Structural Equation Modeling and Its Application to Network Analysis in Functional Brain Imaging

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Abstract: The analysis of brain imaging data has recently focused on the examination of the covariances of activity among neural regions during different behaviors. We present some of the theoretical and technical issues surrounding one of these covariance-based methods: structural equation modeling. In structural equation modeling, connections between brain areas are based on known neuroanatomy, and the interregional covariances of activity are used to calculate path coefficients representing the magnitude of the influence of each directional path. The logic behind the use of structural equation modeling stems from the suggestion that brain function is the result of changes in the covariances of activity among neural elements. The technical foundations for neural structural equation models are presented, emphasizing the ability to make inferential comparisons to evaluate the experimental changes in path coefficients. Simulated data sets were used to test the effects of omitted regions and omitted connections. The results suggested that structural modeling algorithms can give hints as to possible external influences and missing paths, but that the final decision as to model modifications requires the guidance of the researcher. The utility of anatomically based models to distinguish between the direct effect of one region on another, and indirect effects mediated through intervening regions, is demonstrated in an empirical data set that examined the effects of darkness or patterned light on the metabolic activity in the rat visual system. The anatomical framework for the structural equation models revealed that the total impact of ascending thalamocortical influences was modified by corticocortical interactions. Extensions of structural equation modeling to human brain imaging experiments are presented. We conclude by suggesting that neural covariances may be a more accurate way to examine the dynamic functional organization of the central nervous system.

Key words: path analysis, neural pathway, neural systems, visual system, rat, human, 2-deoxyglucose, regional cerebral blood flow, positron emission tomography

INTRODUCTION

Functional neuroimaging techniques have provided a unique opportunity to examine simultaneously the activity within the entire brain of a single subject. New data analysis methods have also taken advantage of this opportunity. Image averaging across subjects, subtraction methods, statistical parametric maps [Fox et al., 1988; Friston et al., 1991], and particle or cluster analysis [Poline and Mazoyer, 1993; Roland et al., 1993] represent a few of the innovative methods for increasing the sensitivity of data analyses to locate changes in regional metabolic activity. The use of more sensitive analytic techniques is particularly im-

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portant for mapping studies of behavioral functions when metabolic changes are subtle.

Recent trends in the analysis of brain imaging data have focused on the interactions among brain regions [Friston et al., 1993a,b; Horwitz et al., 1992a,b; Goldenberg et al., 1989; Lagrèze, et al., 1993; McIntosh and Gonzalez-Lima, 1991; Moeller and Strother, 1991]. They all extract information about neural interactions through decomposition of interregional covariances of activity. One of these methods is structural equation modeling or path analysis. It has proved to be a powerful way to combine functional neuroimaging data with anatomical circuitry to determine the functional neuroanatomy underlying a particular task. We have applied structural equation modeling to autoradiographic 2-deoxyglucose (2-DG) and fluorodeoxyglucose (FDG) data obtained from rats in different behavioral paradigms [McIntosh and Gonzalez-Lima, 1991, 1992a, 1993, 1994]. More recently, structural equation modeling has been applied to human brain imaging data obtained from positron emission tomographic (PET) measures of regional cerebral blood flow (rCBF) [McIntosh et al., 1994a,b]. The goal of this paper is to explain the application of structural equation modeling to functional brain imaging data. The theoretical and technical issues of structural equation modeling in its general use have been extensively researched [e.g., Bentler, 1985; Berry, 1985; Bollen, 1989; Boomsma, 1985; Freedman, 1987; Hayduk, 1987; Jöreskog, 1973; Jöreskog and Sörbom, 1979, 1989; Loehlin, 1987], so the focus here is on issues related to the application of structural equation modeling to neural data.

Since interregional covariances of activity are the basis of all network analytic techniques, we will begin by suggesting that the fundamental organization of the central nervous system makes it ideal for covariance analysis. From that we will present the basic theory underlying structural equation modeling as applied to the central nervous system. Our application of structural equation modeling to neural systems makes use of the neuroanatomy to define a network and to express the interactions among brain regions. Since the method is a modeling technique, it often requires simplifying assumptions about the anatomy that includes leaving out minor connections and, on occasion, brain areas. The effects of an incomplete anatomical model, and the omission of regions that have an impact on other regions included in the model will be examined using simulated data sets. The utility of anatomically based models in the theoretical interpretation of a neural structural equation model will then be presented, followed by recent extensions of structural equation modeling to human brain imaging experiments. A contrast of data-driven versus theory-driven approaches to modeling is then discussed. We conclude this paper by suggesting that covariance-based methods, which explain brain operations in the context of functional interactions, will provide a more realistic picture of the relationship of brain activity and behavior.

WHY STUDY COVARIANCES?

The traditional form of data analysis in all neuroscience techniques has been to look for differences in group or condition means on the measured variable, whether behavioral (e.g., performance on a neuropsychology test) or physiological (e.g., action potentials per second, isotope incorporation). Brain imaging is no exception to this, and focusing on changes in mean regional activity has been a successful approach. For covariance-based analyses to be useful in neuroimaging, they must make a significant contribution to the understanding of the data sets beyond what could be derived from analysis of mean regional activity. Covariance relationships can span many temporal and spatial domains, from milliseconds to minutes and from single neurons to neural ensembles and brain areas. Extraordinary insights have been gained by examining covariances at fine spatial and temporal resolution, in the case of single neuron electrophysiology [Aertsen et al., 1987; Opticon and Richmond, 1987] and across short temporal intervals but larger spatial extents using evoked potentials [Gevins et al., 1985; Gevins and Cutillo, 1993]. With brain imaging and structural equation modeling, the issue is whether similar insights can be gained from examining covariances based on time-integrated activity measures of ensembles or brain regions.

Expressed in terms of neural systems, a measure of covariance represents the degree to which the activities of two regions are related to one another, or how they vary together. A high covariance between areas A and B means that if area A increases its activity, so too will B (in the case of a positive covariance). Covariances are studied in many scientific disciplines, but in neural systems, covariances of activity have a special meaning. The dependent variables (regional activity of brain areas) are anatomically connected to one another, while in other disciplines, such as social science, there may be no a priori connective relationships between dependent variables.

