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White matter networks dissociate semantic control from semantic knowledge representations: Evidence from voxel-based lesion-symptom mapping

Junhua Ding[a,b]*, Keliang Chen[c]*, Nan Zhang[d,e], Mingyue Luo[d], Xiaoxia Du[f], Yan Chen[a,g], Qing Yang[h], Yingru Lv[i], Yumei Zhang[j], Luping Song[f], Zaizhu Han[a] and Qihao Guo[k]

[a]State Key Laboratory of Cognitive Neuroscience and Learning & IDG/McGovern Institute for Brain Research, Beijing Normal University, Beijing, People's Republic of China; [b]Department of Neurosurgery, Baylor College of Medicine, Houston, TX, USA; [c]Department of Neurology, Huashan Hospital, Fudan University, Shanghai, People's Republic of China; [d]Faculty of Psychology, Beijing Normal University, Beijing, People's Republic of China; [e]Department of Human Development and Quantitative Methodology, University of Maryland, College Park, MD, USA; [f]Department of Neurology, China Rehabilitation Research Center, Rehabilitation College of Capital Medical University, Beijing, People's Republic of China; [g]College of Biomedical Engineering and Instrument Sciences, Zhejiang University, Hangzhou, People's Republic of China; [h]Department of Rehabilitation, Huashan Hospital, Fudan University, Shanghai, People's Republic of China; [i]Department of Radiology, Huashan Hospital, Fudan University, Shanghai, People's Republic of China; [j]Department of Medicine Rehabilitation, Beijing Tiantan Hospital, Capital Medical University, People's Republic of China; [k]Department of Gerontology, Shanghai Jiaotong University Affiliated Sixth People's Hospital, Shanghai, People's Republic of China

ABSTRACT

Although semantic system is composed of two distinctive processes (i.e., semantic knowledge and semantic control), it remains unknown in which way these two processes dissociate from each other. Investigating the white matter neuroanatomy underlying these processes helps improve understanding of this question. To address this issue, we recruited brain-damaged patients with semantic dementia (SD) and semantic aphasia (SA), who had selective predominant deficits in semantic knowledge and semantic control, respectively. We built regression models to identify the white matter network associated with the semantic performance of each patient group. Semantic knowledge deficits in the SD patients were associated with damage to the left medial temporal network, while semantic control deficits in the SA patients were associated with damage to the other two networks (left frontal-temporal/occipital and frontal-subcortical networks). The further voxel-based analysis revealed additional semantic-relevant white matter tracts. These findings specify different processing principles of the components in semantic system.

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Introduction

Semantic memory represents a person's conceptual knowledge and understanding of the world. It consists of two processes: semantic knowledge representation and semantic control (Jefferies & Lambon Ralph, 2006; Lambon Ralph et al., 2016; Warrington & McCarthy, 1983). Semantic knowledge representation stores and processes general knowledge of objects, word meanings, facts, and people. To form a concept, information from various modalities is needed (e.g., colour, shape, smell, and motion) which is then integrated through additional processes, including semantic control. Semantic control specifically guides access to semantic knowledge in a task-driven manner such that information relevant to current goals and the context is accessed (Jefferies, 2013; Jefferies & Lambon Ralph, 2006). Based on the task demand, semantic control supports the suppression of semantic associations that are task-irrelevant or which do not serve the current task goal. Most semantic theories have no doubt that these two processes are separable and interactive to accomplish semantic processing (Jefferies, 2013; Jefferies & Lambon Ralph, 2006; Lambon Ralph et al., 2016; Rogers & McClelland, 2004). In cognitive models, there are multiple degrees of separation between two processes (Binder & Desai, 2011; Fedorenko et al., 2018). They can be distinct systems with interaction. Alternatively, they can share the same system with various degrees. Semantic knowledge is represented by a distributed

CONTACT Qihao Guo qhguo@sjtu.edu.cn Department of Gerontology, Shanghai Jiaotong University Affiliated Sixth People's Hospital, Shanghai, 200233, People's Republic of China
*J. Ding and K. Chen are co-first authors.
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network (Barsalou et al., 2003; Caramazza et al., 2014; Dove, 2011). To support interaction with it, semantic control can interact with its whole network or just with a specific part of its network. However, it is still unknown in which way and to what extent these two processes dissociate from each other. Simultaneous direct comparisons between these two processes would help address this important cognitive issue.

Neuropsychological evidence has found that semantic knowledge and semantic control are separable and are selectively impaired in patients with semantic dementia (SD) and semantic aphasia (SA), respectively (Jefferies & Lambon Ralph, 2006). When concepts are impaired in individuals with SD, they fail to complete tasks requiring those concepts regardless of the input modality or manner of access to the information. Their performance depends on the difficulty that they have to access different concepts (e.g., frequency, familiarity, and imageability). As a result, they present high item consistency and performance correlations among semantic tasks, high sensitivity to familiarity and frequency of stimuli, and many semantic coordinate/superordinate errors in naming tasks. In contrast, SA patients do not truly forget concepts. Their performance on semantic tasks highly depends on task demands. In addition, accessing concepts for them becomes easier for simple tasks than difficult tasks. Thus, they present low item consistency and performance correlations among semantic tasks, low sensitivity to frequency or familiarity of stimuli, strong effects of task cueing and many semantic associative errors in naming tasks (Corbett et al., 2009; Jefferies & Lambon Ralph, 2006; Noonan et al., 2013a).

The grey matter cortices underlying these two semantic processes have been widely investigated. The most direct evidence comes from neuropsychological studies of patients with brain damage. Patients with SD and SA provide an ideal lesion model to reveal the underlying grey matter networks of these two semantic processes. For instance, it has been found that the areas of highest atrophy in individuals with SD include bilateral anterior temporal lobes, and damage to those structures is associated with deficits in semantic knowledge. By contrast, lesions in individuals with SA tend to involve the left inferior frontal gyrus and the temporoparietal junction, and damage to those structures is associated with deficits in semantic control (Corbett et al., 2009; Jefferies & Lambon Ralph, 2006; Noonan et al., 2013a). These results have been confirmed by other approaches, such as functional neuroimaging in healthy participants (Noonan et al., 2013b; Peelen & Caramazza, 2012; Whitney et al., 2011), transcranial magnetic stimulation in healthy participants (Lambon Ralph et al., 2009; Pobric et al., 2010; Whitney et al., 2011a, 2011b) and deep electric stimulation in patients (Orena et al., 2019). Thus, this neural dissociation further provides evidence for the separability of these two semantic processes.

In fact, white matter also plays a crucial role in semantic processing. Studies using MRI (de Zubicaray et al., 2011; Han et al., 2013) and direct electrical stimulation (Duffau, 2008; Duffau et al., 2013; Herbet et al., 2019; Maldonado et al., 2011; Mandonnet et al., 2010; Moritz-Gasser et al., 2013) have suggested that general semantic processing is supported by a white matter network, which includes the inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, uncinate fasciculus and anterior thalamic radiation. However, compared with grey matter networks, white matter networks supporting semantic control and semantic knowledge are still unclear in detail. One recent study (Fang et al., 2015) split the semantic white matter network into three parts: the frontal-temporal/occipital network, the frontal-subcortical network, and the medial temporal lobe network. It is possible these networks are associated with semantic knowledge, semantic control, or both. If a similar white matter basis is related to both the semantic processes, it will support a partially shared mechanism of semantic knowledge and semantic control. Otherwise, a dissociated neural pattern will support the distinction between these two processes.

