

RAPID COMMUNICATION

Right Hemisphere Semantic Processing of Visual Words in an Aphasic Patient: An fMRI Study

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This study was designed to identify the neural network supporting the semantic processing of visual words in a patient with large-scale damage to left-hemisphere (LH) language structures. Patient GP, and a control subject, RT, performed semantic and orthographic tasks while brain-activation patterns were recorded using functional magnetic resonance imaging. In RT, the semantic-orthographic comparison activated LH perisylvian and extrasylvian temporal regions comparable to the network of areas activated by non-brain-damaged subjects in other neuroimaging studies of semantic discrimination. In GP, the same comparison activated homologous right-hemisphere regions, demonstrating the ability of the right hemisphere to subserve visual lexicosemantic processes. The results are discussed within the context of the normal right hemisphere's capacity for semantic processing of visual words. Examining results from functional neuroimaging studies on recovery in the context of innate hemispheric abilities may enable reconciliation of disparate claims about mechanisms supporting recovery from aphasia. © 2000 Academic Press

Key Words: language recovery; functional activation; lexicosemantic processing; fMRI; right hemisphere.

INTRODUCTION

Cases of selective recovery of specific language processes in aphasia have implications for the manner in which the brain can compensate functionally to support various processes following injury. Restitution of particular lan-

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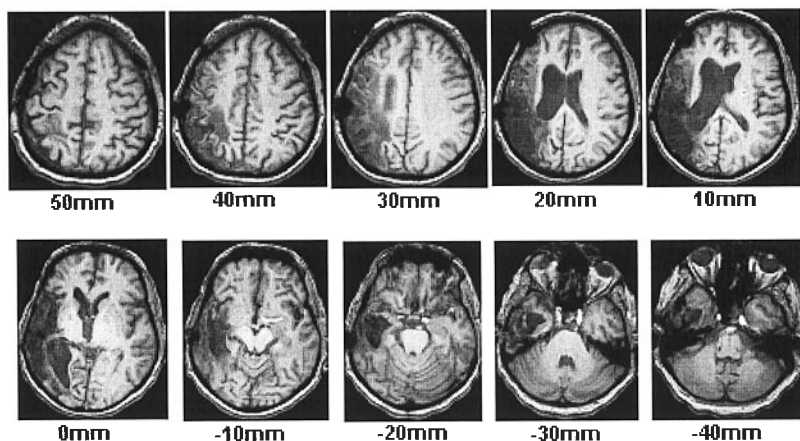


FIG. 1. The extent of GP's cerebral infarct in the left hemisphere, 7 years following stroke. The slices are at 10-mm intervals centered on the anterior commissure–posterior commissure (AC-PC) line.

guage processes following large-scale damage to left-hemisphere (LH) language regions suggests recruitment of other areas to support those processes. Candidate mechanisms are perilesional regions surrounding the infarct, homologous contralateral regions, or a combination of ipsilateral and contralateral areas. The advent of noninvasive functional neuroimaging has made it possible to explore these potential mechanisms in individual cases, and specific language processes, by comparing brain-activation patterns of patients and control subjects during the performance of language tasks (Heiss, Karbe, Weber-Luxenburger, Herholz, Kessler, Pietrzyk, et al., 1997; Weiller, Isensee, Rijntjes, Huber, Muller, Bier, et al., 1995).

In the present study, we used functional magnetic resonance imaging (fMRI) to explore the neuroanatomical correlates supporting the semantic processing of visual words in a patient with a global aphasia. The patient's brain activation patterns were compared with those of a control subject during the performance of lexical and semantic tasks to identify regions that may be involved in functional compensation.

METHODS

GP is a 52-year-old, native English-speaking, right-handed man with no familial history of left-handedness. GP has 15 years of formal education. The control subject, RT, is a 54-year-old, native English-speaking, right-handed man with no familial history of left-handedness. RT has 15 years of formal education and no history of neurological or psychiatric illness.

In October of 1992, at the age of 45, GP suffered a hemorrhagic infarct of unknown etiology. Neuroimaging revealed the destruction of cortical and subcortical regions of the LH supplied by the middle cerebral artery. The extent of damage to GP's brain is seen in Fig. 1, which displays magnetic resonance images at 10-mm intervals. GP's infarct encompasses almost the entire left temporo-parietal region and posterior frontal and lateral occipital areas. Damaged

LH regions are the inferior frontal gyrus (BA 44), precentral gyrus (BA 4,6), postcentral gyrus (BA 1-3), supramarginal gyrus (BA 40), angular gyrus (BA 39), superior temporal gyrus (BA 42), middle temporal gyrus (BA 22), the superior portion of the inferior temporal gyrus (BA 21), and lateral portions of the superior occipital gyrus/cuneus (BA 19). Damaged LH deep structures are the insula, putamen, caudate, internal capsule, and subcortical white matter. Remaining LH brain structures, and the entire right hemisphere (RH), are within normal limits for age without significant sulcal widening.