More formally, the central nervous system is unique in that it is composed of numerous interconnected elements ranging from single neurons to entire ensembles. These connections range from local intra-

regional connections among neurons, to interregional connections among ensembles of neurons across brain areas. Though perhaps somewhat obvious, it is worth noting that communication between neural elements (neurons or ensembles) is along these interconnections and these communications underlie brain function. It follows from this that a change in the observed activity of any element results from a change in the communication with one or more connected elements. In other words, an activity change at any central nervous system site must come about through a change in the influences of one or more afferent pathways. For peripheral sensory receptors, activity changes are the result of environmental stimulation except where central sites influence the receptors (olivocochlear bundle). Under physiological conditions, possible exceptions might be found in the diffuse central effects of non-neuronal origin (e.g., peripheral hormonal or hemodynamic changes). Since one neural element can influence the activity of, and therefore the variance of, another, the relationship between neural elements can be quantified as a covariance. Therefore, interactions between neural elements can be detected by examining the covariances of measured activity within the central nervous system.

The general organizational principles of the nervous system outlined above suggest that *brain function is the result of changes in the covariances among neural elements.* The traditional emphasis on the analysis of changes in regional activity alone is more in line with the contrasting view that brain functions are the responsibility of specialized areas [Horwitz and Sporns, 1994]. As will be demonstrated later, covariance analysis can contribute more to the understanding of brain operations since it implicitly assumes that the central nervous system is a collection of parallel functional networks rather than segregated regions. The importance of covariance of neural activity has been recognized by other researchers dealing with electrophysiological and imaging data [Aertsen et al., 1989, Ahissar et al., 1992, Gerstein et al., 1978; Horwitz et al., 1992a] and implied by some theories of brain function [Damasio, 1989; Luria, 1973; Tononi et al., 1992].

Mathematical extension

The relationship between brain areas can be described using a simple linear mathematical expression of the variance of a region as influenced by the variance of another. The equation for this is:

$$Y = \alpha + \beta_{y \cdot x} X + \psi \qquad (1)$$

where Y and X are measures of the activity in two interconnected brain regions across a sample. Since the measures are across a sample, Y and X also represent the variance in these two regions. Equation (1) also contains the Y-intercept for a line, α, and the slope of the line, $\beta_{y \cdot x}$, indicating the size of the influence of X on Y. The final term ψ is the residual representing the variance in Y that is not determined by X. This representation is simple linear regression. The value of $\beta_{y \cdot x}$ is computed directly from the covariance of Y and X, and when the measures of Y and X are standardized (transformed to z-scores), the intercept, α, becomes zero and the slope $\beta_{y \cdot x}$ would be the zero-order correlation between Y and X. Equation (1) also represents the *general linear model* and forms the foundation for almost all conventional statistical analyses from simple t-tests to canonical correlations [Harris, 1975].

A simple extension of equation (1) can represent effects of an additional area Z on the regional activity of area Y.

$$Y = \alpha + \beta_{y \cdot x} X + \beta_{y \cdot z} Z + \psi \qquad (2)$$

Equation (2) represents the effects of X and Z on Y. The β weights are the degree to which these two areas influence the variance, or activity, of Y. Because of the semi-partialling of variances sources in the computation of the β weights, the influences of Z on Y and X on Y are mathematically independent of each other [Cohen and Cohen, 1983]. Equation (2) is a multiple linear regression.

Equation (2) shows how the effects from multiple influences on regional activity can be derived from looking at covariances. The equation can be further expanded to include more regions and, if expressed as matrices, can be used to define the interconnections of an entire network. The matrix representation is the foundation for structural equation models.

$$\begin{bmatrix} X \\ Z \\ Y \end{bmatrix} = \begin{bmatrix} 0 & 0 & 0 \\ \beta_{z \cdot x} & 0 & 0 \\ \beta_{y \cdot x} & \beta_{y \cdot z} & 0 \end{bmatrix} \begin{bmatrix} X \\ Z \\ Y \end{bmatrix} + \begin{bmatrix} \psi_x \\ \psi_z \\ \psi_y \end{bmatrix} \qquad (3)$$

In equation (3), the variances of all three regions, X, Y, and Z, are represented as a vector that is determined by the weighted influence of the other regions (matrix of β weights) plus the residual influences contained in the vector ψ. The zero values in the matrix β represent connections that do not exist in the model. Equation (3) can be represented graphically, as shown in Figure 1.

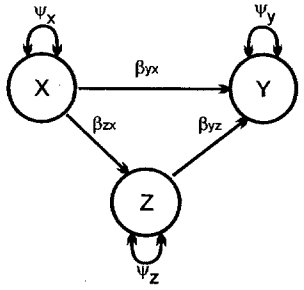


Figure 1.
Graphic representation of structural equation model from equation (1). Circles represent the measured variance from regions X, Y, and Z. Unidirectional arrows represent the path for the influences of these sources of variance on each other, the weighting of the influence given by β. Curved bi-directional arrows represent residual influences whose size is indicated by ψ.

Relationship between experimental variance and covariance

Most of the results obtained from brain imaging studies have been derived from the analysis of the differences in regional activity between tasks or groups. It can easily be demonstrated that this is the same as evaluating the covariance between brain activity and experimental manipulation. Using the general linear model presented in equation (1), the activity in Y is expressed as being partly determined by an experimental manipulation A.

$$Y = \alpha + \beta_{y \cdot a} A + \psi \qquad (4)$$

In this equation, Y represents a set of measures of regional activity (variance) from two experimental conditions, and A represents a binary vector coding for an experimental or control condition (e.g., $A = 1$ for experimental condition, $A = 0$ for control condition; this is also referred to as dummy coding [Pedhazur, 1982; Cohen and Cohen, 1983]). Computation of the influence of A on Y, represented by $\beta_{y \cdot a}$, indicates whether there is a change in the activity of Y related to the two conditions, i.e., whether the mean activity of Y is different in the two conditions. This covariance analysis is identical to a simple t-test [Pedhazur, 1982].

