

## Cognitive Subtractions May Not Add Up: The Interaction between Semantic Processing and Response Mode

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**Determining the areas of brain activity associated with cognitive processing has typically relied on the use of a subtraction paradigm, which is based on the premise that the neural processes underlying behavior are additive. If the additivity assumption is valid then brain regions associated with a semantic processing task should be the same regardless of how participants make a response. To investigate this proposition, participants underwent six PET scans, in which they made semantic or letter word judgments, responding “yes” or “no” in three different modes: mouse-clicking, spoken response, or silent thought. Analyses showed an increase in regional cerebral blood flow associated with semantic processing in the left inferior frontal cortex, anterior cingulate, and right cerebellum for all three response conditions. However, there was a significant interaction: the greatest increase was observed in the mouse-click condition and the weakest change seen with silent thought. Moreover, other areas of the brain were uniquely activated for each response mode. The results indicate that different areas of the brain were recruited for semantic processing depending on how participants had to organize their responses. Implications for the additivity assumption and methods of analysis to be used in conjunction with the subtraction technique are discussed.** © 1997 Academic Press

### INTRODUCTION

The subtraction paradigm has been the foundation of neuroimaging research relating cognitive function to brain activity for a number of years (e.g., Petersen *et al.*, 1988). In the simplest version of this technique, participants are scanned while performing two tasks (target and baseline). These conditions are designed to share a number of processes with the exception of a single process, present in the target task, that is of experimental interest. The pattern of regional cerebral blood flow (rCBF) associated with the baseline task is then subtracted from that related to the target task and

differences in rCBF are attributed to the process in question.

Underlying this method is the assumption that neural structures supporting cognitive and behavioral processes combine in a simple additive manner. So if one takes the baseline task, and adds a new process to create the target task, the effect of the new process should simply add to the already existing pattern of activation, such that the influence of all other task components is constant and a single function can be isolated. Several researchers have pointed out the potential weakness of this premise, suggesting that processes combine in a nonadditive or interactive fashion. That is, a process may be modified by aspects of the task surrounding it, and adding a single process to the baseline task may alter the earlier operations (e.g., Bookheimer *et al.*, 1995; Friston *et al.*, 1996; Sergeant *et al.*, 1992).

Recently, Bookheimer *et al.* (1995) provided an example of such interaction at the cognitive level. They compared PET activations during oral and silent reading and found different patterns of activity associated with reading in the two conditions. This result could pose problems for the additivity assumption, suggesting that oral reading entails more than simply adding a verbal output process to a silent reading task. However, their data were not unexpected from a cognitive perspective; according to the dual-coding hypothesis of reading, oral and silent reading should enlist very different cognitive processes. Oral reading invokes a phonological coding pathway, whereas silent reading relies on a direct lexical route, and these different cognitive processes should be reflected as distinct neurally.

The more critical question, though, is whether the additivity assumption holds at the neural level when adding components to a baseline condition should not have a cognitive effect on prior operations. Unfortunately, it can be difficult to design studies where additivity at the phenomenological level is ensured. For example, a recent study by Friston *et al.* (1996) was carried out to demonstrate an interaction in the infero-

temporal cortex between phonological retrieval and object recognition during an object identification task. Their goal was to isolate and compare object recognition across two sets of image subtractions, one of which included phonological retrieval, to show that the neural processes underlying phonological retrieval and object recognition do not combine additively. However, these authors point out that their design may not have been ideal because phonological retrieval in their subtraction was represented by color naming in one condition and object naming in the other. It is unlikely that these tasks represent equivalent cognitive components (Friston *et al.*, 1996).

While several investigators have suggested that cognitive additivity may not hold neurally, an empirical demonstration is still lacking. The question remains, then, whether there is additivity at the neural level when a cognitive process can be added without influencing prior operations. For instance, consider a task where participants must semantically process information to determine if a word represents something "living" and then give a "yes" or "no" response. There is little reason to suppose that responding "yes" or "no" aloud versus clicking the buttons of a mouse should alter the preceding semantic process. In fact, changing how participants make a response would seem to be trifling with an irrelevant task component. Consequently, if neural processes are additive, one would predict that brain regions associated with a cognitive function, such as semantic processing, should remain the same regardless of differences in how participants give their response.

The present study was designed to evaluate this proposition. Participants underwent six PET scans, in which they made semantic or letter judgments about words, responding in three different modes: mouse-clicking, spoken response, or silent thought. If the additive assumption is valid, then the pattern of rCBF obtained when subtracting letter processing from semantic processing for each response mode should be the same. However, if the pattern of activity associated with semantic processing differs for each response mode, one can conclude that semantic processing and response mode interact, indicating that the additive assumption is untenable.

## MATERIAL AND METHODS

Twelve right-handed, healthy participants (6 male, 6 female) ranging in age from 23 to 34 years ( $M$  age = 27.3) took part in the study. They provided informed consent, and the experiment was conducted with approval from the Human Subject Use Committee of the University of Toronto.