To elucidate the dissociation between semantic knowledge and semantic control from the perspective of white matter basis, we built regression models to investigate the relationship between the white matter integrity values of semantic networks and semantic performance in each subject cohort (19 SD patients and 25 SA patients), controlling for the influence of other potential confounding factors. We used fractional anisotropy (FA) to measure white matter integrity. Semantic performance was measured by the composite score of three semantic tasks (i.e., oral picture naming, picture associative matching, and word associative matching). The potential

confounding factors included brain damage degree, overall cognitive ability, and non-semantic performance. In addition to the abovementioned network-based analyses, voxel-based lesion-symptom mapping analyses were carried out to identify the white matter tracts for which variance in structural integrity is related to variance in the performance on semantic tasks across individuals with SD and SA.

Materials and methods

Participants

Two groups of brain-damaged patients (SD and SA) and healthy controls were recruited. This study obtained informed consents from all the participants and was approved by the Institutional Review Board of the Huashan Hospital, China. The participants have been reported in our previous studies (Ding et al., 2016; Han et al., 2013). They were all right-handed (Oldfield, 1971), had normal or corrected-to-normal hearing and visual acuity and were able to follow the task instructions.

SD Patients and healthy controls

Nineteen patients with SD (12 males) were selected from the Huashan Hospital in Shanghai (age: mean = 61.3, standard deviation = 8.6, range = 46–75 years; duration of formal education: mean = 11.5, standard deviation = 3.3, range = 4–16 years). These patients satisfied the diagnostic criteria for SD (Gorno-Tempini et al., 2011). In other words, they experienced anomia (assessed by the picture naming task) and impaired single-word comprehension (assessed by picture and word associative matching tasks) with relative sparing of the abilities of phonology, episodic memory and executive control (assessed by the oral repetition, Rey-O recall and shape trail tests, respectively; see details in Table 1 and Ding et al., 2016). Furthermore, these patients presented severe cerebral atrophy in the anterior temporal lobes (see Table 1). Their disease duration was on average 3.4 years (standard deviation = 1.5, range = 1–8). The disease duration of each patient was reported by his or her caregiver (i.e., the time since appearance of the first observable symptom).

Twenty healthy controls (eight males) were selected. Their age and formal educational levels were 60.5 years (standard deviation = 3.9, range = 51–69) and 10.5 years (standard deviation = 2.9, range = 2–16), respectively. These demographic variables were comparable with those of the SD patients (p values > 0.15; see Table 1).

SA Patients and healthy controls

Eighteen patients with SA (17 males) were recruited from the China Rehabilitation Research Centre. Their mean age and formal education level were 49.9 years (standard deviation = 10.2, range = 32–68) and 12.6 years (standard deviation = 2.9, range = 6–16), respectively. All the patients had experienced their first brain stroke (six patients with hemorrhage and 12 patients with infarction) and were at least one month post-onset (months from onset: mean = 3.5, standard deviation = 2.7, range = 1–9 months). They did not have any other neurological or psychiatric diseases, were able to follow the task instructions, and were all right-handed. Most of them were diagnosed with aphasia (global = 5; motor = 6; subcortical = 2; anomia = 2; sensory = 1; or conduction = 1). Moreover, the patients satisfied the criteria for SA (Noonan et al., 2013a), in which they exhibited multimodal comprehension deficits (t-scores < −1.69, p < 0.05) with principal lesions in the left hemisphere (eight patients with bilateral lesion and ten patients with only left lesion; see details in Table 2).

Forty-six healthy controls (24 males) were recruited. The subjects' age was 49.5 years (standard deviation = 11.0, range = 26–72), and their formal education level was 13.0 years (standard deviation = 4.0, range = 6–22). The control subjects were comparable to the SA patients in age, educational level, and handedness (p values > 0.70) but included fewer males (p = 0.002; see Table 2).

Behavioural data collection and preprocessing

Data collection

Using the same procedure, each subject was assessed on three cognitive abilities (semantic, non-semantic, and general cognitive abilities). The evaluation was conducted in a quiet room. Each testing session lasted less than two hours, and participants were allowed to pause when necessary. The presentation order of items in each task was pseudorandom but was the same across subjects.

Table 1. Background information of the patients with semantic dementia.