A simple extension of equation (4) can examine experimental effects on both regional activity and interregional covariance.

$$Y = \alpha + \beta_{y \cdot x} X + \beta_{y \cdot a} A + \beta_{y \cdot xa} XA + \psi \qquad (5)$$

Equation (5) represents the effect of area X on Y, the experimental effect of A on Y, and the interaction of the impact of brain area X and the experimental effect A (XA). The interaction assesses whether the relationship between X and Y changes because of the experimental effect. The β weights represent the degree to which these three factors influence the variance, or activity, of Y. The influence of area X on Y, independent of the experimental effect, is evaluated by the testing the statistical significance of $\beta_{y \cdot x}$. The significance of experimentally related regional differences in the activity of Y, independent of the influences of region X, is assessed by evaluating the significance of $\beta_{y \cdot a}$. The significance of the slope $\beta_{y \cdot xa}$ indicates whether the influence of region X changes depending on the experimental condition, i.e., whether the covariance of X and Y changes because of the experimental manipulation.

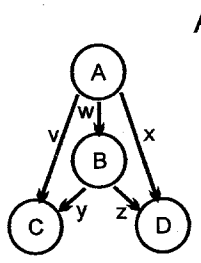
Neuroimaging can be used to assess experiment related functional changes *within* brain areas by examining average activity levels and comparing these levels across groups or tasks. In equations (4) and (5), this is represented by the evaluation of the effect of A on Y ($\beta_{y \cdot a}$). Functional changes *between* brain areas may be inferred from regional activity, but some of the functional changes may not be obvious from regional mean activity. For example, in equation 5, it is entirely possible for the term representing the experimentally induced difference in regional activity ($\beta_{y \cdot a}$) to be nonsignificant, but for the term representing the change in the relationship between X and Y due to the experimental effect ($\beta_{y \cdot xa}$) to be significant. This would be missed if the covariance of X and Y was not evaluated. Given the interconnections among neural elements and that regional activity in the central nervous system is mainly determined by afferent influences, the changes in functional relationships among brain regions can only be quantified by covariance analyses.

FOUNDATIONS FOR STRUCTURAL EQUATION MODELS OF NEURAL SYSTEMS

With the increasing interest and application of covariance-based analyses, new terminology has also been introduced. It is useful at this point to clarify some of these terms and define their relation to the terms we use to describe neural structural equation models. The term *functional connections* (*connectivity*) has been used to refer to the correlations of activity between neural elements in both electrophysiology [Aertsen et al., 1987] and brain imaging [Friston et al., 1993b]. To say that two neural elements (neurons or brain regions) have a functional connection is to say that these elements show statistically significant corre-

lated activity without reference to how that correlation is mediated. *Effective connectivity* is a logical progression from functional connectivity and can be defined as the influence or effect one neural element has on another [Aertsen et al., 1989; Friston et al., 1993b]. The term *functional network* has been applied to the pattern of covariances among evoked potential sites [Gevins and Cutillo, 1993], but could also be applied to a pattern of covariances obtained through other measures of neural activity. For our application of structural equation modeling to neural systems, we have applied the terms *anatomical* model and *functional* model [McIntosh and Gonzalez-Lima, 1993; McIntosh et al., 1994a]. The *anatomical model* simply represents the neuroanatomical connections between brain regions used in the structural equation models. The interregional correlations of activity are used to assign numerical weights to the connections in the anatomical model, leading to the functional model. A *functional model,* therefore, represents the influences of regions within the model on each other through the anatomical connections. In some respects, the functional model is close to the notion of effective connectivity since it depicts the influence of one region on another. The difference, as will be illustrated subsequently, is that the influences in the functional model are depicted as direct and indirect effects through the anatomical model. Effective connections are typically not expressed in this manner.

There are many commercially available computer packages that are specifically designed for structural equation modeling including LISREL [Jöreskog and Sörbom, 1989], EQS [Bentler, 1985] and AMOS [Arbuckle, 1992]. The algorithms used in structural equation modeling have undergone some modifications since the initial development by Wright [1920], but the procedure remains conceptually unchanged. All structural equation models are derived from covariance matrices and from a causal structure. Figure 2 illustrates the basic processes and features of structural equation models. The system, made up of four variables, has a causal structure indicated by the arrows (Fig. 2A). The regions and connections define the *anatomical model* [McIntosh and Gonzalez-Lima, 1993; McIntosh et al., 1994a]. By using this anatomical model, the correlation matrix (i.e., standardized covariances, Fig. 2B) can be decomposed to assign functional weights or *path coefficients*—given by letters *v–z*—to each of the arrows. The addition of the path coefficients defines the *functional model* [McIntosh and Gonzalez-Lima, 1993; McIntosh et al., 1994a]. The path equations (Fig. 2C) and structural equations (Fig. 2D) are mathematically equivalent, but the structural equations provide a more computationally efficient method to solve for the path coefficients as the complexity of the system increases.



B

Correlation Matrix

	A	B	C	D
A	-			
B	rAB	-		
C	rAC	rBC	-	
D	rAD	rBD	rCD	-

C

Path Equations

rAB = w
rAC = v + wy
rAD = x + wz
rBC = y + wv
rBD = z + wx
rCD = yz + vx + vwz + ywz + ywx

D

Structural Equations

A = ψA
B = wA + ψB
C = vA + yB + ψC
D = xA + zB + ψD

Figure 2.

