

Changes in Limbic and Prefrontal Functional Interactions in a Working Memory Task for Faces

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Regional cerebral blood flow, measured with positron emission tomography, was used to identify brain regions that play a special role(s) in a working memory task for faces. Perceptual matching (no retention interval), short-delay (average = 3.5 s retention interval), intermediate-delay (average = 12.5 s), and long-delay (21 s) tasks were considered. From the idea that brain function is the result of neural interactions, the data were analyzed using anatomically based, covariance structural equation modeling. In perceptual matching, the dominant functional interactions were observed among the ventral cortical areas, from extrastriate regions, to the anterior temporal, and into the inferior prefrontal cortex. These interactions decreased with longer delay intervals. In the short-delay functional model, interactions along this ventral stream in the right hemisphere appeared to be rerouted through limbic areas with strong interactions among the hippocampal region, the anterior and posterior cingulate, and the inferior prefrontal cortices. For the intermediate-delay model, the hippocampocingulate interactions continued, but showed a shift to more left hemisphere involvement. In the long-delay network, interactions within the right limbic circuit were reduced in favor of strong bilateral inferior prefrontal and frontocingulate interactions. Effects from the prefrontal cortex, especially from the left hemisphere, to temporal and occipitotemporal cortices were particularly strong in the long-delay model, suggesting recruitment of some of the same circuits primarily involved in face perception. The strong corticolimbic interactions at short and intermediate delays may represent maintenance of an iconic representation of the face during the retention interval. However, at longer delays, where the image was more difficult to maintain, a frontocingulate-occipital network was used that could represent an expanded encoding strategy resulting in a more resilient memory.

Introduction

Functional brain imaging studies in humans using positron emission tomography (PET) to measure regional cerebral blood flow (rCBF) have been extraordinarily successful in exploring parts of the human cortical visual system that are activated during perception and recognition of faces. All of these works confirm that the ventral posterior cortex seems to play a special role in processing faces. Further subdivisions in these ventral cortical areas suggest that the more posterior occipital and occipitotemporal areas are specifically activated by face perception, while more anterior occipitotemporal and temporal regions are associated with perception of the unique identity of a face (Sergent, *et al.*, 1992; Haxby *et al.*, 1994a, 1995).

Building from this, a recent PET study by Haxby *et al.* (1995) sought to examine face recognition processes by adding a memory component. Subjects were scanned in a delayed match-to-sample task for faces where the delay interval was parametrically varied from 1 to 21 s. This design allowed for the assessment of activity changes as both the perceptual and working memory load were changed. The results from the

working memory study demonstrated that as the perceptual load decreased with longer delay, rCBF in the ventral occipitotemporal regions also declined. The right hippocampal and parahippocampal regions (GH) showed activation only at the shorter delays and followed a linear decrease similar to the occipitotemporal regions. With the increase in memory load, increased rCBF was observed in frontal cortices, but the pattern of changes differed between the two hemispheres. The right inferior frontal cortex showed a tendency towards a decrease with increasing delay, while the left inferior, middle frontal and anterior cingulate cortices showed activation at the longest delays. The changes in the patterns of activity across delay were thought to reflect a change of strategy in the performance of the match-to-sample task. Subjects reported using a more 'perceptual' strategy by attempting to hold an image of the face at the shorter delay intervals, which may have recruited right GH and prefrontal areas. At longer delays, when the image of the face was more difficult to maintain in memory, subject reports suggested a more expansive strategy of encoding features of the face, which presumably required more left frontal involvement (Haxby *et al.*, 1995).

One simple question that comes from the working memory study is whether the changes in activity reflect differential activation of the same functional network that underlies normal face recognition, or if there are new areas recruited with the increasing memory load. It has been postulated that brain operations are the result of interactions among parts of the nervous system (e.g., Mountcastle, 1979), and so it is likely that the participation of any particular area in these interactions depends on the behavioral requirements of the task (John and Schwartz, 1978; McIntosh and Gonzalez-Lima, 1994). We have previously shown that the patterns of activity associated with simple perceptual matching of faces in humans may result from the interactions in a network involving ventral cortical areas and extending into the prefrontal cortex (McIntosh *et al.*, 1994). The activation pattern observed in the face working memory study may reflect interactions within this same network, but given the involvement of left frontal and cingulate areas and right GH, the network may have expanded to accommodate the increasing memory demands of the task. The purpose of the present paper is to determine how this basic perceptual network is changed with the additional memory load.

A number of researchers have specifically examined neural interactions at a variety of spatial and temporal levels. All of these methods use the covariances of brain activity either across space or time (or both) as indices of neural interactions (Horwitz, 1989). These covariances have also been called 'functional connectivity', which was originally developed in reference to temporal interactions among single cells (Gerstein *et al.*, 1978; Aertsen, *et al.*, 1987; Singer, 1993) and has more recently been extended to brain imaging (Friston, 1994). A

difficulty with functional connectivity, however, is that the interregional covariances can come about either through direct interactions between regions, indirect interactions, or because of some common influences. An attempt to tease apart these possible outcomes was the impetus for the application of structural equation modeling to brain imaging data (McIntosh and Gonzalez-Lima, 1991, 1992b, 1994). Structural equation modeling allows for the combination of the interregional covariances of activity, and the neuroanatomy that connects the regions, to provide indices of whether covariances are a reflection of direct or indirect neural interactions. Covariances are decomposed in the context of the anatomical network to provide numerical weights, or path coefficients, to each anatomic link. Because these models combine an anatomic model and functional connections, a complete neural structural equation model is called a 'functional model'. The functional models are most closely related to the notion of 'effective connectivity' (Aertsens *et al.*, 1989) since direct and mutual influences can be partly accounted for by using the anatomical constraints. Structural equation modeling has been successfully applied to rat brain imaging studies of auditory classical conditioning (see review by Gonzalez-Lima and McIntosh, 1994), and most recently to human PET studies of visual perception in normal subjects (McIntosh *et al.*, 1994), Parkinson's disease patients (Grafton *et al.*, 1994), and aged and Alzheimer's subjects (Horwitz *et al.*, 1995a). Here, we examine the functional models for working memory of faces.

Materials and Methods

The methodological and theoretical details of our application of structural equation modeling to analyze neural interactions have been described in detail previously (McIntosh *et al.*, 1994; McIntosh and Gonzalez-Lima, 1994) and are summarized here. Brain regions to be used in the models are selected based on univariate analysis of changes in mean rCBF, multivariate analyses, and theoretical guidance. The anatomic connectivity between selected brain regions is derived from the literature on primate neuroanatomy and each connection is assigned a numeric weight. These weights, or path coefficients, are derived through a process of iterative data-fitting to the observed pattern of interregional covariances of activity. The covariances are usually computed within a condition and across subjects. Path coefficients represent the proportion the activity in one area as determined by the activity of other areas that project to it. Since they are based on functional activity measured across subjects, they reflect what could be thought of as an average functional influence within a given task. Furthermore, these path coefficients can be statistically compared between conditions to see if there is a significant change in these functional influences using the approach outlined below.

An important distinction needs to be drawn between neural structural equation modeling and analysis of changes in rCBF between tasks. Since the covariance patterns used in models are based on within-task relations, the functional models represent interactions that occurred during that task. Interactions in one task may differ from those in another, and it is often (though not always) the case that these changes map onto the differences in local activity. The functional models thus allow for the determination of how differences in mean activity are brought about by differences in the interactions in neural systems.

PET Data

The data used for the network analysis were obtained from 12 young subjects (10 males and 2 females, mean age 25 years). Subjects gave written informed consent before participation in the study. The experiment used a delayed match-to-sample task with five intervals between the presentation of the sample face and the two choice faces: 1, 6, 11, 16, and 21 s. One scan was done at each delay interval. Subjects indicated which of the two choice faces corresponded to the sample face by pressing a button with the thumb on the side corresponding to the

correct choice. Three additional scans were made—one in a simultaneous match-to-sample task similar to the one used in previous studies (perceptual matching: Haxby *et al.*, 1991, 1994a), and two scans of a sensorimotor control identical to the control task used by Haxby *et al.* (1994a) where subjects were presented with three identical complex visual patterns in the same configuration as the face stimuli and pressed either response button at random. The PET scans (Scanditronix PC2048-15B tomograph) were performed on each subject after a bolus injection of $H_2^{15}O$ for each scan. Scanning sessions began and ended with the sensorimotor control task, and the order of the other tasks was counterbalanced across subjects.

