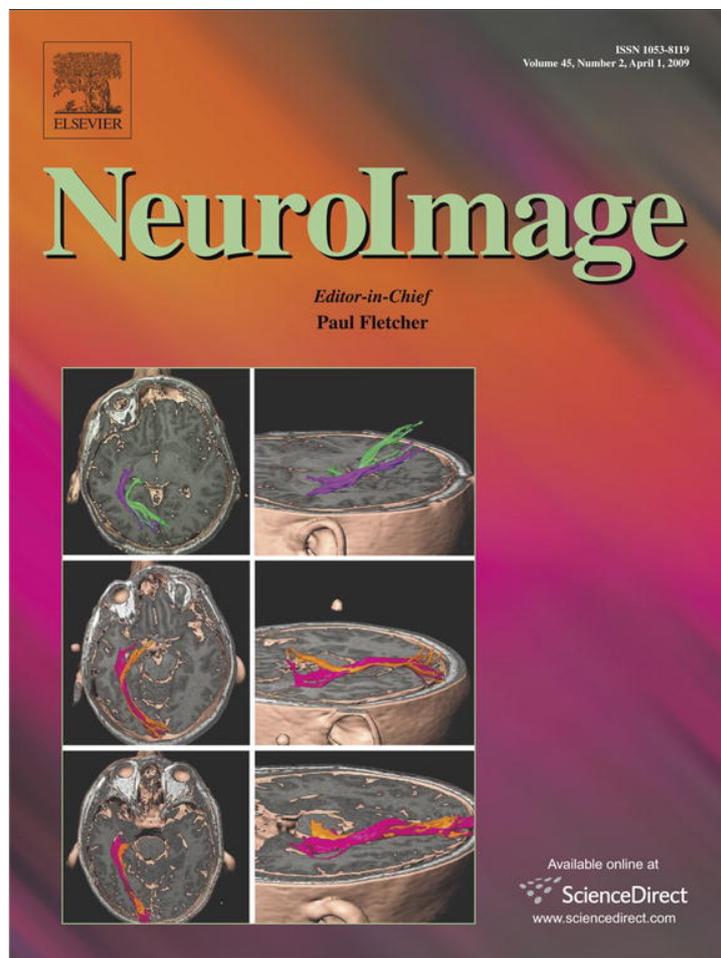


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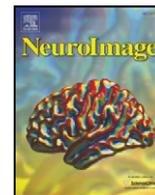
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Domain-specific reorganization of semantic processing after extensive damage to the left temporal lobe

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ABSTRACT

We investigated with fMRI the cortical correlates of recovery of semantic processing in a patient (DL) with left temporal damage. Names of animals, plant, and artifacts (semantic conditions) and reversed words (baseline condition) were auditorily presented to the patient and nine control subjects in a category monitoring task. Data analyses showed large differences between the patterns of domain-specific semantic activation observed in DL and the control subjects, which could be attributed to a cortical reorganization compensating for the damaged part of the semantic processing system in DL. Such reorganization relied on three main mechanisms, first, upholding of a subset of the structurally intact domain-specific regions, second, functional changes (both decreases and increases) of the domain specificity in several structurally intact regions that are normally engaged in the domain-specific network and, third, recruitment of supplementary domain-specific areas. Thus, in DL, animal-specific processing engaged supplementary areas in the left lingual gyrus and right cuneus, which correspond to animal-specific regions usually engaged in more demanding semantic tasks whereas the supplementary areas recruited for artifact-specific processing within the left superior/middle occipital lobe and right angular gyrus probably are endowed with a related but not domain-specific, semantic function. In contrast, no supplementary area contributed to plant-specific processing in DL. These findings suggest that the pattern of cortical reorganization consecutive to damage to the semantic processing network depends on the particular domain-specific function sustained by the damaged areas and the capacity of the remaining areas to assume this function.

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Introduction

The representation and processing of semantic knowledge is sustained by a distributed, left-dominant cortical network that involves a cluster of prefrontal, temporal, temporo-parietal, temporo-occipital, and occipital brain structures (Bookheimer, 2002; Martin, 2003; Vigneau et al., 2006). Damage to part of this network, either resulting from stroke, head injury, herpes simplex virus encephalitis, or degenerative disease, may cause sometimes severe impairments in retrieving the meaning of words and semantic knowledge about concrete and familiar objects. Several months or even years following injury, patients nonetheless may show some improvement if not complete recovery of semantic processing, which may be attributed to the adult human brain being capable of functional reorganization following injury to compensate for lost function or to maximize remaining functions (e.g., Frackowiak, 1997). In this study, we investigated the cortical

correlates of recovery of semantic processing in a patient who suffered extensive damage to the normal semantic processing network. We addressed the issue of which factors influence the location of the compensatory neural regions by examining whether and how one particular factor, the domain of semantic knowledge, influences that location.

Recovery of cognitive functions following brain damage is well known for over a century, particularly in the language domain (e.g., Crosson et al., 2007; Marsh and Hillis, 2006). Recent functional neuroimaging studies carried out with individuals having partially or totally recovered from aphasia showed that recovery of language functions was sustained by either interhemispheric reorganization, by which right hemisphere homologs of left language damaged areas were recruited during language tasks (e.g., Cappa et al., 1997; Leff et al., 2002; Thompson et al., 2000), or intrahemispheric, perilesional reorganization, by which spared regions surrounding lesions in the left hemisphere took over language functions (e.g., Heiss et al., 1999; Perani et al., 2003; Warburton et al., 1999; for recent reviews, see Crosson et al., 2007; Marsh and Hillis, 2006; Price and Crinion, 2005).

The same empirical generalization can be derived from the few activation studies that have specifically addressed semantic

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processing in individuals having recovered from semantic deficits. Thus, Zahn et al. (2002) studied with fMRI two aphasic patients (HP and RC) who, following left middle cerebral artery infarction, presented impaired word comprehension in the context of a transcortical sensory aphasia, which had almost completely recovered at the time of the study, i.e., 6 months post-stroke. Cortical correlates of semantic processing were identified by contrasting activations during a semantic monitoring task on auditory words (animal words had to be discriminated from names of other natural kinds) with activations during a lexical decision task. In the control subjects, semantic processing involved the left posterior middle frontal gyrus and the posterior parietal lobe as well as the posterior inferior or middle temporal gyrus. In RC and HP, whose lesions affected either solely the prefrontal (patient HP) or both the prefrontal and posterior parietal (RC) parts of this network, semantic processing recruited left perilesional prefrontal regions (RC), left Wernicke's area (RC and HP), and the left posterior middle and inferior temporal areas (HP). With the same fMRI paradigm, Zahn et al. (2004) studied seven aphasic patients who presented with severely impaired speech comprehension in the context of a global aphasia and showed at least partial recovery of speech comprehension when the activation study was performed, several months after presentation. These patients suffered from left middle cerebral artery infarction resulting in left fronto-temporo-parietal lesions. In these patients, the most consistently activated regions associated with semantic processing were the left posterior inferior/middle temporal and the right posterior parietal cortex, which also showed activation in normal subjects. Actually, lateralization ratios of activations did not differ significantly between the patients and the normal subjects.

In contrast, in patient GP studied by Gold and Kertesz (2000), semantic processing was largely taken over by right hemisphere regions. GP suffered infarct in the territory of the middle cerebral artery, which left him with global aphasia and extremely poor verbal comprehension. Damaged left hemisphere regions encompassed the superior, middle, and inferior temporal gyri, in addition to inferior frontal, precentral, postcentral, supramarginal, angular, and superior occipital gyri. The fMRI study was conducted 7 years following GP's stroke, when his comprehension considerably improved for visual words. Regions associated with semantic processing were identified by contrasting activations during a semantic association task (which of two written words shared a closer semantic association with a third one) with activation in an orthographic task. The results showed that the control subject activated a network of left-lateralized regions including the inferior frontal gyrus, the inferior and middle temporal gyri, the angular gyrus, and the cuneus whereas, in GP, the network was entirely lateralized to the right hemisphere, i.e., in the right middle frontal gyrus, superior temporal gyrus, angular gyrus, supramarginal gyrus, and precuneus.

The outstanding issue is what are the factors that determine the pattern of cortical reorganization of the damaged semantic processing system. The previous studies were able to show that the relative contribution of left perilesional *versus* right hemisphere regions likely depends on the location and extent of left hemisphere lesions: left frontal and temporal areas were recruited in case of damage to the frontal or fronto-parietal part of the semantic processing network (Zahn et al., 2002) whereas right-hemisphere areas took over semantic processing in case of extensive damage to the left temporal lobe (Gold and Kertesz, 2000). However, the semantic system involves a mosaic of areas each having distinct functional roles. Therefore, to gain real insight into this issue requires that the pattern of cortical reorganization is related not to location and extent of damage *per se* but to the *specific semantic functions* that were sustained by the damaged areas.

Thus, among the functional areas that can be identified within the semantic system, some are neutral to the content of knowledge (domain-general areas) like the anterior temporal lobes, involved in

processing semantic knowledge for all kinds of concepts in all modalities (Jefferies and Lambon Ralph, 2006; Patterson et al. 2007), the left inferior frontal gyrus, which has an executive role in semantic knowledge retrieval (Demb et al., 1995; Devlin et al., 2003; Poldrack et al., 1999; Thompson-Schill et al., 1997, 1998), and the left angular gyrus, which sustains the mapping between the sensory representation of words or objects and meaning (Hickok and Poeppel, 2000; Vigneau et al., 2006). Other areas, located in the left or right temporal, occipital, or parietal lobes, are specific of one domain (living vs. nonliving or animal vs. plant) of knowledge (e.g., Chao et al., 2002; Grezes and Decety, 2001; Lewis, 2006; Moore and Price, 1999; Noppeney et al., 2006; Phillips et al., 2002).