Participants were screened to ensure that none suffered from a major medical, neurological, or psychiatric

disorder. Each participant performed six tasks. For each task, 48 concrete nouns (3–8 letters in length) were presented by video monitor for a duration of 1.5 s followed by a 500-ms interval. For three tasks, participants were asked to make semantic judgments, deciding whether each word represented something that could be considered "living." For the other three tasks, they were asked to make letter judgments, determining whether each word contained the letter "a." Participants answered "yes" or "no" for both types of tasks. In one condition, they responded by clicking the left and right buttons of the mouse (mouse-click condition); in the second, they responded by saying "yes" or "no" aloud (spoken-response condition); and in the third, they simply responded silently in their minds (silent-thought condition). Each response condition was paired with both processing tasks. In short, participants underwent six scans: for three scans, they carried out the semantic task responding by mouse-click, spoken response, or silent thought; for the other three scans, they performed the letter task with the same three response modes (see Table 1).

Following the final scan, participants were given a recognition test in which they were shown 16 words from each task (96 old words) and 96 new words and were asked to indicate if they recognized a word from scanning. This recognition test was included to provide a check on performance in the silent-thought condition. Because participants were not required to make an overt response during this condition, some means of assessing their adherence to task instructions was necessary. If participants were performing the tasks consistently across all three response modes, we would expect to see a levels of processing effect for each condition—recognition memory should be higher in the semantic task than the letter task ( Craik and Lockhart, 1972), and recognition levels should be comparable for all response types. If recognition performance varied with response, then nonadditivity in the brain data could reflect performance differences.

Participants were scanned using a GEMS-Scanditronix PC-2048 head scanner (15 slices, 6.5 mm apart, inplane FWHM 5–6 mm) with a thermoplastic custom-fitted face-mask for head stabilization. Scans were

**TABLE 1**

Experimental Design: Processing Crossed with Response Mode (Six Scans Total)	
Processing task	Response mode
Semantic task	Mouse-click Spoken response Silent thought
Letter task	Mouse-click Spoken response Silent thought

carried out using 40 mCi of [ $^{15}\text{O}$ ]water injected into a forearm vein through an indwelling catheter. Each task began 20 s prior to the 60-s scan, which occurred every 11 min. Task order was counterbalanced, such that each participant received a different ordering with the restriction that tasks using the same response mode never occurred consecutively.

### Image Analysis

Integrated regional counts were used as an index of rCBF. All images were spatially transformed using the SPM95 analysis package (Friston *et al.*, 1995) to facilitate intersubject averaging and identification of common areas of change. For each subject, all images were first registered to the initial scan to correct for head motion during the experiment, then each image was spatially transformed to a rCBF template conforming to Talairach and Tourneaux stereotaxic space (1988). After transformation, each image was smoothed with a 10-mm isotropic Gaussian filter to reduce individual anatomic variability. Pixel values within the transformed images were adjusted for whole-brain CBF by a ratio transformation, in which each pixel value was divided by the average value for whole volume within a scan.

As an initial test of the hypothesis that neural processes combine in a nonadditive manner, pairwise voxel by voxel comparisons, in which the pattern of rCBF associated with the letter task was subtracted from the pattern related to the semantic task, were carried out for each response mode using SPM95. These subtractions specified areas of increased rCBF associated with semantic processing and were considered significant at  $P < 0.001$ . Results were then examined across the three response conditions to determine similarities and differences.

## RESULTS

### Behavior

Participants showed highly accurate performance during the semantic and letter tasks for the spoken-response (0.98 and 0.99) and mouse-click (0.94 and 0.99) conditions. A two-task (semantic, letter) by two-response (mouse, spoken) analysis of variance examining accuracy showed that there was no significant interaction between processing task and response mode [ $F(1, 11) = 4.14, P > 0.05$ ]. Similarly, the recognition data suggested that participants performed the letter and semantic tasks consistently across all three response conditions (Table 2). A two-task (semantic, letter) by three-response (mouse, spoken, thought) analysis of variance revealed a significant levels of processing effect for all three response types—semantic processing produced better recognition than letter pro-

**TABLE 2**

Probability of Responding "Old" to Old and New Items on the Recognition Test for Each Response Mode

Item	Mouse-click		Spoken response		Silent thought	
	Semantic	Letter	Semantic	Letter	Semantic	Letter
Old	0.90	0.52	0.87	0.52	0.79	0.54
New	0.27	0.30	0.22	0.24	0.28	0.23

cessing [ $F(1, 11) = 32.66, P < 0.01$ ]. There was also no significant interaction between processing task and response [ $F(2, 22) < 1$ ], although performance in the silent-thought condition was slightly lower than in the other two modes.

### Image Analysis

Areas of increased rCBF associated with semantic processing obtained from the pairwise subtractions for each response can be seen in Fig. 1. These subtractions revealed several commonalities in activation across the three modes, primarily, increased rCBF to the left inferior frontal gyrus, which could be seen for all three response types. However, the more striking finding lies with the large number of regions that were discrepant across the three conditions. For the mouse-click condition, semantic processing was associated with increased rCBF to the bilateral dorsolateral prefrontal cortex, right anterior cingulate, right cerebellum, right angular gyrus, and left superior temporal gyrus. The spoken-response condition also showed activation of the right anterior cingulate and right cerebellum, but revealed rCBF to the left medial frontal gyrus, left fusiform gyrus, and posterior cingulate. The silent-thought condition also showed activity in the right dorsolateral prefrontal cortex and left fusiform gyrus, but unique activity in the right middle frontal gyrus, right lentiform nucleus, and right inferior parietal lobule was also present.