Schematic representation of methods involved in structural equation modeling of a neural system. **A:** Path diagram of a simple network with four brain regions (*A, B, C, D*) and their anatomical connections (indicated by arrows). **B:** The information about the correlations of activities between regions is used in conjunction with the path diagram (A) to calculate the strength of influences through the connections, known as the path coefficients (*v, w, x, y, z*). **C:** Path equations show how the correlations between regions can be decomposed to solve for the path coefficients. **D:** Structural equations show the variance in activity in each region as a function of the weighted variance of other brain regions and a residual influence (indicated by ψ). These residuals are not shown in A and C for simplicity.

$$\boldsymbol{\eta} = \boldsymbol{\beta}\,\boldsymbol{\eta} + \boldsymbol{\psi} \tag{8a}$$

$$\begin{bmatrix} A \\ B \\ C \\ D \end{bmatrix} = \begin{bmatrix} 0 & 0 & 0 & 0 \\ w & 0 & 0 & 0 \\ v & y & 0 & 0 \\ x & z & 0 & 0 \end{bmatrix} \begin{bmatrix} A \\ B \\ C \\ D \end{bmatrix} + \begin{bmatrix} \psi_A \\ \psi_B \\ \psi_C \\ \psi_D \end{bmatrix} \tag{8b}$$

To construct a model it is useful to refer to equation (8a and b). The model is expressed in matrix notation (8a) and expanded as vectors and matrices in (8b). The equation has a vector, $\boldsymbol{\eta}$, which contains the variances of regional activity from *A* through *D*, a matrix $\boldsymbol{\beta}$, which defines the network and contains the path coefficients, and a vector of residual effects, $\boldsymbol{\psi}$. Model specification is done through indicating which elements in $\boldsymbol{\beta}$ and $\boldsymbol{\psi}$ are *fixed* at zero (indicating no anatomical connection), fixed at a non-zero value, or *free* to be estimated. The zero elements of $\boldsymbol{\beta}$ in equation

(8b) represent fixed coefficients, while the others represent coefficients that are free. The vector ψ is a diagonal matrix in the form presented in equation (8b). It can also be expanded to a full matrix to allow for correlations among residual influences.

Solutions to the structural equations are typically obtained through iterative estimation. The most common form is maximum-likelihood estimation, although different least-squares methods have been used [Bentler, 1985; Jöreskog and Sörbom, 1989]. Initial estimates for the unknown parameters (path coefficients and residuals) in the structural equations are obtained and a set of implied variances and covariances are computed using derivations similar to those presented in Figure 2C. The implied covariance matrix is then compared with the original covariance matrix. On the basis of the differences between these two matrices, modifications to parameter estimates are made using iterative fitting techniques (e.g., Davidon Fletcher-Powell method used by LISREL [Davidon, 1959; Fletcher and Powell, 1963], a modified Gauss-Newton method for EQS [Bentler, 1985]). This data fitting procedure finishes when the differences between the observed and implied covariances matrices are in an acceptable range. The optimization routines are surprisingly well behaved given a reasonable set of equations and initial conditions for iterative estimation, and the methods used for iterative fitting will typically give the same results in data sets in which the covariance matrix is not singular [Jöreskog and Sörbom, 1989]. Departures in the final solution are likely when the numbers of known and unknown parameters are close to being equal or there is singularity in the data set (one or more regions are perfectly related to one another). The ultimate ability of the model to reproduce the data is given through a χ^2 goodness-of-fit statistic (the χ^2 value is the minimum value of the maximum-likelihood fit function, multiplied by $N - 1$, where N is the total sample size [Jöreskog, 1973]).

Effects decomposition

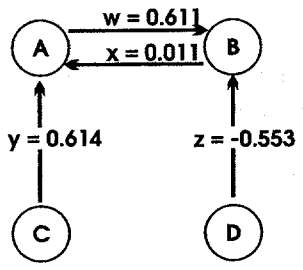
The representation of the system as a set of path equations (Fig. 2C) demonstrates the ability of structural equation models to determine direct, indirect, and total effects. In Figure 2, the effects of region A on C consist of the direct effect, v, and the indirect effects through w and y. The total of effects of A on C is the sum of the direct plus indirect effects. The path equations depicted in Figure 2C do not contain a residual term; therefore, the total effects would be the zero-order correlation between A and C. In the case in which residuals are included, the total effects would be smaller than the correlation coefficient. Evaluating influences within a system as direct, indirect, and total effects is known as effects decomposition and is an important characteristic of structural equation modeling. Effects decomposition can indicate how the influence of a region is modified through indirect influences and whether these change depending on the experimental manipulation. Effective connectivity, as defined by Aertsen et al. [1992], resembles most closely total effects in that an effective connection is the influence of one neural element on another irrespective of direct or indirect influences. In structural equation modeling, effective connections, or total effects, are further decomposed into direct and indirect effects by use of the anatomical model.

Feedback loops

One characteristic of biological neural networks is that many anatomical connections are reciprocal. Structural equation models can solve for the functional weights of reciprocal connections between neural elements and show whether these loops are symmetric or asymmetric [Berry, 1984]. Symmetric relationships have equal influences in both directions of the loop, while asymmetric relations will be larger in one direction. Such information cannot be derived from simple pairwise correlations since correlations are symmetric, but can be determined using structural equation models.

The ability to solve these loops is related to the complexity of the system. At one extreme, there is the two-region model whereby the regions are connected by a loop. In this case there would be only one known quantity, the correlation coefficient, and two unknowns, the path coefficients. The system is undetermined, as there are more unknowns than knowns. Only with additional information could this be solved, so the most parsimonious solution would be to assign each path coefficient the same value equal to half of the correlation between the two regions. On the other hand, an example of a determined system is presented in Figure 3, and explained below.

In this system, two areas (A and B) are connected by a loop, with each area receiving an additional projection from another area. There are six known correlation coefficients and four unknown path coefficients to solve for. The added information provided by the influence of regions C and D makes it possible to solve the structural equation. Moreover, the estimated values for the coefficients within the loop are not equal.



	A	B	C	D
A	1.00			
B	0.48	1.00		
C	0.62	0.16	1.00	
D	0.24	-0.41	0.06	1.00

Figure 3.
A four-region neural network with reciprocal connections, or loop, between regions A and B. Correlations coefficients are given below the network, and the values for each arrow are the maximum-likelihood estimates for the path coefficients. Unlike the information derived from the correlation coefficients, the path coefficients for the influences within the loop are asymmetric.