We put forward the hypothesis that the pattern of cortical reorganization of the semantic processing system should depend on which – domain-general or domain-specific – functions were sustained by the damaged areas and which remaining areas are capable of assuming these functions. The existence of domain-specific regions within the semantic system has been accounted for either by the exemplars within the domain of living things (animal and plant) requiring finer-grained identification processes than man-made objects (Devlin et al., 2002a,b), by the representation of the various categories of objects being differentially weighted in sensory, functional, and motor properties (Martin and Chao, 2001), or by evolutionary pressure having resulted in specialized neural circuits dedicated to representing and processing knowledge related to categories like animals and plant (Caramazza and Shelton, 1998). Beyond their differences, these theories thus all assume that each domain (i.e., animal, plant, man-made object) of conceptual knowledge has its own representational or/and processing requirements that distinct neural structures are capable of fulfilling. On this basis, one can expect that, in case of damage to domain-specific structures, functional recovery should engage distinct compensatory cortical areas as a function of their having processing abilities similar or close to those of the damaged areas.

There is indeed some suggestion in the neuropsychological literature that the processes of recovery after damage to the semantic network are constrained by the domain of semantic knowledge. Thus, Laiacona et al. (1997) reported on two patients LF and EA who, as a consequence of herpetic encephalitis, had extended left temporal damage, which involved the posterior halves of the left superior and middle temporal gyri in EA but not in LF. Both patients presented a semantic deficit that, at the outset, affected living things (animals as well as plant) more than man-made objects. LF manifested a good overall recovery after 13 months whereas EA showed recovery only for man-made objects after 20 months and, 10 years later, recovery for animal knowledge while his knowledge for plant items remained as severely impaired as at the outset (Laiacona et al., 2005). The discrepant pattern of recovery observed between LF and EA suggests that the posterior part of the left superior temporal lobe may be crucial for recovering semantic processing of plant items but not of other domains of knowledge. Moreover, the different rate of recovery observed for man-made objects and animals in a single individual (EA) strongly suggests that distinct plastic processes were recruited to compensate damage to each domain-specific function.

Given the variability in sites and extent of damage to the semantic processing network and the variety of semantic functions that are likely to be impaired in isolation or combination, it is doubtful that insight into how the brain compensates for the various functions involved in semantic processing could be gained by studying groups of patients with heterogeneous patterns of lesions and functional deficits. A single-case methodology seems to be required as a first step before any general predictions and hypotheses can be articulated and tested.

Therefore, in the present study, we adopted a single-case approach to address the issue of whether and how functional reorganization after damage to the semantic system is constrained by the domain of

semantic knowledge, in particular, knowledge related to animal, plant, or man-made objects (artifacts). We used fMRI to investigate the cortical correlates of domain-general and domain-specific semantic processing in a patient, DL, who had extensive left temporal damage due to herpes encephalitis that initially caused a severe loss of semantic knowledge. The study was performed when the patient was in the chronic stage of recovery and only items for which she had good semantic knowledge were presented during the activation task.

Methods

Participants

A post-encephalitis female patient, DL, who was in the chronic stage of recovery (6 years post-onset) as well as nine neurologically intact control subjects participated in the activation study. The nine control subjects were right-handed, French-speaking women with age ranging from 46 to 59 (mean = 53) who had no history of neurological disorder. All the participants gave their informed written consent prior to the fMRI experiment. The study was approved by the Ethics Committee of the Faculty of Medicine of the *Université catholique de Louvain*.

DL was a 61-year-old, right-handed French-speaking woman with 10 years of formal education. In October 2000, at the age 55, she contracted herpes simplex virus. The neuropsychological examination performed 2 weeks after her admission, reported right hemiparesia and aphasia with very profound speech comprehension disorders. The patient could close her eyes on verbal command but the successive simple commands led to perseverations of her first response. The patient could not point to any object or body part named by the examiner and could not read aloud any word or digit. Two months later, the reports still indicated right hemiparesia, jargonaphasia, severely impaired language comprehension (the patient still could not understand even simple commands and she could not repeat any word), and complete anosognosia. In December 2000, the patient was admitted as an in-patient in a rehabilitation hospital, from which she was discharged in May 2001, being then able to live alone with the occasional assistance from relatives. At this time, right hemiparesia had resolved and speech production and comprehension had substantially improved. Formal neuropsychological testing (see Table 1) disclosed impaired verbal short-term memory. Verbal episodic memory could not be tested due to the language disorders. As for visuo-spatial short-term memory, the patient's performance was impaired at the Block Tapping Test but not in the "Span" part of the Span/Supra-Span Test. Likewise, visual long-term memory was impaired in the Doors part of the Doors and People Test but within the normal range at the supra-span visual memory test. Attention, executive functions, and praxis were all within the normal range. Language testing (Table 2) revealed a severe impairment in picture naming (2/80) but better, albeit impaired too, word comprehension of the same items (62/80). Word-picture verification also revealed moderate word comprehension difficulties, with a similar level of performance for living and nonliving things. Semantic association was only mildly impaired with pictures, like her performance in classifying words or pictures into semantic sub-categories.

In sum, in May 2001, 8 months post-onset, DL's performance in tasks requiring semantic knowledge showed that she still presented a semantic deficit affecting all processing modalities (i.e., verbal and visual) and domains of knowledge (i.e., living and nonliving). However, the patient demonstrated substantial recovery from her initial severe word comprehension deficit (although it could not be measured because of the lack of formal testing at the outset). She had knowledge about both the general and the specific semantic features of a subset of the concrete objects probed (Cf. her performance in the word/picture matching and the word/picture verification tasks) and, for most of the objects probed, she had at least knowledge of general

features (Cf. her performance in the categorization task). The large discrepancy between DL's performance in word naming and comprehension suggested that she had an additional deficit at the post-semantic, spoken word retrieval, processing level (see for additional details and discussion, Léonard et al., 2008). On the other hand, the pre-semantic levels of processing (speech perception, auditory and visual word recognition, visuo-structural processing of objects or pictures) were spared in the patient (see Table 2). From 2001, the patient could not be examined with formal tests because of her frequent and severe intractable seizures for which adequate treatment was found only after 2 years trying out. In May 2003, some testing was undertaken, which showed that DL's performance in the tasks requiring semantic knowledge did not differ from her performance 2 years before (Table 2), which suggested that she likely reached a chronic, stable stage of recovery. At that time, an attempt was made at assessing her verbal episodic memory. At the Buschke (1984) test, the patient's performance was impaired in all the subtests assessing recall, but her performance certainly was biased by her still severe word-finding difficulties. However, her performance in the recognition subtest (14/16; -2.4 SD) was mildly impaired as well.

At the time of this study (May 2006), the seizures were completely controlled. According to clinical reports, the patient then presented a

Table 1
Neuropsychological data of patient DL (May 2001)

Test	DL's score	DL's percentile or z-score
Raven matrix	100	P.50
<i>Short-term memory</i>		
Digit span – forward ^a	3	-3.82
Spatial span (block tapping test) ^b	4	P.10
Spatial span (span/supraspan test) ^c	7	-1.6
<i>Long-term memory</i>		
Doors test (Doors and People test) ^d		
Part A	9/12	P.10
Part B	3/12	P.1
Supraspan (span/supraspan test) ^c	8	+0.1
<i>Attention</i>		
D2 sustained attention test ^e		
Total raw score	319	P.27
Errors	16 (5%)	P.50–75
Total score minus errors	303	P.34
Fluctuation	9	P.75–90
<i>Executive functions</i>		
Rey figure ^f		
Copy	Type 2	P.25
Organisation	31/36	P.30–40
Time	5'04"	P.25
Go/no-go inhibition test ^g	459	P.30
<i>Visual processing</i>		
BORB ^h		
View matching	50/50	
Object decision task	104/128	-1.8
<i>Praxis</i>		
Imitation of symbolic gestures	5/5	n.a.
Imitation of meaningless gestures	7/8	n.a.
Pantomiming the use of objects (on verbal command)	14/14	n.a.

n.a. = not available.

^a Wechsler (2000).

^b Smirni et al. (1983).

^c Wilson et al. (1989).

^d Baddeley et al. (1994).

^e Brickenkamp (1962).

^f Rey (1959).

^g Zimmermann and Fimm (1994).

^h Riddoch and Humphreys (1993).

Table 2
Results of the language evaluation in DL

Test	DL's score (May 2001)	DL's score (March 2003)	Control's mean (SD or range)
Discrimination of CV syllables	15/16	n.t.	16/16
Repetition		n.t.	
Words	18/18		18/18
Syllables	15/15		15/15
Pseudowords	5/6		6/6
Short sentences	3/3		3/3
Long sentences	0/3		3/3
Auditory lexical decision task	112/120	n.t.	119.5/120 (117–120)
Visual lexical decision task	117/120	n.t.	117.5/120 (115–120)
Spoken picture naming ^a	2/80	6/80	75.1/80 (SD=2.17)
Spoken word/ picture matching ^a	62/80	62/80	79.3/80 (SD=0.46)
Spoken word/picture verification ^b			
Animals	8/18	7/18	16.2/18 (15–18)
Fruit/vegetables	10/18	9/18	17.0/18 (15–18)
Implements	10/18	9/18	16.2/18 (15–18)
Transport	10/18	9/18	15.2/18 (12–17)
Pyramids and Palm Trees test ^c (pictures)	47/52	47/52	50.2/52 (50–52)
Semantic categorization			
<i>Distant categories</i> (e.g., transport/musical instruments/guns)			
Pictures	34/36	31/36	36/36
Spoken words	35/36	36/36	36/36
<i>Closer categories</i> (e.g., air/sea/land transportation)			
Pictures	32/36	n.t.	36/36
Spoken words	33/36	n.t.	36/36

n.t.=not tested.