These data strongly suggest that semantic processing and response mode do not combine in a simple additive manner at the neural level since the pattern of activation resulting from subtraction was different for each response mode. Instead, semantic processing and response mode seem to interact. However, while the apparent difference in the effects of semantic processing may represent an interaction with response mode, it is not possible from mere visual examination to discriminate which aspects of these differences represent noise versus a true physiological effect. In order to characterize our qualitative impression of an interaction, and to thoroughly explore the main effects of semantic processing and response mode, a new multivariate analysis method, partial least squares (McIntosh *et al.*, 1996), was applied to the data.

Mouse-Click



P A

Spoken Response

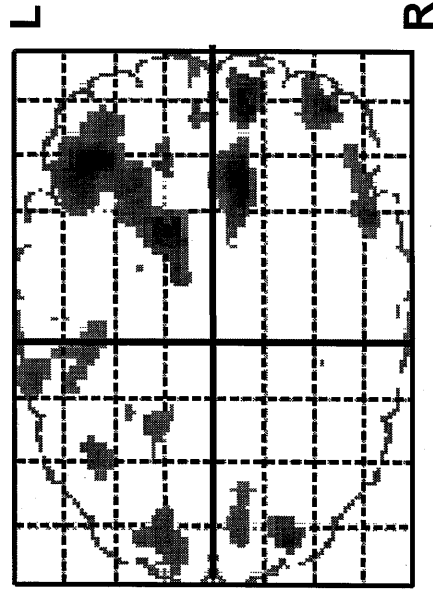


P A

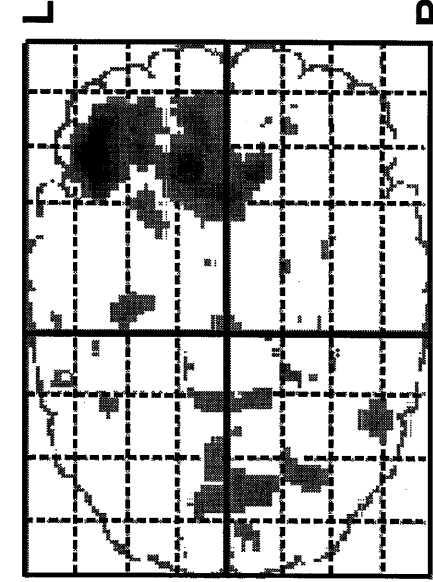
Silent Thought



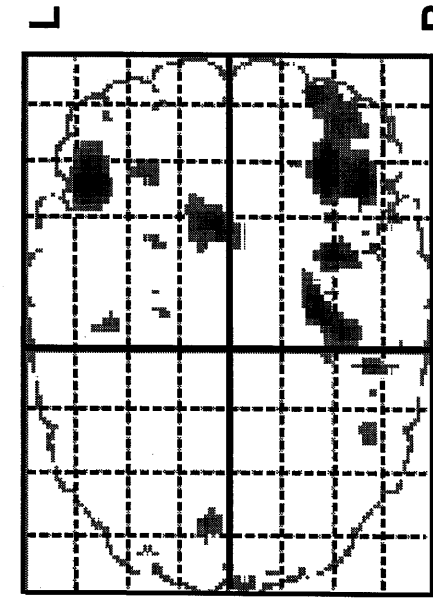
P A



P A



P A



P A

**FIG. 1.** Patterns of rCBF obtained when subtracting the letter-processing task from the semantic-processing task for each response mode. Results are presented on sagittal and transverse glass brain projections.

Partial least squares (PLS) is designed to describe the relationship between an experimental design and the resultant brain images, allowing us to examine changes in the pattern of rCBF across an entire image for each processing task/response mode pairing. Because PLS considers all six conditions and their respective images simultaneously, it reveals similarities, in addition to differences, across conditions. For our experimental design, an index of commonality is essential, providing a means of determining the areas of rCBF that support semantic processing regardless of response mode. More importantly, though, we need a technique to examine interactions between processes.

Several researchers have emphasized that the manifestation of cognitive and behavioral function arises from cooperation of distributed neural systems rather than single isolated regions (McIntosh and Gonzalez-Lima, 1994; Mesulam, 1990). Therefore, interactions between cognitive operations have to be examined in terms of overall patterns of brain activity rather than individual areas. Because voxel-based univariate methods, such as SPM, assess main effects and interactions element by element, it is possible to find experimental effects representing an interaction expressed in an isolated region, but this interaction can be meaningless in terms of the patterns of image-wide activity (distributed neural systems) related to the experimental manipulations. Instead, what is needed is an *omnibus test* that examines main effects and interactions, and, again, because PLS examines changes in the pattern of rCBF across an entire image for each condition, it satisfies this requirement.