	Demographic characteristics				Behavioural performance							Grey matter volume (cm^3)		
Patient	Age (years)	Gender	Education duration (years)	Disease duration (years)	Oral picture naming	Picture associative matching	Word associative matching	Repetition	MMSE	Rey-O recall	STT B-A (s)	Whole brain	Left TP	Right TP
1	75	F	9	5	**.08 (−11)**	**.74 (−5)**	**.60 (−22)**	.83 (−2)	**.43 (−7)**	.36 (0)	**278 (3)**	**340 (−1.87)**	**1.68 (−2.87)**	**1.64 (−4.56)**
2	52	F	7	3	**.34 (−10)**	**.74 (−5)**	**.77 (−18)**	1.00 (1)	**.70 (−4)**	.28 (0)	**173 (3)**	374 (−1.36)	**2.02 (−3.94)**	**2.14 (−5.75)**
3	65	F	12	3	**.12 (−12)**	**.71 (−6)**	**.63 (−23)**	.92 (−1)	**.53 (−6)**	**0 (−3)**		**300 (−3.63)**	**1.97 (−2.84)**	**1.46 (−5.35)**
4	69	M	4	8	**.36 (−6)**	**.80 (−3)**	**.66 (−16)**	.83 (−1)	**.67 (−3)**	.08 (−1)	95 (−1)	394 (−0.28)	**1.22 (−3.92)**	**2.40 (−4.24)**
5	63	M	9	3	**.61 (−4)**	**.79 (−3)**	**.89 (−4)**	1.00 (1)	**.80 (−2)**	.33 (0)	91 (0)	397 (−0.69)	**1.23 (−4.11)**	**1.79 (−5.46)**
6	59	M	11	1	**.10 (−12)**	**.67 (−6)**	**.59 (−26)**	**.58 (−3)**	**.43 (−7)**	.17 (−2)	54 (−1)	416 (−0.40)	**1.10 (−4.35)**	**3.77 (−3.60)**
7	62	M	12	2	**.37 (−8)**	**.66 (−7)**	**.84 (−8)**	1.00 (1)	**.73 (−3)**	**.11 (−2)**	101 (0)	**348 (−2.41)**	**1.65 (−3.74)**	**.33 (−7.40)**
8	65	M	12	2	**.10 (−12)**	**.53 (−10)**	**.60 (−25)**	.92 (0)	.83 (−2)	**0 (−3)**	**201 (3)**	427 (−0.01)	**1.37 (−3.95)**	**4.72 (−2.36)**
9	75	M	16	2	**.50 (−6)**	**.76 (−5)**	.89 (−2)	.92 (−1)	.93 (0)	.39 (−1)	64 (−2)	361 (−2.04)	**2.40 (−2.43)**	**.70 (−6.91)**
10	68	M	16	3	**.11 (−13)**	**.79 (−4)**	**.69 (−19)**	1.00 (0)	**.63 (−5)**	**.22 (−2)**	**192 (3)**	387 (−1.44)	**1.02 (−4.24)**	5.30 (−1.68)
11	57	M	16	3	**.31 (−10)**	.89 (−2)	**.91 (−5)**	1.00 (1)	**.80 (−2)**	.86 (1)	89 (1)	417 (−0.80)	**1.70 (−3.81)**	5.75 (−1.68)
12	46	M	9	3	**.31 (−9)**	**.80 (−3)**	**.67 (−21)**	1.00 (1)	**.73 (−3)**	.28 (2)	83 (2)	408 (−0.75)	**1.21 (−4.39)**	**2.58 (−4.99)**
13	63	F	9	5	**.06 (−13)**	**.56 (−10)**	**.51 (−34)**	**.75 (−2)**	**.43 (−8)**	.36 (0)	12 (−3)	**329 (−2.64)**	**.43 (−4.94)**	**2.93 (−3.95)**
14	48	M	9	3	**.24 (−10)**	**.67 (−5)**	**.69 (−20)**	1.00 (1)	**.67 (−4)**	.11 (−2)	58 (1)	**357 (−2.13)**	**1.80 (−3.82)**	**1.14 (−6.38)**
15	52	F	12	3	**.14 (−14)**	**.61 (−9)**	**.47 (−41)**	.83 (−1)	**.57 (−6)**	**.11 (−2)**		405 (−0.75)	**1.24 (−4.34)**	**4.12 (−3.13)**
16	66	F	14	4	**.25 (−10)**	.91 (−1)	**.84 (−7)**	1.00 (0)	.87 (−1)	.61 (0)	**243 (4)**	394 (−0.84)	**1.40 (−3.19)**	5.81 (−0.33)
17	62	F	15	3	**.12 (−12)**	**.59 (−9)**	**.70 (−19)**	1.00 (0)	**.73 (−3)**	**0 (−3)**		**289 (−4.21)**	**.41 (−4.32)**	**1.58 (−5.22)**
18	49	M	15	3	**.24 (−11)**	.87 (−2)	**.67 (−24)**	.83 (−1)	**.77 (−3)**	**.25 (−2)**	**80 (2)**	**348 (−2.88)**	**1.15 (−4.55)**	**5.47 (−2.29)**
19	68	M	12	5	**.21 (−10)**	**.60 (−8)**	**.73 (−15)**	1.00 (0)	**.70 (−4)**	.22 (−1)	122 (0)	372 (−1.56)	**.64 (−4.64)**	**1.51 (−5.89)**
SD average	61.3 ± 8.6	12:7	11.5 ± 3.3	3.4 ± 1.5	.24 ± .15*	.72 ± .11*	.70 ± .13*	.92 ± .11	.68 ± .15*	.25 ± .22*	121 ± 75	372 ± 39*	1.35 ± .52*	2.90 ± 1.80*
NC average	60.5 ± 3.9	8:12	10.5 ± 2.9		.89 ± .06	.95 ± .03	.96 ± .02	.96 ± .08	.93 ± .05	.45 ± .18	91 ± 36	421 ± 28	5.09 ± .78	6.62 ± .78

The numbers in parentheses are the corrected *t*-scores. The bold font indicates impaired cogntive abilities or severe brain atrophy (STT's corrected *t*-scores > 1.65; others' < -1.65). MMSE: Mini-Mental State Examination; STT: shape trail test; TP: temporal pole; SD: semantic dementia; NC: normal control. *: $p < 0.005$ (comparisons between the patients and controls).

Table 2. Background information of the patients with semantic aphasia.

	Demographic characteristics & etiology						Behavioural accuracy					Neuroimaging summary		
Patient	Age (years)	Gender	Education duration (years)	Months from onset	Cause of disease	Aphasic type	Oral picture naming	Picture associative matching	Word associative matching	Repetition	MMSE	Lesion size (mm^3)	Laterality	Lesion location
1	60	M	16		hemorrhage	global	**.35 (−14)**	**.67 (−6)**	**.71 (−9)**	**.42 (−13)**	**.30 (−14)**	103117	B (L > R)	Frontal-temporal-parietal
2	32	M	15	9	hemorrhage	global	**.23 (−16)**	**.80 (−3)**	**.73 (−8)**	**.33 (−15)**	**.17 (−16)**	33699	L	Frontal-temporal
3	34	M	12	9	hemorrhage	no	**.71 (−5)**	**.86 (−2)**	**.87 (−3)**	.92 (−1)	.90 (−1)	24926	L	Temporal-subcortical
4	42	M	14	5	infarction	global	**.50 (−10)**	**.86 (−2)**	**.79 (−6)**	**.42 (−13)**	**.60 (−7)**	131093	L	Frontal-temporal-parietal
5	49	M	12	3	infarction	global	**.04 (−20)**	**.86 (−2)**	**.83 (−4)**	**.50 (−11)**	**.23 (−15)**	141054	L	Frontal-temporal-parietal
6	51	M	9	1	infarction	anomia	**.81 (−3)**	**.87 (−2)**	**.91 (−2)**	**.58 (−9)**	**.57 (−8)**	60518	L	Frontal
7	56	F	12	5	infarction	subcortical	**.14 (−15)**	**.77 (−3)**	**.76 (−6)**	**.67 (−6)**	**.37 (−10)**	42069	L	Frontal-temporal
8	40	M	16	5	hemorrhage	motor	**.64 (−7)**	**.87 (−2)**	**.91 (−2)**	**.83 (−3)**	**.80 (−3)**	91004	B (L > R)	Frontal-temporal-parietal
9	68	M	16	1	infarction	conduction	**.00 (−22)**	**.79 (−3)**	**.66 (−10)**	**.00 (−23)**	**.00 (−20)**	65693	B (L > R)	Frontal-temporal
10	58	M	9	6	infarction	motor	**.09 (−19)**	**.76 (−4)**	**.74 (−8)**	**.58 (−9)**	**.10 (−18)**	51073	B (L > R)	Frontal-subcortical
11	63	M	12	1	infarction	motor	**.01 (−21)**	**.69 (−6)**	**.60 (−12)**	**.25 (−17)**	**.10 (−18)**	145476	L	Frontal-subcortical
12	58	M	15	1	infarction	sensory	**.59 (−8)**	**.71 (−5)**	**.86 (−4)**	**.42(−13)**	**.10 (−18)**	63830	B (L > R)	Frontal-temporal
13	37	M	12	3	infarction	global	**.26 (−15)**	**.79 (−4)**	**.80 (−5)**	**.75 (−5)**	**.73 (−4)**	54852	L	Frontal-subcortical
14	53	M	12	1	infarction	anomia	**.74 (−4)**	**.84 (−2)**	**.86 (−4)**	1.00 (0)	**.57 (−8)**	23235	B (L > R)	Frontal-temporal-parietal
15	48	M	15	3	hemorrhage	motor	**.84 (−2)**	**.79 (−3)**	**.90 (−2)**	**.75 (−5)**	**.57 (−8)**	10226	B (L > R)	Insula
16	57	M	6	2	infarction	motor	**.66 (−6)**	**.74 (−5)**	**.64 (−11)**	**.83 (−3)**	**.47 (−10)**	11384	L	Subcortical
17	48	M	9	1	hemorrhage	subcortical	**.00 (−21)**	**.79 (−4)**	**.70 (−9)**	**.00 (−4)**	**.10 (−18)**	206777	B (L > R)	Frontal-temporal-parietal
18	45	M	15	4	infarction	motor	**.64 (−7)**	**.81 (−3)**	**.76 (−7)**	**.67 (−7)**	**.33 (−13)**	156637	L	Frontal-temporal-parietal
SA average	49.9 ± 10.2	17:1*	12.6 ± 2.9	3.5 ± 2.7	12:6		.40 ± .31*	.79 ± .06*	.78 ± .10*	.55 ± .29*	.39 ± .27*	78703 ± 56841	10:8	
NC average	49.5 ± 11.0	24:22	13.0 ± 4.0				.94 ± .04	.94 ± .04	.96 ± 03	.98 ± .04	.95 ± .04			