^a de Partz et al. (2001).^b Samson et al. (1998).^c Howard and Patterson (1992).

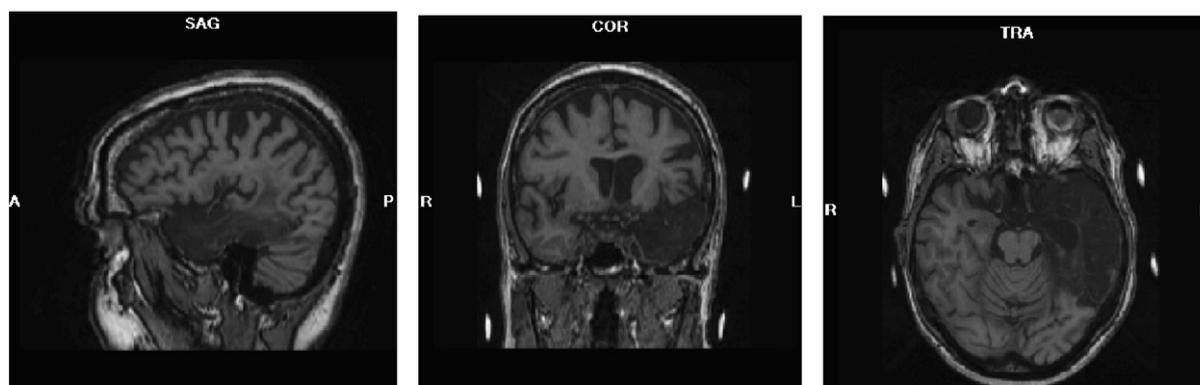
chronic transcortical sensory aphasia with complete anosognosia. The patient lived alone and worked part-time in a library, travelled by herself in public transport, was able to adequately plan her daily activities and never forgot her appointments, which suggested that spatio-temporal orientation as well as attention and executive functions were normal while episodic memory likely was only mildly impaired, if ever.

The MRI performed in May 2006 (Fig. 1) showed, on the left side, a destruction of most of the temporal lobe including the amygdala, the hippocampus, and the parahippocampal gyrus. Only the posterior part of the superior temporal gyrus was partially preserved. The whole insula, most of the rectus and orbital gyri, and the anterior and middle part of the cingulate gyrus were also destroyed. In the frontal lobe, the lesions extended to the precentral gyrus and to the white matter of the inferior frontal gyrus. In the occipital lobe, the lesions extended to the lingual gyrus and the inferior and posterior part of the cingulate gyrus. On the right side, the lesions were much more focused and concerned the insula, the inferior and anterior part of the cingulate gyrus, and part of the rectus and orbital gyri.

In spite of the patient not presenting well-circumscribed lesions, her pattern of impaired/spared functions and of functional recovery presented unique features that motivated selecting her in this study. First, there was no evidence of a differential pattern of recovery or level of performance across the domains of semantic knowledge (animal, plant, man-made object). This feature allowed us to test, in a single patient, the hypothesis that distinct compensatory structures should take over the processing of the different domains of knowledge and thus to overcome the difficulties that would arise from studying compensation of each domain across different patients (e.g., controlling for factors like time from outset, nature and severity of the functional deficits). Second, and importantly, the cognitive abilities that were required to perform the activation task – auditory word recognition, attention, and executive functions – were spared in DL, which greatly minimized the chance of observing abnormalities in brain activity that would be due to unrelated, impaired cognitive processing instead of semantic processing.

Scanning stimuli and task

In order to select items for which she had good semantic knowledge, DL was presented with a pool of items belonging to three semantic categories (animals, plant, artifacts) in an auditory word categorization task, first, and, then, in an auditory word/picture verification task, outside the scanner. In the auditory word categorization task, 167 items were auditorily presented to the patient who was asked to classify them into one of three categories (animals, plant, artifacts). Each item was presented three times in a random order and an item was scored as correct when it was accurately categorized on the three presentations. With this scoring procedure, DL succeeded in 148/167 (89%) items. Then, these succeeded items were used in the auditory word/picture verification task. The patient was presented each item as an auditory word simultaneously with a colour photograph and was asked to tell whether the photograph



SAG = sagittal view; COR = coronal view; TRA = transversal view
L = left; R = right

Fig. 1. MRI sagittal, coronal, and transversal views in the patient DL.

matched the meaning of the word. Each word (e.g., *guitar*) was presented in a random order once with the correct photograph, once with a photograph that depicted a close semantic coordinate of the item (e.g., a violin), once with a photograph depicting a more distant semantic coordinate (e.g., scissors), and once with an unrelated photograph (e.g., a fox). An item was scored as correct if the patient both accepted the correct photograph and rejected the three foils. This specific task and scoring procedure have been shown to be more sensitive than the more widely used multiple-choice word-to-picture matching task in identifying deficits in auditory word comprehension (Breese and Hillis, 2004). DL scored 81/148 (55%) in the word/picture verification task. The stimuli for the scanning session were selected among the 81 items that were scored correct in this task and that allowed us to match as closely as possible the three categories of items (animals, plant, artifacts) according to word frequency. Due to large differences in the distribution of word frequencies across the categories, there were ten items left in each category once word frequency was matched. Word frequency did not significantly differ across the three categories [$F(2, 27)=3.2$; $p>0.1$]. In addition, ten low-pitched reversed words (created from the word stimuli) and ten low-pitched pink noises were selected for the baseline conditions.

During the scanning session, the stimuli from each condition (the three semantic conditions, i.e., names of animals, plant, or artifacts, and the two baseline conditions, i.e., low-pitched reversed words and low-pitched pink noises) were presented to the participants within a block stimulus presentation design. They had to perform a category monitoring task: in each block, they were auditorily presented with the name of a category of items (e.g., “animals” or “low-pitched noises”) followed by a list of items from that category within which an unspecified number of foils were included. Participants were asked to press a response button as soon as they heard a foil within a list. The foils were artifact or plant names within the animal lists, artifact or animal names within the plant lists, animal or plant names within the artifact lists, high-pitched reversed words within the low-pitched reversed-word lists, and high-pitched pink noises within the low-pitched pink-noise lists. In the semantic conditions, this monitoring task amounts to a “go/no go” semantic categorization task.

The whole session comprised five runs of ten blocks each. Each block included six stimuli from one condition, lasted 24 s, and was followed by a 12-second rest epoch. Within a run, the five blocks corresponding to each of the five conditions were repeated twice (in reversed order) and this design was repeated in the five runs. However, the order of presentation of the various conditions within a run and of the stimuli within a block was random. There were zero, one, or two foils within each block, 10 foils per run and, thus, 50 foils in the whole session (10 animal, 10 plant, 10 artifact names, 10 high-pitched reversed words, and 10 high-pitched pink noises).

The animal, plant, or artifact names selected as foils were items extracted from the no-foil lists so that, across the blocks, a given name could either correspond to a foil (“go”) or a no-foil (“no-go”) response. Moreover, no foil name was presented twice as such across the different presentations of a list. Therefore, in spite of the no-foil stimuli being repeated ten times across the whole session, it was not possible for a participant to provide an accurate response in a trial by reminding her previous response(s) to the same stimulus.

The presentation of the stimuli was controlled by a PC running E-prime 1.1 (PST, Inc.). The stimuli were presented binaurally via MR Confon compatible headphones with the volume set to be comfortable for each subject despite the scanner noise.

Data acquisition and analyses

Accuracy and speed of DL's and the control subjects' responses in the monitoring task were recorded via the E-prime software. MR images of brain activity were collected from DL and the controls using

a 1.5 T Philips Gyroscan Intera scanner of the *Université catholique de Louvain* and *Cliniques universitaires Saint-Luc*, Brussels, provided with a six channels phased array coil. In each session, a 3D T1-weighted gradient echo data set encompassing the whole brain was acquired (scan parameters: repetition time (TR)=30, echo time (TE)=3, flip angle (FA)=30°, matrix size=256×183, FOV=240×180, 110 slices, slice thickness=1.5 mm, no gap, SENSE factor=1.5, total scan time=415 s). Single shot gradient-echo-echo-planar imaging (GRE-EPI) was performed using BOLD contrast effect as an indirect marker of local neuronal activity (Ogawa et al., 1990). Thirty-three 3.6 mm axial slices were acquired (TR=3000 ms, TE=45, FA=90°, matrix size=64×64, FOV=230, no gap, total scan time: 420 s including 4 dummy scans).

The fMRI signal in the various conditions was analysed using Brain Voyager QX (Version 1.7 Brain Innovation, Maastricht, The Netherlands). Prior to the statistical analyses, the functional data were subjected to a series of pre-processing operations. Pre-processing consisted of linear trend removal for excluding scanner-related signal, a temporal high-pass filtering applied to remove temporal frequencies lower than 3 cycles per run, and a correction of small interscan head motion by a rigid body algorithm rotating and translating each functional volume in a 3D space. All volumes were then spatially realigned to the first volume in order to minimize effects of head movements on data analysis. The data were temporally smoothed using Gaussian filter of 2.8 s full width at half maximum (FWHM) and spatially smoothed using a Gaussian filter of 4 mm FWHM. Anatomical and functional images (including those of DL) were spatially normalized to the Talairach space (Talairach and Tournoux, 1988). The statistical maps computed were overlaid to the 3D T1-weighted scans to calculate Talairach coordinates for all relevant activation clusters.