The reason for this is illustrated in the structural equations for regions A and B:

$$A = xB + yC + \psi_A \tag{9}$$

$$B = wA + zD + \psi_B \tag{10}$$

Though A and B both influence each other, the structural equations for each one contain additional influences that add information, i.e., the influence of region C on A [equation (9)] and region D on B [equation (10)]. Since path coefficients are similar to semi-partial regression coefficients, and since the correlations among regions are not homogeneous, the resulting path coefficients for the influence of A on B (w) and B on A (x) will not be equal. The maximum likelihood estimates for the path coefficients in Figure 3 illustrate this. The derivation of a path coefficient relies on partialling and semi-partialling of covariances [for a detailed explanation of partial and semi-partial coefficients see Cohen and Cohen, 1983]. Semi-partial coefficients can be obtained through least-square estimation or by using the formula for a semi-partial correlation as follows:

$$\mathbf{r}_{A(B\cdot D)} = \frac{\mathbf{r}_{AB} - (\mathbf{r}_{AD} \times \mathbf{r}_{BD})}{\sqrt{1 - \mathbf{r}_{BD}^2}} \tag{11}$$

In the formula, $\mathbf{r}_{A(B\cdot D)}$ represents the semi-partial correlation coefficient for regions A and B with D held constant or partialled out. With the direction of the influences in the model, this would equal the standardized semi-partial regression coefficient for the influence of A on B, i.e., w. This coefficient will be different from $\mathbf{r}_{A(B\cdot C)}$, which represents the coefficient of the influence of B on A, i.e., x, since the terms that are partialled out of $\mathbf{r}_{AB}$, namely $\mathbf{r}_{AC}$ and $\mathbf{r}_{BC}$, have different values. The standardized semi-partial regression coefficient for the influence of A on B (w) is 0.616, and the standardized semi-partial regression coefficient for the influence of B on A (x) is 0.397 ($y = 0.552$, for C on A, and $z = -0.554$ for D on B).[1] The ability to solve loops is an important feature of structural equation modeling and highlights another important concept. Looped influences can only be solved when the relationships among all regions in a model are considered simultaneously. The partialling procedure that is used in structural equation modeling (and regression) reveals relationships that cannot be deduced from interregional correlations.

Residual effects

Structural equation modeling also allows for influences not measured or not measurable to be incorporated in the model as residuals [Hayduk, 1987; Jöreskog and Sörbom, 1979, 1989]. Residual influences can be represented in at least two forms. One representation of residuals is with variable ψ (PSI) in LISREL terminology and is indicated in equations (3) and (8) and Figure 2D. These residual influences are best thought of as including the combined influences of regions outside the model and the influence of a brain region upon itself [McArdle and McDonald, 1984; McIntosh and Gonzalez-Lima, 1992a,b]. It is important that residuals be allowed to occur in the model for both theoretical and technical reasons. Brain regions that do not have a residual influence imply that all the variance in that region is accounted for by the connections with other regions in the model. This is an unlikely situation in a neural system. For model fitting, fixing the residuals to zero forces that variance attrib-

[1]The values for the semi-partial regression coefficients and the maximum likelihood estimates for the path coefficients (Fig. 3) are close, but not identical, to each other. This is the result of the two different estimation techniques, specifically, least-squares for the regression coefficients and maximum likelihood for the path coefficients. The main reason for the difference is that the estimates for least-squares were obtained separately for each coefficient while the maximum likelihood estimates were obtained simultaneously. It is useful to emphasize that least-squares estimates are often used as starting values for iterative estimation methods like maximum likelihood.

utable to residuals to be expressed from a source within the model, which can seriously impair the ability to locate an appropriate solution for the model. PSI values in LISREL are represented as variances and not path coefficients. They can be converted to a coefficient by taking its square root [Loehlin, 1987], but information about the sign of the influence (positive or negative) is not obtainable unless further model modifications are made [Hayduk, 1987].

Another representation of residuals is as a variable having a direct path to one or more of the regions within the model. Conceptually, this influence would represent a region that has a strong influence on areas within the model, but could not be included, in other words, an influence that is *exogenous* to the model and is unmeasured. In LISREL, exogenous variables are referred to as ξ (KSI) variables, whose influence can be represented by direct paths to the *endogenous* variables (η) in the model (the brain regions in the system). These exogenous paths can be given a weight or path coefficient represented by γ (GAMMA). Path coefficients among endogenous variables are represented as β. KSIs can be useful in accounting for influences of peripheral sensory organs such as the retina or cochlea [for examples, see McIntosh and Gonzalez-Lima, 1992a, 1993]. It must be emphasized that while conceptually the residual input represents a single source, the mathematical reality is that other common residual sources are encompassed in this influence. As a result, it is not a "pure" representation for the single source.

Estimation of residual effects will depend on the complexity of the model. Our typical approach for the estimation of residuals (KSI and PSI) is to fix these values at 35 to 50% of the total variance for a given brain region depending on its connections within the model [McIntosh and Gonzalez-Lima, 1991, 1992a,b]. Regions receiving more inputs will have a lower residual value and for areas that do not receive influences from within the model, the effect of residuals is set to 100%. These residual effects can be modified if it significantly improves the fit of the model. Values for PSI can also be estimated directly as free parameters (but see simulation results below). It is not advisable to free KSI and PSI in the same model since there is no way to differentiate the source of the greatest residual variance that leads to indeterminacy in the final solution.