### Partial Least Squares

Partial least squares comprises four main steps shown in Fig. 2 (for full description, see McIntosh *et al.*, 1996). First, the cross-correlation matrix between the functional PET images for every participant in each condition and contrast vectors coding for the experimental design is calculated. Second, singular value decomposition of this matrix is carried out to produce pairs of latent variables. The number of latent variable pairs is equal to the degrees of freedom associated with the experimental design, or is equal to the number of contrasts if only a subset of the experimental effects are examined (coded). Each latent variable pair depicts a set of brain regions that show the greatest covariance with an experimental effect represented by the contrasts. The first element of each pair consists of a matrix of weights that apply to the design contrasts, and the second element consists of a matrix of weights that apply to all brain voxels. These weights are referred to as *saliences*. For the brain voxels, the salience is an index of the voxel's relation to the experimental effect. For example, if the effect is a main effect of processing task (semantic versus letter), a

positive salience might indicate a voxel that had higher activity during semantic judgments, while a negative salience might indicate a voxel with lower activity during semantic judgments. Saliences for the design contrasts indicate how *strongly* the effects coded in the design contrasts are represented by the pattern of brain activity for a given latent variable. Again, if the effect is a main effect of processing task, and the design contrasts contain a vector for that effect, the design saliencies for that latent variable would be near unity for that vector and at 0 for the other contrasts.

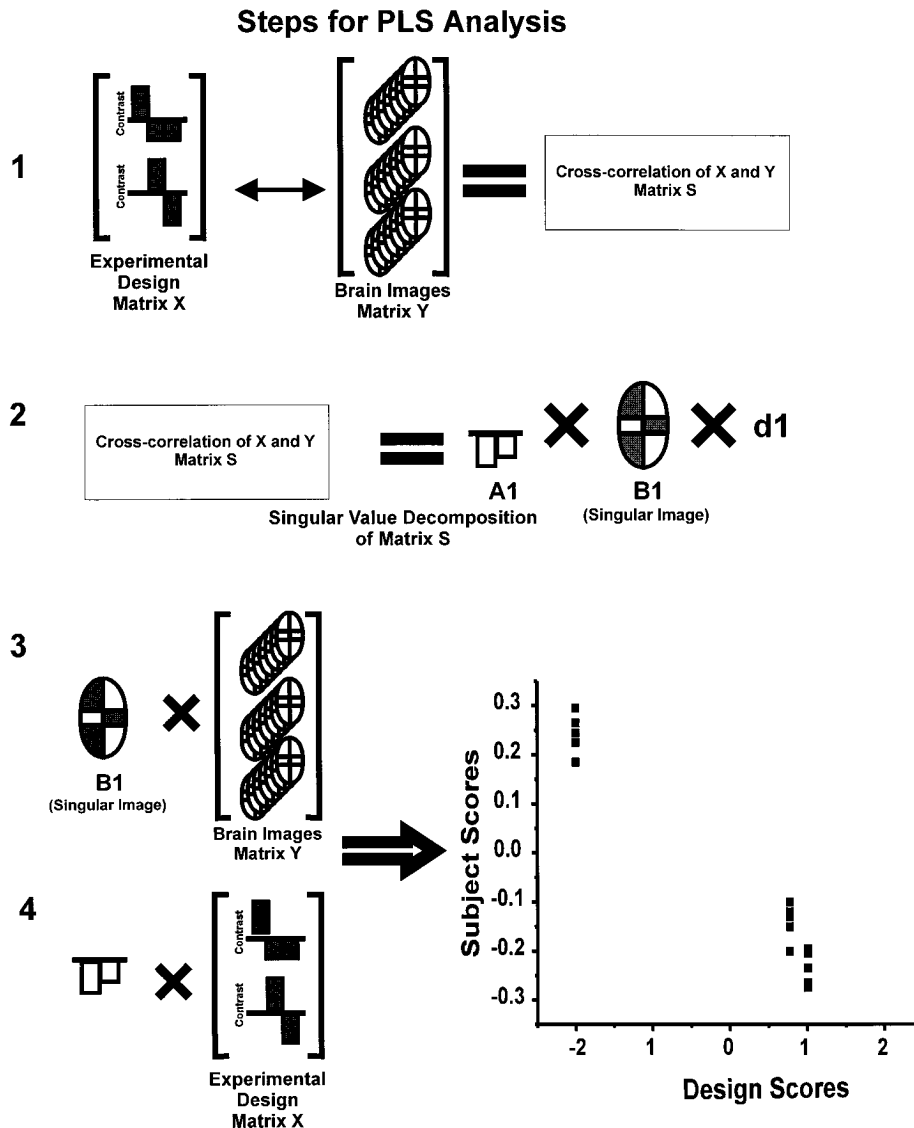
In the third step, participants' scores for each latent variable are derived by multiplying each individual image within a condition by the voxel weights for that latent variable and summing the cross products. This provides a single "subject score" for each participant in every scan condition for a given latent variable. Fourth, design scores for each latent variable are calculated by multiplying the design weights by the original contrast vectors. Subject scores can then be plotted against the design scores to aid in interpreting each latent variable pair. This scatterplot depicts the expression of the "experimental effect." If a main effect of processing task is represented, the scores should distribute themselves such that the semantic judgment tasks are separated from the letter judgment tasks in the scatterplot.

To test the statistical significance of each latent variable, we examined the  $R^2$  obtained from a multiple regression analysis using the contrast vectors and subject scores as predictor and dependent variables. From the  $R^2$  values, we can determine the extent to which the variability in subject scores is related to the design contrasts for each latent variable. The significance of each  $R^2$  was then assessed with a permutation test (Edgington, 1980; Good, 1994), which involved randomly reassigning the data for each subject to a different task condition, and for each reordering, computing a new PLS. Following each PLS, a multiple regression analysis was performed on the permuted subject scores and the design contrasts, and the significance of the  $R^2$  obtained from our actual data was calibrated against the distribution of  $R^2$ 's arising from 500 permutations.