Reaction time and accuracy measures were obtained for the perceptual matching and all delay conditions. The accuracy of memory performance was high across all conditions (96–99% correct), but reaction time did decrease as a function of delay ($F[4,36] = 12.87$, $P < 0.001$).

Activation Analysis

Spatial registration of PET images and activation analysis were performed using the Statistical Parametric Mapping (SPM) program (version 4; Friston *et al.*, 1989, 1991a, 1991b). Comparisons were made for all conditions relative to the average of the two sensorimotor control scans, and each delay condition was compared to the perceptual matching task. The complete results have been presented elsewhere (Haxby *et al.*, 1995). For the present work, trend analysis of linear and quadratic changes in rCBF across delay was performed. A probability level of $P < 0.001$ was adopted for the trend analysis.

The SPM activation analysis gives a limited set of information about the areas that are important in a given experiment. Since it is a univariate technique, each statistical test is performed independent of the others; this reduces sensitivity in a data set where the dependent measures are related to one another (Harris, 1975), such as brain imaging data. To find additional areas, a more sensitive multivariate analysis was performed. This analysis is known as partial least squares (PLS; Bookstein *et al.*, 1990) and has been adapted to operate on the correlation between the brain images and the experimental manipulation. The method entails performing a singular value decomposition on the cross-correlations of the functional images for all subjects in all conditions with a matrix that contains weighted contrasts that code the experimental design. What results are patterns of brain regions whose activity is most related to the experimental manipulation. A full description of this method is the subject of another paper (McIntosh *et al.*, 1996).

The network analysis relies heavily on interregional correlations, and therefore spatial autocorrelations introduced by image normalization were of some concern. The severe spatial filtering that is typically done to PET images works well for analysis of regional activity changes between conditions (Friston *et al.*, 1991a), but it is detrimental for examination of regional interactions within a condition. Since the smoothing procedure adds a wide spatial autocorrelation, it would be difficult to distinguish correlations that reflect a functional link from correlations that are caused by spatial filtering. This would especially be a concern for regions that were closer together. Smoothing also reduces subject variability which will reduce error variance, but will also attenuate within-condition covariances. To minimize this potential confound, a 15 mm Gaussian filter was used instead of the 20 mm filter that is the conventional choice. Although the smaller filter increased the total error variance (20 mm filter: full image mean-squared error = 7.02; 15 mm filter: full image mean-squared error = 12), it did not affect the patterns of activation and the highest effect size was about the same for both filter levels (20 mm filter: $r^2 = 0.501$; 15 mm filter: $r^2 = 0.510$).

Structural Equation Modeling

Voxels that were identified as having a key relation to the experimental conditions using the SPM analysis and multivariate PLS analyses were selected for the structural equation models. Once the brain regions, represented by a voxel, were selected, interregional correlations of activity were computed within each condition (Horwitz *et al.*, 1995b). The interregional correlations and the anatomic models were combined to create a structural equation model using LISREL (version 8, Scientific Software Inc.). The correlations were corrected for the subject block effect, as a result of the repeated measures design, using a regression

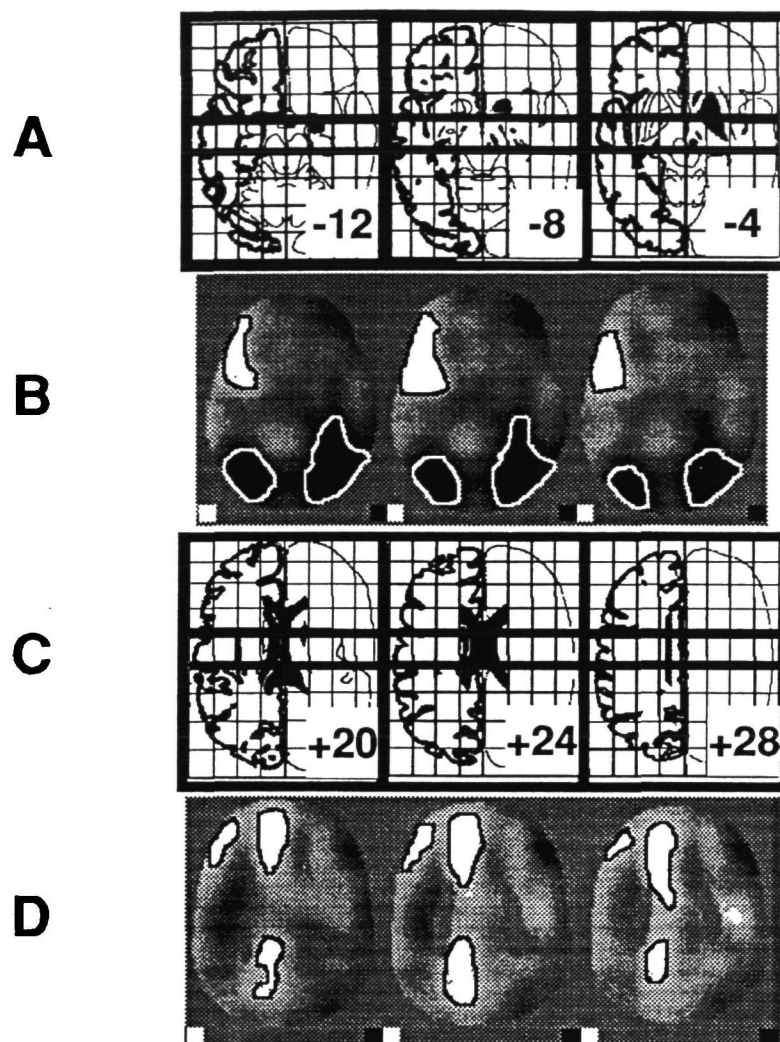


Figure 1. Results of linear trend analysis across the five delays. Rows *B* and *D* depict statistical maps of *z*-scores ($P < 0.001$). Regions highlighted in white are voxels that showed significantly increased rCBF with increased delay, while those in black are regions that showed significant decreases. Rows *A* and *C* represent atlas plates (Talairach and Tournoux, 1988) to aid in approximate locations. The number within each plate is the location of the section relative to the AC–PC line in mm. Top is anterior and left is left in all images.

procedure (Pedhazur, 1982; McIntosh and Gonzalez-Lima, 1992b). The regression procedure helps reduce the impact of individual variability across the entire experiment while maintaining the variability attributable to the experimental manipulation.

Omnibus Tests

Omnibus comparisons between conditions were done using the stacked model or multiple group approach in LISREL (Jöreskog and Sörbom, 1989; McIntosh and Gonzalez-Lima, 1992a; McIntosh *et al.*, 1994). Rather than estimating a model for each condition separately, the models were combined in a single program run. The process involved statistically comparing functional models where path coefficients were constrained to be equal between conditions (null model) with those where the coefficients were allowed to differ (alternative model). The comparison of models is done by subtracting the goodness-of-fit χ^2 value for the alternative model from the χ^2 value for the null model. If the alternative model, where the coefficients were allowed to differ between conditions, had a significantly lower χ^2 value, then the coefficients that were allowed to vary between conditions were statistically different. This χ^2_{diff} is

assessed with the degrees of freedom equal to the difference in the degrees of freedom for the alternative and null model. Comparison of models where all path coefficient estimates were constrained between conditions versus models where the estimates were unconstrained served as an omnibus test for changes in functional interactions.

Regional Tests.