The numbers in parentheses are the corrected *t*-scores. The bold font indicates impaired cognitive abilities (corrected *t*-scores < -1.65). MMSE: Mini-Mental State Examination. SA: semantic aphasia; NC: normal control.
*: $p < 0.005$ (comparisons between the patients and controls).

Semantic ability. Three tasks were implemented, all involving semantic processing but varying in the modalities of stimuli input and response output. (1) *Oral picture naming*. This task included 140 object pictures designed by our lab (Ding et al., 2016; Han et al., 2013), with 20 from each of seven categories (animals, tools, common artefacts, fruits and vegetables, large nonmanipulable objects, faces, and actions). The pictures of the faces were black and white face photos of famous Chinese people. The pictures of actions were black and white line drawings depicting somebody's actions. The other pictures were coloured photos of real objects. The word frequency was balanced among the five object categories. Each picture was visually presented on the screen, and participants were instructed to speak the name of the picture. (2) *Picture associative matching*. This task had the same format as the Pyramid and Palm Trees Test (Howard & Patterson, 1992). It included 70 items, with ten from each category in the oral picture naming. For each item, three object pictures from the same semantic category were simultaneously presented in the form of an equilateral triangle. Participants were instructed to decide which of the two bottom pictures (e.g., spoon, ruler) was semantically closer to the top one (e.g., chopsticks). The targets' frequency was balanced between the object categories and the answers and foils' frequency was balanced within each object category. The response was made by pressing the corresponding picture. (3) *Word associative matching*. This task was the same as the picture associative matching task except that the object pictures were replaced with their corresponding written names, and the items were presented in a new order.

Non-semantic repetition ability. The examiner spoke eight words and four sentences, and participants were asked to repeat what they heard.

General cognitive ability. This ability was evaluated using the MMSE (Folstein et al., 1975). The conventional collection procedure for this test was adopted. Of note, the meaning of the MMSE score for stroke patients is still unclear.

Episodic memory. We used the Rey-O complex figure task to test the episodic memory ability of SD patients (Osterrieth, 1944). First, we showed a complex figure to participants. After 30 min, participants were asked to recall the complex figure based on their memory.

Executive control. We used the shape trail test to assess the executive control ability of SD patients (Zhao et al., 2013). There were two sets for this task. In set A, there were numbers in circles. Participants were instructed to connect circles based on the order of numbers. In set B, there were numbers in both circles and squares, and the subjects needed to draw lines alternatively between circles and squares based on the order of numbers.

Data preprocessing

The response to each item was scored as correct or incorrect. Regarding the two oral production tasks (oral picture naming and repetition) and two object associative tasks (picture and word associative matching), each item was scored by participants' first complete oral response and first pressing response, respectively. The MMSE and Rey-O recall tests were scored using their conventional score method. The score of the shape trail test was calculated by subtracting the time of set A from the time of set B. A higher score indicates that patients have more executive control impairments.

Although demographic variables matched well between the patients and healthy controls, Demographic variables still had large variances within the patient group. In this case, a raw patient score might not reflect the severity of the deficit. To eliminate the influence of demographic characteristics (i.e., age, gender, and education level), the task score of each patient was transformed into a corrected *t*-score by considering the distribution of healthy controls (Crawford & Garthwaite, 2006; Han et al., 2013). Specifically, we first built a regression model for each task in healthy subjects, in which the demographic variables were treated as the predictors and the task accuracy was treated as the dependent variable. Then, we obtained the predicted task scores of the patients by introducing the patients' demographic data into the model. The *t*-score was further obtained by dividing the discrepancy of real and predicted task scores by the standard error of controls. Finally, a semantic composite score for each subject was calculated by averaging the *z*-transformed *t*-scores (based on the patient group) of the three semantic tasks

(the same method used in Ding et al., 2016; Han et al., 2013).

Imaging data acquisition and preprocessing

Imaging data acquisition

Two types of neuroimaging data were collected: 3D T1-weighted MPRAGE and diffusion-weighted images. FLAIR T2 images were additionally collected for the SA patients, and were used as a reference during the manual drawing of lesion contours.

SD patients and healthy controls. Patients were scanned by a Siemens 3 T scanner at Huashan Hospital in Shanghai. (1) T1 images. Images were acquired in the sagittal plane with the following parameters: matrix size = 240 × 256, voxel size = 1 × 1 × 1 mm, repetition time = 2300 ms, echo time = 2.98 ms, field of view = 240 × 256 mm, flip angle = 9°, and slice number = 192 slices. (2) diffusion weighted images. Images were acquired in the transverse plane with the following parameters: matrix size = 128 × 128, voxel size = 1.8 × 1.8 × 3 mm, repetition time = 8500 ms, echo time = 87 ms, inversion time = 0 s, field of view = 230 × 230 mm, flip angle = 90°, slice number = 42 slices, slice thickness = 3 mm, and direction number = 20. Each direction was scanned twice to improve the image quality.

SA patients and healthy controls. Patients were scanned by a 1.5 T GE Signa Excite scanner at the China Rehabilitation Research Centre. (1) *T1 images.* Images were acquired in the sagittal plane with the following parameters: matrix size = 512 × 512, voxel size = 0.49 × 0.49 × 0.70 mm, repetition time = 12.26 ms, echo time = 4.2 ms, inversion time = 400 ms, field of view = 250 × 250 mm, flip angle = 15°, and slice number = 248 slices. (2) *diffusion weighted images*. Images included two separate sequences. The parameters for the first sequence were 15 diffusion weighting directions, matrix size = 128 × 128, voxel size = 1.95 × 1.95 × 2.6 mm, repetition time = 13000 ms, echo time = 69.3 ms, inversion time = 0 s, field of view = 250 × 250 mm, flip angle = 90°, and slice number = 53 slices. The second sequence had the same parameters but included 17 different directions. (3) *FLAIR T2 images*. Images were acquired in the axial plane with the following parameters: matrix size = 512 × 512, voxel size = 0.49 × 0.49 × 5 mm, repetition time = 8002 ms, echo time = 127.57 ms, inversion time = 2 s, field of view = 250 × 250 mm, flip angle = 90°, and slice number = 28 slices.

