological studies have converged to find that idely distributed left-lateralized gray matter (GM) regions in the lateral and ventral temporal, inferior parietal, and inferior and medial frontal cortices are implicated in this process [Binder et al., 2009; Dronkers et al., 2004; Mahon and Caramazza, 2009; Martin, 2007; Wei et al., 2012]. In diffusion tensor imaging (DTI) and electrostimulation studies on healthy and brain-damaged patients, several major WM path ays have been observed to support semantics, including the left inferior frontooccipital fasciculus (IFOF; also referred to as the extreme capsule fiber system), the left uncinate fasciculus (UF), and the left anterior thalamic radiation (ATR), such that the disruptions of these tracts have been associated ith inferior semantic processing abilities [Acosta-Cabronero et al., 2010, 2011; Aralasmak et al., 2006; de Zubicaray et al., 2011; Duffau et al., 2002, 2005; Friederici and Gierhan, 2013; Han et al., 2013].

A critical gap bet een these GM findings and the WM path ay findings is that their correspondence is elusive, and the most crucial information—the precise GM regions that are anatomically connected to process semantics—has rarely been tested directly, but rather through various deductions. The major WM path ays that are commonly studied and identified are composed of large numbers of fiber bundles connecting large numbers of GM areas, ith the exact terminations controversial and various subcomponents ith distinct functions being identified [Catani and Thiebaut de Schotten, 2008; Fernández-Miranda et al., 2008; Martino et al., 2010; Sarubbo et al., 2013]. For instance, these previously identified semantic-associated WM tracts, such as the IFOF, UF, and ATR, all connect frontal regions ith other cortices, but it is not kno n hether it is the same frontal regions that connect these different systems for semantics. Several studies performed WM tracking bet een specific GM regions of interest, defined from lesions or task-based functional MRI studies, and found WM path ays, including the IFOF, arcuate fasciculus (AF), middle, inferior longitudinal fasciculi, the transcallosal, and a ventral path ay via the extreme capsule among these regions [Binney et al., 2012; Graves et al., 2014; Saur et al., 2008; Turken and Dronkers, 2011]. Kümmerer et al., [2013] subsequently reported a negative correlation bet een the lesion volume in the tract that connected anterior/posterior middle temporal gyrus ith ventrolateral prefrontal cortex and semantic performance, indicating a critical role of the WM path ay among these ventral cortical regions in semantic processing. These studies significantly advanced the understanding of the anatomical properties of the semantic anatomical connections. Ho ever, the fiber tract of interest spanned multiple regions, and the specific connections bet een GM node pairs that support semantics remained unplotted. With such a gap, a semantic WM net ork has yet to be constructed.

An anatomical net ork, or connectome [Sporns et al., 2005], for semantic processing can be constructed if both the WM connections (edges) and the GM regions (nodes) that they connect are elucidated. Once such a net ork is mapped, graph analyses can be performed to characterize its underlying topological architecture [Bullmore and Sporns, 2009; He and Evans, 2010], including the potential anatomical/functional subdivisions (i.e., modules), hich may in turn shed light on the anatomical substrate of cognitive components ithin the semantic system.

The goal of the current study is to construct an anatomical net ork (connectome) for object semantic processing, on the basis of hich e could understand the specific communication patterns across GM regions in support of semantics, including the potential subdivisions. We first tracked WM connections (edges) among 90 GM regions (nodes, based on Automated Anatomical Labeling [AAL] atlas) using diffusion imaging data from 48 healthy participants. This net ork contained 688 WM "edges" across 90 GM "nodes." We then tested the relationship bet een the integrity of the WM edges (lesion volume from structural imaging and mean fractional anisotropy [FA] from diffusion imaging) and semantic performance across 80 brain damaged patients. Such analyses render WM edges necessary for semantic processing, and the GM nodes that they connect are elucidated. Finally, to understand hether the semantic WM net ork is further organized by subcomponents, e performed graph analyses to detect the potential modular partition of the semantic WM net ork. The analysis scheme is sho n in Figure 1.

MATERIALS AND METHODS

Participants

Forty-eight healthy subjects and 80 patients ith brain damage participated in the present study. Neuroimaging data for both subject groups ere collected using identical procedures, and behavioral data ere collected for patients. All participants ere native Chinese speakers, ere paid for their participation, and provided informed ritten consent. This study as approved by the Institutional Revie Board of the State Key Laboratory of Cognitive Neuroscience and Leaning, Beijing Normal University.

Healthy participants

For the 48 healthy subjects (25 males), the mean age as 50 years (SD = 11; range: 26-72 years), and mean years of formal education as 13 (SD = 4; range: 6-22). They ere recruited from patients' acquaintances and the local