For the present modeling effort, it was possible that interactions in only certain parts of the network would change significantly. We therefore distinguished those paths in the network that showed significant changes from those that did not. Given a significant omnibus test, comparisons were made by removing constraints from sections of the model one at a time across all tasks and testing whether this represented a significant change (e.g., testing to see whether influences on the occipitotemporal cortex were different). Pairwise comparisons between conditions were not performed. Portions of the network that did not significantly differ were constrained to be equal across conditions. In the tests for significance for different regions, no corrections were made for multiple comparisons so the probability levels reported for tests of individual parts

of the network should be understood to be descriptive. The inferential aspect of our application of structural equation modeling comes from the omnibus tests.

Results

Regional Activity Changes

The activation results have been presented in detail elsewhere (Haxby *et al.*, 1995) and are summarized here. Relative to the sensorimotor control task, the perceptual matching condition showed strong increased rCBF in ventral posterior cortical areas extending from occipital into occipitotemporal areas of the fusiform gyrus in both hemispheres (areas 18 and 37). This pattern has been demonstrated in previous PET studies using face matching (Haxby *et al.*, 1991, 1994a). The fusiform area showed reduced relative activation across the delay conditions, and by the 11 s delay fusiform rCBF was not significantly greater than the control task. However, even at the 21 s delay, rCBF in these fusiform areas was not significantly lower than during the control task. Regions in the inferior frontal lobes showed delay-related activations when compared to the control condition. The right frontal areas showed the highest activation at the 1 s delay, which then decreased at longer delays. The left prefrontal region showed a somewhat more complicated nonlinear pattern with initial activation at 1 and 6 s, none at 11 s, and then an increase again at 16 and 21 s.

A trend analysis examined the relation of rCBF and a linear and quadratic function across the delay intervals excluding the perceptual matching task. Linear decreases with delay were noted in the ventral occipital and right GH as reported before (Haxby *et al.*, 1995). Linear increases were most prominent in the left hemisphere and were observed mainly in prefrontal, anterior, and posterior cingulate cortices (Fig. 1). This trend was driven by the 21 s delay condition since reanalysis eliminating the 21 s delay yielded no regions showing a significant linear increase across delay. No regions showed a significant quadratic trend across delay.

The PLS analysis revealed essentially the same pattern as the linear trend analysis, but with some additional areas. This included the right inferior and middle prefrontal cortices and the right anterior and posterior cingulate cortices. The location of areas ultimately selected for the structural equation models are presented in Table 1. For most areas, equivalent locations were selected in both hemispheres. Differences in the voxel locations in the frontal cortex were suggested by the SPM and PLS analysis and may reflect asymmetries in the functional organization of the two hemispheres.

Structural Equation Models

Model Construction

To limit the complexity of the structural equation models, we averaged the data from the 1 and 6 s delay into a short-delay condition, and the 11 and 16 s delay into an intermediate-delay condition. The grouping of conditions was based on the patterns of regional means obtained from the linear trend analysis (Haxby *et al.*, 1995). Four conditions were analyzed using structural equation modeling: perceptual matching, short-delay (1 + 6 s), intermediate-delay (11 + 16 s), and long-delay (21 s) conditions.

The anatomical model is depicted in Figure 2. The connections between these areas were based on the neuroanatomy in nonhuman primates (Petrides and Pandya, 1988; Ungerleider *et al.*, 1989; Pandya and Yeterian, 1990; Felleman and Van Essen, 1991; Knierim, and Van Essen, 1992; Distler, *et al.*, 1993; Van

Table 1

Location of representative voxels used in the network analysis. Gyral locations are given using the coordinate system of Talairach and Tournoux (1988)

Brodman area	Gyrus	x	y	z
17	Cuneus	-15	-70	4
17	Cuneus	15	-70	4
19d	Cuneus	-30	-78	20
19d	Cuneus	30	-78	20
18v	Fusiform	-30	-84	-4
18v	Fusiform	28	-84	0
37	Fusiform	-34	-44	-8
37	Fusiform	34	-44	-8
21/20	Inferior temporal	-53	-35	-12
21/20	Inferior temporal	53	-35	-12
47	Inferior frontal	-35	22	-12
47	Inferior frontal	35	22	-12
10	Inferior frontal	-30	50	8
10	Inferior frontal	34	40	-4
45/46	Middle frontal	-45	24	12
45/46	Middle frontal	41	25	20
23	Cingulate	-5	-55	20
23	Cingulate	5	-52	32
24	Cingulate	-8	32	20
24	Cingulate	5	20	32
—	Hippocampal	-28	-32	-4
—	Hippocampal	28	-32	-4

Hoesen *et al.*, 1993). To construct the functional model, we assumed homologies between Brodmann areas 17/18 and V1/V2; areas 18v and V4v; areas 19d and dorsal V4; areas 37 and TEO; and areas 21 and TE. The frontal lobe connections were determined assuming the dorsal/ventral, anterior/posterior connection patterns demonstrated in monkeys (Pandya and Yeterian, 1990; Petrides and Pandya, 1994) would be equivalent in humans. It needs to be emphasized that these anatomic designations should be regarded as tentative until they can be confirmed experimentally.

For clarity of presentation, the anatomical model was divided into three networks. The first (Fig. 2a) was the visual cortical network. It was a modification of the one used in our initial analysis comparing object and spatial vision (McIntosh *et al.*, 1994). The present network has additional paths from area 37 directly to the inferior frontal lobe, more feedback paths and reciprocal connections, and a path from ventral area 18 to anterior temporal area 21 (Distler *et al.*, 1993). Parietal area 7 was not part of the present model. The second, a corticolimbic network (Fig. 2b,c), involved the connections between these cortical visual areas and limbic regions: the anterior and posterior cingulate cortices (areas 24 and 23) and the hippocampal gyrus (GH). The third network, shown in Figure 4d, represented the connections between homologous areas of the left and right hemisphere. We considered only homologous connections in order to simplify the model. Unlike our previous analysis (McIntosh *et al.*, 1994), there were no strong indications of heterogeneous contralateral influences, and hence the interhemispheric network seemed adequately to represent this data set.

Functional models were constructed as follows: (i) the path coefficients for the feedforward connections starting from areas 17 and 18, through to the frontal and limbic areas were tested within each hemisphere; (ii) the estimates from this analysis were fixed and the effects through the feedback connections from frontal areas were compared between conditions, again within hemisphere; (iii) the estimates from analysis (ii) were