Imaging data preprocessing

SD patients and healthy controls. For each subject, T1 images were resampled into $1.5 \times 1.5 \times 1.5\ mm^3$, segmented into different tissue types (i.e., grey matter, white matter, and cerebrospinal fluid) and normalized into the MNI space using SPM8 (https://www.fil.ion.ucl.ac.uk/spm/). Grey matter volume images were further generated via affine and nonlinear warpings and smoothed using an 8-mm FWHM Gaussian kernel. The diffusion weighted images were preprocessed using PANDA (Cui et al., 2013). The brain mask was created from the b0 image. To correct for the eddy-current distortion and simple head motion, other images were registered to the b0 image with an affine transformation. To evaluate the white matter integrity, fractional anisotropy (FA) values were computed by a tensor model in the native space and were normalized into the MNI space through nonlinear registration. Finally, to carry out the voxel-based analysis, images were smoothed with 6 mm FWHM.

SA patients and healthy controls. With regard to T1 images, two sequences were first coregistered using trilinear transformation and averaged together. Then, the T2 image was coregistered to the averaged T1 image using the same method. Lesion maps were manually drawn on T1 images, referring to T2 images, by our experienced colleagues. The colleagues were not the authors of this article and were blind to the purpose of this study. To reduce the registration problem induced by brain damage, manual and automatic registrations were implemented. Manual registration was carried out via the "3D Volume Tools" from Brain-Voyager QX v2.0 (http://www.brainvoyager.com/) to transfer the lesion maps from the native space to the Talairach space, which provides detailed anatomical information to modify the location of damaged areas. The automatic registration was applied by the "WarpImageMultiTransform" from ANTS (http://stnava.github.io/ANTs/) to estimate affine transformation from the Talairach space to the MNI space. Finally, the lesion maps were transformed into the MNI space using the affine parameter. With regard to diffusion data, we

merged the two sequences. The other procedures were the same as those in the SD patients.

Statistical analyses

Identifying semantic-relevant grey matter regions

To replicate the grey matter dissociation of semantic knowledge and semantic control, we performed the following analyses. For the SD patients, we calculated a partial correlation between the grey matter volume of each voxel and the semantic composite score, controlling for the total brain volume (summing all the voxels' grey matter volumes in the whole-brain grey matter mask), general cognitive state (*t*-scores of the MMSE test) and repetition ability (*t*-scores of the repetition test). The threshold was set at voxel $p < 0.001$ and cluster $p < 0.05$ (GRF correction). For the SA patients, due to the binary nature of the lesion measure, we carried out a voxel-based lesion-symptom mapping (VLSM; Bates et al., 2003) analysis instead of a partial correlation, controlling for the total lesion volume (number of total damaged voxels), general cognitive state and repetition ability. This VLSM analysis was run on voxels damaged in at least 10% (i.e., two) of the patients. For each voxel, the semantic composite scores in the patients with lesion were compared with the semantic composite scores of those without lesion. The threshold was set as voxel $p < 0.05$ and cluster $p < 0.05$ (GRF correction).

Identifying semantic-relevant white matter networks

To determine the relationship between the white matter networks and two semantic processes, we performed a network-based white matter lesion-symptom mapping analysis. Masks of the three networks were obtained from the previous study (Fang et al., 2015). In that study, tracts were tracked in 48 controls, and FA values of the tracts were extracted in 80 brain-damaged patients. Then, 53 tracts related with the patients' semantic deficits were chosen to carry out a modular analysis (Newman, 2006). Three semantic-related networks were generated. These networks included tracts among different grey matter regions: the medial temporal network included four regions (the left hippocampus, parahippocampal gyrus, amygdala, and pallidum); the left frontal-subcortical network included nine regions (the left middle frontal, inferior triangular and opercular frontal gyri; insula; thalamus; Heschl's gyrus; putamen and bilateral caudate); and the frontal-temporal/occipital network included nine regions (the left orbital superior, middle and inferior frontal gyri, superior temporal pole, middle and superior temporal gyri, calcarine fissure and lingual gyrus).

We first extracted the mean signals of the three networks from the FA maps. Then, we established a regression model in each patient group, with one dependent variable (semantic composite score), three predictors (FA values of three networks) and three covariates (total grey matter volume for SD/total lesion size for SA, general cognitive state, repetition ability). This enabled us to identify the network whose integrity can significantly predict the severity of deficit for semantic knowledge or semantic control after controlling for the influence of confounding factors.

Regarding the SD patients, more validation analyses were carried out. The regression models included the same dependent and independent variables as above, but the covariate was replaced with episodic memory ability (*t*-scores of Rey-O figure recall), executive control (*t*-scores of the shape trail test) or laterality index (differences of grey matter volumes between bilateral temporal poles).

Identifying semantic-relevant white matter tracts

This analysis was used to explore the semantic-relevant tracts beyond the abovementioned networks. The white matter mask for this analysis was generated by binarizing the "ICBM-DTI-81 white matter labels" atlas with 60% probability (Mori et al., 2005). First, the FA maps were compared using voxel-based independent *t*-tests between the patient and control cohorts within the white matter mask (GRF correction: voxel $p < 0.001$, cluster $p < 0.05$). Then, the voxel-based partial correlations between the FA values and the semantic composite scores were carried out in each patient cohort, controlling for the confounding variables used in the abovementioned grey matter analyses at a threshold of uncorrected $p < 0.05$, cluster size > 50 voxels (Agosta et al., 2013; Iaccarino et al., 2015). To report the location of significant areas, we used the TRACTOTRON (http://www.bcblab.com/BCB/Tractotron.html) to calculate the overlap ratios of significant areas relative to different tracts and networks. The tract-based atlas was constructed from healthy controls with a probability of 50% (Rojkova et al., 2016).

Results

Demographic and neuropsychological profiles

Tables 1 and 2 display the demographic information and neuropsychological performance of the SD and SA patients, respectively. There were no significant differences in demographic variables between the patients and their controls (p values > 0.15), except for the gender distribution between the SA patients and their controls ($\chi^2 = 10$, $p = 0.002$). The accuracies of all the semantic tasks and MMSE in both the SD and SA patients were significantly lower than those in the healthy controls (SD: t-values < −6.98; SA: t-values < −7.31; p values < 0.001). With regard to the repetition task, scores of the SA patients were lower than those of the healthy controls ($t = -6.36$, $p < 0.001$), whereas the SD patients had comparable scores with the healthy controls ($t = 1.46$, $p = 0.15$). Moreover, the SD patients had significant deficits in episodic memory ($t = -3.08$, $p = 0.004$) but not in executive control ($t = 1.46$, $p = 0.16$). At the individual level, most of the SD and SA patients showed deficits in semantic tasks (SA: $n = 18$; SD: $n > 16$) and MMSE (SA: $n = 17$; SD: $n = 16$). Most of the SA patients had a repetition problem ($n = 17$). The SD patients varied substantially in non-semantic functions. Some patients had impaired abilities of repetition ($n = 2$), episodic memory ($n = 7$) or executive control ($n = 6$), but others did not (see Table 1). This difference was because the SD patients in both mild and severe stages were recruited. When atrophy reaches the lateral frontal lobe, medial frontal lobe and medial temporal lobe, it will lead to the impairment of repetition, executive control, and episodic memory, respectively (see Figure 1).