In comparing the PLS and SPM results, it should be noted that the local maxima coordinates from the two statistical analyses will differ slightly because of differences between the multivariate (PLS) and the univariate (SPM) approaches. To identify whether PLS and SPM regions were the same, voxels were considered comparable if they were within 10 mm of one another in the  $x$ ,  $y$ , and  $z$  directions.

### PLS Results

The PLS analysis produced five patterns of covariation (latent variables) with Helmert contrasts used to code for the design contrasts. For Helmert contrasts, a



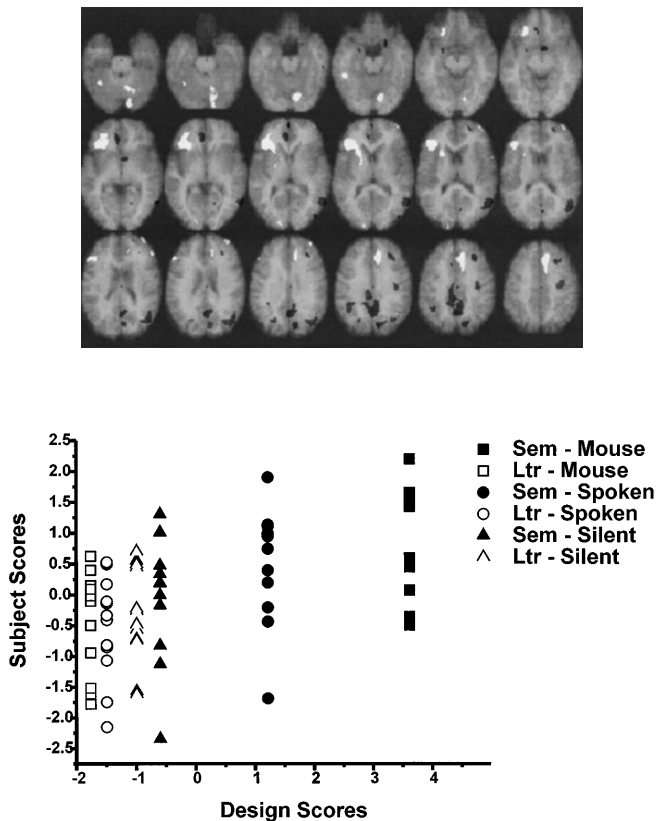
**FIG. 2.** Schematic representation of the four steps underlying the PLS analysis: (1) Calculation of cross-correlation matrix, (2) singular value decomposition, (3) calculation of subject scores, and (4) calculation of design scores.

level of a factor is compared with the mean of subsequent levels of that factor. In the present case, the first two contrasts were  $[5, -1, -1, -1, -1, -1]$  and  $[0, 4, -1, -1, -1, -1]$ . This descending pattern continued for the other three contrasts. It is worth noting that the outcome of the PLS analysis would have been identical had we chosen any other set of five orthogonal contrasts (Bookstein, 1991; McIntosh *et al.*, 1996).

The first two latent variables identified two main effects of response mode. Latent Variable 1 isolated brain regions that distinguished the spoken-response condition from the other response modes regardless of processing task ( $R^2 = 0.34$ ,  $P < 0.0001$ ). Areas of increased rCBF related to the vocal response included the left somatomotor area, bilateral somatosensory areas, and the left cerebellum, whereas areas of decreased

rCBF included the left orbital frontal gyrus, left superior frontal gyrus, medial frontal gyrus, right parahippocampal gyrus, and left inferior parietal lobule. Latent Variable 2 also revealed a main effect of response, differentiating mouse-click responses from the other two modes ( $R^2 = 0.37$ ,  $P < 0.0001$ ). Regions of increased rCBF associated with mouse-click responding included the left inferior parietal lobule, bilateral anterior cingulate, right vermis, and the left posterior cingulate. Areas associated with decreased rCBF included the left orbital frontal gyrus, bilateral uncus, right cerebellum, and inferior occipital gyrus.

The remaining three latent variables represented the main effect of semantic processing and interactions between semantic processing and response mode. Latent Variable (LV) 3 identified regions of rCBF that



**FIG. 3.** Singular images and latent variable scores from Latent Variable 3 representing experimental task variance. The singular images (top) present activations imposed on MRI slices ranging from  $z = -28$  to  $z = 44$  (Talarach and Tourneaux, 1988), with increases of 4-mm intervals. Positive saliences are indicated in white and negative saliences are indicated in black. Right is right on the image. A scatterplot of subject scores and design scores for each subject is presented below. Subject and design scores have been transformed to  $z$  scores.

distinguished semantic from letter processing regardless of response ( $R^2 = 0.26$ ,  $P < 0.0001$ ). These areas can be seen graphically in Fig. 3 and listed by coordinates in Table 3. Positive saliences indicate areas of increased rCBF associated with semantic processing. These regions include the left inferior frontal cortex (BA 45), left orbital frontal gyrus (BA 11), right anterior cingulate (BA 32), right cerebellum, and left striate cortex (BA 17). Areas of decreased rCBF (negative saliences) corresponding to the semantic processing task included the left precuneus (BA 7), right middle temporal gyrus (BA 37), and posterior cingulate gyrus (BA 31).

