

Mapping Neural Interactivity onto Regional Activity: An Analysis of Semantic Processing and Response Mode Interactions

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Neuroimaging studies of cognition have typically been designed to identify brain regions that are active during a cognitive process. However, identifying how brain regions *interact* may be equally important. In a recent study we found that the pattern of activation associated with a semantic task *differed* depending on how subjects made a response, suggesting that there was an interaction between the neural systems underlying response mode and semantic processing (J. M. Jennings *et al.*, 1997, *NeuroImage* 5, 229–239). This result raises two important questions, which we examined here: (1) How did the regions underlying semantic performance influence one another, or interact, to produce a different pattern of activation in each case? (2) What can be learned about the neurobiology of semantic processing when different regions are identified as a function of response? We addressed these questions using structural equation modeling. This technique produced functional network models representing the effect of different regions on each other during the semantic task for each response. A common network of regions associated with semantic processing was observed and included the left inferior frontal and left superior temporal cortices, with other regions brought into that network depending on response (e.g., right middle frontal). Moreover, changes in the influences among these regions across response condition predicted the pattern of activation found previously. These results show how an arbitrary response can affect the neural pathways associated with a cognitive process, likely due to the parallel and reentrant organization of the brain, and emphasize the importance of examining functional connections when studying cognition. © 1998 Academic Press

INTRODUCTION

Brain imaging techniques provide an invaluable tool for exploring the neural basis of cognition. For many studies, the aim is to determine whether particular brain regions are more or less *active* than other regions

through the subtraction of regional cerebral blood flow (rCBF) patterns between different tasks (e.g., Petersen *et al.*, 1988). The results of this work have provided fundamental knowledge about the neural areas underlying various cognitive activities (Cabeza and Nyberg, 1997). However, recently, we found that neural processes may not always combine in the additive manner that is assumed when using the subtraction technique (Jennings *et al.*, 1997), a concern which has been voiced in the neuroimaging literature with increasing frequency (Bookheimer *et al.*, 1995; Friston *et al.*, 1996; Sergent *et al.*, 1992; for an interesting debate on this issue see papers by Poeppel, 1996a,b; and Demonet *et al.*, 1996).

In our study, PET scans were obtained while subjects carried out a semantic task, in which they decided whether a word represented something “living,” and a letter task, in which they determined whether words contained the letter “a” (Jennings *et al.*, 1997). The two tasks were designed to differ only in the access and utilization of word meaning, as discussed elsewhere (Kapur *et al.*, 1994). Subjects performed each task three times, and each time answers were indicated by use of a different response mode (mouse clicking, spoken responding, or silent thought). According to the subtraction paradigm (e.g., Petersen *et al.*, 1988), there should be an additive relationship between response type and semantic processing. That is, subtracting the letter task from the semantic task for each response mode should result in the same pattern of rCBF. In actuality, the pattern of activation following subtraction varied with response. There was a different pattern of brain activation in each case, and statistical testing revealed a significant interaction between processing task and response mode.

These results suggest that the neural basis of the semantic task was not simply the addition of the neural components subserving the semantic process *plus* the neural components underlying a response, but arose from the interactive engagement of both sets of components. Such interactions do not seem surprising when

one considers the biological organization of the brain. As pointed out by Sergent (Sergent *et al.*, 1992; Sergent, 1994), the additivity assumption requires information processing to occur in a serial, feed-forward manner without retroactivation or feedback. However, there is evidence that higher cognitive functions involve the rapid integration of information across several sensory and behavioral domains through reciprocal and long-range feedback connections among widely distributed brain regions (Edelman, 1987; Mesulam, 1990; Tononi *et al.*, 1992, 1994). In addition, a particular site often subserves multiple cognitive operations depending on its functional connections with other areas (McIntosh *et al.*, 1996, 1997). Given the interconnectedness of the brain, determining the neurobiology of a cognitive process may be better accomplished by examining how regions *influence* one another during task performance rather than regional localization.

One effective technique for exploring the relationships among regions is network analysis using structural equation modeling (McIntosh and Gonzalez-Lima, 1994; McIntosh *et al.*, 1994). A thorough discussion of the practical and theoretical issues surrounding the use of this approach in neuroimaging has been covered elsewhere, particularly in a review by McIntosh and Gonzalez-Lima (1994). Their paper details the mathematical foundation of neural structural equation modeling and addresses the use of anatomical constraints for modeling using simulations and empirical demonstrations. Briefly though, the method produces brain models that represent the *effect* of different regions on each other through their *neuroanatomical* connections. The influence of different regions is represented by path coefficients, which indicate the strength and type (positive or negative) of an effect and provide an idea of how regions interact as a network to support cognitive performance.