To confirm SD and SA patients had deteriorations of semantic knowledge and semantic control respectively, we calculated their item consistency among three semantic tasks and their semantic error types in the picture naming task. Relative to the SA group, the SD group presented significantly higher item consistency values between naming and associative tasks (t-values < −2.33, p values < 0.03) but comparable consistency between associative matching tasks ($t = 0.66$, $p = 0.63$). Moreover, the SD patients generated more coordinate/superordinate errors, while the SA patients generated more associative errors ($t = -4.18$, $p < 0.001$). These results are consistent with the

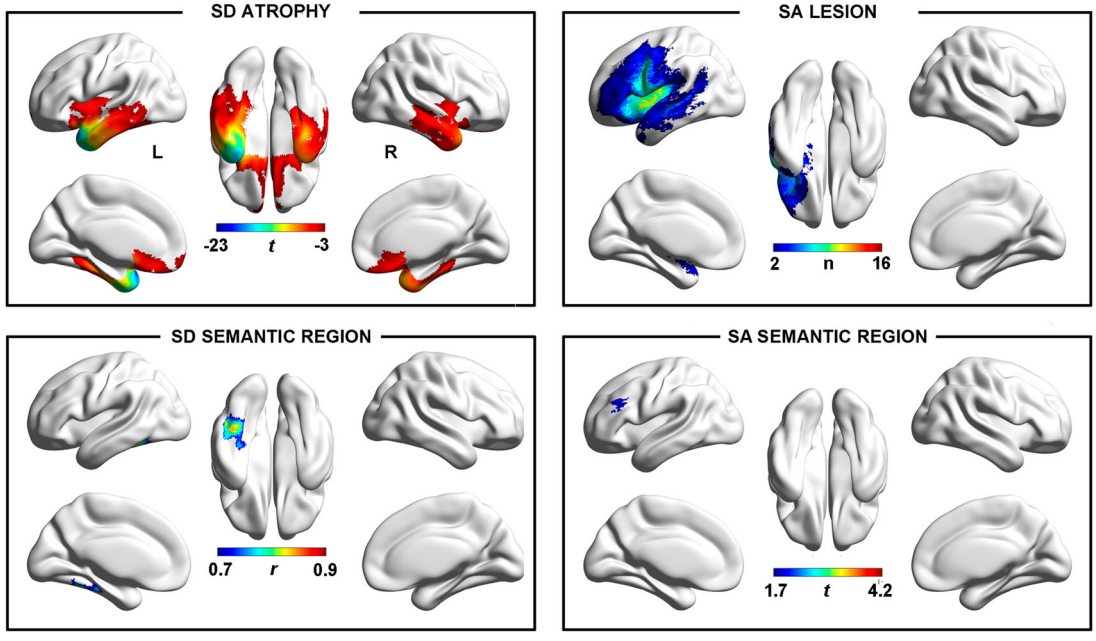

Figure 1. Damaged and semantic-relevant grey matter regions derived from the voxel-based analysis in each patient group. Left top: the brain atrophy map of the SD, which is from the comparison between grey matter volumes of the patients with SD and the healthy controls. Right top: the lesion overlap map of the SA patients, which is the sum of lesion maps of the SA patients. Left bottom: the map of significant regions in the SD patients, which is from the correlation analysis between grey matter volumes of the SD patients and their semantic composite scores. Right bottom: the map of VLSM significant regions of the SA patients, which is from the comparison between semantic composite scores of the patients with intact voxels and those with damaged voxels. SD: semantic dementia; SA: semantic aphasia; VLSM: voxel-based lesion-symptom mapping.

assumption that SD and SA individuals impair semantic knowledge and semantic control, respectively (Jefferies & Lambon Ralph, 2006).

Semantic-relevant grey matter regions

These two patient groups presented distinctive patterns of grey matter abnormalities (Figure 1). The SD group had marked atrophy in the bilateral temporal poles (right side: peak $t = -11$; peak coordinates: 27, 21, −43; 23448 voxels; left side: peak $t = -23$; peak coordinates: −54, 18, −24; 29286 voxels), extending bilaterally into the whole temporal lobe, insula and ventral frontal lobe. In contrast, the SA group had the most severe damage in the left dorsal white matter (peak coordinates: −29, 7, 24), extending into the whole left frontal lobe, lateral temporal lobe, insula, and subcortical areas. More importantly, the grey matter region related to semantic deficits in the SD patients was the left fusiform gyrus (peak $r = 0.85$, peak coordinates: −45, −49, −21; 1577 voxels), while the grey matter regions related to semantic deficits in the SA patients were the left inferior frontal gyrus (BA 45) and the middle frontal gyrus (peak $t = 1.75$; peak coordinates: −37, 29, 18; cluster size: 1182 voxels; see Figure 1). These results replicate the previous findings that semantic knowledge and semantic control are supported by separate grey matter regions.

Semantic-relevant white matter networks

The mean FA values of all the white matter networks were significantly lower in the patient groups than their healthy control groups (SD: t-values < −2.53; SA: t-values < −8.79; p values < 0.02; see Table 3).

To determine the white matter network associated with semantic knowledge or semantic control, we established regression models using the networks' FA values to predict the severity of semantic deficits in the SD or SA patients controlling for the influence of other confounding variables (see Figure 2 & Table 4). This analysis revealed that the semantic performance of the SD patients was significantly predicted by the FA value of the left medial temporal network (beta = 0.86, $p = 0.02$). Moreover, when other covariates were controlled, the effect of the medial temporal network still existed (controlling for episodic memory: beta = 2.64, $p = 0.02$; executive control: beta = 2.89, $p = 0.02$; laterality: beta = 3.31, $p = 0.005$). In contrast, the performance of the SA patients was predicted by the FA values of the left frontal-subcortical (beta = 1.54, $p = 0.04$) and the left frontal-temporal/occipital networks (beta = −1.02, $p = 0.05$). These results indicate that the left medial temporal network and the other two networks might contribute to semantic knowledge and semantic control, respectively.

Table 3. Mean FA values of the white matter networks in the patient and their corresponding control groups.

	Network	Patients	Controls
Semantic dementia	medial temporal network	.29 (.01)**	.31 (.01)
	frontal-subcortical network	.28 (.02)*	.29 (.01)
	frontal-temporal-occipital network	.32 (.02)*	.33 (.01)
Semantic aphasia	medial temporal network	.27 (.02)**	.33 (.01)
	frontal-subcortical network	.23 (.03)**	.31 (.02)
	frontal-temporal-occipital network	.26 (.03)**	.33 (.02)

The numbers in parentheses are the standard deviations. FA: fractional anisotropy. *: $p < .05$, **: $p < .001$ (comparisons between the patients and controls).

Semantic-relevant white matter tracts

To further validate and extend the findings of the abovementioned network-based analyses, we performed voxel-based white matter analyses. Compared with the healthy controls, the SD patients presented decreased FA values in the ventral pathways (e.g., bilateral inferior fronto-occipital fasciculi, inferior longitudinal fasciculi, uncinated fasciculi, anterior commissure and fornix; overlap ratio with the frontal-temporal/occipital network: 9%, overlap ratio with the medial temporal network overlap: 9%). Meanwhile, the SA patients showed a widespread white matter abnormality (overlap ratios > 25%; see details in Figure 3, Table 5 & Supplementary Table).