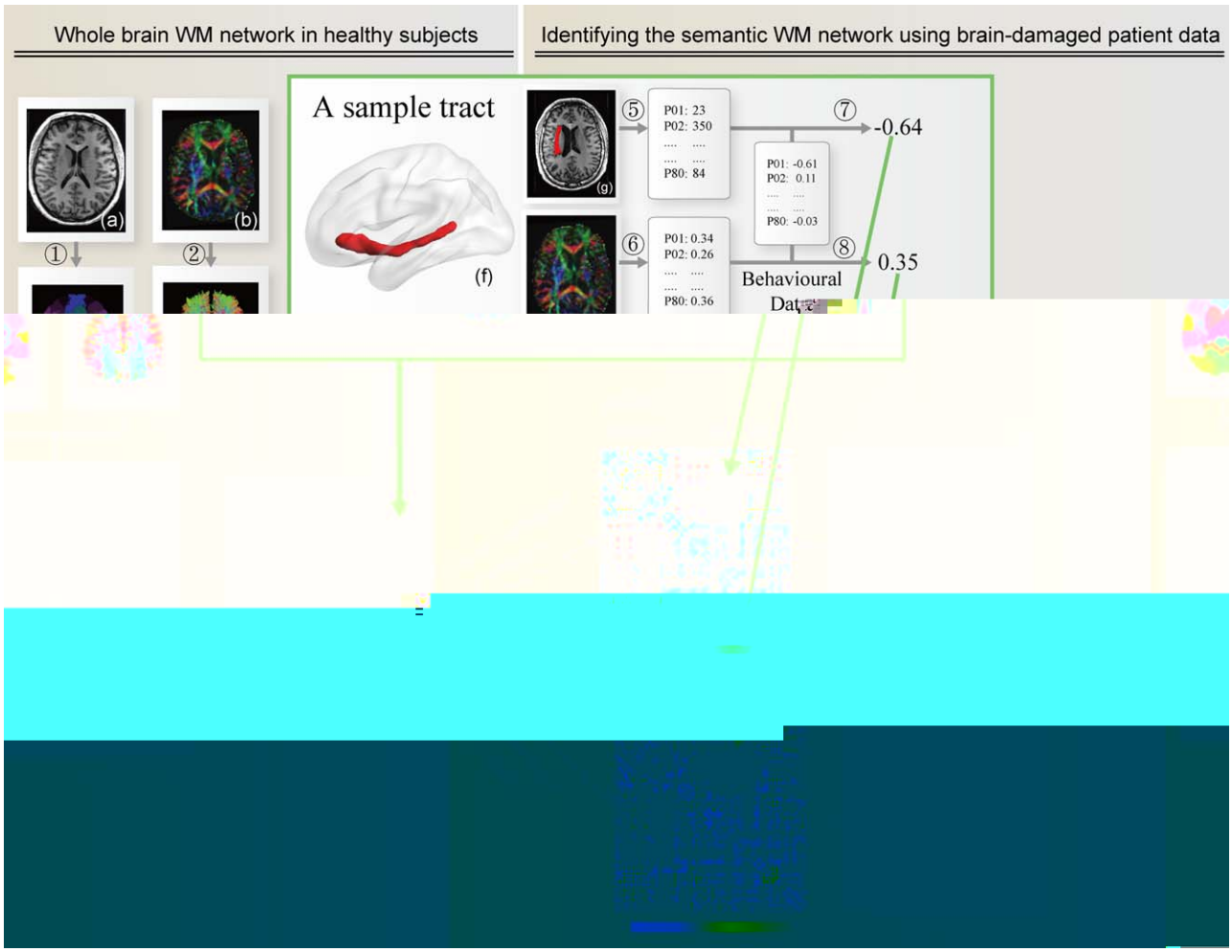

Figure 1.

A flowchart for the construction of the semantic WM network. ① Transforming the AAL atlas in the MNI space to the native diffusion space by applying the inverse transformation obtained from the native T1-weighted image (**a**), resulting in a subject-specific AAL mask in the DTI native space (**c**). ② Reconstructing all WM fibers (**d**) in the whole brain from the native FA image (**b**) using DTI deterministic tractography. ③ Determining the WM fibers connecting every pair of gray matter regions for each healthy subject. All tracts in the native space were transformed to the MNI space. ④ Identifying the network matrix (**e**, black: 1; white: 0) and building binary tract maps. The inset shows a 3D view of an exemplar tract map (**f**), which connects the orbital part of the inferior frontal gyrus and the middle temporal gyrus. ⑤ Calculating the lesion volume in a tract for each patient by overlapping the binary tract map with the lesion image (**g**) in the MNI space. ⑥ Calculating the mean FA in a tract for each patient by overlapping the binary tract map with the FA image (**h**) in the MNI space. ⑦⑧ Correlating the lesion volumes/FA values and the semantic PCA score (extracted from eight behavioral tasks), controlling for confounding variables (see Method for details) in each tract and constructing weighted lesion network matrices (**i**) and FA network matrices (**k**) using partial correlation coefficients. ⑨ ⑩Transforming the weighted network matrices into binary network matrices by applying statistical thresholds (FDR corrected qs < 0.05), resulting in 41 semantic tracts in the lesion network matrices (**j**) and 36 tracts in the FA network matrices (**l**). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

community, 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] as administered as a measure of general cognitive state (mean- = 28.46; SD = 1.35; range: 24–30). All subjects ere right

handed, ith laterality quotient [LQ = (R − L)/(R + L) × 100] higher than 40 [Edinburgh Handedness Inventory, Oldfield, 1971].

Patients

Eighty patients ith brain damage (see Supporting Information Table 1 for details; 60 males) ere recruited from the China Rehabilitation Research Center ith the follo ing inclusion criteria: no previous brain injury; at least 1 month post-onset (mean = 6.09 months; SD = 11.69; range: 1–86 months; number of patients in the chronic phase, that is, > 4 months postonset: 41; e did not have exact post onset time information of five patient and all reported to be longer than 1 month); no other neurological or psychiatric disease; able to follo task instructions; and premorbidly right handed. The majority suffered from stroke ($n = 67$), and others suffered from traumatic brain injury ($n = 13$). The patients' mean age as 45 years (SD = 13; range: 19–76 years), and mean years of formal education as 13 (SD = 3; range: 2–19). The mean score on the MMSE as 21.90 (SD = 7.58; range: 3–30). The patients and healthy groups ere comparable in education years ($t = -0.29$, $P = 0.77$) and different in age ($t = -2.135$, $P = 0.04$) and gender distributions ($\chi^2(1) = 7.1$, $P = 0.01$).

Behavioral Data Collection

The semantic processing abilities of patients ere determined using PCA based on eight cognitive tasks that vary in the degree of semantic involvement and input/output modalities (visual and auditory; verbal and nonverbal): oral picture naming, oral naming to definition, oral sound naming, picture associative matching, ord associative matching, ord-picture verification, oral ord repetition and oral ord reading. The details of each task and procedures are presented in Supporting Information Methods. The semantic PCA factor as defined as a component that had a high loading eight on the tasks in hich semantic processing is highly relevant (oral picture naming, oral sound naming, oral naming to definition, picture associative matching, ord associative matching, and ord-picture verification) relative to those tasks in hich semantic processing is not central (oral ord reading and oral ord repetition). The semantic PCA score as computed as the linear combination of the standardized task scores and factor score coefficients. The nonverbal semantic task (picture associative matching) as also analyzed separately for validation purpose.

Imaging Data Collection

Each subject as scanned using a 1.5 T GE SIGNA EXCITE scanner ith 8-channel split head coil at the China Rehabilitation Research Center. We collected three types of images: (1) high-resolution 3D T1- eighted MPRAGE images in the sagittal plane ith a matrix size = 512 × 512, voxel size = 0.49 × 0.49 × 0.70 mm^3, repetition time = 12.26 ms, echo time = 4.2 ms, inversion time- = 400 ms, field of vie = 250 × 250 mm^2, flip angle=15°, and slice number = 248 slices; (2) FLAIR T2- eighted images in the axial plane ith a matrix size = 512 × 512, voxel size = 0.49 × 0.49 × 5 mm^3, repetition time = 8002 ms, echo time = 127.57 ms, inversion= 2 s, field of vie - = 250 × 250 mm^2, flip angle = 90°, and slice number = 28 slices; and (3) diffusion- eighted imaging ith t o separate sequences ith different diffusion eighting direction sets. The parameters for the first acquisition ere 15 diffusion eighting directions, matrix size = 128 × 128, voxel size = 1.95 × 1.95 × 2.6 mm^3, repetition time = 13000 ms, echo time = 69.3 ms, inversion time = 0 s, field of vie - = 250 × 250 mm^2, flip angle = 90°, and slice number = 53 slices. The other acquisition had the same parameters but included 17 different directions. The first t o volumes ere b0 volumes, and the b-value of the other volumes as 1000 s/mm^2 in each sequence. All of the sequences except the FLAIR T2 images ere scanned t ice to improve the quality of the images.

Imaging Data Preprocessing

Structural MRI data

We first coregistered the t o T1 images using a trilinear interpolation method in SPM5 (http:// .fil.ion.ucl.ac.uk/spm/soft are/spm5) and then averaged them. The FLAIR T2 images ere coregistered and resliced to the native space of the averaged T1 images. T o trained personnel manually dre each patient's lesion contour on averaged T1 images slice-by-slice, visually referring to the FLAIR T2 images. Both investigators reached a reasonable degree of inter-rater reliability ith an experienced radiologist during the training phase (mean percentage volume difference, 9% ± 8% and 4% ± 3%; mean percentage of discrepant voxels, 7% ± 4% and 6% ± 2%, ith discrepant voxels defined as t o voxels from the other manually dra n lesion volume [Fiez et al., 2000]. The lesion dra ing of each patient as double checked by the radiologist. To deal ith the challenges in registration of brains ith lesions, e applied a t o-step method including the manual registration and the automated non-linear transformation First, each patient's structural images ere resliced into 1 × 1 × 1 mm^3 voxels and then manually normalized into Talairach space via the "3D Volume Tools" in BrainVoyager QX v2.0 (.brainvoyager.com), and the manual registration as completed on the 3D visual interface. Then, e used the ANTs soft are (Advanced Normalization Tools, http:// .picsl.upenn.edu/ANTS/) to estimate the affine transformation bet een the native and Talairach spaces, hich as further applied to transform the lesion masks into the Talairach space using the "WarpImageMultiTransform" program. The lesion masks ere then transformed into Montreal Neurological

Institute (MNI) space. We manually checked the registration quality for each subject.