Network analysis is particularly advantageous for making sense of the discrepant patterns of activation mentioned above. By determining the functional networks associated with the semantic task for each response, we can compare them to establish whether the different patterns of activation associated with semantic processing can be attributed to differential influences among the same brain regions as a function of response. Moreover, we can learn more about the neurobiology of semantic processing. Trying to identify the specific regions associated with semantic performance through activation analysis alone is problematic because different regions would be specified depending on which response condition was considered. Instead, examining the influences among brain regions allows us to determine whether they are any common connections that are maintained regardless of response and can thus be attributed to semantic processing.

In summary, the following study was carried out

using functional network analysis to determine: (1) whether differences in effective connectivity among the brain regions associated with semantic processing in each response condition (mouse clicking, spoken responding, silent thought) can account for the statistical interactions that were found in our previous study (Jennings *et al.*, 1997) and (2) whether there is a network of regions that appear to support semantic processing regardless of response mode.

MATERIAL AND METHODS

The methodology for data collection and rCBF analysis have been reported elsewhere (Jennings *et al.*, 1997). However, these details are presented briefly below since the activation analyses provide the basis for incorporating regions into the functional models.

PET and Behavioral Data

Data were obtained from 12 right-handed participants (6 male/6 female) with a mean age of 27.3 years. Each participant underwent six PET scans. For three of the scans they made semantic judgments, deciding whether each word presented on the computer screen could be considered living or nonliving; for the other three scans they carried out a letter processing task, checking each word presented on the computer screen for the letter "a." For each task, 48 concrete nouns (three to eight letters in length) were presented visually for a duration of 2 s followed by a 500-ms interval. Participants responded "yes" or "no" during each task by clicking the response buttons of a computer mouse (mouse-click condition), responding aloud (spoken response condition), or by thinking silently to themselves (silent thought condition). Each response condition was paired with both processing tasks (i.e., six different scan tasks). 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.

Participants were scanned using a GEMS-Scanditronix PC-2048 head scanner (15 slices, 6.5 mm apart, inplane FWHM = 5–6 mm) with injections of 40 mCi of [¹⁵O]water for each scan. Integrated regional counts were used as an index of rCBF. Following the final scan, participants were given a recognition test to ensure that they were performing both the semantic and the letter processing tasks consistently across each response mode. If so, there should be a levels of processing effect—recognition memory should be higher in the semantic task than the letter task (Craik and Lockhart, 1972) for each response condition, with comparable levels of recognition regardless of response. Because we found this pattern of memory performance, we can assume that any nonadditivity in the brain data did not arise from discrepancies in effort or attention during

the tasks as a function of response. Moreover, all subjects showed highly accurate performance during the semantic and letter tasks for the spoken response (0.98 and 0.99, respectively) and mouse click (0.94 and 0.99, respectively) conditions, with no significant interaction between processing task and response mode.

Activation Analyses

Images were spatially transformed, smoothed with a 10-mm isotropic Gaussian filter, and corrected for individual differences in whole brain CBF through ratio transformation using SPM95 (Friston *et al.*, 1995).

Statistical testing for a processing task \times response mode interaction was performed with a new multivariate analysis method, partial least squares (McIntosh *et al.*, 1996). Partial least squares (PLS) describes the relationship between a set of contrasts that code for the experimental design and the resultant brain images, allowing the examination of 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 is more appropriate when the experimental question is aimed at the level of entire neural systems (McIntosh *et al.*, 1996). Moreover, in a fully parameterized orthonormal design matrix, in which all experimental degrees of freedom are represented, PLS provides an *omnibus* index of whether main effects and interactions are significant (McIntosh *et al.*, 1996). Because the PLS solutions are invariant to orthonormal rotation of the design matrix (Bookstein, 1991). In contrast, the univariate complement of tests for main effects and interactions (the conventional ANOVA) is better used to assess interactions when the hypothesis is focused on a particular brain area (Friston *et al.*, 1996).

Structural Equation Modeling

To determine the functional network underlying semantic processing for each response mode, we applied structural equation modeling to the data. We first chose a set of regions, which were identified in the PLS analysis, for the reasons outlined below. Each region was represented by its peak voxel, and the globally scaled activity counts of each peak were used to compute interregional correlations of activity among the brain regions for each response mode, as done elsewhere (Horwitz, 1989; Horwitz *et al.*, 1995; McIntosh *et al.*, 1994; Nyberg *et al.*, 1996). The anatomic connectivity between these regions was then derived from the literature on primate neuroanatomy, with a focus on the connectivity of prefrontal and anterior temporal regions (Pandya and Yeterian, 1990; Petrides and Pandya, 1988). Recent neuroanatomical work has suggested that strong cytoarchitectural similarities exist between the monkey and human prefrontal cortex,

which implies that the use of primate connectivity for functional modeling is a reasonable approximation for humans (Petrides and Pandya, 1994).