Stacked models for statistical comparison of structural equation models

An issue in examining neural interactions is whether there is a change dependent on experimental conditions or groups of subjects (e.g., clinical population). In structural equation modeling, it is possible to compute the functional models within each condition and then provide a descriptive comparison of where the models differ [e.g., McIntosh and Gonzalez-Lima, 1991]. The inferential power of such a strategy is, however, rather limited. Most structural modeling programs allow for a *multiple group* or *stacked models* analysis, where instead of estimating a functional model for each condition separately, the models are combined in a single program run. The process involves statistically comparing functional models, using the χ^2 index of model fit, whereby path coefficients are constrained to be equal between conditions (null model) with those in which the coefficients are allowed to differ (alternative model). The comparison of models is made by subtracting the χ^2 value for the alternative model from the χ^2 value for the null model. If the alternative model, in which the coefficients were allowed to differ between groups, 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. The procedure is similar to a simple *t*-test for differences in group means in which the null hypothesis is that a single estimate of the mean is adequate for both groups (i.e., the group means do not differ). For the stacked models approach, the null hypothesis is that a single estimate for each path coefficient is adequate for both groups (i.e., the path coefficients between groups do not differ). This feature of structural equation modeling has the benefit of not only allowing for inferential evaluation of different models, but also improves the statistical fitness of the models by increasing degrees of freedom [Hayduk, 1987]. When models are estimated simultaneously, each covariance matrix operates as a set of observed values. By constraining certain parameters to be equal between conditions, the ratio of knowns (observed values) to unknowns (parameters to be estimated) is increased, making parameter identification of the models more likely.

Measurement model for neural systems

As of yet, an undeveloped capacity of neural structural equation modeling is the ability to account for errors of measurement in the model. A complete structural equation model (Fig. 4) separates the variance of the system into two main components, a measurement model and a structural model [Loehlin, 1987]. The measurement model is depicted as the area

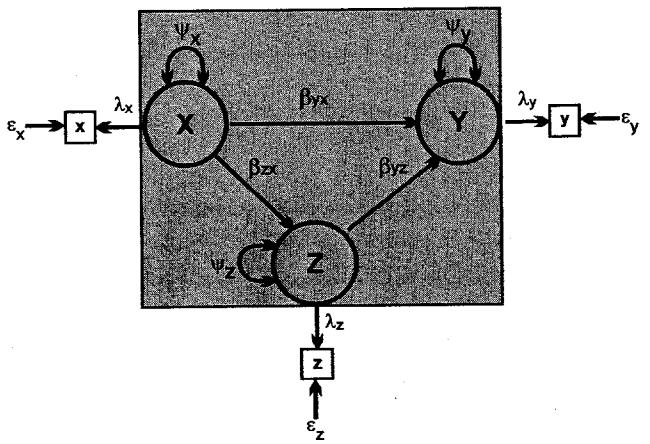


Figure 4.
Division of complete structural equation model into a measurement and structural model. The structural model is depicted by elements contained in shaded grey box. The measurement model is those elements outside the box. A measurement model implies that the activity observed in *x*, *y*, and *z* (indicator variables) is a function of the influence of the actual activity of the area (*X*, *Y*, and *Z*, latent variables) plus some error of measurement (ϵ). The degree that a measured variable reflects a latent variable is given by the values for λ.

outside the grey box in Figure 4 and in matrix notation is:

$$\begin{bmatrix} x \\ z \\ y \end{bmatrix} = \begin{bmatrix} \lambda_x & 0 & 0 \\ 0 & \lambda_z & 0 \\ 0 & 0 & \lambda_y \end{bmatrix} \begin{bmatrix} X \\ Z \\ Y \end{bmatrix} + \begin{bmatrix} \epsilon_x \\ \epsilon_z \\ \epsilon_y \end{bmatrix} \qquad (12)$$

The measurement model represents three variables, *x*, *y*, and *z*, that are directly measured by the researcher. These variables represent, or *indicate*, some latent variables (*X*, *Y*, and *Z*) that cannot be directly observed. The degree to which a *latent variable* (e.g., *X*) is expressed in an *indicator variable* (e.g., *x*) is given by the weighting, λ (e.g., λ_x). Since the relationships of the latent variables and indicator variables are not perfect, part of each indicator variable will be composed of measurement error (ϵ_x, ϵ_y, and ϵ_z). The structural model for this system was presented in equation (3).

In many senses, this depiction of a neural structural equation model from brain imaging data is more accurate, as it implies that what is measured, whether 2-DG or rCBF, is a function of the actual regional activity plus some error of measurement. In mapping data this measurement error may represent everything from errors in quantification of glucose utilization or blood flow, machine drift, and recovery coefficients, to individual differences in functional and anatomical organization. The measurement model accounts for the reliability of the measuring device. Such a depiction of a neural structural equation modeling may help to stabilize the estimates of the path coefficients, as it would reduce the potential amount of variance to account for. This also cleans up the structural model since the measurement error is removed from the residual term of the structural model. If a measurement model is not used, then part of the residual term in the structural model would include this measurement error.

The meaning of a path coefficient

The technical definition of a path coefficient (expressed in terms of neural pathways) is the direct proportional functional influence one region has on another region through their direct anatomical connection, with all other regions in the model left unchanged. A path coefficient is the expected change in the activity of one region given a unit change in the region influencing it. If a path coefficient for the influence of region *A* on *B* is 0.5, then a unit increase in the activity of *A* would lead to an increase of half of that unit in *B*; assuming no other regions connected to *B* show any change. For instance, if rCBF in region *A* increases by 10 ml/100 g/min, then rCBF in region *B* would increase by 5 ml/100 g/min.

The path coefficient indicates the average influence across the time interval measured. If a structural equation model was constructed for multi-site single neuron data, the path coefficients would be the influences on a millisecond time scale. For metabolic mapping data, activity is time integrated and is the sum of activity in a region. Path coefficients, in this case, show the average influence across that time interval. Going back to the previous example, if we measure rCBF in *A* and *B*, then the path coefficient of 0.5 indicates that across the time interval measured (e.g., 1 min) the influence of area *A* accounted for 25% (square of path coefficient) of all the influences on *B* (25% of the variance in *B*).