Results of the voxel-based correlation analysis are illustrated in Figure 3, Table 5 and supplementary table. This analysis obtained highly consistent results with those of the network-based analysis. Specifically, the semantic deterioration of the SD patients was associated with the left posterior cingulum (peak $r = 0.74$, peak coordinates: −20, −28, −20, 2 clusters, cluster size > 50 voxels). This area overlapped with the left medial temporal network (overlap ratio = 3%). The semantic deterioration of the SA patients was associated with the left anterior cingulum, anterior thalamic projection, frontal-striatal tract, right arcuate fasciculus, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus and optic

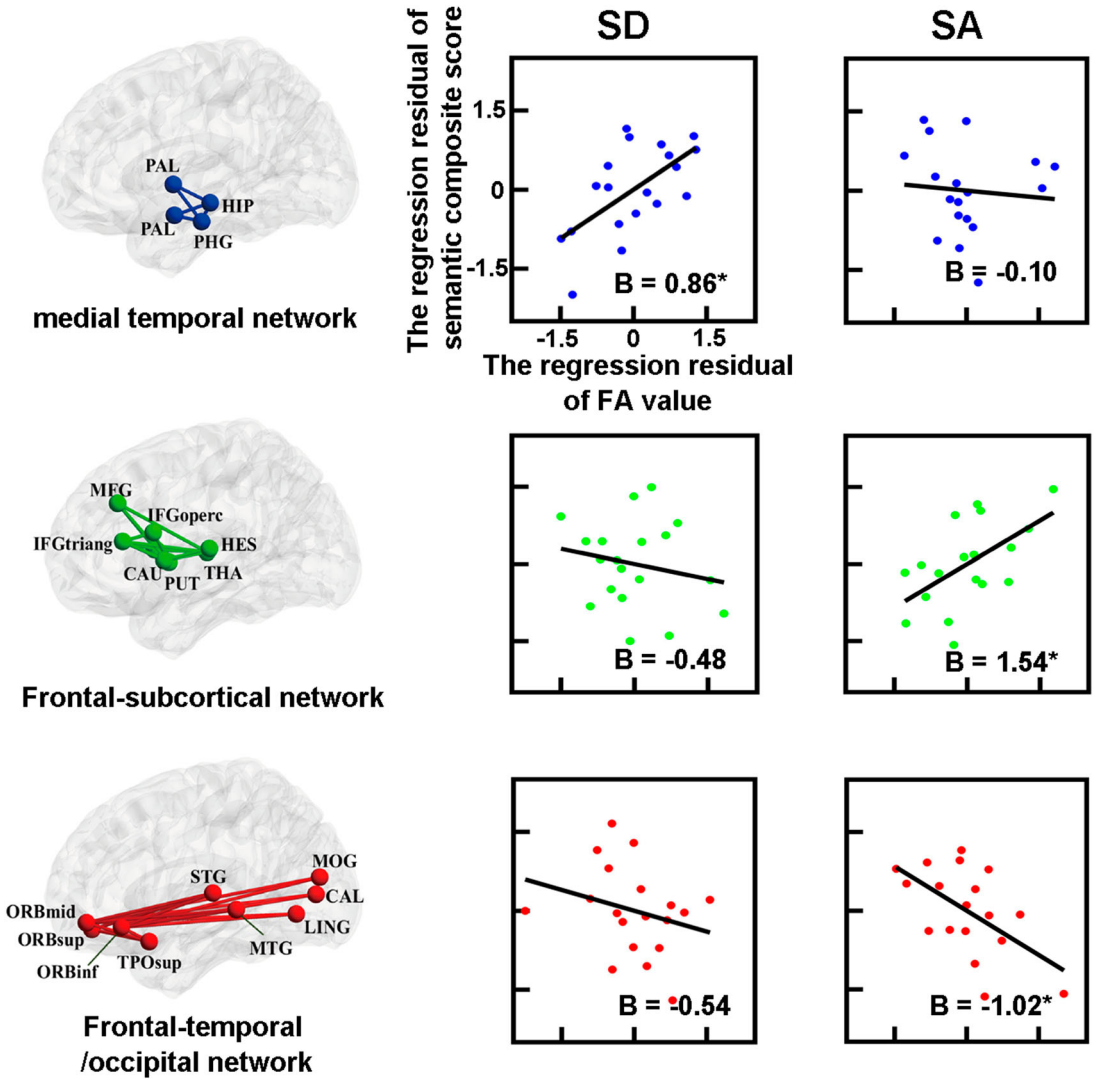

Figure 2. Semantic-relevant white matter networks derived from the network-based analysis in each patient group. *: $p < 0.05$. B: beta value; CAL: calcarine fissure; CAU: caudate; FA: fractional anisotropy; HES: Heschl's gyrus; HIP: hippocampus; IFGoperc: inferior frontal gyrus, opercular part; IFGtriang: inferior frontal gyrus, triangular part; LING: lingual gyrus; MFG: middle frontal gyrus; MOG: middle occipital gyrus; MTG: middle temporal gyrus; ORBmid: middle frontal gyrus, orbital part; ORBinf: inferior frontal gyrus, orbital part; ORBsup: superior frontal gyrus, orbital part; PAL: pallidum; PHG: parahippocampal gyrus; PUT: putamen; THA: thalamus; TPOsup: superior temporal pole; SA: semantic aphasia; SD: semantic dementia; STG: superior temporal gyrus.

radiations (peak $r = 0.82$, peak coordinates: −18, 40, 30; 8 clusters, cluster size > 50 voxels), which had a high overlap with the left frontal-subcortical network (overlap ratio = 2%).

Table 4. R^2 and beta values of the regression models in the two patient groups.

	Semantic dementia	Semantic aphasia
R^2	0.87*	0.87**
frontal-temporal-occipital network	−0.54	−1.02*
frontal-subcortical network	−0.48	1.54*
medial temporal network	0.86*	−0.10
MMSE	0.50*	0.92**
whole brain damage	−0.01	0.52
repetition	0.13	−0.07

The first row indicates the R^2 of the models. The other rows indicate the beta values of the variables. *$p < .05$, **$p < .01$.

Discussion

The purpose of this study is to investigate in which way and to what extent two semantic processes (semantic knowledge representation and semantic control) dissociate from each other. One recent study (Fang et al., 2015) split the semantic white matter network into three left-hemispheric subnetworks: the medial temporal, the frontal-temporal/occipital, and the frontal-subcortical networks, providing an opportunity to reveal the evidence for a dissociation between semantic knowledge and semantic control from a white-matter perspective. The present study found that semantic knowledge was associated

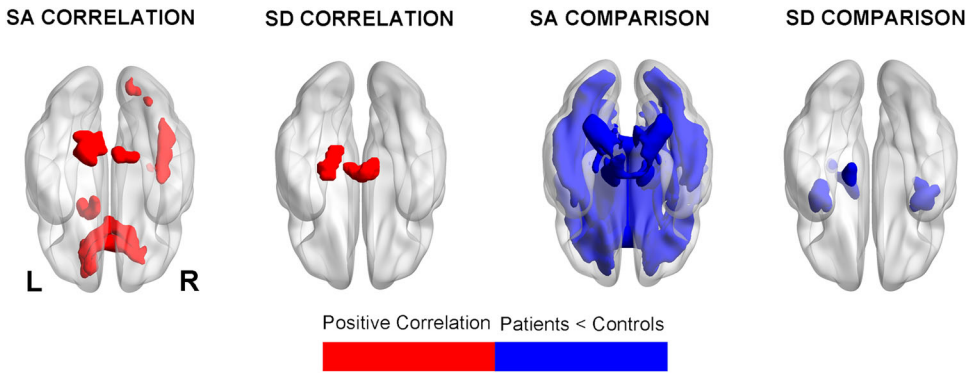

Figure 3. Semantic-relevant white matter tracts derived from the voxel-based analysis in each patient group. SA: semantic aphasia; SD: semantic dementia.

with the medial temporal network, because its white matter integrity value could effectively predict the severity of semantic deficit in the patients with SD (a semantic knowledge disorder). In contrast, semantic control was associated with the other two networks because their white matter integrity values could effectively predict the severity of semantic deficit in the patients with SA (a semantic control disorder). Thus, our results underlined the dissociation between these two semantic processes from the perspective of white matter basis.