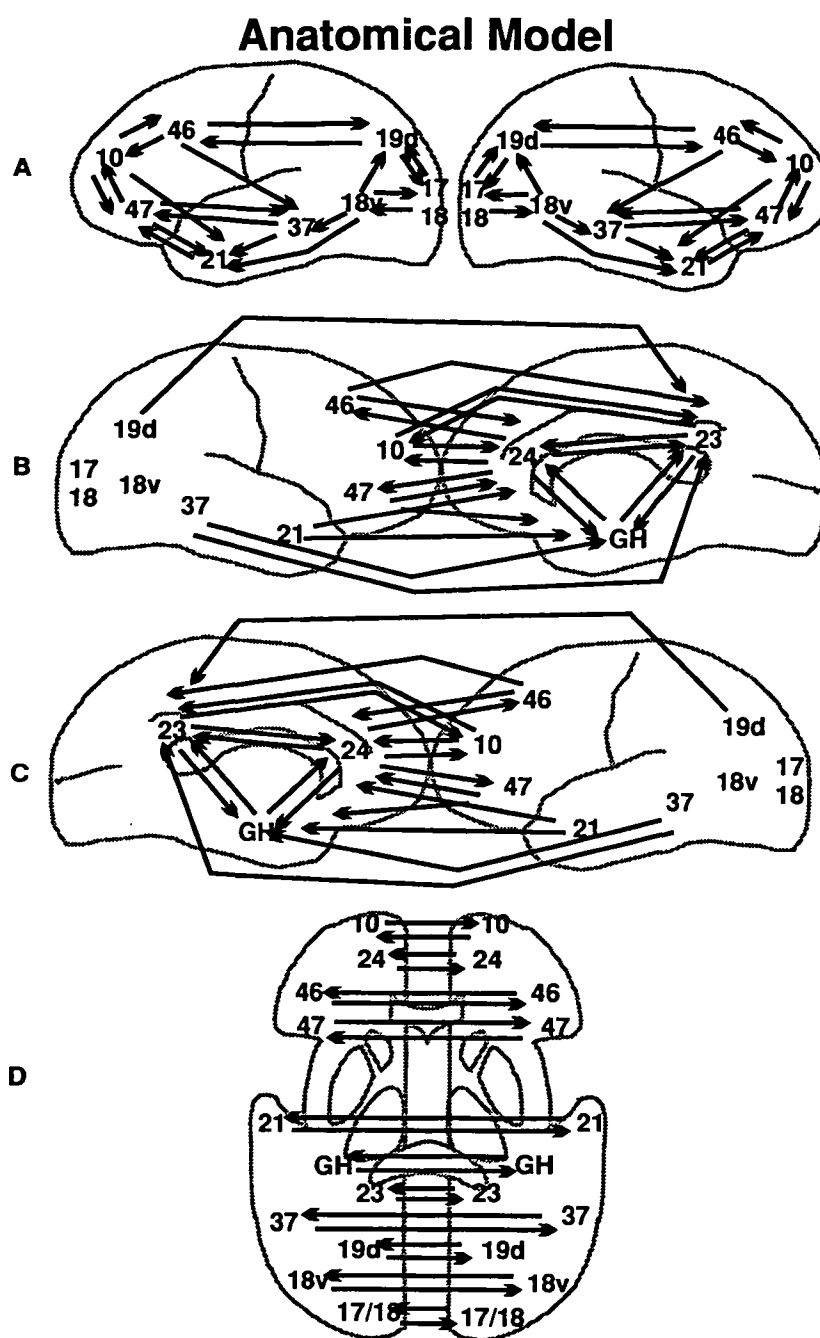


Figure 2. Anatomical model for the network analysis. Arrows represent the anatomic connections considered and were obtained from primate neuroanatomy studies. (A) The cortical visual model in the left and right hemispheres. (B,C) The corticolimbic models for the right and left hemisphere, respectively. (D) The interhemispheric model. It should be noted that the locations of the areas on the brain schematic are not accurate and are placed to maintain the clarity of the figure. For the exact location of these areas, the reader is referred to Table 1.

fixed and the interhemispheric network was tested. To ensure that the solutions were not exceedingly influenced by the order of analysis, steps (i) and (ii) were reversed and the results compared. The path coefficients and significance test outcomes were virtually identical regardless of the order of the analysis, and thus we are confident that, within the constraints of the modeling technique, the final solution is unique. This strategy has been used before when the number of total path coefficients

for the full model were in excess of the total number of correlations (the total number of paths for both hemispheres and interhemispheric connections across all conditions = 262; total number of areas (M) = 2; total number of correlations = $(M^2M - 1)/2 = 231$) (McIntosh and Gonzalez-Lima, 1992a).

Omnibus Statistical Tests

The omnibus statistical comparisons suggested that there were

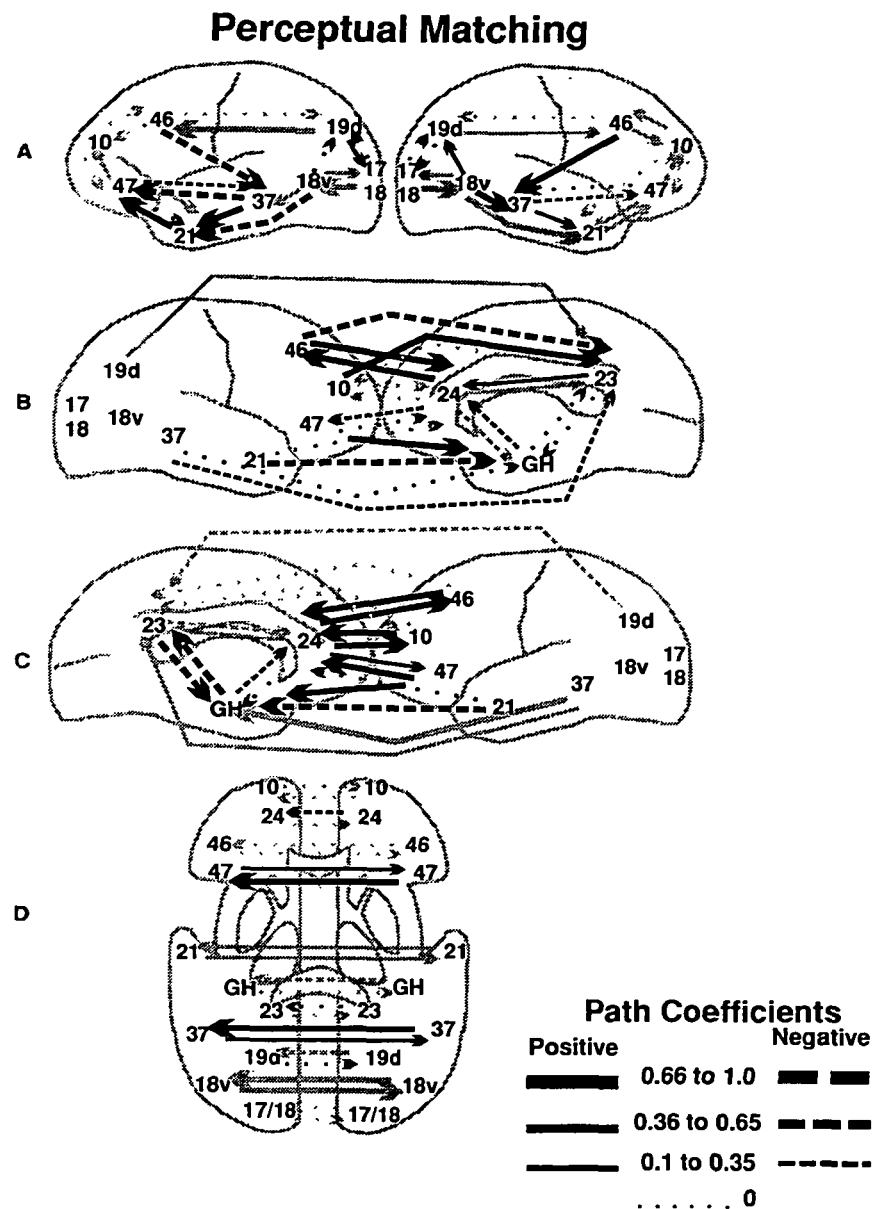


Figure 3. Functional model for perceptual matching. Magnitude of the direct effect is proportional to arrow width for each path. Values for the width gradient for this and all subsequent figures are given in the legend at the bottom of the figure. Positive path coefficients are shown as solid arrows, whereas negative ones are shown as segmented arrows. Arrows colored black represent path coefficients that significantly differed across conditions, while those in gray did not significantly change.

significant task-related differences in all networks. In general, feedforward effects in the right hemisphere cortical visual network interactions were reduced among ventrally located areas across delay, with an increase in corticolimbic interactions (right hemisphere feedforward test: $\chi^2_{\text{diff}}(66) = 112.48$; $P < 0.001$). A similar pattern of reductions was observed in the left hemisphere cortical visual network, but with a more complicated change in corticolimbic interactions (left hemisphere feedforward test: $\chi^2_{\text{diff}}(66) = 181.69$; $P < 0.001$). Feedback effects also differed, with the right hemisphere showing the most prominent changes at shorter delays [right hemisphere feedback test: $\chi^2_{\text{diff}}(57) = 124.13$; $P < 0.001$], while in the left hemisphere the dominant shift was at the longest delay [left hemisphere feedback test: $\chi^2_{\text{diff}}(57) = 143.05$; $P < 0.001$]. Of the three

networks tested, the interhemispheric models showed the weakest changes [$\chi^2_{\text{diff}}(66) = 88.36$; $P < 0.05$], with differences involving mainly occipitotemporal area 37 and frontal area 47. Below we present the functional models for each of the four conditions, highlighting the differences. It should be understood that these specific differences were significant at $P < 0.05$ without any correction for multiple comparisons. In most cases the differences were highly significant ($P < 0.001$), so adopting a more conservative criterion would not alter these results.