Administration of the Western Aphasia Battery (WAB; Kertesz, 1982) 4 years following stroke indicated that GP had a global aphasia characterized by extremely poor auditory-verbal comprehension, speech output limited to expletives and stereotypic utterances, and severe alexia and agraphia. GP also demonstrated initial right hemiparesis, from which he has since recovered. A recent language examination was performed in March of 1999, 7 years following GP's stroke. GP's diagnosis remained global aphasia at this time. However, selective improvement was observed in the comprehension of written words, accounting for a small overall increase on the reading section of the WAB (from 19 to 34; out of 100). GP remains right-hand dominant.

In a series of experiments, GP demonstrated considerable ability for semantic processing of visual words despite continued extreme impairment of auditory-verbal comprehension, speech and writing (Gold & Kertesz, under review). GP identified superordinate and subordinate visual words with a high degree of accuracy. He could distinguish proper written names from frequent nouns matched for initial letter and length and printed words representing living things from nonliving things. GP was also able to draw more fine-grained distinctions between semantically related visual words on the Pyramids and Palm Trees Test (Howard & Patterson, 1992). The extent of GP's visual lexicosemantic abilities was striking considering the site and size of his lesion.

Functional Magnetic Resonance Imaging

The fMRI study was conducted 7 years following GP's stroke. Informed consent for the fMRI study was obtained from both subjects, and the research protocol was approved by the University of Western Ontario Ethics Review Board. In a semantic-processing task modeled on the Pyramids and Palm Trees Test (Howard & Patterson, 1992), the subjects made decisions about word triads presented visually. A target word was positioned above two probe words, and subjects were asked to decide which of the probes shared a closer semantic association with the target. Nouns were of medium to high frequency (Kucera & Francis, 1976). An equal number of correct probes were presented on the left and right sides of the screen. Sample items are provided in the Appendix. This task has been used in a series of neuroimaging studies with normal subjects (Mummery, Patterson, Hodges, & Price, 1998; Price, Moore, Humphreys, & Wise, 1997; Price, Mummery, Moore, Frackowiak, & Friston, 1999; Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996). Each of these studies reported activation of a distributed network of LH regions, extending from the temporo-occipito-parietal (T-O-P) junction, (BA 37/19/39) through the inferior and middle temporal lobe (BA 21/22) to inferior frontal regions (BA 45/47), with additional RH activation reported occasionally in the temporal pole (Mummery et al., 1998) and cerebellum (Price et al., 1997, 1999).

Comparison to an orthographic control task was used to identify regions associated with semantic processing. In the orthographic task, the subjects were asked to decide whether all of the words in a triad were spelled correctly. The same items from the semantic task were used to ensure that differences in functional activation would not result from exposure to different stimuli. Minor modifications to half of the items in the orthographic task were made by changing one letter of one word to create misspelled items. The spatial positioning of incorrectly spelled words was counterbalanced across trials.

An LCD 1280 multisync projector was used to display stimuli through a projection screen onto a mirror fastened to the head coil. Subjects responded by pressing hand-held buttons. In

the orthographic condition, the right-hand button indicated "yes" and vice versa. In the semantic condition, the right-hand button indicated selection of the word on the right side of the screen and vice versa. Buttons were hooked to a Macintosh computer that controlled stimulus presentation and recorded reaction times and responses. Based upon pilot data, the interstimulus interval for each task was 3 s, and subjects were encouraged to respond as quickly and accurately as possible.