Statistical analysis of fMRI data was performed by multiple linear regression of the signal time course at each voxel. The expected BOLD signal change for each predictor (experimental conditions)¹ was modelled by a linear relation between neural activity and hemodynamic response, assuming a rectangular neural response during the phases of auditory stimulation (Boynton et al., 1996).

The data analyses first aimed to identify which part of the normal domain-general and domain-specific processing networks was structurally damaged or showed abnormal activity in DL. To this end, the regions consistently associated with domain-general and domain-specific semantic processing in the control group were identified and activity within these regions of interest (ROIs) was then directly compared in DL vs. the control subjects. The second step in the data analyses aimed to identify the compensatory regions engaged in domain-general and domain-specific processing in DL. DL data were thus analysed to identify regions that were significantly associated with domain-general and domain-specific semantic processing in the patient and that were not identified in the control group. Activity within these ROIs was then directly compared in DL vs. the control subjects.

Activation associated with domain-general semantic processing was assumed to be reflected in the clusters commonly activated in the three semantic conditions (animals, plant, artifacts) and was identified in DL and the control group, separately, by performing a conjunction analysis that combined each category condition *versus* the reversed word condition [(animals–reversed words)+(plant–reversed words)+(artifacts–reversed words)]. The patterns of domain-specific semantic activation, i.e., the clusters preferentially activated in each semantic category condition, were identified in DL and the control group, separately, by performing three subtraction analyses contrasting each semantic category condition with the two remaining category conditions [animal-specific: (animals)–(plant+artifacts); plant-specific: (plant)–

¹ The data related to the low-pitched pink noise condition were discarded in the present report.

Table 3

Number and percentage of correct “go/no go” responses and mean response times (RT, in ms) of “go” responses for DL and the control group in the category monitoring task, according to the condition (animals, plant, artifacts, reversed words)

		Animals	Plant	Artifacts	Reversed words	Mean
DL	Correct responses	53/60 (88%)	55/60 (92%)	54/60 (90%)	51/60 (85%)	53.25/60 (89%)
	RT	1548	1338	1355	1054	1324
Control group	Correct responses	59/60 (98%)	59/60 (98%)	60/60 (100%)	57/60 (95%)	58.75/60 (98%)
	RT	1185	1239	1247	1249	1230

(animals+artifacts); artifact-specific: (artifacts)–(plant+animals)]. Every conjunction and contrast applied to the control group data was based on a random effect analysis running a multisubject GLM with predictors separated for each control subject. Significantly activated regions were defined as clusters that showed a differential response for a given condition compared to another at $p < 0.01$ ($t > 3.2$), uncorrected for multiple comparisons. The analyses applied to DL data were based on fixed-effect analyses and only regions activated at $p < 0.001$ ($t > 3.3$), uncorrected, were reported. In all analyses of both groups, only clusters of more than 30 voxels were considered, a criterion that was likely to drastically reduce Type I errors.

In order to directly compare the condition effect (i.e., conjunction or contrast between the conditions) in DL versus the control subjects within the ROIs identified in the control group data, on one hand, and within the ROIs identified in DL data, on the other hand, a separate subject design including both DL and the control subjects was performed and the mean beta weights of each condition in each of these ROIs were extracted from the GLM analysis, for DL and every control subject. We then computed the value of the mean beta weight for each conjunction or contrast and used these values as the dependent variable to test, with the modified t statistics (Crawford and Howell, 1998), whether the condition effect was significantly different in DL and the control subjects in each ROI. The modified t -test was developed by Crawford et al. for the statistical analysis of single case data in neuropsychology. It allows us to compare a single test score obtained from an individual with a control sample that has a small N . It overcomes the disadvantage of the standard z -score method, which exaggerates the rarity/abnormality of an individual's score and inflates the Type I error rate, by treating the statistics of the control sample as statistics rather than as population parameters and using the t -distribution (with $n - 1$ degrees of freedom) rather than the standard normal distribution. It provides a point estimate of the abnormality of the patient's score (a p value)². Here we used a < 0.01 p value within the framework of a bilateral hypothesis.

Finally, for every ROI identified in DL data that showed a significantly increased condition effect compared to the control subjects (compensatory regions), we examined whether the region was likely a “supplementary” region (unique to DL) by examining how many control subjects showed activation reaching threshold in this region when investigated on a single-case basis with the same procedure and criteria as those used for DL data (fixed-effect analysis, $p < 0.001$, uncorrected). A significantly activated cluster in a control subject was deemed to be in the same region as a cluster found in DL if both clusters had at least one overlapping voxel or one cluster in close proximity, that is, in the same Brodmann area and at a distance of less than ten Talairach points along the x , y or z axis in the Talairach space.

Neural activity in the eyes, outside the brain, in the white matter, or in subcortical regions was not reported.

Results

Behavioural results

As displayed in Table 3, DL's accuracy in the category monitoring task was very good (mean of 89% correct responses) albeit significantly lower than the control group's in each condition [Crawford and Garthwaite's (2002) modified t -tests: $-14.23 < t < -2.8$; $0.001 < p < 0.05$]. DL's incorrect responses were both misses ($n = 8$) and false alarms ($n = 19$). However, no significant effect of condition on response accuracy was observed in DL [$0.3 < \chi^2 < 1.3$; all $ps > 0.1$] or in the control group [all $\chi^2 < 1$]. As for response speed, DL's mean response times did not significantly differ from the control group's in any condition [Crawford and Garthwaite's (2002) modified t -tests: $-1.2 < t < 0.4$; all $ps > 0.1$] and no significant effect of condition on response times was observed in DL [$F(3, 28) = 1.2$, $p > 0.1$] nor in the control group [$F(3, 32) < 1$].

Neuroimaging results

Semantic activation in the control group

In the control group (Table 4), domain-general semantic processing involved the left superior frontal gyrus, the right parahippocampus, and the left angular gyrus. The animal-specific semantic network was left dominant and involved regions in the left frontal lobe, left anterior superior temporal gyrus, and the left temporo-occipital junction. The right inferior occipital and the left postcentral gyri were also activated. The plant-specific semantic network was much more widespread and involved numerous clusters distributed bilaterally over frontal, temporal, occipital, and parietal regions. However, at the temporo-occipital junction, only right hemisphere activation was detected (in contrast to left activation in case of animal-specific processing). Finally, the artifact-specific semantic network was bilateral in frontal areas but left lateralized in occipital and parietal regions.

Comparison of semantic processing networks in DL and the control subjects

Table 4 displays the significant t values resulting from the comparison of the size of the condition effect in DL versus the control subjects within the ROIs identified in the control group (hereafter, “normal” regions) as well as the location of damage within these regions. Table 5 displays the compensatory semantic processing regions in DL, that is, semantic processing regions identified in DL and not in the control group, which showed a significantly greater condition effect in DL than in the control subjects. Table 5 also reports the number of control subjects showing a significant condition effect in DL's compensatory regions when analysed in an individual basis.

- The normal domain-general regions were all structurally intact in DL and did not show any significant differential effect in DL compared to the control subjects. The analyses of DL data disclosed no additional area associated with domain-general semantic processing.

² Essentially, this method is a modified independent samples t -test in which the individual is treated as a sample of $M = 1$.

Table 4
List of the regions consistently associated with semantic processing in the control group and significant differences between DL and the control subjects within these regions

Localization of significant clusters in the control group (random-effect analysis, $p < 0.01$, uncorrected)								DL vs. controls modified t
Lobe	Region	BA	Side	Talairach coordinates			k	* $p < 0.01$ ** $p < 0.001$
				x	y	z		
<i>Domain-general semantic processing</i>								
Frontal	Superior	10	L	-2	52	11	46	
Temporal	Parahippocampus	35	R	28	-39	-11	34	
Parietal	Angular	39	L	-33	-71	23	65	
<i>Animal-specific semantic processing</i>								
Frontal	Orbital	11	L	-24	29	-4	118	-3.6*
		11	L	-12	46	-1	351	+6.0**
Temporal	Anterior cingulate	24	L	-3	34	0	178	...
		38	L	-35	11	-26	31	...
T-O junction	Anterior superior	19/37	L	-54	-43	-5	43	...
Occipital	Inferior	18/19	R	38	-75	-23	35	...
Parietal	Postcentral	1/2/3	L	-23	-40	48	46	-4.3*
<i>Plant-specific semantic processing</i>								
Frontal	Superior	6	L	-11	-9	56	706	
		6	L	-35	12	43	41	
		6	R	14	-9	57	47	
		6/8	R	1	21	48	658	
	Superior/middle	6	L	-34	-6	48	120	
		6	L	-20	-13	57	59	
	Middle	9/10	R	25	52	17	1490	-4.0*
		9/10	L	-32	36	42	56	
		9/10	L	-30	30	37	41	+12.0**
		6	R	14	-9	57	47	
	Middle/precentral	4/6	R	41	-6	48	372	-6.2**
		45/46	R	46	11	7	590	-4.3*
	Orbital	11	R	30	37	-5	36	
		44	L	-47	9	29	50	
	Inferior	44	R	50	19	26	154	-4.2*
		45/47	L	-38	39	13	292	
	Precentral	4/6	R	41	-6	16	522	-6.2**
		23/24	L	-10	-13	39	268	...
	Anterior cingulate	23/24	L	-7	-26	35	358	...
		23/24	R	13	-10	40	83	
		23/24	R	12	0	42	155	
		24	L	-6	14	33	32	...
		24	R	13	35	19	112	
		24	R	6	-35	39	263	
	Insula	13	L	-45	15	3	221	...
		13	L	-31	15	-8	149	...
		13	L	-24	21	11	329	...
		22/38	L	-49	3	4	243	...
Temporal	Anterior superior	22	R	44	-16	1	200	-3.4*
		22	R	53	-23	6	60	
	Middle	21	R	67	-15	-4	74	
		41	R	41	-27	15	63	...
	Anterior transverse	42	L	-43	-37	16	36	
		36	R	24	-43	-18	190	
T-O junction	Fusiform	19/37	R	53	-49	8	406	-3.5*
		19/37	R	42	-54	11	96	-5.9**
		18/19	L	-49	-56	-26	68	
		18	L	-16	-76	21	83	-4.3*
Occipital	Cuneus	18	M	0	-76	4	586	-3.6*
		18	L	-7	-74	-6	197	
	Lingual	18	R	2	-59	4	195	-4.5*
		7	R	19	-60	19	861	-4.6*
P-O junction	Superior	7	L	-21	-60	49	53	
Parietal		7	L	-21	-55	46	46	
		40	L	-57	-32	23	288	
	Supramarginal	40	L	-51	-30	34	239	
		40	L	-42	-39	41	126	
	Supramarginal/angular	39/40	R	49	-44	32	1399	
		7	L	-1	-65	40	292	-3.4*
	Precuneus	7	L	-1	-49	58	364	
		7	L	-3	-73	31	49	-3.4*
		7	R	13	-67	42	202	-4.2*
		7	R	7	-53	38	53	
	Posterior cingulate	23	L	-8	-40	27	129	
		23	R	3	-44	10	243	-7.0**
	Angular	39	L	-39	-54	40	60	
		39	R	32	-52	44	222	
		39	R	42	-59	26	51	