Diffusion MRI data

For the diffusion- eighted imaging data of each participant, e first merged each of the 15 directions and 17 direction-paired sequences into a single 4D image and then preprocessed the images, as typically performed using PANDA [Cui et al., 2013] (http:// .nitrc.org/projects/panda/). The pre-processing procedure included (1) BET, skull removal; (2) Eddycorrect, correction of eddy current distortion; (3) DTIFIT, building diffusion tensor models and obtaining the FA maps; and (4) Registration of all the individual images to MNI space ith target voxel size of $2 \times 2 \times 2$ mm^3.

Constructing the Whole-Brain WM Network Using Data From Healthy Participants

We follo ed the approach used by Gong et al. [2009] to construct the hole brain anatomical net ork.

Gray-matter node selection

We adopted the AAL atlas [Tzourio-Mazoyer et al., 2002] to define GM (cortical and subcortical) nodes for our net ork construction. This atlas as chosen for our anatomical net ork study because it is an anatomy (gyrus/sulcus)-based GM parcellation template and is commonly used in patient studies [Caeyenberghs and Leemans, 2014; Cao et al., 2014; Lo et al., 2010; Zhang et al., 2011]. We parceled the entire cerebral GM into 90 regions to define GM (cortical and subcortical) nodes for our net ork construction. We dilated (thickened) each of the regions by three voxels (voxel size: $2 \times 2 \times 2$ mm^3) using the "fslmaths" tool of FSL (http:// .fmrib.ox.ac.uk/fsl/data/atlas-descriptions.html# m). For the pairs of regions hose intervals fe er than six voxels, the dilation stopped once the t o regions touched so that different regions did not have overlapping voxels. For each individual, the 90 dilated nodes in MNI space obtained ere masked and then transformed back to the native diffusion space, ith each representing a net ork node.

White-matter connections extracted from diffusion MRI tractography

Deterministic tractography as performed in the native diffusion space for each healthy participant using the FACT tracking algorithm [Mori et al., 1999]. Fiber tracking as terminated hen the angle bet een t o consecutive orientations as greater than 45° or hen the FA value as smaller than 0.20. Given that the outcome of tractography is affected by the initial position of the seed points ithin the voxel [Cheng et al., 2012], 100 seeds ere randomly selected ithin each voxel to avoid biases from initial seed positioning.

For every t o AAL region masks, the tracts ere filtered out as connecting the t o regions if one of their endpoints terminated ithin one region and the other endpoint terminated ithin the other region. In total, 4,005 regional pairs ere determined. For each node pair (regions a and b), the filtered-out tract (if it existed) as projected onto the voxels in the native diffusion space, resulting in a binary map. This binary map as further transformed to MNI space. The binary maps of the MNI space for all subjects ere then overlaid to generate a count map, in hich the value of each voxel represented the number of subjects ho had WM fibers in that area. Finally, a group-level threshold as set at voxel value $> 25\%$ of subjects (i.e., 12 subjects); cluster size > 300 voxels (2,400 mm^3), hich as used to determine hether the node pair as anatomically connected. The procedure as repeated for all of the 4,005 node pairs, ith 688 pairs passing the threshold and therefore being considered directly connected by WM tracts (Figure 2A).

Identifying Semantic Anatomical Networks Using Brain-Damaged Patient Data

Tract integrity (lesion volume and mean FA) and semantic performance correlation analyses

The main procedures are sho n in Figure 1. To elucidate hich of the bet een-node tracts identified in healthy controls (in total 688) are related to semantic processing, e correlated t o types of measures of the tract integrity and semantic performances across patients: lesion volume, reflected by structural imaging, and the FA value, reflected by diffusion imaging. Only tracts ith more than five patients ith lesions ere included in the lesion volume analyses. Demographic variables, including age, gender, and education level ere al ays included as covariates in the analyses. Additionally, the hole brain lesion volume (total number of damaged voxels in the hole brain excluding the t o connecting nodes) and the lesion volume of the t o GM nodes (number of damaged voxels in each node) ere included as covariates to reveal specific effects of the WM tracts. The false discovery rate (FDR), ith a threshold of $q < 0.05$, as adopted to correct for multiple comparisons.

Overlaps with major WM tracts

To understand ho the observed semantics-related WM tracts may converge ith the classical major tracts, e calculated the extent of overlay for each observed tract ith conventional WM tracts in the 'JHU WM tractography atlas' from FSL. The 25%-threshold subtemplate as used, hich contained 20 major tracts [see Han et al., 2013 for details]. Each of observed tracts and atlas tracts as masked. The overlay percentage of each