Images were obtained with a Varian UNITY INOVA whole-body imaging system (Varian, Palo Alto, CA; Siemens, Erlangen, Germany) at 4.0-T field strength. A birdcage head coil specific for high-frequency applications was used for reception and transmission of radio frequencies. Foam padding was used to limit head motion within the coil. Scout MR images were acquired in sagittal planes. A set of 64 contiguous high-resolution T1-weighted axial anatomical images was chosen from the sagittal scout, parallel to the anterior commissure-posterior commissure (AP-PC) line. Functional images were acquired in the same planes using a T2*-weighted gradient echo, echoplanar imaging (EPI) sequence (TR = 3000 ms, TE = 15 ms, 24-cm field of view). A total of 18 contiguous 5-mm axial slice locations were imaged (64² matrix, with in-plane resolution = 3.75²). The semantic and orthographic conditions were alternated every 60 s for a total of 10 min, resulting in the collection of 200 functional images (100 per task) per voxel location. Functional imaging was preceded by 20 s of "dummy" gradient and radio-frequency pulses to approach tissue steady-state magnetization.

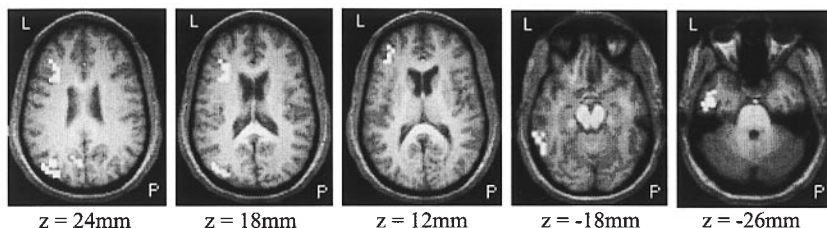
The raw data was transferred to a SUN Sparc workstation. Head motion during the performance of cognitive neuroimaging tasks can result in faulty localization of function and may be more likely in patient populations. Therefore, an automated algorithm was applied to minimize the influence of head motion on subsequent functional maps (Cox, 1996). The algorithm coregisters images spatially using an iterative procedure that minimizes variance in voxel intensity differences between images (Cox, 1996). Data was then smoothed spatially by convolution with a 5-mm-voxel FWHM Gaussian kernel to optimize signal-to-noise ratio. Functional images were evaluated with a cross-correlation technique (Bandettini, Jesmanowica, Wong, & Hyde, 1993). The cross-correlation technique identifies voxels corresponding to the timing of the expected activation, based on the temporal parameters of stimulus presentation, with the best match retained to account for hemodynamic lag. Voxels satisfying a conservative correlation coefficient of $r = .50$ were selected for construction of functional activation maps. A minimum cluster size threshold of four voxels ($p < .001$) was stipulated to reduce the influence of isolated voxels that exceeded $r = .50$, but were not part of a coherent spatial cluster, and could therefore reflect false positives (potential type I errors) (Bandettini et al., 1993). (Activated regions shown in Fig. 2 meet these criteria.) Activated voxel maps were then overlaid onto corresponding T1-weighted high-resolution anatomical images. Anatomical location of activated regions was determined using a computer-based stereotaxic coordinate system (Talairach & Tournoux, 1988).

RESULTS

Accuracy rates on the semantic task ($M = 93\%$) and the orthographic task ($M = 95\%$) were not significantly different. There was also no significant difference between RT's semantic scores ($M = 94\%$) and GP's semantic scores ($M = 91\%$). Finally, there was no significant difference between RT's orthographic scores ($M = 95\%$) and GP's orthographic scores ($M = 93\%$) ($p > .05$ for all tests). The uniformly high scores suggest that subjects engaged the tasks appropriately.

Semantic reaction times ($M = 2.49$, $SD = .16$) were not significantly different than orthographic times ($M = 2.38$, $SD = .19$). GP took significantly longer ($M = 2.51$, $SD = .21$) to respond to tasks than RT ($M = 2.38$,

A



B

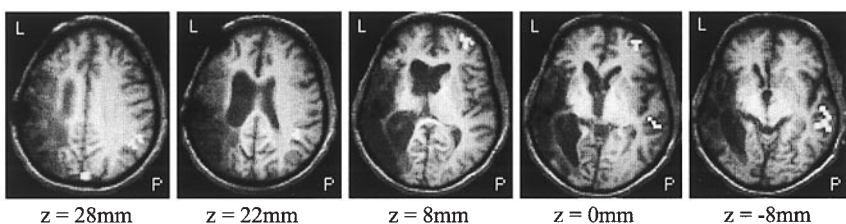


FIG. 2. Summary of the areas activated during the semantic task, compared to the orthographic task, superimposed on subjects' anatomical images. Areas activated at $r = .50$, or higher, $p < .001$, are displayed in white. Activated regions correspond to Brodmann areas and Talairach and Tournoux coordinates provided in Table 1. (A) Control subject, TR's data. (B) GP's data. L, left hemisphere; P, posterior; z, distance in millimeters from the AP-PC line.