The physiological interpretation of a neural path coefficient, based on brain imaging data, is somewhat less obvious in relation to cellular electrical events. Since the physiological interpretation of a change in a metabolic marker related to cellular electrical activity depends on the brain region under consideration [Gonzalez-Lima et al., 1992], giving a purely physiological interpretation to a path coefficient is likely misleading. One temptation is to interpret a negative path

coefficient as an inhibitory influence and a positive path coefficient as excitatory in reference to electrophysiological postsynaptic events. However, an increase in metabolism can result from an increase in either postsynaptic excitation or inhibition depending on the energy demands and cellular geometry of the region [e.g., Batini et al., 1983; Heil and Scheich, 1986; Nobrega and Coscina, 1983; Nudo and Masterton, 1986]. This does not allow a direct translation of path coefficients based on metabolic mapping data as indices of postsynaptic excitation or inhibition. This difficulty is not unique to metabolic mapping. Similar interpretative difficulties exist in evoked or field potential work, in which a change in the electrical activity cannot be accurately interpreted as excitatory or inhibitory postsynaptic activity unless additional information about the specific cell populations recorded from is obtained. The pure physiological interpretation of a path coefficient therefore depends on the activity measures from which the interregional covariances are computed.

If covariances between neural elements underlie brain operation, then path coefficients may be interpreted as an indication of functional influences or how much of the observed variance in a brain region is due to the direct effect of an interconnected region. Here the emphasis is on whether the path coefficients show a change across tasks or between groups. If, across tasks, a path coefficient shows a large increase, or decrease, in absolute magnitude, this suggests a quantitative change in functional influence. If the absolute magnitude remains the same, but the sign of a coefficient changes across tasks (e.g., positive to negative), this may imply a qualitative change across tasks. Dichotomies such as this are seldom complete, so it is likely that both magnitude and sign changes will occur. When evaluated in this manner, path coefficients can indicate whether there are task- or group-related differences in functional influences within the same anatomical pathways.

Nonlinearities in covariance analysis

All models discussed so far have assumed that the relationship of the metabolic activity between brain areas is predominantly linear. Most biological systems, including the central nervous system, have nonlinearities in their responses. The implications of applying a linear model to a nonlinear system, at a simple level, would be a loss of information. Physiological responses typically follow a sigmoidal function, which is essentially a bounded linear function. By assuming a purely linear response, information about responses at the bounds of the actual physiological response would be lost, and at worst the degree of linearity would be overestimated. However, some researchers have suggested that for metabolic mapping data, a linear approximation to the data is a reasonable one under most physiological conditions [Friston et al., 1992; Nudo and Masterton, 1986]. The ability to incorporate feedback loops into structural equation models is a step towards introducing nonlinearities. More formal nonlinearities can be evaluated before modeling by examining the significance of nonlinear trends using polynomial expansions [Pedhazur, 1982], and these nonlinearities can be incorporated into the structural equation models [Kenny and Judd, 1984]. There are currently two methods by which this can be done. The first involves modifying the measured activity before modeling the system, and then adding an extra variable into the model representing this modification. For example, if it is suspected that region Y is a function of both linear effect of X and the square of the effect of X, measures from X would be squared and an additional variable would be added to the model to represent the square of X [for examples, see Kenny and Judd, 1984 and Hayduk, 1987]. The second method involves constraining the estimate of the influence of one region on another to be some nonlinear function, which could have significant utility in modeling nonlinear output in response to a linear input. An example would be constraining the output of X (its effect on Y) to be the inverse of the linear effect of input from variable Z. This feature has been incorporated into many of the programs for structural equation modeling such as EQS and newer versions of LISREL (version 8).

SIMULATIONS FOR INCOMPLETE ANATOMICAL MODELS

One important feature in neural structural equation modeling is the use of anatomical paths to define the causal structure and assess functional interactions. The issue of the accuracy of the anatomical model and how this affects the utility of the model has not yet been explored. Moreover, neural structural equation models are by necessity simplifications of reality since any given region can be influenced by numerous other areas, some of which may not be included in the model. Simulations were carried out to provide some indication of the impact of a missing pathway and of regions that were not included in the model. These simulations were grossly oversimplified and were meant only to illustrate the behavior of the structural

equation modeling algorithms under the two conditions indicated above.

Methods

The model was constructed using EQS version 4 [Bentler and Weeks, 1980; Bentler, 1985]. Six "regions" (variables V1 to V6) were simulated from a unit normal distribution with a sample size of 100 (to avoid confounds due to sample size issues [Boomsma, 1985]). In the population structural equation model, regions receiving influences from within the model had residual variances equal to 0.25, and those not receiving input from within the model had residual variances set at 1.0. The sample covariance matrix used for the analysis is presented in Table I. The specific values for the path coefficients and residuals are given in Table II. The base model was essentially a feedforward network with one loop between V3 and V6. A graphic depiction of the base model and the simulation results is presented in Figure 5.

Three simulations were conducted to determine the effect of region or path elimination. The first test model was an elimination of the path from V4 to V5, the second was an elimination of V1 from the model, and the final was an elimination of the feedback from V6 to V3. The effects of these omissions were assessed by examination of changes in path coefficients from the base model and by evaluation of *modification indices*. [Jöreskog and Sörbom, 1989; Hayduk, 1987]. Modification indices are computed from the first- and second-order partial derivatives for each possible parameter in the model—path coefficients and residuals. They suggest parameters that should be freed to improve the fit of the model. A high modification index suggests that allowing the estimate of the parameter to change (usually from zero) would significantly improve the fit of the model. They can be evaluated as a χ^2 value with 1 degree of freedom [Jöreskog and Sörbom, 1989]. Residual influences (PSI) were fixed at the values obtained from the base model to determine whether the most promising improvement to the fit of the model would come from increasing a residual, or adding a path. It has been noted by other researchers that there is a tendency for unaccounted variance to be expressed in the residual term if the estimate for that term is unconstrained because it is usually the fastest way to minimize the fit function [Hayduk, 1987]. Fixing the residual influences in the test models avoided this possible problem.