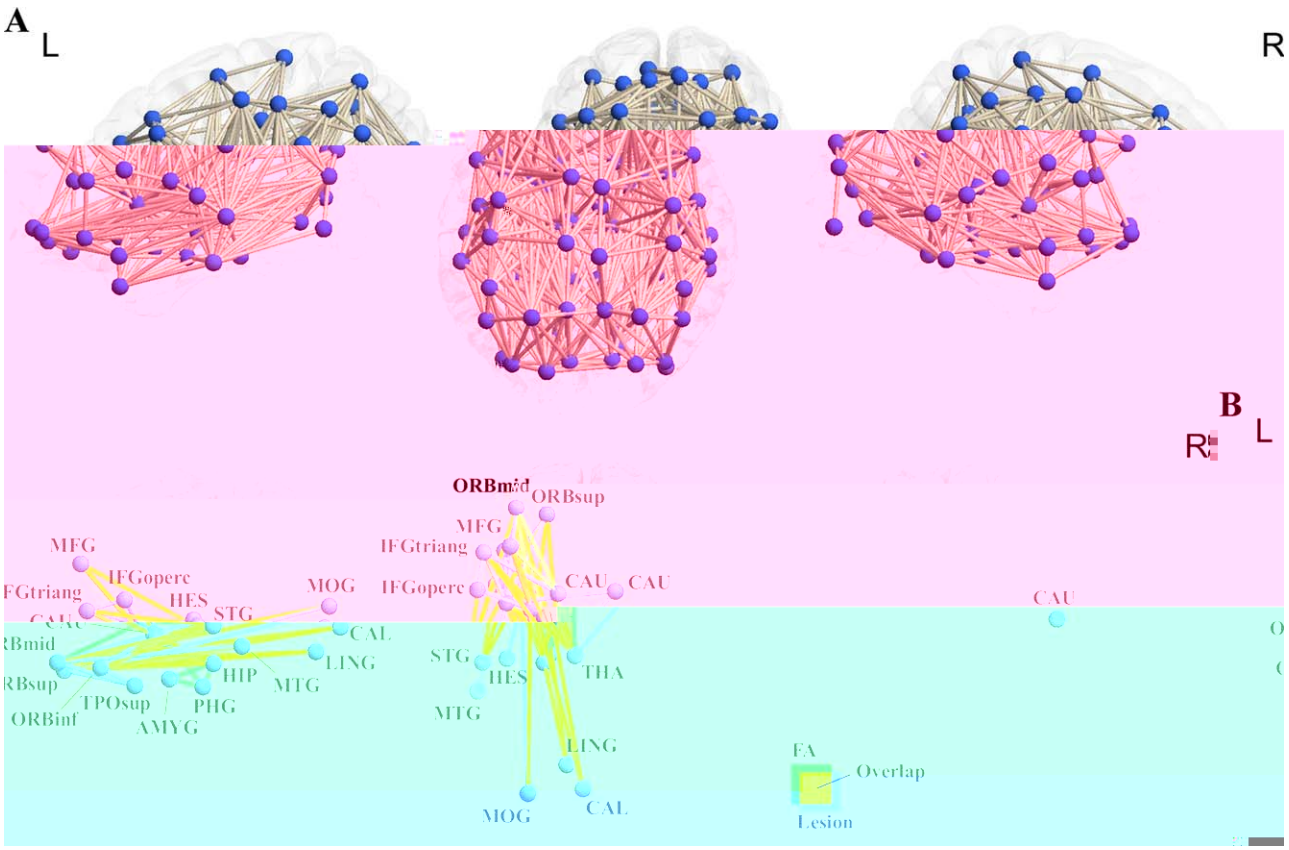

Figure 2.

Whole brain anatomical network and the semantic anatomical network. (**a**) Six hundred and eighty-eight WM tracts were successfully tracked between the 90 AAL regions in 48 healthy adults, resulting in a whole-brain anatomical network. (**b**) The WM tracts whose integrity values (lesion volume or mean FA value) significantly correlated with the semantic PCA scores across 80 patients, regressing out demographic variables and lesion volume variables (FDR corrected qs < 0.05). Most semantic tracts (24 tracts) were observed in both lesion volume and FA analyses (yellow); 17 were significant only in the lesion volume analysis (blue); 12 only in the FA analysis (green; see Supporting Information Table 3 for details). These edges and the gray matter nodes they connect constitute the semantic anatomical network. The network was visualized using in-house BrainNet Viewer [Xia et al., 2013]. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

observed tract ith each atlas tract as computed using the formula: (the number of common voxels bet een the observed tract and the atlas tract)/(the total number of voxels in the atlas tract). Observed tracts ith more than 5% of overlay percentages ere presented (Supporting Information Table 3).

Controlling for the effects of types and post-onset time of brain damage

Because e included both stroke and traumatic brain injury patients, e examined hether the semantic tracts identified above ere influenced by the type of brain damage by performing t o further analyses. In the first analysis, e computed partial correlations bet een the patients' semantic PCA scores and lesion volume or mean FA values, ith lesion type as an additional covariate. Lesion type as coded as 1 for stroke and 2 for trauma. In a second analysis, e computed the lesion volume and FA-behavior correlation in only the 67 stroke patients. The threshold as set at FDR correction $q < 0.05$ (corrected across all 688 WM tracts). In both analyses other confounding variables ere also controlled for (demographic variables, the hole brain lesion volume, and the lesion volumes of the t o GM nodes). Given the large variation in terms of post-onset time of brain damage (1–86 months), e further excluded potential confounding effects of this variable by correlating the patients' semantic PCA scores and lesion volume or mean FA values ith covariates being the time post-onset (month), the demographic variables, the hole brain lesion volume, and the lesion volumes of the t o GM nodes.

Testing the relative specificity of the semantic anatomical network

To examine the extent to hich the observed WM tracts ere specifically relevant for semantic processing, e computed the partial correlation coefficients bet een semantic PCA scores and lesion volumes or mean FA values ith patients' performances on t o cognitive tasks in hich semantic involvement as not central (oral ord reading and oral ord repetition) as covariates in addition to the other confounding variables. The threshold as set at FDR correction $q < 0.05$ (corrected across all 688 WM tracts).

Characterizing the Semantic Anatomical Network Using Graph Analysis

In this section, e applied graph-analysis measures to characterize the modular pattern of the semantic net ork to determine hether the semantic net ork is composed of relatively independent sub-components (modules). First, e reconstructed the semantic anatomical net ork comprising all semantic-tracts found in the above lesion- and/or FA- analyses. Then, e transformed the net ork as a binary and undirected graph, here edges represented semantic-related WM tracts and nodes represented the GM regions that these WM tracts connected. To evaluate the stability of the critical nodes and net ork modular pattern, e considered semantic net orks that ere derived from t o additional thresholds in addition to the current threshold in the lesion- and FA-behavior correlation analyses (FDR corrected, $q < 0.05$, equaling uncorrected $P < 0.0028$ in lesion analysis and $P < 0.0026$ in FA analysis): a more stringent threshold (uncorrected $P < 0.001$) and a more liberal threshold (uncorrected $P < 0.01$).

We partitioned the semantic anatomical net ork into subnet orks using Ne man's spectral optimization algorithm [Ne man, 2006]. Modularity (Q) is a measure that compares the number of ithin-module and bet een-module connections to reveal the strength of a graph's modular organization, and the maximum Q is used to choose an appropriate division of the net ork. Intramodularity and intermodularity are identified after the division of the net ork. To test hether the modular Q as significantly higher than random net orks, ten thousand random net orks ere constructed. Each of the random net orks as constructed to have the same number of nodes and edges and the same degree distribution as the actual net ork using Maslov's iring algorithm [Maslov and Sneppen, 2002]. A Z score as then generated by the Q in the real net ork relative to the Q in the random networks to determine the significance level.

After various modules ithin the semantic net orks ere identified, e elucidated the roles of each node in the communication across different modules by computing their participation coefficient (PC) [Guimera and Nunes Amaral, 2005]:

$$\mathrm{PC}_i = 1\text{-}\sum_{S=1}^{N_M}\left(\frac{k_{is}}{k_i}\right)^2$$

here k_i is the total number of connections of node i and k_{is} is the number of connections bet een node i and nodes in module s. The PC value is 0 hen the connections of a node are restricted to one module and 1 hen all of the connections of a node are ith other modules. The modularity analysis and the PC scores ere computed using the "Net ork - Modularity" package and the "gretna_parcoeff" function in Gretna toolkit, respectively (http:// .nitrc.org/projects/gretna/).