Perceptual Matching Network

Figure 3 presents the functional model for the perceptual matching task. The cortical visual network in the right hemisphere (Fig. 3a) showed a pattern similar to the one we

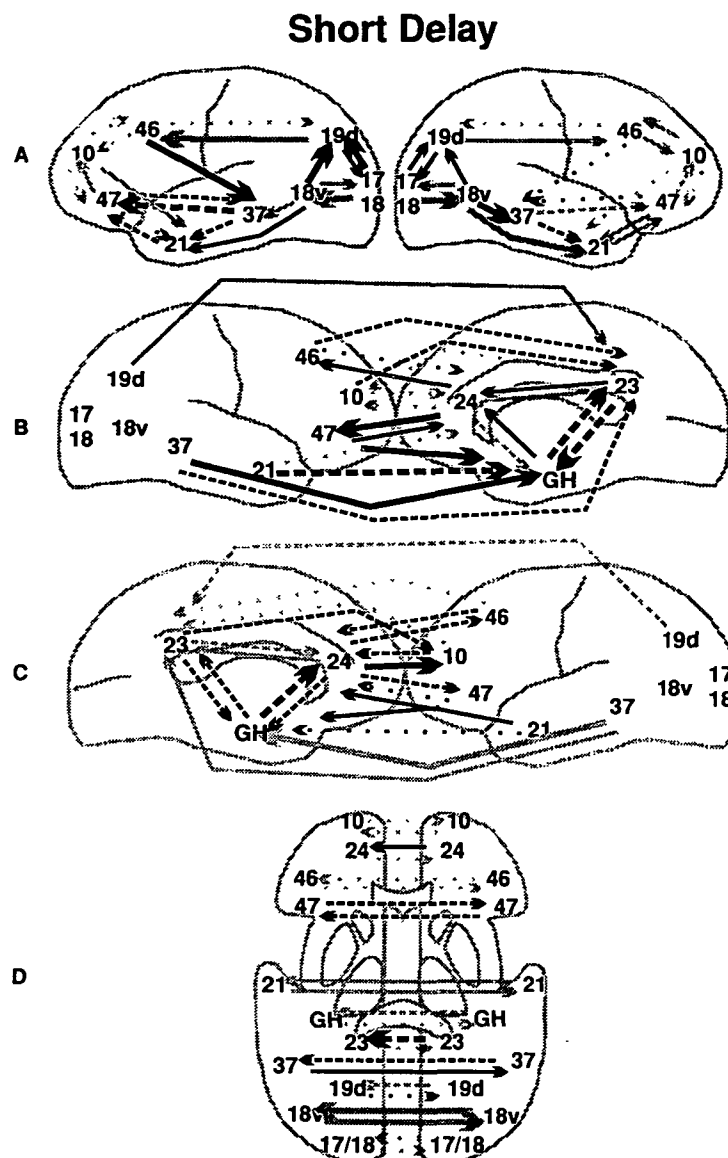


Figure 4. Functional model for the short delay condition (average of 1 and 6 s delay scans). Compared to perceptual matching, some differences of interest were in paths from area 37 to area 21 (A), area 37 to GH, and stronger inferior frontal paths (B).

previously reported for face matching (McIntosh *et al.*, 1994). There were strong interactions extending from the striate cortex along a ventral path through area 18v to areas 37 and 21, and terminating in inferior frontal area 47. The path from striate to dorsal extrastriate cortex was relatively weak, suggesting that most interactions were along the ventral cortical stream. The left hemisphere showed a pattern similar to that of the right hemisphere, but with more negative path coefficients. This left hemisphere pattern has been reported in our previous study (McIntosh *et al.*, 1994).

Corticolimbic interactions in the right hemisphere were dominated by cingulate-frontal paths while paths to GH were mainly near zero or negative (Fig. 3b). The left corticolimbic model showed similar strong cingulate-frontal interactions but also had stronger interactions involving GH (Fig. 3c). Finally, interhemispheric interactions, shown in Figure 3d, were strongest for ventral occipital and occipitotemporal cortices,

with a slight right hemisphere bias for the occipitotemporal interactions. Interactions between left and right frontal area 47 were similar to area 37 with a slight right hemisphere bias.

Delay Networks

The functional models for the delay conditions are presented sequentially in Figures 4–6. The main trends of interest were a decrease in the interactions along the ventral stream in the right hemisphere, more corticolimbic interactions in the short and intermediate delays, and more frontal involvement in the long delay. Below, we highlight some of these changes.

Short Delay

The cortical visual network in the short-delay condition (Fig. 4a) showed two major differences compared to perceptual matching (Fig. 3a). First, the dorsal interactions between area 17/18 and area 19d increased in both hemispheres, while the

Intermediate Delay

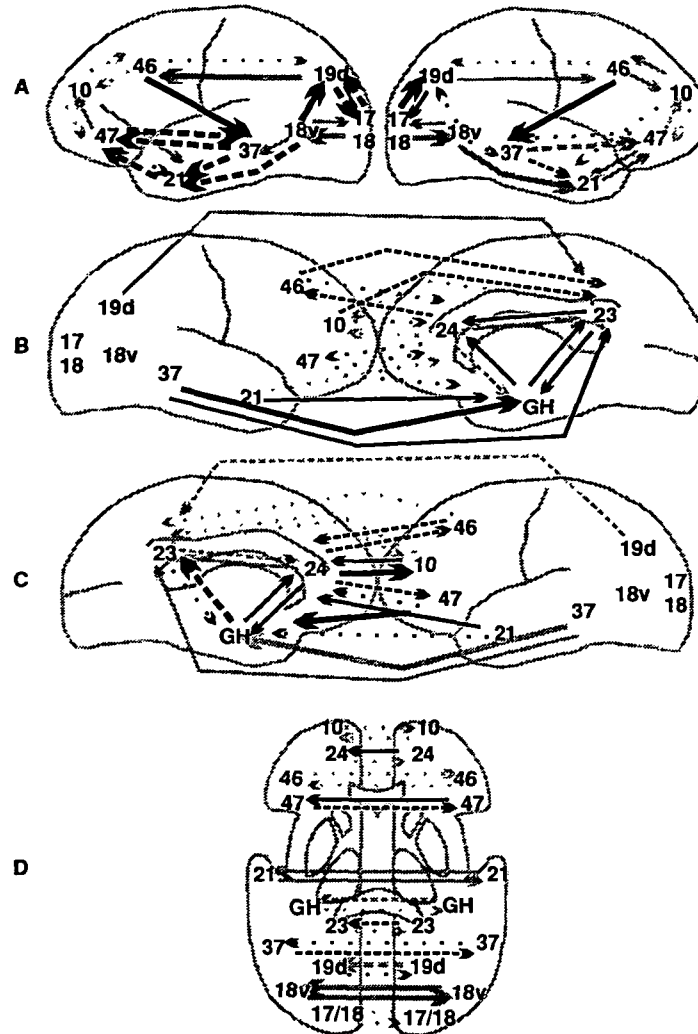


Figure 5. Functional model for the intermediate delay condition (average of 11 and 16 s delay scans). Interactions in ventral visual paths further reduced (A) as were inferior frontocingulate paths (B).

influence from area 37 to area 21 had weaker negative coefficients in both hemispheres. Feedback effects from area 46 were reduced in the right hemisphere, and in the left, the feedback reversed sign and was positive. Compared with perceptual matching (Fig. 3*b*), the right corticolimbic network (Fig. 4*b*) shows a general reduction of interactions of middle frontal areas 46 and 10 and posterior and anterior cingulate cortices. A similar pattern was observed in the left hemisphere (Fig. 4*c*). The decrease in middle prefrontal influences was accompanied by increased interactions between the right inferior frontal and the anterior cingulate cortex. Additional changes were an increase in the influence of area 37 on GH and from GH to the anterior cingulate. With these changes, a small positive loop developed involving frontal area 47, anterior cingulate area 24, and GH. The SPM activation analysis suggested that increases in right frontal and GH rCBF was greatest at short delays, which may reflect the loop enhanced effects within this trinodal circuit. The interaction between GH and the posterior

cingulate was characterized by a strong negative loop. The interhemispheric network (Fig. 4*d*) showed a general decrease in the interactions between right and left areas 37 and between right and left areas 47, with some additional sign changes. Finally, cingulate cortex area 23 had an increased coefficient going from right to left, and area 24 showed a sign change to a positive coefficient.