A more striking result obtained with the third latent variable was the absence of a pure main effect of semantic processing. The plot of subject scores versus design scores showed that the degree to which the pattern of activity in Fig. 3 distinguished semantic and letter processing varied with response mode. Specifically, the magnitude of increase and decrease in rCBF associated with semantic processing was greatest for

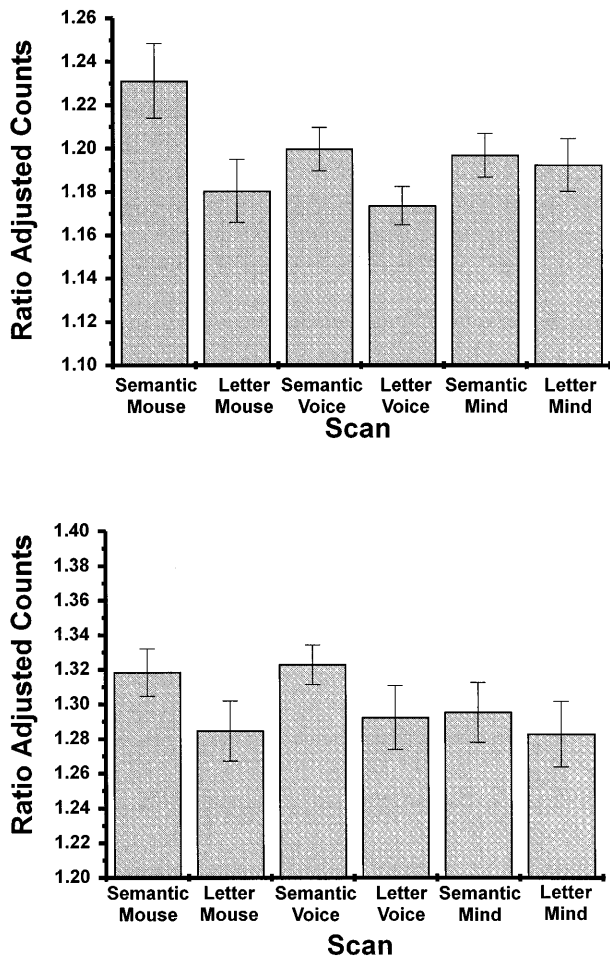
the mouse-click condition, somewhat less for the spoken-response condition, and very small with silent thought. This interaction is illustrated in Fig. 4, where activity counts from the left inferior prefrontal cortex and right cerebellum are plotted as a function of task. The magnitude of difference between the semantic and the letter tasks becomes progressively smaller across the mouse-click, spoken-response, and silent-thought conditions. This result sheds some light on the subtraction data, which showed activation of the right anterior cingulate and right cerebellum with mouse-click and spoken response but not with silent thought. It appears that those regions were too weakly activated in the silent-thought condition to be considered significant in a pairwise subtraction.

The fourth and fifth LVs provided stronger evidence for an interaction effect, further clarifying the subtraction results. Plotting subject scores as a function of design scores for both LVs revealed that the pattern of activity associated with semantic processing changed depending on response condition. For LV4, the pattern of rCBF associated with semantic processing in the mouse-click condition differed for the spoken-response and silent-thought conditions ( $R^2 = 0.37$ ,  $P < 0.0001$ ). Specifically, some areas of the brain that showed increased rCBF for the semantic task during the mouse-click response showed decreases with the spoken-response and/or silent-thought conditions. These results

**TABLE 3**

Coordinates and Brodmann's Areas Identified for Latent Variables 3–5

Latent variables	Positive saliences			Negative saliences					
	<i>x</i>	<i>y</i>	<i>z</i>	Brodmann's areas		<i>x</i>	<i>y</i>	<i>z</i>	Brodmann's areas
LV3	6	22	36	R. 32		30	-12	40	R. 4
	-34	28	4	L. 45		-8	-30	32	L. 31
	10	-76	-16	Cerebellum		-2	-58	32	L. 7
	-24	28	-8	L. 11		50	-62	8	R. 37
	10	-88	-28	Cerebellum		-8	36	0	L. 32
	-34	40	0	L. 45					
LV4	-16	-94	4	L. 17					
	-8	60	12	L. 10		-8	16	40	L. 6/8
	10	54	-4	R. 10		16	-34	-8	R. 35
	-56	-4	-12	L. 21		-28	-22	-20	Fus. gyrus
	-62	-36	8	L. 22		38	24	24	R. 46
	-58	8	12	L. 44/6		-22	0	0	L. 22
LV5	26	-88	20	R. 19					
	-42	44	24	L. 46					
	42	30	28	R. 9		-10	38	8	L. 32
	40	48	12	R. 10		0	-26	36	31
	16	18	-16	R. 47		20	38	36	R. 8
	58	-36	16	R. 22		-6	4	-8	L. 25
	36	44	28	R. 46		-60	-56	0	L. 21
	44	10	40	R. 6/8					
30	-14	0	R. NL						
46	-34	36	R. 40						



**FIG. 4.** Plots of means and standard errors of ratio adjusted activity counts for (top) the left inferior prefrontal cortex ( $-34, 28, 4$ ) and (bottom) the right cerebellum ( $10, -76, -16$ ) across the six scan conditions.