RESULTS

Behavioral Results

The semantic processing abilities of patients ere determined using principal component analysis [Jolliffe, 2002], hich as based on eight cognitive tasks varying in the degree of semantic involvement and input/output modalities (Supporting Information Table 2). The Kaiser–Meyer–Olkin measure of sampling adequacy (0.87) and Bartlett's test of sphericity ($\chi^2(28) = 560$, $P < 0.001$) sho ed that the behavioral dataset as suited for PCA analysis (Supporting Information Table 2). T o components sho eigenvalues > 1 and ere extracted: Component 1 accounted for 40% of the model variance (under varimax rotation), ith the five oral production tasks having higher loading values (0.74–0.80) and the three tasks that did not require oral production having lo er loading values (-0.01 to 0.34). We thus labeled this component as the oral production component. The second component accounted for 39% of the model variance, ith the six semantic tasks (oral picture naming, oral naming to definition, oral sound naming, picture associative matching, ord associative matching, and ord-picture verification) having higher loading values (0.51–0.87) and the t o nonsemantic tasks (oral ord reading, oral ord repetition) having lo er loading values (-0.13 to 0.33). We considered this component to be the semantic component and derived scores for each patient's semantic processing ability based on this component. The remaining components (3–8) had eigenvalues belo one and did not sho any trend associating ith semantic processes. Note that five of the six semantic tasks involve language (ord) processing, a caveat to consider is that the semantic component may primarily be driven by lexical-semantic processes. We thus also carried out the main brain-behavior analyses using the nonverbal semantic task—picture associative matching—for validation. Moreover, given that PCA results may be influenced by the tasks being included, e further conducted a PCA analyses including t o

additional perceptual tasks (face verification and the visual form perception from the size match task A of Birmingham object recognition battery) [Riddoch and Humphreys, 1993] to maximize the variation in degree of reliance on various processing components. In face verification, stimuli ere six male faces, each ith three different vie s. The participants ere asked to judge hether the t o

more than five patients ith lesions, 106 (16%) had more than 50% of patients ith lesions, 276 (41%) had 30–50% of patients ith lesions, and 275 (41%) had 10-–30% of patients ith lesions.

The results of the correlation analyses bet een tract integrity measures (lesion volume and mean FA values) and semantic PCA scores for the 673 tracts are presented in Figure 2B and Supporting Information Table 3.

Lesion volume-behavior correlation

The lesion volume of 41 WM tracts significantly negatively correlated ith semantic PCA scores across patients hen the effects of demographic variables (age, gender, and education level) and hole brain lesion volume, as ell as lesion volumes on the GM nodes ere partialed out (partial *r*s: −0.35 to −0.71; FDR corrected qs < 0.05). Larger lesions ere associated ith more severe semantic deficits. There ere five intra-lobe tracts (one connecting frontal lobe regions and four connecting subcortical regions) and 36 interlobe tracts (15 connecting frontal and subcortical regions, 13 connecting frontal and temporal regions, six connecting frontal and occipital regions, and t o connecting temporal and subcortical regions). By overlaying our results ith the major WM tract mask in the JHU tractography atlas, e found that the 41 tracts observed here ere mainly located on three left hemisphere major tracts: the ATR (94% overlapping voxels), the UF (89%), and the IFOF (88%). Minimal overlaps ere found ith the left inferior longitudinal fasciculus (ILF, 7%) and the left superior longitudinal fasciculus (SLF, 6%) (Supporting Information Table 3). Note that JHU atlas, the SLF ere divided into "Superior longitudinal fasciculus" and "Superior longitudinal fasciculus (temporal part)," and e found the effects of SLF, not the SLF (temporal part) here and hereafter.

Mean FA-behavior correlation

The mean FA value of 36 WM tracts significantly positively correlated ith semantic PCA scores across patients, ith the effects of demographic variables (age, gender, and education level) and lesion volumes of the hole brain and of the t o connecting nodes partialed out (partial *r*s: 0.35 to 0.55, corrected qs < 0.05). Lo er mean FA values ere associated ith poorer semantic performances. All tracts ere left lateralized, ith seven intralobe tracts (three connecting temporal regions and four connecting subcortical regions) and 29 inter-lobe tracts (12 connecting frontal and subcortical regions, nine connecting frontal and temporal regions, five connecting frontal and occipital regions, and three connecting temporal and subcortical regions). The tracts ere predominantly located on the left ATR (100% overlapping voxels), cingulum (hippocampus) (94%), IFOF (85%), UF (47%) and corticospinal tract (46%), and minimally on the minor forceps (5%) and ILF (7%).

Convergence between Lesion- and FA-behavioral analyses and with the nonverbal semantic task

T enty-four tracts sho ed significant effects (FDR corrected qs < 0.05) in both the lesion volume and the mean FA analyses (Supporting Information Table 3): one tract connecting subcortical regions and 23 interlobe tracts, including eight connecting frontal and subcortical regions, nine connecting frontal and temporal regions, five connecting frontal and occipital regions and one connecting temporal and subcortical regions. Seventeen tracts ere significant in only the lesion analyses and 12 in only the FA analyses, and ere likely to reflect properties that ere more sensitive to one specific measure. For instance, lesion analyses address properties of WM tract integrity beyond FA; FA values may capture the influence of lesion on intact voxels in a WM tract. We thus treated the union of the t o measures, resulting in 53 WM tracts hose integrity is associated ith semantic PCA score in either of the analyses. These 53 tracts ere located on four major left tracts on the JHU tractography atlas: the ATR (90%, overlay percentage), IFOF (85%), UF (47%), and ILF (5%). Note that several language-relevant tracts like the middle longitudinal fasciculus or the AF ere not included in the JHU tractography atlas, and thus the correspondences ere not tested.

When the nonverbal semantic task—picture associative matching— as considered on its o n, its scores significantly correlated ith 36 tracts in the lesion analysis (partial *r*s: partial *r*s −0.34 to −0.63, corrected qs < 0.05) and 53 tracts in the FA analysis (partial *r*s 0.34 to 0.53, corrected qs < 0.05). In total 58 WM tracts ere significant in either the lesion volume or FA analyses, 50 of hich overlapped the ones found ith the semantic PCA scores analyses (Supporting Information Figure 1), suggesting that the results obtained ith the semantic PCA score ere not likely driven by only lexical variables but rather reflected semantic processing more generally.

Controlling for the types and the post-onset time of brain damage

There as no systematic difference in the semantic PCA scores across stroke and traumatic brain injury patients ($t = 0.30$, $P = 0.76$). When lesion type as included as a covariate in addition to the demographic variables (age, gender, and education level) and the lesion volumes of the t o nodes and hole brain, the effects in the tracts observed above remained significant. For the 41 tracts obtained in the lesion analyses, the partial correlation coefficients bet een lesion volume and semantic scores ere −0.35 to −0.71 (corrected qs < 0.05); for the 36 tracts obtained in the FA analyses, the partial correlation coefficients bet een mean FA values and semantic scores ere 0.35 to 0.55 (corrected qs < 0.05; Supporting Information Table 3). The pattern persisted at an uncorrected threshold hen e considered only the 67 stroke patients (lesion

volume tracts: partial rs: −0.31 to −0.76, uncorrected Ps < 0.01; mean FA: partial rs: 0.33 to 0.59, uncorrected Ps < 0.01). When included the post-onset time as a further covariate in addition to the demographic variables (age, gender, and education years) and the lesion volume of the t o nodes and the hole brain, the overall pattern remained. For the 41 tracts of lesion analyses, the partial correlation coefficients bet een lesion volume and semantic scores ere −0.22 to −0.62 (uncorrected Ps < 0.07). For the 36 tracts in the FA analyses, the partial correlation coefficients bet een mean FA values and semantic scores ere 0.24 to 0.43 (uncorrected Ps < 0.05). Virtually identical results ere obtained hen all the potentially confounding variables (the types and the post-onset time of brain damage, the demographic variables and the lesion volume of the t o nodes and hole brain) ere controlled together in one model.