The general feature of the short-delay network, compared to matching, was predominantly increased interactions among the right hemisphere occipitotemporal cortex, inferior frontal and GH, and reduced interactions in both hemispheres between the middle frontal and cingulate cortices, and among the occipitotemporal and temporal regions.

Intermediate Delay

Patterns of interactions similar to those in the short-delay network appeared in the functional model for the intermediate-delay condition (Fig. 5). The influence of the ventral visual

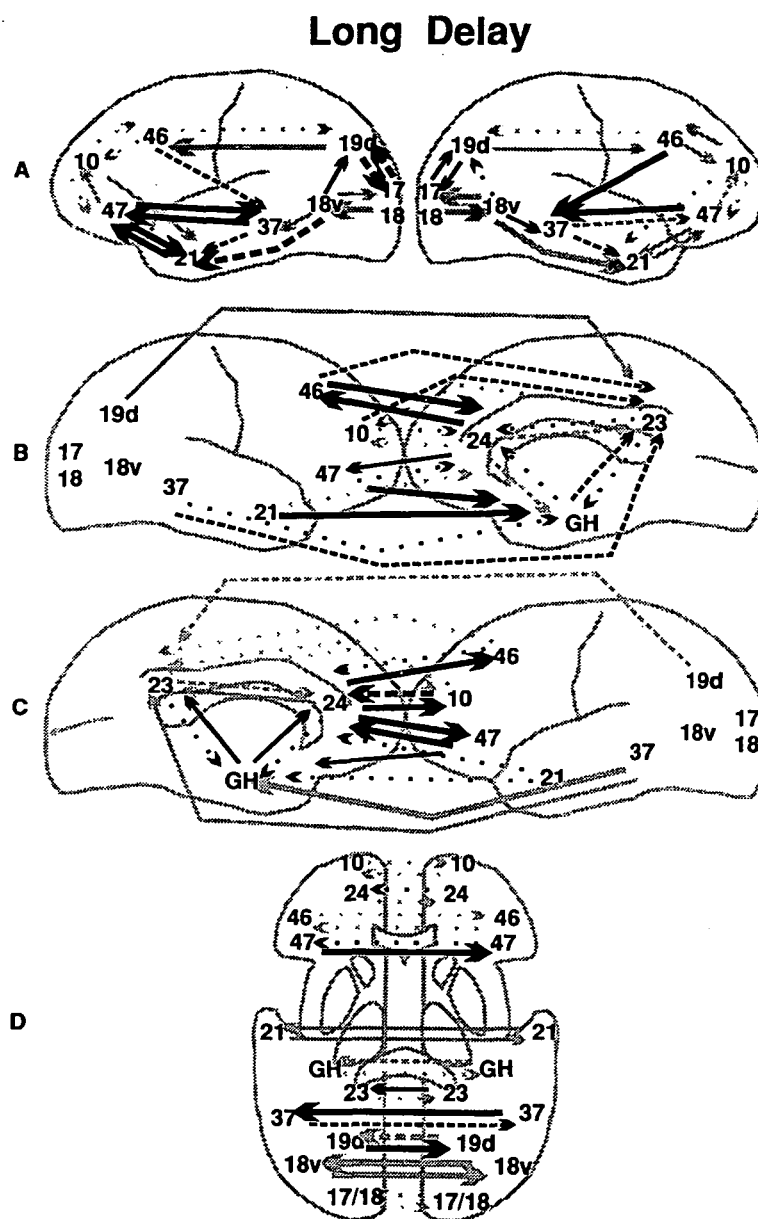


Figure 6. Functional model for the long-delay condition. Frontal feedback from area 47 to areas 37 and 21 (A) were one of the most prominent features of this network.

stream in the right hemisphere, and particularly area 18v, was further reduced both in the path to area 37 and to area 19d (Fig. 5a). Frontal feedback from area 46 returned to the pattern observed for perceptual matching. Strong positive interactions between areas 37 and 21 with GH and the posterior cingulate were observed in the right corticolimbic network (Fig. 5b). Furthermore, GH and the posterior cingulate showed a positive loop, changing from the negative loop observed in the short-delay network. The loop for area 24 to area 47 to GH observed in the short-delay network (Fig. 4b) was zero in the intermediate-delay network. Compared with the short-delay model, there were stronger left frontocingulate and hippocampocingulate interactions (Fig. 5c) involving both areas 10 and 47. Interhemispheric interactions for area 37 were reduced and there was a negative loop between left and right area 47.

The intermediate-delay network could therefore be characterized as showing less right inferior frontal involvement,

compared to the short-delay network, but still maintaining the right corticolimbic interactions with a positive loop between the posterior cingulate and GH. The intermediate-delay model also showed some increased left frontolimbic interactions relative to the short-delay model.

Long Delay

Substantial network changes, compared to other conditions, were observed in the long-delay functional model (Fig. 6). The main differences were in the feedback from the frontal lobe regions to the ventral cortical visual stream, and reduced right corticolimbic involvement compared to the other delay models. Interestingly, the right ventral cortical visual stream showed a pattern that was more similar to the short, rather than intermediate, delay (cf. Figs 4a and 6a). The unique feature of the long-delay model was the addition of strong frontal feedback from area 47. This increase of frontal feedback was also observed

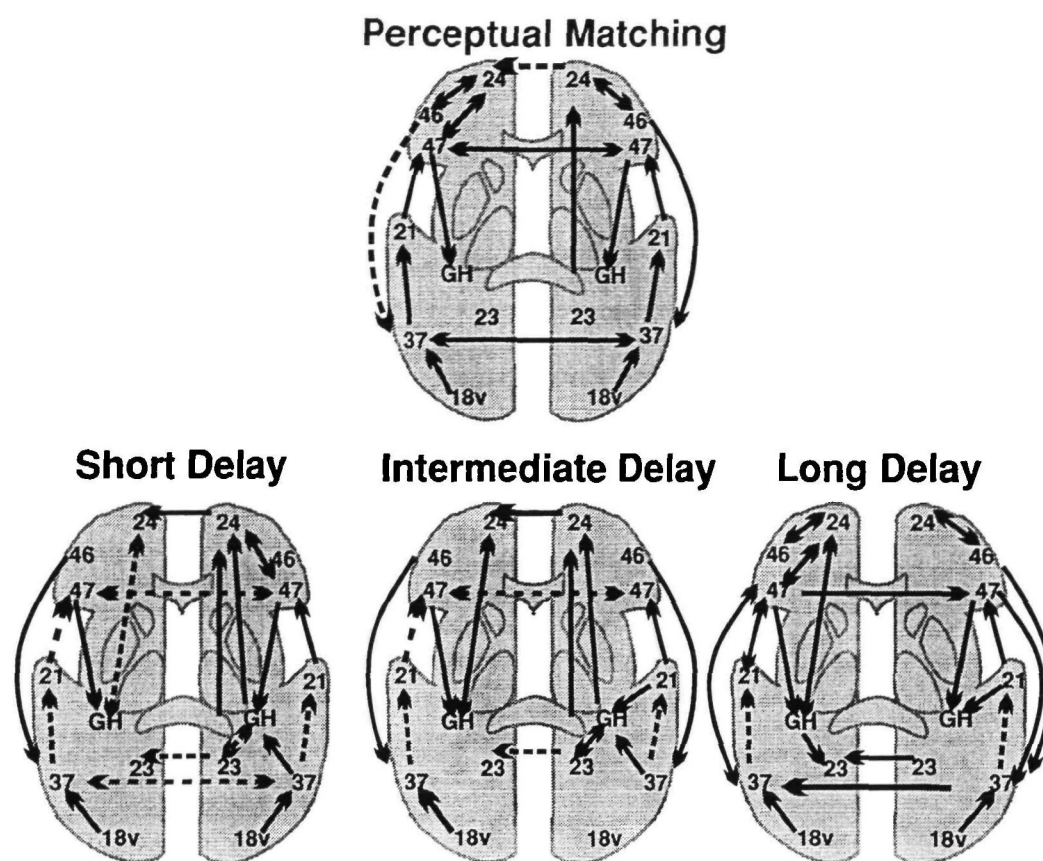


Figure 7. Summary diagram representing some of the dominant changes in functional interactions. Interactions are depicted on a horizontal schematic. To maintain clarity, the locations of these areas are approximate and the reader is referred to Table 1 for their exact location. Positive path coefficients are shown as solid arrows, whereas negative ones are shown as segmented arrows. Two-headed arrows represent reciprocal functional interactions.