Table 4 (continued)

Localization of significant clusters in the control group (random-effect analysis, $p < 0.01$, uncorrected)								DL vs. controls modified t
Lobe	Region	BA	Side	Talairach coordinates			k	* $p < 0.01$ ** $p < 0.001$
				x	y	z		
<i>Plant-specific semantic processing</i>								
Parietal	Postcentral	43	L	-54	-13	14	134	
		1/2/3	R	54	-18	29	55	
	Inferior	40	L	-41	-29	30	35	
		40	R	51	-26	31	102	
		40	R	53	-25	19	39	
<i>Artifact-specific semantic processing</i>								
Frontal	Middle	6	R	37	12	54	265	
		6	R	34	8	42	157	
	Insula	13	L	-37	-15	18	44	...
		24	R	14	20	31	117	
Occipital	Cuneus	18	L	-8	-89	24	49	
		18	L	-11	-78	22	42	-7.1**
Parietal	Angular	39	L	-52	-50	41	53	

BA = Brodmann area; L = Left; M = Medial; R = Right; T-O junction = Temporo-occipital junction; P-O junction = Parieto-occipital junction; "..." means that the area was damaged in DL.

- Within the normal animal-specific semantic network, only one region, the right inferior occipital gyrus, did not show differential activity in DL compared to the control subjects. The left anterior cingulate gyrus, the left anterior superior temporal gyrus, and the left temporo-occipital junction were damaged. Moreover, a significantly decreased condition effect was noted in DL compared to the controls in the left postcentral gyrus. Inspection of the beta weights (Fig. 2a) showed that this functional abnormality in DL was not caused by a general decrease in semantic activity within this region but, rather, by this region tending to be more active for artifacts than animals, in contrast to what was found in the controls. A cluster in the left orbital gyrus [-24, 29, -4] also showed a significantly decreased effect in DL in comparison with the controls but another cluster within the same region [-12, 46, -1] showed an increased effect in DL. Animal-specific compensatory processing

regions were found in DL within the frontal lobe bilaterally (orbital, inferior, and precentral gyri), the right anterior middle temporal gyrus, the left middle occipital gyrus, the left lingual gyrus, right cuneus and right precuneus. The clusters within the orbital and precentral gyrus, the right anterior middle temporal gyrus, and the left middle occipital gyrus were significantly activated as well in a number of controls when analysed individually, but the clusters in the left inferior frontal gyrus, left lingual gyrus, right cuneus, and right precuneus were not found in any control subjects. The effect size of each semantic condition in DL and the control subjects in these supplementary areas is displayed in Fig. 3.

- A large subset of the numerous clusters involved in normal plant-specific semantic processing was structurally intact and functionally normal in DL, whether in the frontal, temporal, occipital, or parietal lobes. The damaged part of the normal network involved

Table 5

List of the regions associated with semantic processing in DL and with significant differences between DL and the controls

Localization of significant clusters in DL (single-subject analysis, $p < 0.001$)								DL vs. controls		
Lobe	Region	BA	Side	Talairach coordinates			k	Modified t * $p < 0.01$ ** $p < 0.001$	Nr of controls with activation in the same cluster (single-subject analysis, $p < 0.001$)	
				x	y	z				
<i>Animal-specific semantic processing</i>										
Frontal	Orbital	11	L	-7	41	-2	600	+5.3**	4	
		11	R	25	25	-1	562	+4.7*	4	
		11	R	13	46	8	59	+4.9*	3	
		11	R	5	41	-4	70	+5.9**	1	
	Inferior	45/47	L	-33	21	3	278	+7.2**	0	
		4	R	49	-8	44	62	+4.8*	4	
	Temporal	Anterior middle	21	R	59	-11	-17	152	+3.6*	3
	Occipital	Middle	19	L	-45	-81	10	82	+3.5*	2
18			L	-16	-67	-14	129	+5.6**	0	
Lingual		18	L	-2	-69	-5	124	+4.1*	0	
Parietal	Cuneus	18	R	6	-85	5	41	+4.8*	0	
		7	R	5	-57	60	145	+4.7*	0	
<i>Plant-specific semantic processing</i>										
Frontal	Superior	10	L	-18	60	10	171	+3.9*	8	
	Superior/middle	9/10	L	-33	41	25	366	+3.4*	9	
<i>Artifact-specific semantic processing</i>										
Frontal	Superior	6/8	L	-20	12	44	356	+4.7*	2	
		10	L	-20	46	6	189	+7.7**	1	
		10	L	-19	48	20	215	+7.2**	1	
	Inferior	44/45	R	28	21	22	259	+7.2**	1	
		19	L	-26	-77	26	406	+7.3**	0	
Occipital	Superior/middle	19	L	-26	-77	26	406	+7.3**	0	
Parietal	Angular	39	L	-39	-66	17	410	+5.4**	2	
	Angular/IPS	39/40	R	31	-53	29	32	+3.7*	0	

BA = Brodmann area; L = Left; R = Right; IPS = Intraparietal sulcus.