Testing the relative specificity of the semantic tracts

We examined hether the semantic-relevant tracts obtained above ere at least relatively specific to semantic processing, as opposed to cognitive processing in general, by considering the t o tasks (ord reading and repetition) in hich semantic involvement as not central and the semantic component loadings ere lo er. When the scores on these t o tasks ere included as covariates in addition to demographic variables (age, gender, and education level) and lesion volume values of the t o nodes and the hole brain, the correlation ith semantic composite scores remained significant for both the 41 tracts obtained in the lesion analyses (partial rs bet een the semantic score and lesion volume: −0.36 to −0.66, corrected qs < 0.05) and the 36 tracts obtained in the FA analyses (partial rs bet een the semantic score and mean FA: 0.35 to 0.61, corrected qs < 0.05; Supporting Information Table 3).

Finer analyses within the temporal gyrus

We used the AAL template in the study because it is idely used in the brain structural connectome research, allo ing us to compare our results ith the literature [Gong et al., 2009; He et al., 2009; Lo et al., 2010]. There is an important concern that AAL regions are rather large and may contain heterogeneous functional subregions. In the context of semantic processing, looking ithin the temporal regions further is particularly motivated because the roles of anterior and posterior middle/superior temporal regions have been highlighted in past research and yet in AAL template MTG spans idely on the anterior–posterior axis (STG: MNI $y = -60$ to 16; MTG: MNI $y = -82$ to 16; excluding temporal pole area hich is a specific AAL region). We thus carried out an analysis dividing the STG and MTG into halves (STG: MNI $y = -22$; MTG: MNI $y = -33$) to check hether the six semantic-relevant WM tracts from left STG and MTG e obtained originated from the middle or posterior parts. Deterministic tracking from subdivided regions revealed t o WM tracts using the original group-level threshold (cluster size > 300 voxels, voxel value > 12 subjects), bet een the posterior MTG and orbital part of inferior frontal gyrus, bet een the middle part of STG and orbital part of inferior frontal gyrus. At a slightly lo er threshold (cluster size > 150 voxels, voxel value > 10 subjects), eight tracts ere obtained: the posterior MTG connecting ith the orbital parts of inferior/middle frontal gyrus, both middle and posterior STG connecting ith the frontal lobe (the middle STG connects the orbital parts of inferior/middle/superior frontal gyrus; the posterior STG connects orbital parts of inferior/middle frontal gyrus and triangular part of inferior frontal gyrus). We then tested the role of these tracts in semantic processing and found that the lesion volume of these tracts significantly negatively correlated ith the semantic PCA factor (partial rs: −0.54 to −0.68; $P < 0.001$), the mean FA value of these tracts significantly positively correlated ith the semantic PCA factor (partial rs: 0.29 to 0.45; $P < 0.05$), hen the confounding variables ere included as covariates. These results converge ith the literature about the important roles that posterior MTG and large portion STG play in semantic processing [e.g., Binder et al., 2009; Dronkers et al., 2004; Turken and Dronkers, 2011].

Topological Characteristics of the Semantic Anatomical Network

The 53 WM tracts sho ing effects in semantic processing observed in the lesion volume and/or FA-behavior analyses above and the 22 GM regions ith hich they connect form a WM anatomical net ork (Fig. 2B). Using graph analysis, e can characterize the net ork's topological properties, including its subcomponents (modules) and hub nodes (connectors) for communication bet een different modules [Bullmore and Sporns, 2009]. A binary net ork as reconstructed for this purpose.

Modularity analysis (Ne man's spectral optimization algorithm, [Ne man, 2006] sho ed that the semantic anatomical net ork could be subdivided into three separate modules (Fig. 4A, $Q = 0.27$; Z score = 2.30, $P < 0.028$ relative to 10,000 random net orks). The net ork contained 34 intramodule and 19 intermodule connections. The first module (labeled as the orbital frontal-temporal/occipital module) comprised edges connecting the orbital part of the frontal lobe ith the (posterior) temporal or occipital lobes. The second module (the opercular/triangular/middle frontal-subcortical module) mainly contained tracts connecting prefrontal regions ith subcortical regions (thalamus, putamen, and caudate). The third module (medial temporal lobe [MTL] module) contained tracts mainly ithin the limbic system, especially the MTL (hippocampus, amygdala, parahippocampal gyrus and pallidum). To identify connector nodes that are important in communication across these different modules, e further

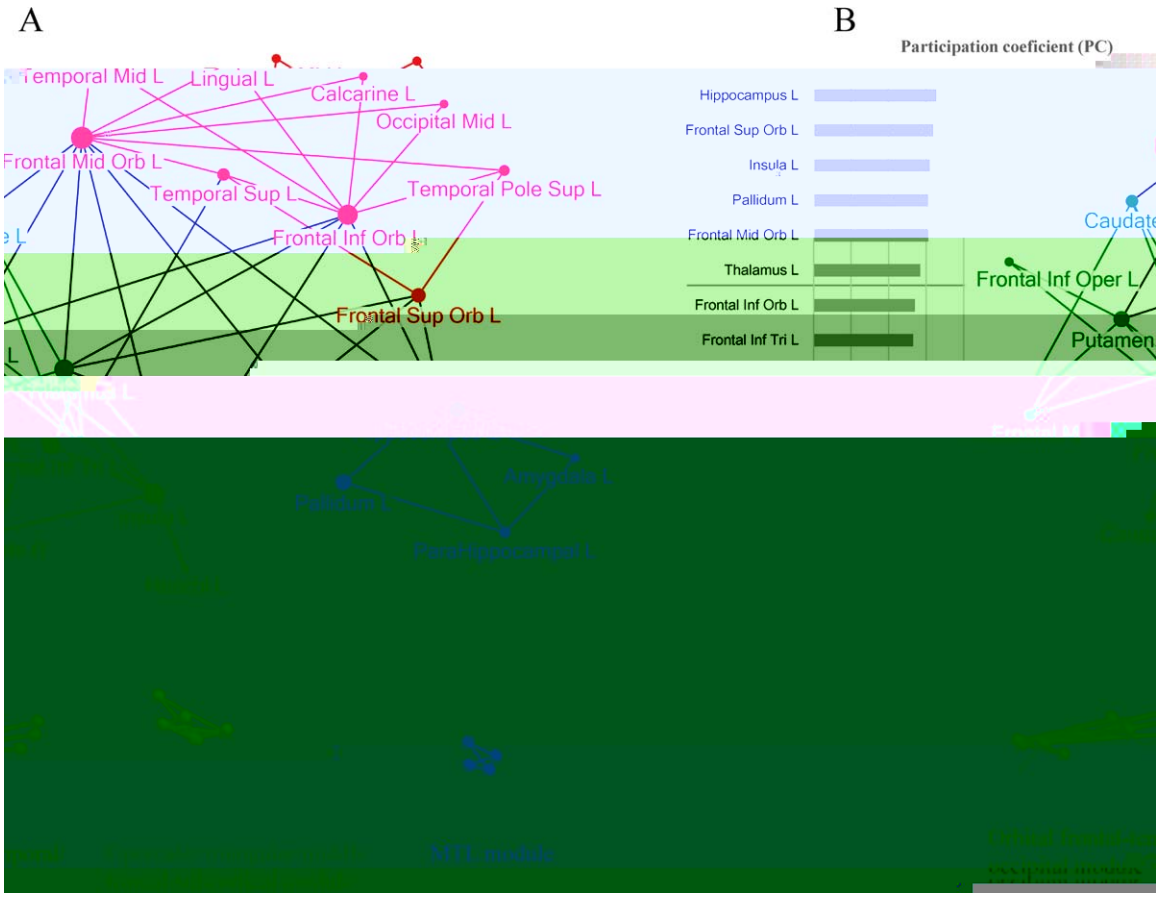

Figure 4.