The interregional correlations and anatomic model were combined to create structural equation models using LISREL (Version 8, Scientific Software Inc.) to determine the weights or path coefficients for each anatomic connection. These values represent the influence of each region on its efferent areas and reflect how much a unit change in activity in one region affects activity in the region to which it projects. Path coefficients were derived through a process of iterative data fitting to the observed pattern of interregional covariances of activity. Since they were based on functional activity measured across participants, they reflect an "average" functional influence within a given task and indicate the stability and direction of that influence within the sample.

Because the value of a path coefficient represents the direct effect that one region has on another in the model, coefficients can be regarded as indices of "effective connectivity" (Aertsen *et al.*, 1989). Effective connectivity contrasts with "functional connectivity" (Friston *et al.*, 1993), which describes interregional correlations of activity without indicating how these correlations are mediated. The interpretation of an effective connection, as derived from a neural systems-level model (McIntosh and Gonzalez-Lima, 1994), can best be conceived of as the overall effect that several cell ensembles in one area has on the ensembles in another. The sign and strength of the coefficients can be thought to reflect ensemble excitation (positive coefficient) or inhibition (negative coefficient). Ensemble excitation/inhibition are statements about the nature of the influences between brain areas, as presently defined by the pattern of covariances in rCBF; they do not necessarily map onto the level of individual neurons or columns of neurons. This point follows from demonstrations showing that the emergent pattern of influences on one level of organization (i.e., single cells) may not correspond directly to another level, such as large-scale neural systems (Douglas *et al.*, 1995; Somers *et al.*, 1995). Further elaboration can be found elsewhere (Nyberg *et al.*, 1996).

Task-related changes in functional influences or networks were assessed statistically by comparing a model, where all path coefficient estimates were fixed to be equivalent between conditions, versus a model in which the estimates were unconstrained. These omnibus comparisons between conditions were carried out using the stacked model or multiple group approach in LISREL (Joreskog and Sorbom, 1989; McIntosh and Gonzalez-Lima, 1992; McIntosh *et al.*, 1994). Rather than estimating a model for each condition separately, the models were combined in a single program run. This process involved statistically comparing the null functional

model (equivalent path coefficients between conditions) with the alternative model (coefficients allowed to differ) by subtracting the goodness-of-fit χ^2 value for the alternative model from that of the null model. If the alternative model produced a significantly lower χ^2 value, then the coefficients that were free to vary between conditions could be considered statistically different across the three response modes, indicating that the functional networks associated with semantic processing vary with response. The significance of this χ^2 test was assessed using the difference in degrees of freedom between the two models. It is important to note that the overall models (i.e., all connections together) were statistically compared rather than individual connections within a model because our interest lies in how the functional network as a *whole* is organized and how a given region in the model is influenced by all other regions acting together.

RESULTS AND DISCUSSION

Regional Activation Changes

Detailed results from the PLS analysis have been described previously (Jennings *et al.*, 1997), but will be summarized here to highlight the main findings. The analysis showed several commonalties in activation patterns when semantic processing was compared to letter processing across the three response modes, primarily increased rCBF to left BA 45 (inferior frontal gyrus). However, this main effect was not pure—the degree to which these common regions distinguished semantic and letter processing varied significantly with response. Specifically, the magnitude of increase 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 (Jennings *et al.*, 1997).

Further evidence for a significant interaction between semantic processing and response was evident in the large number of active regions that were discrepant across the three conditions (Jennings *et al.*, 1997). For the mouse-click condition, semantic processing was associated with increased rCBF to left BA 10 (superior frontal gyrus), right BA 9 and 10 (middle frontal gyrus), and left BA 22 (superior temporal gyrus) whereas the spoken response condition revealed increased rCBF to left BA 6/8 (medial frontal gyrus), left fusiform gyrus, and BA 31 (posterior cingulate). The silent thought condition was similar to the other two responses showing activation in right BA 9 and 10 (middle frontal gyrus) and left fusiform gyrus, but there was also additional unique activation in right BA 9/46 (middle frontal gyrus), the right lentiform nucleus, and right BA 40 (inferior parietal lobule).

Structural Equation Models

From the set of activated regions identified in our PLS analysis, we selected a subset of regions, which included left BA 45, right BA 32, right cerebellum, left BA 10, and bilateral BA 22. These regions were chosen because they have all been identified in previous neuroimaging studies of semantic processing (for review see Cabeza and Nyberg, 1997) yet showed intriguing interactions as a function of response type. In addition, we included right BA 9 and BA 10, which are not typically found during semantic processing but figured prominently in our results. These eight regions, the coordinates of their peak voxels in stereotaxic space (Talairach and Tournoux, 1988), and the response condition(s) for which they were significantly activated are listed in Table 1. The interregional correlations between these regions and the anatomic connections among them (Fig. 1) were combined to create the structural equation models.