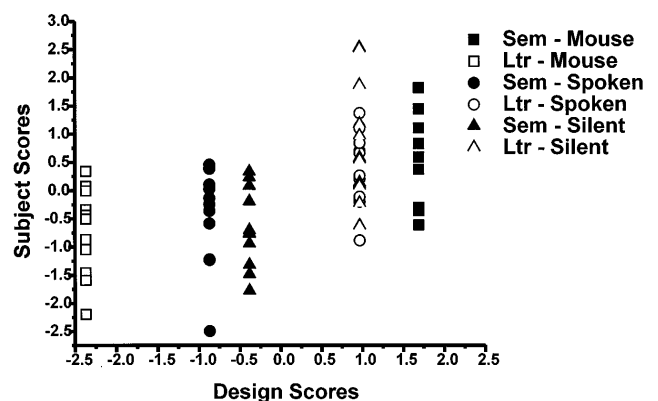
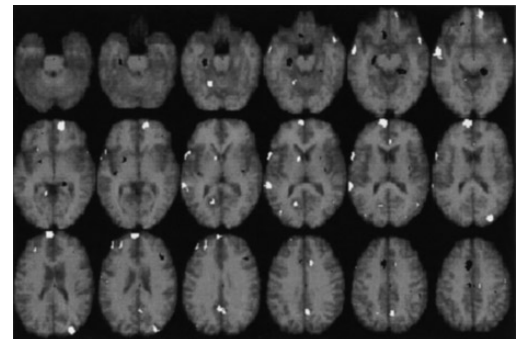
can be seen in Fig. 5 and Table 3, where positive saliences reflect regions of increased rCBF related to semantic processing for the mouse-click response and regions of increased rCBF associated with letter processing in the spoken-response and silent-thought conditions. Negative saliences represent decreased rCBF for the semantic task in the mouse-click condition and the letter task with the other two responses. A similar result can be seen with the fifth latent variable ( $R^2 = 0.21, P < 0.0001$ ). The pattern of rCBF associated with semantic processing was similar for the mouse-click and silent-thought conditions, but changed with spoken response (Fig. 6; Table 3).

In short, the PLS analysis extended the SPM results, indicating that the relationship between the brain and semantic processing varies with response mode. Based on both analyses, the brain regions associated with increased rCBF during semantic processing for each response can be seen in Table 4. This table shows areas that were commonly activated for all three responses,

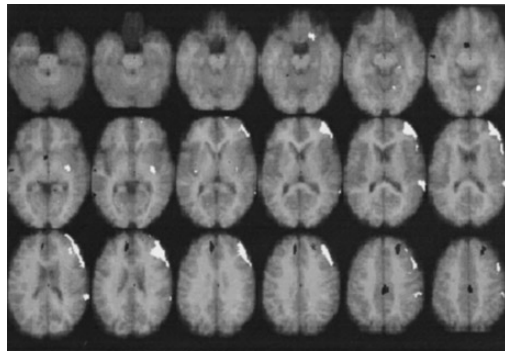
areas that were active for only two conditions, and areas completely unique to a given response. These data clearly signify an interaction between processes at the neural level rather than a simple additive effect.

## DISCUSSION

The PLS and SPM analyses suggest that semantic processing activates several brain regions regardless of response mode, such as the left inferior frontal cortex (BA 45). However, there was also compelling evidence for an interaction between semantic processing and response: the magnitude of rCBF to these common areas differed depending on condition. Moreover, specific areas of rCBF associated with semantic processing were unique to a given response mode or shared across only two responses. These results suggest that the neural processes underlying semantic processing and response do not combine in a simple additive manner, a finding which should not be surprising when the biologi-



**FIG. 5.** Singular images and latent variable scores from Latent Variable 4 representing experimental task variance. The singular images (top) present activations imposed on MRI slices ranging from  $z = -28$  to  $z = 44$  (Talarach and Tourneaux, 1988), with increases of 4-mm intervals. Positive saliences are indicated in white and negative saliences are indicated in black. Right is right on the image. A scatterplot of subject scores and design scores for each subject is presented below. Subject and design scores have been transformed to  $z$ -scores.



**FIG. 6.** Singular images and latent variable scores from Latent Variable 5 representing experimental task variance. The singular images (top) present activations imposed on MRI slices ranging from  $z = -28$  to  $z = 44$  (Talarach and Tourneaux, 1988), with increases of 4-mm intervals. Positive saliences are indicated in white and negative saliences are indicated in black. Right is right on the image. A scatterplot of subject scores and design scores for each subject is presented below. Subject and design scores have been transformed to  $z$  scores.

cal organization of the brain is considered. The additivity assumption requires information processing to occur in a serial, feedforward manner without any retroactivation, which could modulate a preceding process (e.g., Sergeant, 1992). However, one of the characteristics of the brain is the abundance of feedback projections. In cortex, it is common to observe reciprocal connections between adjacent areas, as well as feedback connections from higher order to primary and secondary regions (e.g., Felleman and Van Essen, 1991). Moreover, large-scale neural models suggest that reciprocity may be central to the functional organization of the cortex (e.g., Tononi *et al.*, 1992).