The results of the graph analysis for the semantic anatomical network. (**a**) Three separate modules shown on a two-dimensional pseudostructural map and a three-dimensional structural brain. The edges and nodes are colored according to their module membership. The radius of each node denotes its degree value. (**b**) The participation coefficients of the network nodes, ranked by value. The line denotes > 1 SD. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

computed PC for each node. The results are sho n in Figure 4B. Six regions had PC values higher than 1 SD ($PC > 0.56$), including hippocampus, orbital part of the superior frontal gyrus, insula, pallidum, orbital part of the middle frontal gyrus, and thalamus, indicating that they are important in integration across modules.

Validation analyses

To confirm that our results are robust across various threshold settings, in addition to the conventional threshold adopted above in the lesion- and FA- behavior correlation analyses (FDR corrected qs < 0.05, corresponding to an uncorrected $P < 0.0028$ in lesion analysis and $P < 0.0026$ in FA analysis; ith 22 nodes and 53 edges), e performed the same graph analyses at a more stringent threshold (uncorrected $P < 0.001$, ith 21 nodes and 46 edges) and a more liberal threshold (uncorrected $P < 0.01$, ith 27 nodes and 67 edges). The modularity and connectors results ere largely consistent across these different thresholds (Supporting Information Figure 2), ith the exception that at the more liberal threshold the opercular/triangular/middle frontal-subcortical module further split into t o components.

DISCUSSION

Combining the structural and diffusion imaging data of healthy subjects and patients ith brain damage, e mapped the WM anatomical net orks of semantic processing. We first performed deterministic fiber tracking in 48 healthy participants among 90 AAL GM regions, obtaining 688 WM tracts connecting these GM nodes. Across 80 patients ith brain damage, e found that the integrity of 53 tracts associated ith semantic performance, such that greater lesion and/or lo er mean FA

values correlated ith more severe semantic deficits. Most tracts are left lateralized, densely connecting inferior and middle prefrontal regions ith temporal, occipital, and subcortical regions. The effects of these WM tracts could not be attributed to the effects of GM lesions, total lesion volume, type of brain damage, or cognitive abilities in general. Using graph analyses on the constructed WM net- ork, e observed that the semantic anatomical net ork could be partitioned into three modules: an orbital frontal-temporal/occipital module, an opercular/triangular/middle frontal-subcortical module and an MTL module, ith hippocampus, insula, middle frontal gyrus, and thalamus being important in integration across modules.

Our results are consistent ith the rich literature on the involvement of several major WM path ays necessary for semantic processing—the left IFOF, ATR, and UF [Acosta-Cabronero et al., 2011; Agosta et al., 2010; Aralasmak et al., 2006; de Zubicaray et al., 2011; Duffau, 2008; Duffau et al., 2002, 2005, 2009, 2013; Friederici and Gierhan, 2013; Han et al., 2013; Mandonnet et al., 2007]. The semantic-relevant WM edges sho ed the greatest overlap ith these path ays. While the GM endpoints of these large WM path ays are diverse and ambiguous, our study elucidated the effects of WM connections among specific GM regions underlying semantic processing. While the IFOF, ATR, and UF all connect the frontal lobe ith other regions, our results sho that the temporal and occipital regions connected ith the orbital inferior frontal part of the frontal cortex (part of the IFOF and UF), and the subcortical regions connected ith the opercular/triangular/middle part of the frontal cortex (ATR), to support semantics. Our analyses also revealed smaller tracts that are not fully covered by the major WM path ays, sho ing the effects of connections bet een the hippocampus and parahippocampal gyrus and the amygdala and pallidum. These results, combined ith the previous understanding of the functions of finer regions ithin the frontal and temporal cortices, allo for a more specific hypothesis and interpretation of the potential organizational principles of the semantic frame ork.

With kno ledge of both WM connections (edges) and the GM that they connect (nodes), e can establish the semantic anatomical connectome and analyze its internal net ork architecture using mathematical graph approaches. Modularity analyses revealed that the anatomical connections associated ith semantic preprocessing ere clustered into three components: an orbital frontal-temporal/occipital module, an opercular/triangular/middle frontal-subcortical module, and a MTL module, hich may roughly follo s three key WM bundles—IFOF, striatal-frontal connections and the cingulum bundle. While the semantic system can be dissected along multiple cognitive dimensions such as modality of kno ledge and/or relationship ith verbal and other cognitive systems, the manner in hich the anatomical semantic net ork is structured sheds light on the organizational dimensions of the cognitive system. Belo , e discuss the potential roles of each of these subnet orks in light of their distinct effects implicated in semantic processing.

Orbital Frontal-Temporal/Occipital Module

This module is composed of 14 WM edges among 9 GM nodes, primarily bet een the left orbital frontal regions and distributed occipital and lateral temporal regions. The occipital ends include the middle occipital gyrus, lingual gyrus, and calcarine; the temporal ends include a large portion of the temporal lobes, encompassing the anterior temporal and superior/middle temporal gyrus. This stream has been referred as the "ventral semantic stream" [e.g., Duffau et al., 2013]. The occipital regions are classical visual regions processing visual shape, color, and the spatial properties of objects [Renier et al., 2010; Wang et al., 2013] and have been sho n to be activated hen such object properties are retrieved by verbal stimuli [Chao and Martin, 1999; Hsu et al., 2011; Wang et al., 2013]. The superior and middle temporal gyri, especially the posterior portions, are robustly involved in semantic tasks ith various input and output modalities, including visual ords and pictures [Vandenberghe et al., 1996], auditory ords [Hickok and Poeppel, 2004], and tactile inputs [Stoeckel et al., 2003]. Damage to this territory commonly leads to language comprehension and semantic deficits [Bates et al., 2003; Chertko et al., 1997; Dronkers et al., 2004; Hart and Gordon, 1990; Sch artz et al., 2009]. Using resting-state fMRI, e previously demonstrated that both the intrinsic fluctuation amplitude of the region and its functional connectivity strength ith frontal and parietal regions, including the orbital frontal cortex, correlate ith semantic behavior across healthy individuals [Wei et al., 2012]. The anterior temporal lobe has been presumed to be a potential hub region for binding together various modalities of semantic kno ledge, primarily motivated by the semantic dementia profile, ith peak atrophy in this region associated ith cross-modal semantic impairment [Lambon Ralph, 2014; Lambon Ralph et al., 2010; Patterson et al., 2007]. While semantic dementia involves atrophy and functional abnormalities beyond the anterior temporal lobe [Guo et al., 2013; Mion et al., 2010; Seeley et al., 2009], hich may be the actual cause of semantic deficits, functional imaging studies ith healthy subjects have also sho n that it processes abstract property kno ledge of objects [Peelen and Caramazza, 2012; Simmons et al., 2010] and that its anterolateral subregion is functionally connected ith the semantic net ork during the resting-state [Pascual et al., 2015]. The orbital frontal gyrus is frequently active in imaging studies [Vandenberghe et al., 1996, but see Price et al., 1999]. Intriguingly, both posterior and anterior temporal regions, as ell as the orbital frontal cortex, are strongly implicated in semantic processing across tasks and approaches in the literature, and have been considered potential hub regions binding various modalities of object properties, including the visual properties in the

occipital regions in the current module. The orbital frontal cortex is particularly important because many temporal and occipital regions are anatomically connected through this area and sho ed relatively high PC. Taken together, this module is likely to be a "core" system that assembles various aspects of object properties.