The resulting functional networks proved to be significantly different across the three response modes, χ^2 diff(48) = 114.04, $P < 0.001$. However, examining the networks for each response suggested that they comprised two distinct components. One, there were a number of effective connections underlying the semantic task that were similar for each response mode (Fig. 2), such as the influence between left BA 22 and left BA 45. However, the strength of these connections varied with response. The strongest connections were evident in the mouse-click condition and weakest seen with silent thought. Two, the remaining connections were highly discrepant across the three conditions (Fig. 3). For example, the input connection from the cerebellum to right BA 9 varied markedly with response, being highly positive in the mouse-click condition, weakly positive with spoken responding, and strongly negative with silent thought. Both aspects of the models are explored further below.

TABLE 1

Areas of Increased rCBF Associated with Semantic Processing

<i>x</i>	<i>y</i>	<i>z</i>	Brodmann's areas	Mouse	Spoken	Thought
-34	28	4	Left area 45	*	*	*
6	22	36	Right area 32	*	*	
10	-88	-28	Right cerebellum	*	*	
40	48	12	Right area 10	*		*
42	30	28	Right area 9	*		*
58	-36	16	Right area 22	*		*
-8	60	12	Left area 10	*		
-62	-36	8	Left area 22	*		

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

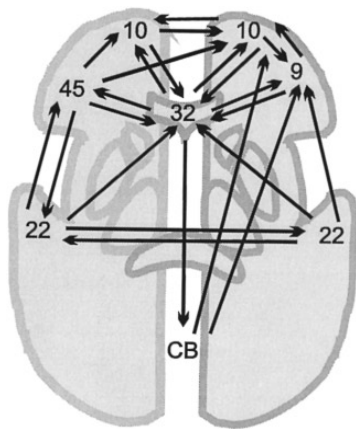


FIG. 1. Graphic representation of the regions included in the functional network analysis and the neuroanatomical connections among them.

Common Network

The set of effective connections that were similar across each response condition consisted of influences between left BA 22 and left BA 45; left BA 22 and BA 32; left BA 45 and right BA 10; right BA 10 and left BA 10; and right BA 10 and BA 32 (Fig. 2). These connections could comprise a common functional network, which is largely responsible for semantic processing, since they were comparable in effect (positive or negative) regardless of response, although the magnitude of influence varied.

To determine if this network of connections could be considered consistent or common, we tested whether the changes in effective strength were significantly different by comparing a null model (all connections held constant) with an alternative model, in which only

the “common” network connections were allowed to vary with condition. The results showed that there was no significant difference between the null and alternative model; the influences among these “common” regions did not differ significantly with response, χ^2 diff(12) = 15.11, $P > 0.05$. As further confirmation, we tested whether the significance of our initial χ^2 test stemmed mainly from the connections that were highly discrepant across each response condition and were not part of the common network. The same null model was compared against a second alternative model, in which only the “discrepant” network was free to vary and the common network was fixed. This comparison proved to be significant, χ^2 diff(36) = 98.99, $P < 0.001$, suggesting that the discrepant effective connections were the strongest source of difference across the three response conditions.

Although these post hoc tests help confirm the idea of a common semantic network, those connections may not be solely associated with semantic processing but may be part of a more general processing network which is also present in the letter task. That is, the common connections between left BA 22 and left BA 45 or left BA 22 and BA 32, for example, may also be seen in a functional model representing the letter condition across all three response modes. To examine this possibility we used the same regions and anatomical network to determine a set of effective connections for letter detection. This analysis yielded a model that was significantly different across the three response conditions, χ^2 diff(48) = 81.22, $P < 0.005$, and showed no evidence of consistently duplicating the common connections we identified with the semantic task. In short, our common network seems to be specific to semantic

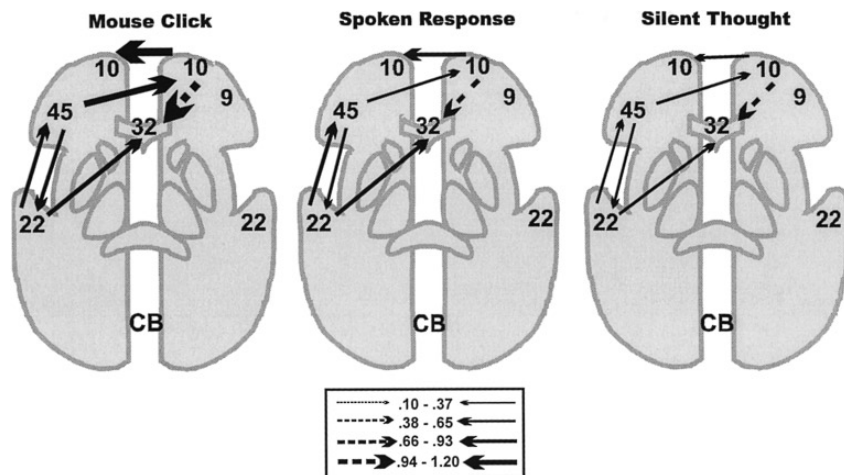


FIG. 2. Graphic representation of the effective connections associated with the semantic task that were *common* across the three response modes. The direct effect is proportional to the arrow width for each path. Values for the width gradient are given in the legend at the bottom. Positive path coefficients are represented as solid black arrows, and negative path coefficients are represented as dashed arrows. Paths where the coefficient was at or near zero are not shown.