$SD = .17$), $F(1, 396) = 187.2$, $p < .05$, but there was no interaction between subjects and tasks.

Table 1 provides a summary of the cerebral regions showing significantly higher blood-oxygenation levels during semantic processing than orthographic processing in each subject. Figure 2 provides a visual summary of these activated areas superimposed on subjects' anatomical images. Analyses revealed strikingly different patterns of functional activation in RT and GP. Compared to orthographic processing, RT activated a network of left-lateralized regions similar to that reported in other neuroimaging studies of semantic processing using visual word triads, including the inferior frontal gyrus, the inferior and middle temporal gyri, the angular gyrus, and the cuneus. In GP, the same semantic-orthographic comparison produced activation lateralized to the right hemisphere. Regions activated in GP were the right middle frontal gyrus, superior temporal gyrus, angular gyrus, supramarginal gyrus, and precuneus.

To explore the possibility of some LH contribution to GP's semantic processing of visual words activation maps were reexamined at $p < .01$. In GP,

TABLE 1
Cerebral Regions Showing Significantly Higher Blood-Oxygenation Levels during
Semantic Processing Than Orthographic Processing

Region at center of mass	Brodmann's areas	Center of mass coordinates			Size (cm ³)
		Semantic-orthographic			
		x	y	z	
Control RT					
Left inferior temporal gyrus	20	-55	-6	-26	21.09
Left inferior frontal gyrus	45	-50	26	16	20.39
Left angular gyrus	39	-42	-72	24	16.87
Left middle temporal gyrus	21	-61	-23	-18	13.36
Left cuneus	18	-4	-87	24	6.33
Patient GP					
Right superior temporal gyrus	42/22	58	-22	-8	16.87
Right middle frontal gyrus	46	42	43	4	14.76
Right supramarginal gyrus	40	53	-29	26	11.25
Right angular gyrus	39	44	-65	0	6.33
Right precuneus	7	2	-61	30	2.81

lowering the significance level produced additional activation in the inferior frontal gyrus, bilaterally (BA 47 on the left, BA 45 on the right), and in the left inferior temporal gyrus (BA 21), surrounding his infarct. In RT, additional areas activated were the left supramarginal gyrus (BA 40) and the superior temporal gyri, bilaterally (BA 22/42).

DISCUSSION

The present fMRI study demonstrated that GP's partially recovered visual lexicosemantic processing is subserved by a network of RH regions homologous to LH sites recruited by neurologically intact, right-handed subjects in studies using similar tasks and partly homologous to areas activated by control subject RT. Other neuroimaging studies of semantic discrimination using printed-word triads have reported activation of a left-lateralized network involving superior occipital, inferior and middle temporal, and inferior prefrontal regions (Mummary et al., 1998; Price et al., 1997, 1999; Vandenberghe et al., 1996). Relative to RT's pattern of functional activation, the only mirror region activated by GP was the right angular gyrus. Nevertheless, each of the other areas recruited by GP was located in close proximity to areas homologous to those activated by RT. Compared to orthographic decisions, semantic decisions activated the left superior temporal gyrus in RT and the right inferior and middle temporal gyri in GP. Semantic decisions activated the left inferior frontal gyrus in RT and the right middle frontal gyrus in GP. Finally, RT recruited a small region of the left cuneus, and GP activated a

small area of the right precuneus. Activation was also observed in GP's left inferior frontal and temporal gyri when significance was lowered, indicating some contribution to his semantic processing from preserved LH regions.

It is not surprising that GP's pattern of functional activation was homologous to the network of regions recruited by normal subjects in other neuroimaging studies of semantic judgement of word triads, but did not mirror entirely areas activated by RT. In the other studies mentioned, functional maps were averaged across subjects and reflect modal regions activated. Analysis of individual subject data in these studies would likely reveal some variability in the neural regions supporting semantic processing of visual words.

The late age of onset of GP's left-hemisphere stroke resulting in a persisting global aphasia, and lack of any prior brain damage, suggest normal lateralization of language in this strongly right-handed man. One potential interpretation of GP's data therefore involves a quantitative functional reorganization characterized by strongly increased RH contribution to semantic processing of visual words in the context of dramatically decreased contribution from LH language regions typically involved. Another potential interpretation involves a more passive form of reorganization involving removal of LH "inhibition" (i.e., Lennenberg, 1967).