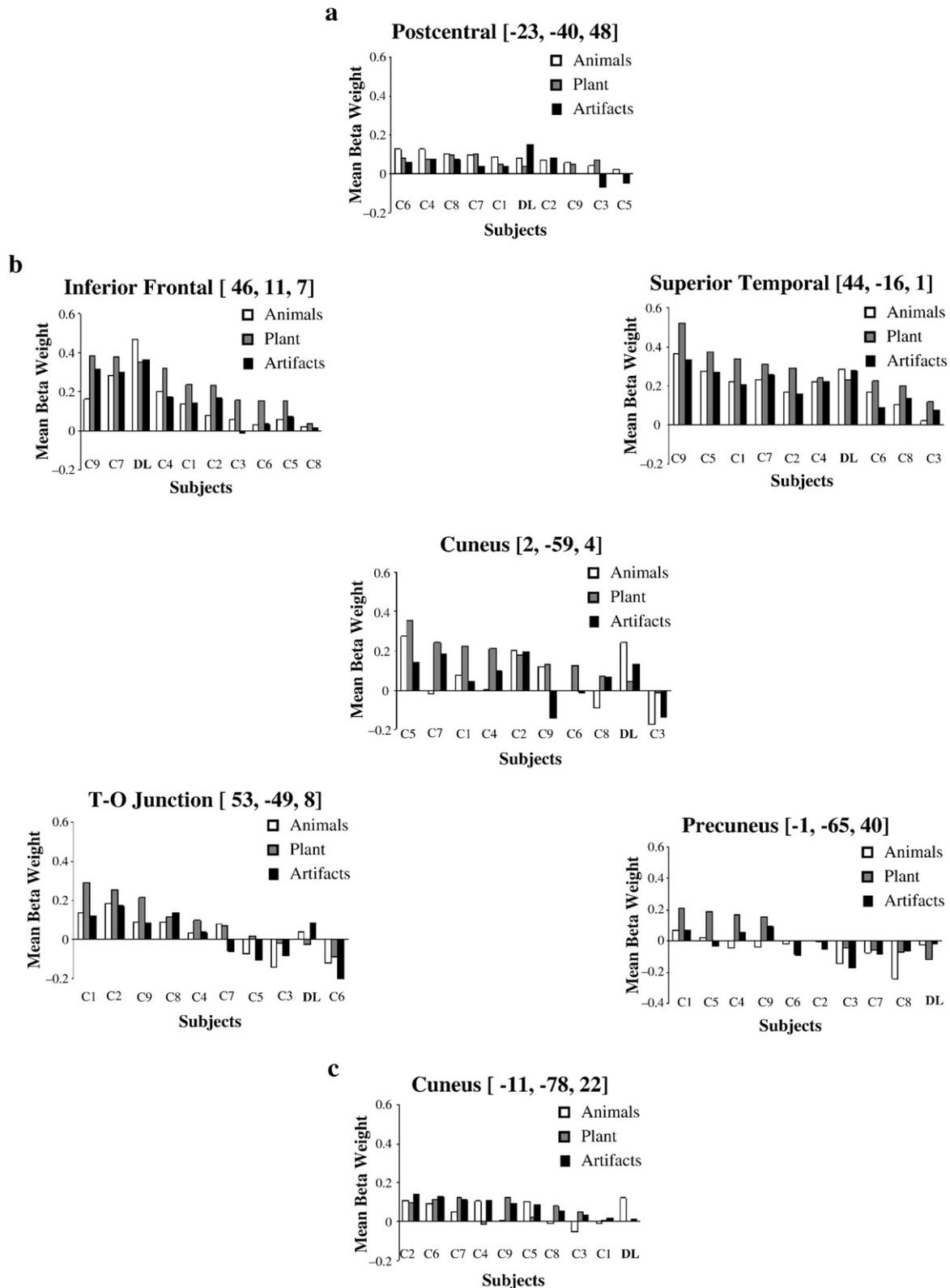


Fig. 2. Regions consistently associated with domain-specific semantic processing in the control group, which showed a significant decrease in domain specificity in DL compared to the control subjects ($t < 0.01$). The mean beta weight for DL and every control subject in these regions for each semantic condition (Animals, Plant, Artifacts) is displayed for regions associated with (a) animal-specific processing, (b) plant-specific processing, and (c) artifact-specific processing. DL and the control subjects are ranked along the x-axis according to the value of the mean beta weight corresponding to the condition of interest, i.e., (a) Animals, (b) Plant, and (c) Artifacts.

the left anterior cingulate gyrus, the left insula, and the left anterior superior temporal gyrus. A number of structurally intact areas, mainly in the right hemisphere, showed a decreased

condition effect, i.e., in the right frontal lobe, the right posterior superior temporal lobe, and the right temporo-occipital junction. A decreased condition effect was also noted bilaterally in occipital

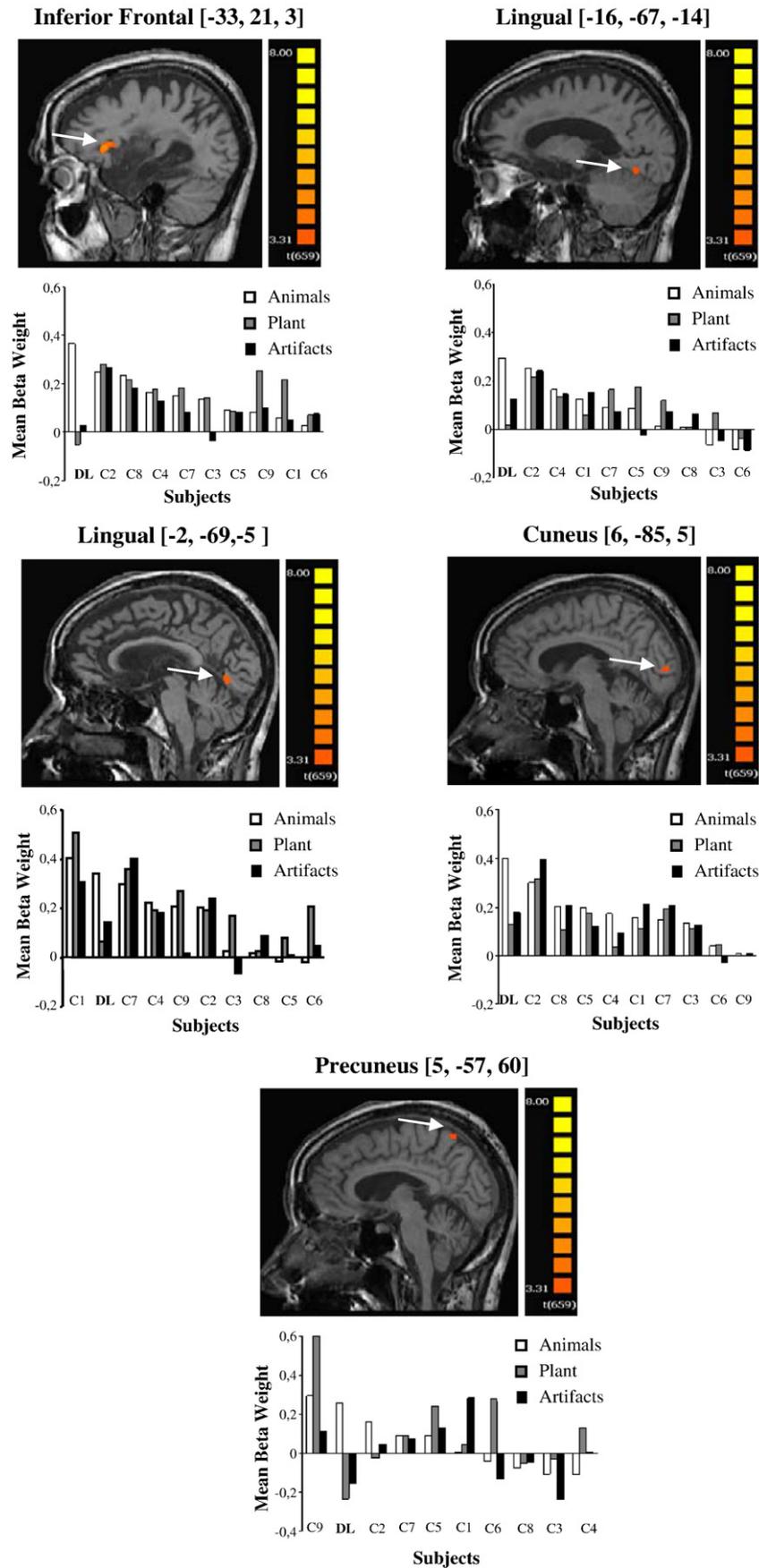
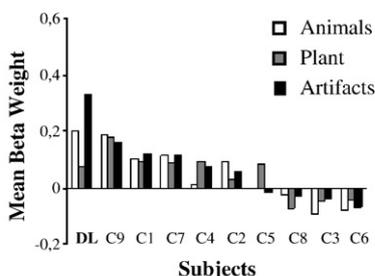
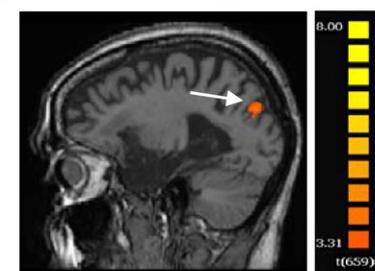


Fig. 3. Activation map in DL showing the location of the supplementary animal-specific semantic regions and mean beta weight for DL and every control subject in these regions for each semantic condition (Animals, Plant, Artifacts). DL and the control subjects are ranked along the x-axis according to the value of the mean beta weight corresponding to the “Animals” condition.

Superior/Middle Occipital [-26, -77, 26]



Angular/IPS [31, -53, 29]

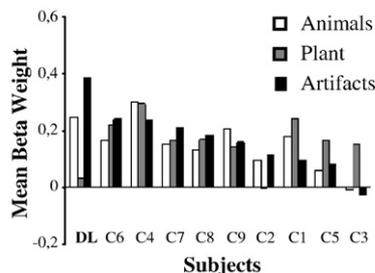
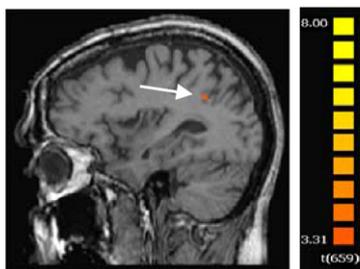


Fig. 4. Activation map in DL showing the location of the supplementary artifact-specific semantic regions and mean beta weight for DL and every control subject in these regions for each semantic condition (Animals, Plant, Artifacts). DL and the control subjects are ranked along the x-axis according to the value of the mean beta weight corresponding to the "Artifacts" Condition.

and parietal regions. Inspection of the beta weights within these regions, here again showed that, in most cases, the differential effect in DL and the controls was not due to these regions contributing less to semantic processing in general or not contributing to plant processing at all but, instead, to these regions not contributing more in the processing of plant compared to the other semantic categories. The only exceptions to this pattern were found in both the clusters within the right temporo-occipital junction and one cluster within the right and the left precuneus, where no contribution to plant or to any semantic category processing was detectable (see Fig. 2b). Plant-specific compensatory processing regions were found in three clusters, i.e., within the left superior, left superior/middle, and left middle frontal gyrus (Tables 4 and 5). These areas were also involved in plant-specific processing in the control subjects.

- Finally, the normal artifact-specific network was damaged in DL in the left insula only and a significantly decreased condition effect was noted in left cuneus (Fig. 2c). Compensatory regions were found in the left superior and right inferior frontal gyrus, the left superior/middle occipital gyrus, and the left and right angular gyrus. When analysed individually, no control subject showed a significant condition effect in the left superior/middle occipital gyrus or the right angular gyrus. The effect size of each semantic condition in these supplementary areas for DL and each control subject is displayed in Fig. 4.

Discussion

The results indicated that the neural network normally activated during an auditory monitoring task that requires retrieving object category knowledge involved both domain-general and domain-specific areas. The domain-general areas were located in the left superior frontal gyrus, left angular gyrus, and right parahippocampus. The location of these domain-general areas is consistent with what is currently known on the involvement of these regions in cognitive processing. Thus, the left superior frontal gyrus has been associated with executive functions like maintaining a goal while performing a task (Koechlin et al., 2000). In our study, activation in this region likely reflected the maintenance in memory of the category name during the monitoring of the category properties of objects. Activation within the left angular gyrus probably reflected the domain-general process of mapping between the sound and the meaning of words. As for the right parahippocampus activation, it could be the consequence of the repeated exposure of the same words across the runs in our experiment and of the resulting formation of memory traces for these words. Chao et al. (2002), for example, reported right parahippocampal activation when contrasting covert naming of pictures that were previously trained versus untrained outside the scanner.