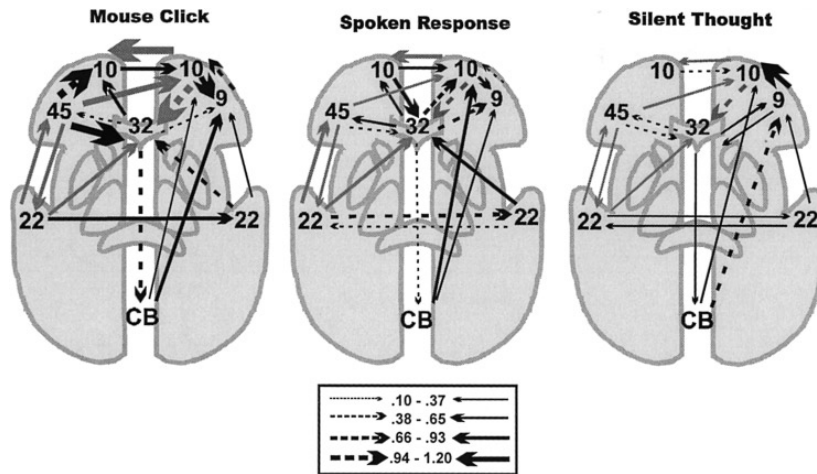


FIG. 3. Graphic representation of the semantic networks for each response condition. The direct effect is proportional to the arrow width for each path. Values for the width gradient are given in the legend at the bottom. Positive path coefficients are represented as solid black arrows, and negative path coefficients are represented as dashed arrows; paths where the coefficient was at or near zero are not shown. The common network is represented by gray arrows.

processing in our experiment. It should be noted that this model of letter detection was not meant to offer any information about that task, since the regions included in the model were only used to provide a check on the semantic condition.

Neural Influences Underlying Semantic/Response Interactions

As mentioned above, a number of connections in the models differed significantly across the three response conditions (Fig. 3), and it is these differential influences that seem to reflect the statistical interactions found between semantic processing and response mode. The same regions appear to affect one another very differently during the semantic task depending on how subjects make a response. Moreover, these variations are in keeping with the interaction effects seen in the original PLS analysis. Before considering interpretations of these network connections though, one needs to remember that the models are not complete representations of the semantic task. Due to parametric constraints, only a subset of the regions activated during response performance can be included for modeling. Nonetheless, even these somewhat limited models shed light on why certain regions were activated during the semantic task in only one or two response conditions.

Consider the afferent influences to right BA 10 (Fig. 3). In the mouse-click condition there was a strong positive common connection from left BA 45, a weak positive input from the cerebellum, and a moderately strong influence from left BA 10 with a moderate negative connection from right BA 9. The silent thought condition showed a weaker positive connection from left BA 45 and a weak positive path from the cerebellum combined with a very strong positive influence

from right BA 9 and only a weak negative influence from left BA 10. In contrast, the spoken response condition showed weak positive connections from left BA 45 and left BA 10 with only a moderate positive influence from the cerebellum and two negative connections (right BA 9 and BA 32). The absence of significant activation seen in right BA 10 with spoken responding relative to the other two modes could be attributed to those weaker positive connections and additional negative pathway.

A similar type of explanation can be applied to the activation found in BA 32 (Fig. 3). This region was significantly more active in the mouse-click and spoken response conditions than with silent thought, a result which is consistent with the inputs identified in the models. In the mouse-click condition, there was a very strong positive connection from left BA 45 with a moderate positive common connection from left BA 22, regions which, in turn, were most strongly activated with that response type. There were also two negative pathways acting on BA 32, although their influence did not cancel out the positive effects. The spoken response condition also had several positive influences acting on BA 32 from left BA 22, left BA 10 and right BA 22, with only weak negative influences from left BA 45 and right BA 10. In contrast, the silent thought condition showed only two weak positive influences (left BA 22 and right BA 9) with negative inputs from left BA 45 and right BA 10. This pattern of weaker positive connectivity helps explain the lack of activation in BA 32 during the silent thought condition compared to the other two responses. Inspection of the other connections in the models provide further insights about the pattern of activation found with the original PLS analysis. The differential patterns of activation for all areas, except the cerebellum

lum and right BA 22, which had too few inputs to draw meaningful conclusions, can be related to their network connections.