in the left hemisphere involving area 47 and areas 21 and 37. In this case, there were strong positive loops between areas 47 and 21, and 47 and 37. Recall that, in the linear trend analysis, the left prefrontal and temporal areas showed the strongest increase in rCBF across delay, and that it was due mainly to their relative activation at the 21 s delay. The positive loops between these areas would amplify effects transmitted between the areas and probably underlies the observed activation pattern.

Right corticolimbic interactions in the long-delay model showed patterns most similar to those observed during perceptual matching (cf. Figs 3*b,c* and 6*b,c*). The path from area 37 to GH reduced to zero in the right hemisphere while the relations of middle prefrontal area 46 and anterior cingulate area 24 increased, compared to the short- and intermediate-delay models. The left hemisphere corticolimbic network also closely resembled the small positive loop composed of areas 24, 47 and GH in the short-delay, right-hemisphere model. Perhaps this circuit subserved similar operations in the long-delay network as those performed by the right hemisphere during the short delay.

The interhemispheric network for long delay showed a division between posterior and anterior interactions. Area 37 and cingulate area 23 showed strong right to left influences, while dorsal area 19 showed the reverse pattern with stronger left to right influences. Anteriorly, area 47 showed stronger left to right influences.

To summarize, prefrontal lobe effects seemed to play a stronger role in the long-delay model compared to the other

functional models. Right corticolimbic interactions were essentially zero, while left corticolimbic interactions increased. Frontal effects on occipitotemporal and temporal areas were especially strong in the long-delay model. This feedback, along with the changes in interhemispheric interactions, resulted in an interesting interhemispheric circuit involving prefrontal area 47 and posterior cortical area 37.

Model Summary

The diagrams in Figure 7 summarize what we feel are primary changes in the interactions across the three delay intervals. In the perceptual matching network, the dominant interactions were in the ventral cortical visual stream, extending into inferior frontal area 47 and GH bilaterally. Frontocingulate interactions were also strong in both hemispheres. Interhemispheric interactions showed a slight right hemisphere bias but were essentially equal for areas 37 and 47. In the short-delay network, there was a sign change in the path from area 37 to temporal area 21 in both hemispheres, and in the right hemisphere the interactions shifted to the GH. This shift was accompanied by a general increase in right hippocampocingulate interactions and inferior frontal-cingulate interactions. In the intermediate-delay network, the inferior frontal-cingulate interaction decreased, but the strong interactions among area 37, GH, and anterior cingulate continued, with some additional left hemisphere involvement. In some respects, the intermediate-delay network represented a transition between the short- and long-delay

networks. The right corticolimbic participation essentially dropped out of the long-delay model, replaced by the left corticolimbic circuit, and the feedback influences of the frontal lobe regions increased bilaterally. This frontal lobe increase set up an interhemispheric circuit involving the occipitotemporal areas (area 37) and the inferior frontal regions.

Discussion

The models obtained in the present paper showed how some of the neural circuits engaged in a working memory task depended on the retention interval. This change in interactions maximized memory operation in the match-to-sample task since behavioral performance did not differ across tasks (Haxby *et al.*, 1995). During short-delay conditions, the right hemisphere corticolimbic circuits seemed most active. These circuits were involved in the intermediate delays, but additional left hemisphere corticolimbic circuits were recruited, representing a transition to the long-delay network. At the longest delay, the dominant interactions were among inferior prefrontal, cingulate and areas 37 and 21.

Network analysis of brain imaging data works on the assumption that brain operations are carried out through the interactions among neural ensembles (McIntosh and Gonzalez-Lima, 1994). The patterns of activity that are observed stem from changes in neural interactions, and, therefore, a full appreciation of brain operation can only be gained by quantifying these interactions. In the present paper, we have demonstrated, using network analysis, how the observed patterns of rCBF differences may have been mediated by changing interactions. We extended these observations by showing that the functional models extend beyond areas specifically activated in each task. By incorporating the results of the activation analysis and network analysis, a more complete appreciation for the brain operations engaged in the experiment was obtained.

As noted in the Introduction, reports from the individuals scanned indicated that they could maintain a mental image of the sample face at short delays, but that it tended to degrade over the longer delays. From this, it was felt that the strategy at shorter delays was to rely on maintenance of the iconic representation of the face, while at longer delays, an elaborative rehearsal and encoding strategy was employed that emphasized distinctive local or global features of the face (Haxby *et al.*, 1995). The corticolimbic interactions during shorter delays may therefore reflect the attempt to hold the image of the face, while the frontal-cingulate-temporal interactions may represent elaborative rehearsal and encoding. One caveat should be noted here: the logic of the design was such that there was an inverse relation between perceptual load and memory load. With the decreased perceptual load as delay increased, there would also a decrease in the number of events occurring during the scan interval. It is possible that some of the changes in rCBF, and in the interactions, reflect the decreased number of stimulus-response events. While it is unlikely that all the changes can be explained through this, such an alternative should be kept in mind when the functional models are examined.

The pattern of activations observed for these data corresponded well to the changes in the interactions among brain areas. The linear trend analysis showed a decrease in the activity of ventral posterior cortical areas (areas 18v and 37) with increasing delay. The network analysis follows this with a decline in the positive interactions in the ventral stream from area 18v, to area 37, and then to area 21. Since fewer faces were presented

with increasing delay, the decreased interactions most likely reflect reduced processing in the visual stream. The strong interactions between area 37 and GH, and GH and areas 47 and 24 during the short delay are congruent with the greater activation at shorter delays. [Interestingly, a similar pattern of activity in the GH has been obtained in 2-deoxyglucose mapping studies of working memory tasks in the rhesus monkey (Adcock *et al.*, 1992).] This circuit was weaker in the intermediate-delay network and weaker still in the long-delay network, following the linear decline in rCBF for the right GH. Linear increases in rCBF were noted in left hemisphere regions, mainly in the frontal, cingulate, and temporal cortices. The functional models showed that these areas formed a strong functional circuit in the long-delay network.

Interactions between areas 17/18 and area 19d were greater in the delay networks, and in the long-delay network, the interhemispheric effects of left area 19d on the right hemisphere were stronger than in other conditions. If part of the encoding strategy during the delay conditions was a reliance on salient local/global relations, such as eye position or size of the nose, then this could account for the increased interactions with area 19d. Also noteworthy is the observation that the influence of area 19d on the dorsal prefrontal cortex did not change across networks. The occipitofrontal connection is part of the network mediating spatial vision (McIntosh *et al.*, 1994) and would therefore not be expected to change dramatically. This attests to the specificity of structural equation modeling when applied to neural systems.