We did not find any significant domain-general activation in the anterior temporal lobes, which yet are thought to critically support amodal and domain-general aspects of semantic knowledge processing (e.g., Jefferies and Lambon Ralph, 2006; Rogers et al., 2004). This view is supported by studies of patients with semantic dementia, a syndrome arising from progressive and focal atrophy of the inferior lateral parts of the anterior temporal lobes, more pronounced in the left hemisphere but involving both (Snowden et al., 1989; Mummery et al., 2000). Patients with semantic dementia are impaired on any task requiring semantic knowledge, in all modalities of reception and expression, and for all semantic categories (Bozeat et al., 2000; Hodges et al., 1995). However, the vast majority of functional imaging studies with healthy participants did not report anterior temporal activation for semantic tasks (Rogers et al., 2006), like in the present study. In studies using fMRI, the most commonly used technique, this failure might be a consequence of the well-known MRI susceptibility-induced signal loss in these regions (Devlin et al., 2000). To overcome this susceptibility artifact, Rogers et al. (2006) recently used PET in a study with healthy individuals and found bilateral activation of the antero-lateral temporal cortices when the semantic task required category verification at a specific ("is it a labrador?"), relative to intermediate ("is it a dog?") or general ("is it an animal?") levels.³ In the present study (like in most previous ones), the semantic task did not require identification of the stimulus at a

³ In Rogers et al.'s (2006) study, the activation of the anterior temporal lobes was equally robust for specific categorization of animals and vehicles. However, some studies found more robust activation for living than nonliving things in these regions (e.g., Devlin et al., 2002a,b; Gorno-Tempini and Price, 2000, 2001; Moore and Price, 1999), which can be accounted for by the living things imposing more demands on specific identification processes than nonliving things because of the higher similarity existing between the members of the living things category.

specific nor intermediate level, but at a more general level (e.g., “animal”). Therefore, it is very likely that this domain-general area was only minimally, if ever, involved in the category monitoring task of the present study, even if we cannot rule out some signal loss in the more anterior part of the temporal lobes.⁴

Further to domain-general areas, the data analyses disclosed domain-specific areas: animal-specific areas in the left anterior superior temporal gyrus, the left temporo-occipital junction, and the right inferior occipital gyrus, plant-specific areas in the left anterior temporal gyrus, at the right temporo-occipital junction, and in the occipital gyrus bilaterally and, finally, artifact-specific areas in the right premotor and left occipital and posterior parietal regions.

The location of these domain-specific areas of semantic processing is largely consistent with the findings from previous neuroimaging studies, although the categories that were mostly investigated were animals and a subcategory of artifacts, namely, tools. Animal-specific activation generally involved anterior temporal regions in the left hemisphere or bilaterally (Thioux et al., 2005; Lewis, 2006; Phillips et al., 2002), the lateral fusiform as well as occipital regions bilaterally (e.g., Chao et al., 2002; Noppeney et al., 2006) while tool-specific activation was consistently found in the left posterior middle temporal gyrus, the medial fusiform, the left ventral premotor area, and the left posterior parietal area (Chao et al., 2002; Creem-Regehr and Lee, 2005; Grezes and Decety, 2001; Noppeney et al., 2006). Plant-specific activation, which was much less explored, was found in the right lateral occipital area (Kawashima et al., 2001) or the left anterior temporal area (Moore and Price, 1999).

However, there are some apparent discrepancies between our findings and those reported previously. First, we found *left* anterior temporal activation associated with animal processing whereas *bilateral* temporal activation was frequently reported in previous neuroimaging studies (e.g., Okada et al., 2000; Lewis et al., 2005). This discrepancy was likely due to the results of these studies being based on the [Animal>Tool] contrast while we performed a [(Animal)>(artifact+plant)] contrast. Thus, activation that was attributed to animal-specific processing in previous studies in fact might have been located in areas sustaining both animal and plant processing. Second, it has consistently been found that tool processing recruited the left posterior middle temporal gyrus (Chao et al., 2002; Creem-Regehr and Lee, 2005; Grezes and Decety, 2001; Lewis, 2006; Moore and Price, 1999; Noppeney et al., 2006; Phillips et al., 2002) whereas, in the present study, no activation was found in this region for artifacts. It is likely that this discrepancy resulted from the different types of artifact items used across the studies. Most previous studies used only tool stimuli as artifact items while in our study the artifact category included vehicles, clothing, and tools. Direct evidence in favour of this interpretation is provided by the findings of Moore and Price's (1999) study, in which the correlates of both tool and vehicle processing was investigated, and posterior middle temporal activation found for tools but not vehicles (see also the results of the meta-analysis by Devlin et al., 2002a).

This study also brought new findings. First, the results revealed that the animal- and the plant-specific processing network displayed a very contrasting pattern, the plant-specific network being much more widespread and bilateralized than the animal-specific network. No previous neuroimaging study, including those that selected plant stimuli in their material (Gerlach et al., 2002; Kawashima et al., 2001; Moore and Price, 1999; Spitzer et al., 1995), had performed the particular contrast which allowed us to disclose these animal- and

plant-specific patterns of activation. Second, in addition to the distinct temporal, temporo-occipital, occipital, or parietal regions involved in domain-specific processing, the results revealed distinct loci of left and/or right frontal activation and distinct loci of left and/or right angular gyrus activation for each domain of knowledge. These findings suggest that both executive processing (located in frontal areas) and sound-meaning mapping (within the left angular gyrus) are liable to further functional specialization according to the type of knowledge processed. The neural substrates of both these processes may consist of several sub-networks whose spatial distribution of activation varies as a function of the cortical distribution of semantic representations that are manipulated or onto which an auditory word is being mapped.

Our patient DL had damage to part of the semantic processing network consistently identified in the healthy participants of this study and nevertheless she performed the semantic category monitoring task with high accuracy and normal speed. It is important to note that, given the nature of the stimuli presented in this task, it is very unlikely that the patient used alternative cognitive strategies to perform the task. Whereas, for instance, stimuli like pictures of objects are likely to provide clues to the object category on the sole basis of the general visual shape, there is no other way of retrieving the category of an object from its name than retrieving (at least part of) its semantic representation. Hence, we are allowed to assume that, in DL, compensatory neural structures took over the representation and processing of semantic knowledge required for the accurate classification of objects within the broad categories of animal, plant, or artifacts and, importantly, that the abnormal pattern of cortical activation observed in the patient during the semantic task indeed reflected neuronal rather than cognitive reorganization of semantic processing.

The lesions in DL however did not affect equally the various functional areas within the normal semantic processing network. The normal domain-general areas were structurally intact in DL and there was no evidence of functional abnormality within these areas or of recruitment of additional domain-general resources.⁵ In contrast, the animal-, plant-, and artifact-specific networks were all affected by lesions in the left frontal lobe; in addition, the plant-specific network was affected by lesions in the left anterior temporal gyrus and the animal-specific network by lesions at both the left anterior temporal gyrus and the left temporo-occipital junction.⁶ At the same time, the spatial distribution of the activation associated with animal-, plant-, and artifact-specific semantic processing showed large differences between DL and the healthy participants, which we take as reflecting the functional reorganization of each domain-specific processing network. The findings indicated that such functional reorganization relied on three main mechanisms: first, upholding of a subset of the structurally intact domain-specific regions, second, functional changes, that is, both decreases and increases in domain specificity within several structurally intact regions that are normally engaged in the domain-specific network and, third, recruitment of supplementary domain-specific areas.

Thus, after damage to the left anterior temporal and temporo-occipital regions within the normal network, the reorganized animal-specific semantic network in DL involved a normal and structurally

⁴ However, in our study, signal loss probably was limited, since we did find consistent activation in the left anterior superior temporal gyrus for animal- and plant-specific processing in the control group (see Table 4), like in previous studies (Devlin et al., 2002; Moore and Price, 1999), and activation in the right anterior middle temporal gyrus for animal-specific processing in DL (see Table 5).

⁵ This observation adds support to the view that the monitoring task likely involved the same cognitive processes or strategies in DL and the healthy participants. Were important differences in the way DL and the control subjects performed the task, these should have been reflected in the pattern of domain-general activation. This observation also suggested that other possibly impaired cognitive processes in DL which were not required in the task, like verbal episodic memory, did not influence the pattern of cortical activation associated with semantic processing.