Predicting Regional Activation Levels from the Functional Models

The differences in regional activation between the three response conditions, identified with PLS, seem to be attributable to the discrepant influences seen across our models. If this idea is valid then the activity level of any region within a condition should be predicted by the activity levels of the other regions in the model. We tested this notion by carrying out a multiple regression analysis within each response condition, in which activity in a given region was regressed on the activity of areas that projected to it (Fig. 1). For example, activity in left BA 45 was regressed on the activity of left BA 22 and BA 32. If there is a strong positive correlation between the predicted activity values from the regres-

sion and the actual activity counts, then the notion that activity levels of a region are determined by the influences identified in our models would be confirmed.

This result proved to be the case. The regression analysis showed positive correlations between the predicted and actual activity values for all regions in the model for each response condition. For instance, a scatterplot of the observed values plotted against the predicted values for right BA 10 (Fig. 4) depicts the strong correlation between the predicted and actual activity values for each response mode. The results of the regression analyses for all regions in the model with the exception of the cerebellum and right BA 22, which had too few inputs for this analysis, can be seen in Table 2. Almost all regions show strong correlations between the predicted and actual activity values with the exception of left BA 10, left BA 45, and BA 32 in the silent thought condition, where a number of the afferent influences are weak or even zero. In short, the observed level of activation in a region seems to be well

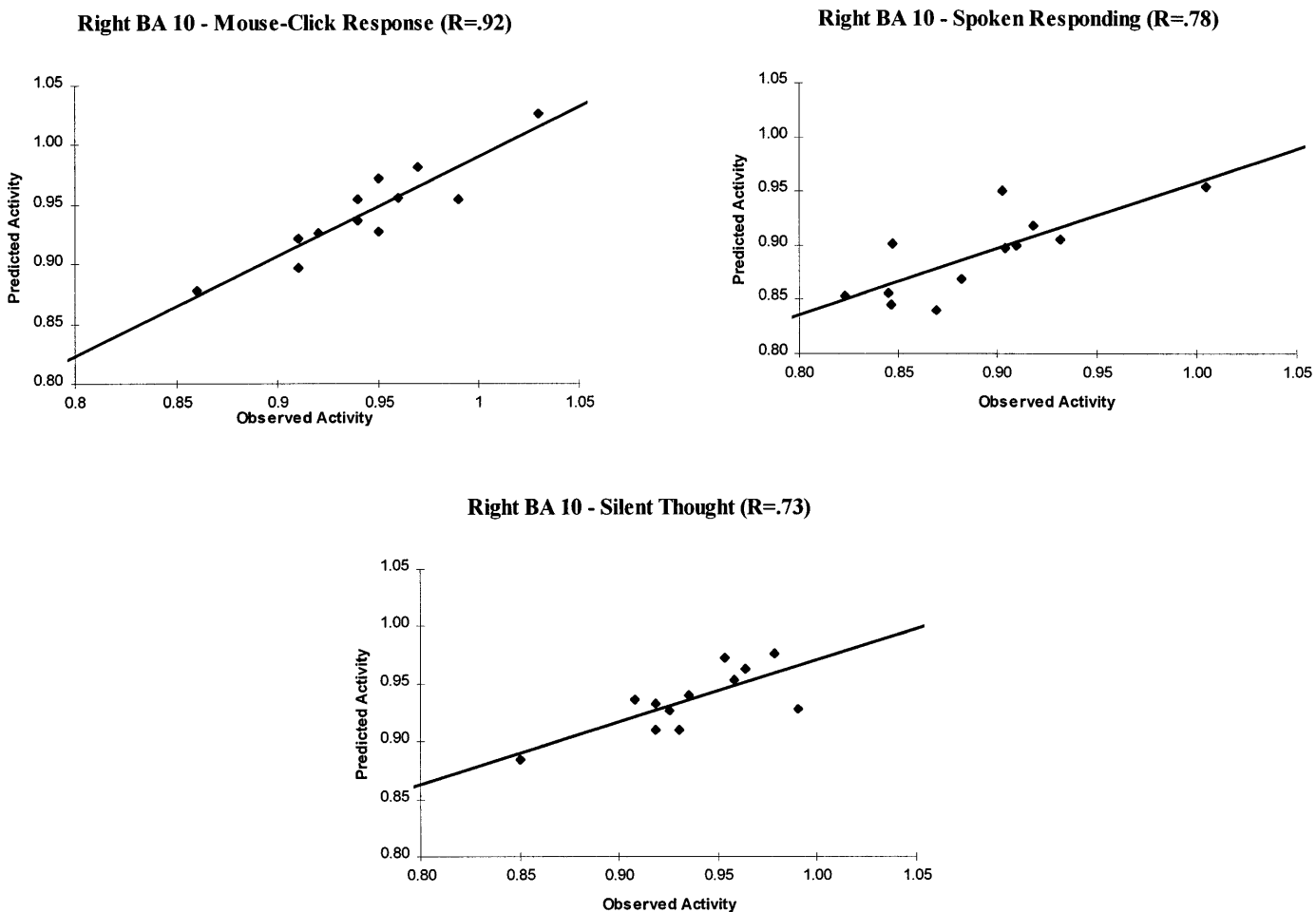


FIG. 4. Scatterplots of observed activity values versus predicted activity values for right BA 10 following regression analysis for each response condition.