Given these principles of reciprocity and feedback, applying a simple additive approach to the study of brain-cognition relationships can be problematic. Reliance on only the subtraction method can result in an inadequate representation of the regions underlying a task by failing to find participation of a specific brain region, or by indicating activation even when a region is

**TABLE 4**

Areas of Increased rCBF Associated with Semantic Processing

$x$	$y$	$z$	Brodmann's areas	Mouse	Spoken	Silent
Areas of increased rCBF common to all response modes						
-34	28	4	Left area 45	*	*	*
-24	28	-8	Left area 11	*	*	*
-16	-94	4	Left area 17	*	*	*
6	22	36	Right area 32	*	*	*
10	-76	-16	Right cerebellum	*	*	*
Areas of increased rCBF common to two response modes						
10	-88	-28	Right cerebellum	*	*	
40	48	12	Right area 10/46	*		*
42	30	28	Right area 9	*		*
-8	16	40	Left area 6/8		*	*
-28	-22	-20	Fusiform gyrus		*	*
Areas of increased rCBF unique to a single response mode						
10	54	-4	Right area 10	*		
-62	-36	8	Left area 22	*		
26	-88	20	Right area 19	*		
-42	44	24	Left area 46	*		
0	-26	36	Area 31		*	
38	24	24	Right area 9/46			*
44	10	40	Right area 6/8			*
30	-14	0	Right NL			*
46	-34	36	Right area 40			*

*Note.* Asterisks indicate regions that were active for each response mode.

not playing a significant role (Horwitz and Sporns, 1994). These weaknesses are evident here. Using the subtraction technique to draw conclusions about the areas of rCBF involved in semantic processing would produce substantially different results depending on the chosen response.

Nonetheless, we did identify a core area associated with semantic processing, namely left inferior frontal, that has been found across a number of studies (Kapur *et al.*, 1994; Petersen *et al.*, 1988; Raichle, 1994). This result suggests that studies based on the additivity assumption do reveal commonalities across experiments and tasks (Cabeza and Nyberg, 1997), and that replication can be helpful in revealing a pattern of rCBF associated with given process. Unfortunately, replication is not sufficient since it provides no means for interpreting differences between studies. Consider the subtraction results for the spoken-response and silent-thought conditions. Silent thought did not show activation of the anterior cingulate or right cerebellum, whereas spoken response did not show any right frontal activation. The subtraction technique alone does not allow one to determine whether such discrepancies arise from statistical noise or from biological causes, such as the interactive effects of processes.

The present study was designed to examine interactions at the neural level when there is no corresponding interaction at the behavioral level, which was corroborated by the results of our recognition test. Participants did not show a significant difference in memory performance as a function of response modality. However, that is not to say that there can *never* be a behavioral interaction between response modality and cognitive processing. It is possible to design situations where response mode interferes with cognitive operations (Brooks, 1968). Given this possibility, the obvious question to address is whether the interaction effects we found arise because response modality modulates the systems concerned with semantic processing or vice versa? The order of these effects is difficult to establish from activity patterns alone, and is not relevant to our main goal of investigating the additivity assumption. Moreover, to better understand the influence that semantic processing and response modality have on one another, an explicit quantification of the functional networks is necessary (see below and McIntosh and Gonzalez-Lima, 1994). A preliminary exposition of such an exploration has been reported elsewhere (Jennings *et al.*, 1996).

Recognizing the nonadditivity of neural processes thus suggests that subtraction can provide only a limited analysis of brain activity, and that additional analytic tools should be applied in conjunction with subtraction to understand brain-behavior relationships. A number of techniques are viable in this context. One approach involves applying parametric manipulations to a target process and looking for variations in rCBF across parametric variation. Only brain areas associated with the target process would be expected to appear or vary across different levels of the task. Moreover, these variations can reveal nonlinear functions or nonadditivity in processes (Haxby *et al.*, 1995). A second option entails using the PLS technique adopted here. Because PLS relies on covariances between task design and functional brain images, the overall pattern of brain activity associated with a given task is explored in the context of all other experimental effects and the main effects and interactions associated with different processes teased out (Nyberg *et al.*, 1996). As was shown here, explicit tests for the interaction between processes revealed the important finding, unobtainable from simple subtractions, that there were differences in the magnitude of activation associated with semantic processing for each response. Similarly, the univariate complement of tests for main effects and interactions (the conventional ANOVA) can be used to assess such influences when the hypothesis is focused on a particular brain area (Friston *et al.*, 1996), but, unlike PLS, may not be appropriate when the focus of the investigation is on entire neural systems (McIntosh *et al.*, 1996; Fletcher *et al.*, 1996). A third alternative

encourages fully exploring the functional interactions underlying a given task through path analysis (McIntosh *et al.*, 1994). This approach eliminates the emphasis on finding specific regions responsible for a process, and instead maps out the overall network supporting performance. With all these techniques the need to assume additivity is eliminated, and questions ranging from which regions underlie a task to how these regions interact during processing can be addressed. More importantly, these approaches bring us closer to the goal of understanding the relation between the interactive biology of the brain and cognitive function.

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