Another interesting pattern of relations was the strong frontocingulate and frontotemporal interactions during perceptual matching that diminished during short and intermediate delays, and reappeared in the long-delay network. Since the interactions were present in both functional models, it seems unlikely that it represents some memory operation. The portion of the anterior cingulate is close to the that identified by Paus *et al.* (1993) as being related to response selection (see further elaboration of this below), so it is possible that these interactions represent some aspect of the response. The anatomical relation between the 'motor' anterior cingulate and regions of the prefrontal cortex has been documented (Bates and Goldman-Rakic, 1993) and would predict strong interactions. The weaker or absent middle frontal-cingulate interactions in the short- and intermediate-delay networks may suggest that they were reduced to facilitate the strategy used to encode and hold the face in memory in these delay conditions, possibly by recruiting the anterior cingulate into a different circuit involving a more ventral part of the prefrontal lobe. Encoding strategies that rely on maintenance rehearsal are more susceptible to interference (Greene, 1987), so it is possible that the middle frontal-cingulate interactions were suppressed to minimize interference and to optimize the inferior frontal-cingulate and hippocampal interactions.

It may have been unnecessary to suppress these interactions at longer delay given the change in strategy. During the long-delay condition, it is reasonable to assume that most of the events occurring during the scan reflected rehearsal and encoding of the face rather than recognition. The pattern of cortical activation observed at the longest delay was similar to that observed in another PET experiment during encoding of new faces (Haxby *et al.*, 1994b; Grady *et al.*, 1995b). The strong frontal influences in the long-delay model may therefore reflect the more elaborate encoding strategy involved in some of the primary areas of face perception (i.e., area 37). Since there was

no effect of delay on performance, the elaborative strategy that recruits this frontotemporo-cingulate circuit was highly successful and robust. There are a number of possible reasons for the involvement of area 37 in the long-delay condition. One is that the feedback to area 37 may represent extraction of perceptual information to aid elaborative encoding and maintenance strategy. A second possibility is that involvement of area 37 reflects the matching of the test face to the features that are held in working memory. Either of these possibilities could be tested by comparing a functional model derived from an encoding task with a functional model from a retrieval task (Haxby *et al.*, 1994b; Grady *et al.*, 1995), or using methods that have finer temporal resolution, such as functional magnetic resonance imaging or evoked potentials, and focusing on covariances between frontal and occipitotemporal cortices during the delay interval.

The anterior cingulate in both hemispheres was a key region in the changing functional interactions in all delay conditions. One commonality in PET studies that have shown activity changes in the anterior cingulate is that this region appears to have some general relation in selection of the appropriate motor output in a given situation (Posner *et al.*, 1988; Pardo *et al.*, 1990). Electrophysiological studies by Gabriel and colleagues (Gabriel *et al.*, 1991; for review, see Gabriel, 1993) show that the anterior cingulate codes the significance of stimuli and rapidly changes activity in response to changes in stimulus meaning. This has led to the speculation that the anterior cingulate may play a strong role in working memory given this capacity for rapid plasticity. The results of this network analysis agree with this speculation. In the context of functional models, the anterior cingulate indeed appears to be a part of the frontal system speculated to subserve working memory operations (Goldman-Rakic, 1988).

Paus *et al.* (1993) have suggested that the portion of the anterior cingulate that is most often identified in PET studies (dorsal just prior to the genu of the corpus callosum) plays a more general role in response selection, beyond simply memory operations, and may be specifically involved when the task is new or difficult. It is reasonable to suggest that, within the delay conditions, task difficulty was also increasing and so the anterior cingulate played a more central role in coordinating responses as the difficulty of the task increased. It is also possible that the recruitment of other areas also reflects the increased demands with increasing delays, particularly with frontal systems. In a recent functional MRI study of nonspatial working memory, Cohen *et al.* (1994) also speculated that part of the reason for frontal lobe involvement in these working memory tasks may reflect increased effort or difficulty. Such a possibility could be tested empirically in tasks where difficulty or effort is manipulated without a strong memory component (Grady *et al.*, 1995a).

The prefrontal cortex is thought to play a special role in working memory (Goldman-Rakic, 1988; Fuster, 1990). However, these frontal systems also appeared to be involved during perceptual matching, especially in the left hemisphere. An argument could be made that the interactions during perceptual matching also reflect some working memory component related to task execution, but this would require further experimental validation. What the network analysis brings to this is the intriguing observation that regions may play a part in more than one functional network (e.g., anterior cingulate) and it is the interactions with other brain regions that determine what operations are being served at that time. Left

hemisphere frontocingulate interactions were present in all models. What changed between tasks was the nature of these interactions, indicated by the sign of the path coefficient, as well as some changes in magnitude.

Similar changes in covariance patterns were observed for the hippocampal region. In the right hemisphere, it was clear that when the memory load was increased in the short-delay task compared with perceptual matching, interactions between occipitotemporal and GH, and GH with cingulate cortices increased. These interactions were maintained at intermediate delay, implying that the hypothesized iconic strategy was facilitated through strong hippocampal-cingulate interactions. A PET rCBF investigation that distinguished face encoding and recognition operations showed that the right GH was activated only during encoding (Haxby *et al.*, 1994b; Grady *et al.*, 1995b). Given this, the corticolimbic interactions in the right hemisphere observed for the present work probably reflect aspects of the encoding of the face, and perhaps holding the image during the delay interval. There was a switch to more left hemisphere limbic involvement in the intermediate-delay network, which may represent a transition to the elaborative strategy that we presume to be used at the longest delay intervals. In the long-delay network, a frontocingulate-hippocampal circuit was established similar to that observed in the right hemisphere during short delay. Relatively few brain imaging studies have noted reliable changes in mean hippocampal rCBF in memory tasks (Sergent *et al.*, 1992; Haxby *et al.*, 1994b; Nenov *et al.*, 1994; Tulving *et al.*, 1994; Grady *et al.*, 1995b; Kapur *et al.*, 1995; for a discussion of this, see Fletcher *et al.*, 1995). When examined in the context of covariance relationships, part of the reason for the lack of detectable changes in average rCBF may be that the interactions of this area are always strong and what changes with memory load are the nature of these interactions. Research on the functional connectivity of neurons within the hippocampus has shown memory-related changes in the patterns of interactions (Wilson and McNaughton, 1994). Similar changes in interactions may underlie the relation of the hippocampus with other brain areas. This speculation could easily be tested across the many different PET studies of memory.

Concluding Remarks

The conclusions drawn from the original report of this study (Haxby *et al.*, 1995) are not incongruent with those drawn from the analysis of functional networks. Right prefrontal involvement at shorter delay intervals is associated with an icon-like representation of the face, while the left prefrontal involvement at longer delays is associated with a face representation resulting from a more elaborate encoding and rehearsal strategy. The network analysis adds to the original conclusions by indicating that interactions mediating the different encoding and maintenance strategies were more extensive than revealed by the analysis of regional means. The maintenance rehearsal strategy used in shorter delays appears to have been subserved by a network involving area 37, the hippocampal region, and the cingulate and inferior prefrontal cortices all in the right hemisphere. As the delay interval increased, and the maintenance strategy proved less effective, a more elaborative rehearsal strategy was employed that involved much more extensive interactions. A network involving strong prefrontal feedback in both hemispheres to area 37, as well as strong interhemispheric interactions, appeared to underlie this strategy. We have thus demonstrated that the functional

networks mediating working memory for faces appear to change depending on the memory load. While there are some common regions that are involved in all delay intervals, the role of these regions was not constant for all conditions. This finding is similar to other applications of structural equation modeling to brain imaging studies, and emphasizes that both changes in regional activity and the interactions are important functional operations.

The impetus for the characterization of neural functional operations, using interregional covariances, arises from the supposition that brain function is the result of changes in the covariances among regions of the nervous system. The importance of covariance of neural activity on many different spatial and temporal levels has been recognized by other researchers dealing with electrophysiological (Gerstein *et al.*, 1978; Aertsen *et al.*, 1989; Bressler *et al.*, 1993; Gevins and Cutillo, 1993) and brain imaging data (Horwitz, 1989; Friston, 1994), and implied by some theories of brain function (Edelman, 1979; Mountcastle, 1979). The combined use of functional neuroimaging with structural equation modeling in this study provides further empirical validation that changes in interregional covariance underlie the functional neuroanatomy of the brain.

Notes

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