TABLE 2

Correlations (R) between Predicted and Actual Activity Counts Following a Multiple Regression Analysis, in Which the Activity in a Given Region Was Regressed on the Activity of the Areas That Projected to It for Each Response Condition

	L BA 22	L BA 45	BA 32	L BA 10	R BA 9	R BA 10
Response						
Mouse	0.73	0.73	0.68	0.67	0.75	0.90
Spoken	0.75	0.56	0.89	0.64	0.83	0.78
Silent thought	0.49	0.44	0.32	0.13	0.77	0.74

predicted from the afferent influences in the model, suggesting that differential activation of these regions is caused by changes in the effective connectivity among them.

While few of the correlations from the regression analysis would be significant by conventional test, the fact that these correlations are even moderately high is surprising when one considers that the models were not meant to account for all influences on a region. For instance, a more veridical model would include effects from additional areas and influences from diffusely acting neurotransmitter systems (e.g., locus ceruleus, basal forebrain). However, such a complete depiction has never been the goal of network analysis (McIntosh and Gonzalez-Lima, 1994). Rather, we have demonstrated, with structural equation modeling, that changes in effective connectivity correspond to the differential patterns of activation obtained from PLS. The regression analysis extends this result by showing that the regions included in the models provide a good, albeit not perfect, prediction of within-task activity patterns. These results are important because there is no a priori reason to expect a relationship between the within-task subject variance that is used for path analysis and the between-task variance used for PLS and univariate methods. The fact this relationship exists validates the approach of using within-task covariances to draw inferences about task-related changes in functional networks.

GENERAL DISCUSSION

We previously demonstrated that the pattern of rCBF associated with a semantic processing task varied as a function of how participants were asked to make a response (Jennings *et al.*, 1997). This interaction effect took two forms. One, the semantic task activated several brain regions consistently (e.g., left BA 45) regardless of response mode. However, the degree of activation in those areas varied with condition, with the greatest activation seen in the mouse-click condition, somewhat less with spoken responding,

and least with silent thought. Two, other regions proved to be uniquely activated for a given response or activated with only two response modes. For example, activation of left BA 10 was unique to the mouse-click condition, while the cerebellum was activated only with mouse-click and spoken responding.

These interactions can be startling if one holds the assumption that the neural processes which underlie cognition and behavior are additive. Subtracting the pattern of rCBF during a letter checking task from that obtained during a semantic task should produce the same pattern of activation regardless of whether subjects respond to each task by clicking a mouse, speaking aloud, or thinking silently to themselves. Whatever the task differences between the semantic and letter processing conditions may be, response mode or output would be assumed to be a constant across the two tasks that should not have an interactive effect with processing.

To understand why such interactions may have occurred, we undertook a functional network analysis of our semantic task for each response. The ensuing models showed how the patterns of rCBF revealed by our PLS analysis may have arisen from the operation of a common network of regions with other areas recruited into that network depending on response (e.g., right BA 9, cerebellum, right BA 22). These models help explain the original statistical interaction effects that were found. The activation of regions common to all response conditions, such as left BA 45, seem to have varied with response because the common pathways among those regions differed in strength across conditions (strongest connections in the mouse-click condition and weakest seen with silent thought) and because the other influences among these regions were highly disparate. The network analysis further revealed that regional differences, unique to a single response mode or shared across only two conditions, also arose from changes in neural interactions as a function of response. For example, activation of left BA 10, which was only significant with the mouse-click response, seems to have been related to stronger positive afferents in that condition relative to the other two modes.

These findings are particularly important because they are unobtainable from examination of regional activation alone. For instance, some regions identified as part of the common network through network analysis (e.g., left BA 22) were not found to be significantly active for all three response conditions (see Table 1). Moreover, even the simplified network used here produced network analysis and multiple regression results which demonstrate that activity changes within a given region are determined by influences of other anatomically related regions.