Although the present research design does not allow us to select between the "active" and "passive" explanations, continued severe impairment of GP's phonological, syntactic, and verbal output processes suggest that mere "disinhibition" is unlikely to account fully for selective recovery of his semantic processing of visual words. Mechanisms related to disinhibition would be expected to become functional shortly following stroke. GP's slow improvement (4–7 years postonset) is suggestive of gradually increased RH involvement in his visual lexicosemantic processing. Support for RH contribution to long-term recovery of language comes from a recent neuroimaging study which found that aphasic patients with continued improvement showed significantly higher RH cerebral blood flow at rest than patients with stable language impairment, 7 years following stroke (Mimura, Kato, Kato, Sano, Kojima, Naeser et al., 1998).

The natural capacity of the RH for visual lexicosemantics makes it unnecessary to postulate functional reorganization of previously uninvolved neural structures in GP's case. Evidence for RH contribution to semantic processing of visual words comes from research conducted with hemispherectomy patients (Patterson, Vargha-Khadem, & Polkey, 1989; Zaidel, 1985), split-brain patients (Bogen, 1985; Gazzaniga & Sperry 1967; Zaidel, 1982, 1983), and patients with large LH lesions (Cossu, da Prati, & Marshall, 1995; Cummings, Benson, Walsh, & Levine, 1979). In general, this research suggests that the RH can process the meaning of frequent concrete nouns presented visually. Split-field studies with normal subjects using lateralized primes report that brief exposure to a probe word facilitates subsequent recognition

of target words that are semantically related to the probe in the RH as well as in the LH (Chiarello, Senehi, & Nuding, 1987).

Based on a general profile of RH language that has emerged from research with patients and normal subjects, the most parsimonious conclusion of the present findings is that GP's pattern of functional activation reflects increased recruitment of a preexisting network of RH regions capable of semantic processing of visual words. Given this conclusion, it is not clear why neuroimaging studies of visual word semantic judgement (Mummery et al., 1998; Price et al., 1997, 1999; Vandenberghe et al., 1996) have reported only modest RH activation in the normal brain. RH areas reaching significance in these studies were the temporal pole (Mummery et al., 1998) and cerebellum (Price et al., 1997, 1999). Similarly, in the present study, activation of the right superior temporal gyrus in RT was observed only at lowered significance. A speculative interpretation of these functional neuroimaging results is that, in the normal brain, LH inhibition contributes to reduced RH involvement in semantic judgement of visual words relative to what would be expected from the findings of research examining the RH in isolation.

Although general language recovery mechanisms involving the left (Heiss et al., 1997) or right (Thulborn, Carpenter, & Just, 1999) hemispheres have been proposed, the neural regions supporting the restitution of language are likely to be specific to particular processes. Studies reporting significantly greater RH response in recovered patients compared to control subjects have tended to involve processes for which the RH is known to have some innate capacity, such as sound categorization (Engelien, Silbersweig, Stern, Huber, Döring, Frith, et al., 1995), auditory word comprehension (Weiller et al., 1995), and reading comprehension (Thulborn et al., 1999). Similarly, significantly greater recruitment of LH regions by recovered patients than controls has been reported in studies examining processes for which the RH has been shown to have little natural capacity, such as speech (Heiss, Kessler, Karbe, Fink, & Pawlik, 1993), word repetition (Heiss et al., 1997), and verb generation (Warburton, Price, Swinburn, & Wise, 1999).

GP's case provides an example in which increased RH contribution to the semantic processing of visual words is able to compensate functionally to some extent for large-scale damage to a network of LH perisylvian temporoparietal and extrasylvian temporal regions. Investigation of functional brain activation patterns in future cases of selectively recovered language function will be needed to characterize further the right hemisphere's ability to compensate functionally for visual lexicosemantic processing and other language processes.

APPENDIX

Sample Semantic Items

1.	Shoe		9.	Table	
Sock		Hat	Chair		Sofa
2.	Orange		10.	Tiger	
Carrot		Apple	Elephant		Lion
3.	Horse		11.	Square	
Zebra		Rabbit	Cube		Circle
4.	Blouse		12.	Velvet	
Tie		Dress	Cotton		Satin
5.	Guitar		13.	Banana	
Violin		Flute	Pear		Tomato
6.	Hammer		14.	Mug	
Nail		Screw	Glass		Cup
7.	Fox		15.	Honey	
Cat		Dog	Bee		Fly
8.	Jacket		16.	Doctor	
Coat		Pants	Nurse		Teacher

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