⁶ This pattern is consistent with the view that the initial deficit in DL affected the three domains of knowledge because each of the corresponding domain-specific functions was damaged, and not (or not only) because of damage to some domain-general function.

intact region in the right inferior occipital gyrus, decreased engagement of a normal animal-specific region within the left postcentral gyrus, and increased contribution to animal-specific processing of several areas, i.e., in bilateral prefrontal regions, the right anterior middle temporal gyrus, the left middle occipital gyrus, the left lingual gyrus, and right cuneus and precuneus. Of these areas, most of the right prefrontal ones as well as the right anterior middle temporal and the left middle occipital were also found as animal-specific areas in a number of control subjects when analysed individually. However, one area in the left inferior frontal gyrus (BA 45/47) as well as those in the left lingual (BA 18), right cuneus (BA 18) and precuneus (BA 7) did not reach threshold in any control subject. Previous neuroimaging studies of semantic processing with healthy participants have consistently reported animal-specific activation in similar regions within the occipital lobe, bilaterally, regardless of whether the stimuli were pictures of objects (Chao et al., 1999; Joseph, 2001; Perani et al., 1995) or their written names (Grossman et al. 2002; Martin et al., 1996). In these studies, the semantic task generally required the retrieval of more fine-grained semantic information than in our category monitoring task, in particular, the semantic features needed to distinguish between close category members (e.g., picture naming). Chao et al. (1999) suggested that the engagement of occipital areas in animal processing reflected top-down activation from more anterior, animal-specific processing sites in the temporal lobes. In this context, the supplementary occipital areas recruited in DL for animal processing can be seen as neural structures that are normally endowed with animal-specific processing functions but usually engaged in more demanding semantic tasks. On the other hand, the role of the precuneus in animal-specific processing is unclear. The precuneus has been implicated in episodic memory retrieval and mental imagery (Cavanna and Trimble, 2006). Activations in similar regions also have been reported in previous studies on lexical-semantic processing (e.g., Cardebat et al., 2003; Henson et al., 2002; Orfanidou et al., 2006; Rissman et al., 2003) but are generally not taken to subserve semantic-related functions.

With damage to left frontal and left anterior superior temporal regions within the normal plant-specific network, plant-specific semantic activation in DL showed, in comparison with the normal pattern, decreased contribution to plant-specific processing of several structurally intact frontal, temporal, occipital, and parietal regions, mostly in the right side, and increased contribution to plant-specific processing of three areas within the left middle and superior frontal gyrus. Plant-specific activity was found in these areas in most if not all the control subjects as well. Functional reorganization thus has shifted plant-specific processing areas from bi-hemispheric to mostly left-hemisphere locations. That only frontal structures, thus, likely executive resources, were additionally engaged in DL for plant-specific processing, and not any temporal, occipital, or parietal regions, might be due to many structurally intact areas remaining normally engaged in plant-specific processing within these regions and, especially, in the left posterior transverse gyrus. Left Wernicke' area was found as a compensatory semantic region in both patients RC and HP reported by Zahn et al. (2002). In patient EA reported by Laiacona et al. (1997, 2005), damage to this area was associated with a total lack of recovery of plant semantic knowledge 10 years post-onset while the patient had recovered semantic knowledge of both animals and man-made objects. In contrast, patient LF (Laiacona et al., 1997), whose left temporal damage did not extend to the posterior part of the superior temporal gyrus, manifested a good overall recovery. Therefore, we speculate that the posterior region of the left superior temporal lobe might contribute to compensate plant-specific semantic functions in case of damage to the left anterior superior temporal gyrus.

Finally, within the normal artifact-specific network, only the left insula was damaged in DL whereas all other areas within the right middle frontal gyrus, left cuneus, and left angular gyrus, with the

exception of one cluster within left cuneus, did not show any functional abnormality. Nevertheless, several areas within left and/or right frontal, occipital, and parietal regions showed increased contribution to artifact-specific processing in DL compared to healthy participants. Most of these areas were also found as artifact-specific regions in some control subjects analysed individually. However, the areas within the left superior/middle occipital gyrus (BA 19) and right angular gyrus (BA 39/40) were supplementary artifact-specific regions in DL. Yet the angular region of the right hemisphere is normally not involved in this domain-specific function. In previous neuroimaging studies of semantic processing in healthy individuals, activation of the right angular gyrus was generally not reported (Martin and Chao, 2001). In the seldom studies that reported right angular activity, it was not specific to artifacts – it was found for both animals and artifacts (Devlin et al., 2002b) or even specifically for living things (Mummery et al., 1996) – nor to auditory semantic processing – it appeared in a visual semantic categorization task (Devlin et al., 2002b) or in a task requiring the production of category exemplars (Mummery et al., 1996). There is one report of tool-specific activation in this region but it was in a picture naming task (Martin et al., 1996). It thus seems that, in DL, compensation of the artifact-specific processing function recruited a region that was endowed with a related but not an artifact-specific, semantic function. The same held for the left superior/middle occipital gyrus, where activation has also been found in tasks that were very different from ours – e.g., a semantic association and visual attribute verification task in Vanderberghe et al. (1996), a picture naming task in Chao et al. (2002) and Damasio et al. (2004) – either for all categories (Vanderberghe et al., 1996), for animals relative to tools (Chao et al., 2002; Damasio et al., 2004), or tools relative to animals (Noppeney et al., 2006).

The findings of this study provided a detailed and complex picture of the cortical reorganization sustaining semantic recovery in a patient with extensive left hemisphere damage. They showed that the question of whether recovery is sustained by intra- or interhemispheric reorganization is oversimplified, at least as far as a complex, internally-structured system like the semantic processing system is concerned. First, the functional reorganization does not necessarily engender a compensatory system made up of structurally intact areas plus one or more perilesional or contralesional areas supplementing the damaged ones. Instead, our findings indicated that no perilesional area and, only exceptionally, contralesional areas were recruited within the compensatory system, which in fact emerged from a wide re-distribution of functions within the remaining structurally intact regions. Moreover, our findings indicated that the location of these functional changes depends on the domain-specific function assumed by the damaged areas and the capacity of the remaining intact areas to assume these functions. Thus, the supplementary areas recruited in DL were located within the left lingual gyrus and right cuneus for animal-specific processing but in the left superior/middle occipital gyrus and the right angular gyrus for artifact-specific processing, which suggests that each of these regions has a distinct capacity to assume representational domain-specific functions. The location of the additional resources recruited within prefrontal regions which, by assumption, assume executive semantic processing functions, also varied according to the domain of knowledge. This observation is consistent with the hypothesis that the spatial distribution of activation associated with executive semantic processes also depends on the cortical distribution of the domain-specific representations that are manipulated.

The results of this study did not support the general view according to which extensive left hemisphere lesion should lead to mostly right-lateralized compensatory processing. In particular, they are at variance with the findings of Gold and Kertesz's (2000) study that showed a complete (i.e., fronto-temporo-parietal) shift of semantic processing to the right hemisphere in a patient (GP) having recovered from a semantic deficit after extensive left hemisphere damage.

A first factor that must be considered as a possible cause for the contradictory pattern between GP and our patient is timing of the study in the course of recovery. In the aphasia domain, there are several lines of evidence suggesting that language functions initially shift to the right hemisphere and often re-shift to left-hemispheric language areas in a subsequent phase of recovery (Marsh and Hillis, 2006; Saur et al., 2006). However, both GP and DL were at the chronic stage of recovery and they participated in the scanning experiment, respectively, 7 and 6 years after onset. Several other factors, which are not mutually exclusive, thus are more likely responsible for these contradictory patterns. First, the study of Gold and Kertesz used a semantic association task (deciding which of two words shared a closer semantic association with a third one). This task is more demanding than our category monitoring task, both in terms of executive resources and retrieval of semantic knowledge, since it requires retrieving and comparing the specific semantic properties of each of the three words in a triad. It thus remains an open question whether a task requiring access to more specific semantic knowledge would yield a different, more right-lateralized, activation pattern in our patient. Second, GP, the patient in the study of Gold and Kertesz, recovered the semantic processing of visual but not auditory words, while our patient's capabilities in semantic processing recovered similarly in both modalities, and Gold and Kertesz used written word stimuli in their activation task, while we used auditory words. Hence, the pattern of functional compensation observed in Gold and Kertesz's study was specific to recovery of *visual* word semantic processing. There are reasons of not generalizing such pattern to the auditory modality. The natural capacity of the right hemisphere for semantic processing of visual words is well known in neuropsychology for a long time. Evidence coming from studies with hemispherectomy patients (e.g., Patterson et al., 1989), split-brain patients (Gazzaniga and Sperry, 1967) and patients with large left hemisphere lesions (e.g., Cossu et al., 1995) indicated that the right hemisphere is able to process the meaning of visually presented words, at least frequent and concrete ones. Finally, the lesion in GP encompassed the left inferior frontal and temporal gyri, like in DL, but it extended more posteriorly than in DL, to the left angular gyrus and lateral portions of the superior occipital gyrus. Such extension might have had two consequences. First, it obviously left less available intact regions in the left hemisphere on which compensation could rely. Second, and more interestingly, on the assumption that the left angular gyrus sustains the primary function of mapping between the sensory representation of words and their meaning, its destruction in case GP could have determined the overall right-hemispheric shift of speech comprehension processes, at least as far as written words are concerned.

In conclusion, we investigated with fMRI the cortical correlates of domain-general and domain-specific semantic processing in a patient having partially recovered from a semantic impairment consecutive to extensive left temporal damage. We found that, in that patient, reorganization of domain-specific semantic processing involved both functional changes in domain specificity within structurally intact regions normally engaged in semantic processing and recruitment of supplementary areas whose location and functional specificity varied as a function of the domain of knowledge being processed. These findings, added to the findings from the few previous studies that have investigated the cortical basis of semantic recovery, lend support to the hypothesis that the pattern of cortical reorganization after damage to the semantic system depends on which domain-general or domain-specific functions were damaged within this system and which remaining areas are capable of assuming these functions. Hence, the outcome of this study should encourage further studies of the cerebral basis of recovery – especially when complex, internally-structured functions like semantics or also language are under consideration – to explore the issue not by asking “how does the neural system underlying semantics or language reorganize once damaged?” but, instead, “how do the specific functions that were

damaged within the semantic or the language system reorganize?”. To this end, the cortical reorganization of semantic processing should be examined in single or small groups of patients selected on the basis of the domain-general or domain-specific semantic function(s) that was (were) damaged within the semantic processing system.

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