Implications for the Neurobiology of Semantic Processing

What have we learned then about the neurobiology of the semantic task from path analysis? The presence of left BA 45 in the common network associated with the semantic task replicates numerous studies that have shown preferential activation of this region in semantic processing (for review see Cabeza and Nyberg, 1997; Kapur *et al.*, 1994). The feedback loop between left BA 45 and left BA 22 found for each response mode also suggests that this latter region is important for semantic processing, although the magnitude of its activation seems to be mediated by response—it was only significantly active in the mouse-click condition. This result is in keeping with other studies that have shown inconsistent activation of left BA 21/22 during a semantic task as a function of response mode and presentation rate (Raichle, 1994; Wise *et al.*, 1991).

An interaction between cognitive processing and response also seems critical when examining activation of BA 32 (anterior cingulate) during a semantic task. Identified in a number of semantic studies, it has been described as part of an anterior attentional system that is engaged in selection for response (Petersen *et al.*, 1988; Petersen and Fiez, 1993). However, a more recent view suggests that the anterior cingulate is critical for modulating and funneling a cognitive/motor command from cortical regions to the motor system (Paus *et al.*, 1993). Our path analysis data suggest this latter view is probable. Although the models allow feedback from BA 32 to other regions, the strongest influences seem to be inputs, suggesting that BA 32 may be more associated with orchestrating a response after semantic processing is complete, a view that makes sense given the relatively diminished activation in that region with silent thought.

One of the more surprising findings, perhaps, involves right BA 10. Most rCBF data show that left frontal activation is largely related to semantic retrieval whereas right frontal activation is more tied to episodic retrieval (Nyberg *et al.*, 1996). However, our functional network suggests that right BA 10 may play more of a role in a semantic processing task than has previously been suspected. A positive input from left BA 45 with a positive output back to left BA 10, common to all response modes, suggests that the right frontal region does participate in the semantic task. One reason this region may be frequently overlooked in other work lies with the weak positive and additional negative influence found in the spoken response condition, which appears to reduce right frontal activation below a significant level. Given most semantic processing studies involve vocal responding, right frontal involvement may have been consistently suppressed in these tasks and gone unidentified (see also Martin *et*

al., 1996, for right frontal activation during silent naming).

Neural Context

In summary, network analysis demonstrated that there were a set of common influences that could be related to the semantic processing task with certain interactions between constituents of this network dependent on response mode. These results can be understood as a manifestation of a more general principle thought of as “neural context,” in which the role a given region plays in a particular process is affected by the context of its interactions with other regions, which, in turn, are influenced by task demands (McIntosh *et al.*, 1997). The neural substrates of cognitive operations may thus be more sensitive to the specifics of task demands than previously thought, which could allow a richer repertoire of operations to be subserved by the same brain regions.

The path analysis results do contain instances where the same brain region may be activated in two task conditions for potentially different reasons. For example, if we consider right BA 10 we can see that activation in the mouse-click condition arose from the common positive input from left BA 45 and from a positive connection from left BA 10. In contrast, the silent thought condition had a weak common connection with left BA 45 but a strong positive influence from right BA 9. Although, right BA 10 was part of the common network, it seems to also be activated for additional and different purposes through a disparate pattern of connections. It should be pointed out that neural context is not meant to imply that there are no consistencies in brain activation patterns related to cognitive function. As mentioned, some of the components of the common network, such as left BA 45, have been identified in other imaging studies of semantic performance (Cabeza and Nyberg, 1997).

Implications for Cognitive Neuroscience

The influence of task demands or response modality on semantic processing is not only apparent at the neural level with rCBF analysis. Such effects can also be identified in behavior. One compelling example comes from case studies of patients suffering with optic aphasia. Individuals with this disorder cannot name visually presented objects, but can indicate access to semantic information through other response modalities, such as gesturing. Moreover, they can correctly name items that they have explored in the tactile domain, suggesting that an interaction between input, semantic processing and output modality must occur (Coslett and Saffran, 1992; Hillis and Caramazza, 1995; Manning and Campbell, 1992). Although we

found no differences in behavioral measures as a function of response, such interactions can be seen with healthy individuals (Brooks, 1968).

Studies of other cognitive domains have also found that task demands can have a strong impact on the neural regions and pathways associated with a particular process. For example, Bookheimer *et al.* (1995) used PET to show that oral reading activates a different neural pathway from that of silent reading, again suggesting that response modality or output can influence the neurobiology of a cognitive operation. Additional evidence has been obtained in the visual domain by Goodale and colleagues (Milner and Goodale, 1993). They propose that the inferior parietal lobule and areas in the premotor and prefrontal cortex are involved in a form of visual processing that is necessary for action, while an occipitotemporal processing stream is more concerned with the visual processes that support perception. Similar to the reading example, the pathways associated with visual processing appear to differ depending on the output requirements of a task. Although the output or response modes required in our semantic task would appear to be an irrelevant task component added to a semantic function, the network analysis results correspond to the data described above. Our findings suggest that even an arbitrary response can strongly affect and alter the neural pathways associated with a cognitive process.

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