Opercular/Triangular/Middle Frontal-Subcortical Module

This module connects the opercular/triangular/middle frontal regions (middle frontal gyrus and dorsal inferior frontal gyrus (BA44/BA45)) and subcortical regions including the thalamus, insula and the basal ganglia (putamen and caudate). These regions have been termed the "basal ganglia thalamocortical circuit" given their anatomical adjacency [Ullman, 2006]. They tend to be implicated in tasks ith high cognitive control in various contexts. For instance, they are coactivated by semantic ord generation tasks here heavy semantic control is involved. For the dorsal inferior frontal gyrus, its activation is positively modulated by the difficulty of the semantic tasks, possibly due to the increased demand of semantic memory and execution of control [Poldrack et al., 1999]. The TMS on the dorsal inferior frontal gyrus disrupts semantic tasks that are executively demanding [Whitney et al., 2011]. For thalamus, its lesion leads to semantic deficits, at least in the lexical tasks [Cox and Heilman, 2011; Crosson, 1984; Nadeau and Crosson, 1997; Segal et al., 2003], and it is activated by semantic associative matching [Assaf et al., 2006; Kraut et al., 2003] and semantic object memory tasks [Hart et al., 2007]. The insula engages in the control and suppression of natural urges [Lerner et al., 2009] and is an integral hub for saliency, s itching, attention, and control functions [Menon and Uddin, 2010]. Lesions in the basal ganglia may cause sentence comprehension deficits [Grossman et al., 2002]. Specifically, the left caudate has been suggested to be a "language control" region in bilingual studies, being important in the s itching bet een different languages [e.g., Crinion et al., 2006]. This "opercular/triangular/middle frontal-subcortical module" may thus serve as the anatomical basis of the executive control component in semantic processing, controlling the retrieval of the appropriate semantic properties for specific tasks and/or contexts. This component is likely to communicate ith other semantic components through the insula and thalamus because they sho rich bet een-module connections and are classified as connectors.

MTL Module

Another module identified links the hippocampus, parahippocampal gyrus, amygdala, and pallidum. The MTL is classically vie ed as critical for episodic memory, being involved in the consolidation of information from short-term memory [Squire et al., 2004; Tubridy and Davachi, 2011]. There is a tight interaction bet een episodic memory and semantic memory, and accumulated evidence has sho n the MTL's role as the "crossroad" bet een the t o memory systems [de Curtis and Paré, 2004; Ranganath and Ritchey, 2012]. The anterior hippocampus is intrinsically functionally connected ith the anterior-temporal lobe, amygdala, anterior parts of the middle and inferior temporal gyrus, and the ventromedial frontal cortex. Semantic dementia is associated ith a reduction of this functional net ork, hile Alzheimer's disease is associated ith reduction of functional connectivity of the posterior hippocampus [La Joie et al., 2014]. Tan et al., [2014] further sho ed that atrophy of the left anterior thalamus and the body of the hippocampus positively correlated ith the severity of semantic dementia. Intriguingly, human neurophysiological studies have found in these regions so-called concept cells, neurons that respond to concepts that are salient for episodic memory across various input modalities [e.g., Quiroga et al., 2008]. There are several explanations of the specific mechanism of the episodic system in semantic processing that are not mutually exclusive; subjects rely on episodic memory to help retrieve semantic information [Ryan et al., 2010]; episodic memory is critical to form ne semantic memories, particularly in the construction of detailed and complex semantic representations [Henke, 2010]. The MTL may also support the creation of multi-attribute representations by indexing memories stored in the neocortex [Giovanello et al., 2004; Wixted and Squire, 2011].

Taken together, the WM net ork for semantic processing is partitioned into structurally segregated modules that encompass regions more salient in processing general kno ledge for objects, controlling for semantic activation for specific task contexts, and interacting ith the episodic memory. Such modularity analysis results motivate ne hypotheses regarding the organization principles of the semantic system and invites studies that empirically test these specific functions for these subnet orks, hich might be more informative than focusing on isolated GM regions.

Note that hile e observed a predominantly left-lateralized WM semantic net ork, task-based neuroimaging studies have reported bilateral activation in semantic processing [e.g., Binder et al., 2009]. Neuropsychological studies also found that the right hemispheric lesions such as right temporal pole and fusiform gyrus associated ith semantic processing deficits [e.g., Duffau et al., 2008; Mion et al., 2010; Thiel et al., 2005; Tranel et al., 1997; Winhuisen et al., 2007]. To examine hether the potential right hemisphere effects ere shado ed by left hemisphere effects, e carried out an analysis on the 15 patients ith unilateral right hemisphere lesions. In these patients, no significant correlation as found bet een semantic scores and lesion volume or mean FA values ith the confounding variables controlled for (demographic variables, hole brain lesion volume, and lesion volumes on the GM nodes). It remains to be further investigated hether right hemisphere WM effects becomes visible ith larger sample size.

Finally, there are several methodological caveats to consider. Patient studies, by nature, are constrained by the lesion distribution patterns [Rudrauf et al., 2008]. In stroke patients, the lesion is strongly associate ith attracted vascular territory [Phan et al., 2005]. Certain WM connections are less likely to be injured by brain damage, and thus their effects less easily assessed. Furthermore, the diffusion imaging is an indirect measure of real fiber connections, is especially prone to errors in resolving fiber crossings [Mori and van Zijl, 2002] and may have great signal loss in certain regions including anterior and ventral temporal cortex because they ere close to air-tissue boundaries [Embleton et al., 2010]. These might explain hy WM connections ith parietal regions, especially the angular gyrus and ventral temporal cortex hich have been sho n to be important in semantic processing in healthy adults [e.g., Binder et al., 2009; Seghier et al., 2010] ere not revealed in our study. Additionally, our study is based on the AAL template, and hile it is idely used in the brain structural connectome research, its regions are rather large and may contain heterogeneous functional subregions. Thus convergent evidence from other imaging techniques and parcellation schemes are arranted.

In conclusion, by combining structural and diffusion imaging of both healthy and patient populations, e mapped an anatomical net ork for semantic processing, ith GM "nodes" and WM "edges" elucidated. This anatomical net ork is composed of three subnet orks that correspond to general semantic kno ledge representation, semantic control, and interplay ith the episodic system. Our findings highlight the critical roles of distributed WM connections among specific temporal and frontal regions and the modular organization in semantic processing. Our results provide an anatomical frame ork for the human semantic net ork, advancing our understanding of the structural substrates underlying normal and impaired semantic processing.

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