Different symptom profiles of SD and SA

Item consistency and semantic error types have been considered as sensitive indexes to differentiate the deteriorations of semantic knowledge and semantic control (Jefferies & Lambon Ralph, 2006). If a patient had semantic knowledge deterioration, the patient would have difficulty in processing the knowledge of impaired concepts, regardless of tasks with different stimuli inputs or response outputs. As a result, it leads to high item consistency across semantic tasks. In addition, when naming objects, the patient would replace the lost concepts with their coordinate or superordinate concepts. In contrast, a patient with semantic control deterioration would present different symptom profiles for tasks or items with varied control requirements. The patient would show a low item consistency across semantic tasks because the patient would produce less correct responses in more difficult tasks. The patient would also make substantial semantic associative errors on difficult items (Lambon Ralph et al., 2016; Rogers et al., 2015). In the current study, the SD patients presented higher item consistency between semantic tasks and made more semantic coordinate/superordinate errors in the naming task than the SA patients. These results nicely replicated the findings in the literature (Corbett et al., 2009; Jefferies & Lambon Ralph, 2006), that SD patients have semantic knowledge deterioration, while SA patients have semantic control deterioration.

Note that previous studies also used presence or absence of the familiarity effect as a measure to differentiate semantic knowledge and semantic control deteriorations (Corbett et al., 2009; Forster & Chambers, 1973; Jefferies & Lambon Ralph, 2006; Lambon Ralph et al., 1998; Scarborough et al., 1977). However, a recent study demonstrated that this measure might not be appropriate (Rogers et al., 2015). Therefore, it was not adopted in our study.

Table 5. Overlap ratios of voxels identified by the voxel-based analysis relative to the white matter networks.

	T test		Correlation analysis	
	Semantic aphasia	Semantic dementia	Semantic aphasia	Semantic dementia
Frontal-temporal-occipital network	0.53	0.09	0.00	0.00
Frontal-subcortical network	0.36	0.01	0.02	0.00
Medial temporal network	0.25	0.09	0.01	0.03

Medial temporal network and semantic knowledge

Our study found that the integrity of the medial temporal network correlated with the severity of semantic deficits in the SD patients, indicating this network is related to semantic knowledge representation. The voxel-based white matter analysis further found that

the posterior cingulum in the medial temporal network was associated with the semantic performance of the SD patients. This tract was found to be associated with memory loss, especially in patients with Alzheimer's disease (Zhang et al., 2007). The other study (Hirni et al., 2013) observed that the part of this tract connecting with the left perirhinal cortex was specialized for semantic processing. However, in general, researchers have not paid attention to its function in semantic processing.

Frontal-subcortical network and semantic control

The present study found a pivotal role of the frontal-subcortical network in semantic control. The regions in the frontal-subcortical network (such as the middle frontal cortex, thalamus, basal ganglia, and inferior frontal gyrus) are engaged in executive control of general cognitive and specific language tasks (Abutalebi & Green, 2007; Duncan, 2010; Jeon et al., 2014). Thus, the white matter tracts in the frontal-subcortical network might be used to connect these regions and transfer information among them.

Our voxel-based analysis further found that the anterior thalamic projection and fronto-striatal tract were related to semantic control. These tracts connect the thalamus and basal ganglia to the frontal lobe. The anterior thalamic projection is related to executive control, episodic memory (Sexton et al., 2012), and semantic processing (Han et al., 2013). More evidence for the fronto-striatal tract underpinning semantic processing is needed. We speculate that this tract might be dedicated to transferring information between regions related to semantic control (e.g., inferior frontal gyrus) and general control (e.g., thalamus, basal ganglia, and dorsal frontal lobe). For example, the inferior frontal gyrus transfers semantic control information to the basal ganglia, while the basal ganglia transfers general control information back to the inferior frontal gyrus. Then, the integration of different information occurs in these regions.

Frontal-temporal/occipital network and semantic control

Note that this network had a negative influence on the semantic performance of the SA patients after controlling for the effect of the frontal-subcortical network, which means that more preserved tissues lead to more severe deficits. We suppose this unexpected result reflects a complicated relationship between these two networks and semantic control. Researchers need to determine how this network collaborates with the frontal-subcortical network to contribute to semantic control in the future.

Implications for semantic processing

Given that cognitive processing is shaped by the underlying biology, an investigation of the neuroanatomy supporting cognitive processing would help clarify the corresponding cognitive theory. Semantic knowledge representation and semantic control, two processes within semantic system, are separable from various perspectives, such as different cognitive models, different neuropsychological performance and different underlying grey matter bases (Jefferies, 2013; Jefferies & Lambon Ralph, 2006; Lambon Ralph et al., 2016). Here, we further found that they are also separable in white matter bases. Compared with grey matter areas, white matter tracts can not only be involved in a specific process, but can also guide the interaction between processes. Thus, our findings support that these two processes are based on distinct systems with limited interactions (Lambon Ralph et al., 2016) but do not support the theories that they have redundant interactions or share one system with graded changes (Fedorenko et al., 2018). The remaining question is how the limited interactions between these two processes work. We speculate that specific white matter tracts connecting these two systems, such as uncinate fasciculus or inferior fronto-occipital fasciculus (Catani & Thiebaut de Schotten, 2008) might be crucial for these interactions.

Limitations

First, the two patient groups had different pathological bases (i.e., dementia and stroke). Thus, the pathological features might affect the findings. Second, due to the constraint of patient scanning, the two patient cohorts were scanned using different scanners and parameters. Although we did not compare these two groups' imaging data directly, the difference in scanning is still

a possible confounding factor influencing the results. Third, we found a significantly negative relationship between the integrity of the frontal-temporal/occipital network and the SA patients' semantic performance. This counterintuitive result might be driven by the effect of the frontal-subcortical network. This issue will be continuously investigated in the future.

Conclusion

This study reveals two dissociable processes in the semantic model. The comparison of item consistency and naming error types indicates that the SD patients had semantic knowledge deficits, while the SA patients had semantic control deficits. Furthermore, the semantic knowledge deficits in the SD patients were associated with damage to the medial temporal network, while the semantic control deficits in the SA patients were associated with the frontal-temporal/occipital and frontal-subcortical networks. These findings enhance our understanding of the separability between semantic knowledge representation and semantic control.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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