TABLE I. Covariance matrix used for data simulations

	V1	V2	V3	V4	V5	V6
V1	0.949					
V2	−.093	1.060				
V3	−.032	−.210	0.272			
V4	0.438	−.057	−.005	0.413		
V5	0.585	0.466	−.146	0.386	1.013	
V6	0.009	0.440	−.001	−.032	0.061	0.484

TABLE II. Results from simulations*

	V1	V2	V3	V4	V5	V6
Base model						
V1	—	—	—	—	—	—
V2	—	—	—	—	—	—
V3	—	—	—	—	—	−.478
V4	0.461	—	—	—	—	—
V5	0.453	0.712	—	0.515	—	−.494
V6	—	0.563	0.848	—	—	—
PSI	1.00	1.00	0.382	0.211	0.248	0.322
Test model 1: omission of path from V4 to V5						
V1	—	—	—	—	—	—
V2	—	—	—	—	—	—
V3	—	—	—	—	—	−.505
V4	0.461	—	—	—	***10.48***	—
V5	0.692	0.726	—	***21.67***	—	−.544
V6	—	0.601	0.940	—	—	—
PSI	1.00	1.00	0.382	0.211	0.248	0.322
Test model 2: omission of V1						
V1	—	—	—	—	—	—
V2	—	—	—	—	—	—
V3	—	—	—	—	—	−.505
V4	—	—	—	***45.31***	***20.13***	—
V5	—	0.664	—	0.995	***7.61***	−.411
V6	—	0.601	0.940	—	—	—
PSI	—	1.00	0.382	0.211	0.248	0.322
				45.31	***7.61***	
Test model 3: omission of path from V6 to V3						
V1	—	—	—	—	—	—
V2	—	—	***11.46***	—	—	—
V3	—	***11.46***	***4.07***	—	—	***15.49***
V4	0.461	—	—	—	—	—
V5	0.453	0.712	—	0.515	—	−.494
V6	—	0.489	0.374	—	—	***4.28***
PSI	1.00	1.00	0.382	0.211	0.248	0.322
			4.07			***4.28***

* Each section contains path coefficients. Rows list variables being affected and columns list source of effect. The two final rows (PSI) show the residual influences on each variable. Items for test models 1–3 shown in bold italics are the modification indices for the expected improvement in the model fit (evaluated as χ^2 with 1 degree of freedom) if estimate for that parameter were changed. Values are given for all parameters whose modification index exceeds a probability of 0.05 (3.84). Cells containing a dash (—) indicate path coefficients that were set to zero.

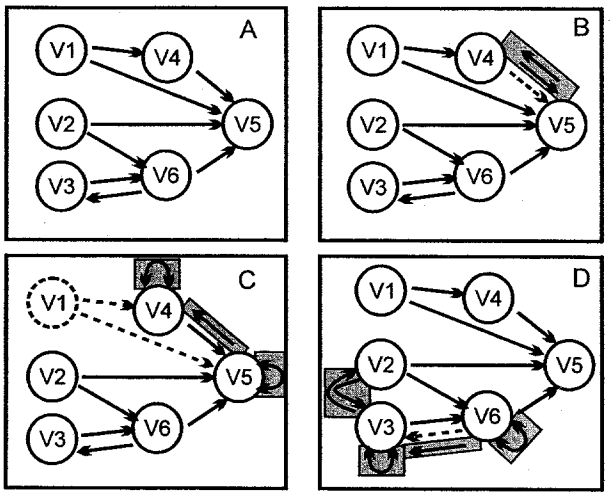


Figure 5.
Graphic depiction of results from data simulations to test the effects of omitted paths or regions. **A:** Base model from which the data set was generated. **B–D:** Results from three test models in which a part of the base model was omitted. Elements that are shown by segmented lines are omissions from the model, while elements highlighted by a gray box are suggested changes to the test models derived from modification indices (see text). Values for the path coefficients, residuals, and modification indices are presented in Table II.

Results

Test model 1: elimination of path from V4 to V5

In the first test model (Fig. 5B), the estimates for the path coefficients did not appear to change substantially. The largest modification index was for the path from V4 to V5 and the second largest was for the path from V5 to V4. For test model 1, the modification indices accurately identified the missing path.

Test model 2: omission of V1

There was a large change in the path coefficient for the influence of V4 on V5 (from 0.515 in the base model to 0.995 in test model 2). This is likely a reflection of the attempt to account for the variance attributable to the missing variable (i.e., to fit the original covariance matrix better). The largest modification indices were for the residual influence on V4 (PSI and influence of V4 on itself) path from V5 to V4, and the residual influence on V5 (PSI and influence of V5 on itself) (Fig. 5C). Examination of the modification indices suggested that an external influence was missing, since the indices for the residual influences were high. However, the modification index for the path from V5 to V4 was higher than the modification index for the residual influence on V5. In this simulation, only one missing element would have been accurately identified, the residual influence on V4. The residual influence on V5 would likely have been missed since the modification index for this was lower than that of the path from V5 to V4.

Test model 3: elimination of path from V6 to V3

There was a reduction in the path coefficient for the influence of V3 on V6 (0.848 in the base model to 0.374 in test model 3) as a result of the removal of the negative feedback path. The largest modification indices were for V6 to V3, a reciprocal path between V2 to V3, and the residuals of V3 and V6 (Fig. 5D). The reciprocal path likely represents an alternative way to account for the variance in V3 when the influence of V6 is omitted. Though the modification indices identified the omitted path, the differences between indices were not as great as in test models 1 and 2.

Conclusions from simulations

It appears that the modification indices obtained from structural equation modeling algorithms are able to indicate possible omissions from the anatomical model, and where regions are omitted. Consistent with intuition [McIntosh and Gonzalez-Lima, 1992b], omitted regions will result in increased residuals. However, the modification indices alone were not completely accurate. In test model 2, only one missing component was accurately identified, and in test model 3 the differences among indices were not as great as in models 1 and 2. Therefore, modification indices can provide clues as to possible omissions, but the final decision of whether to add a path or increase a residual should be made by the researcher. Usually the regions that are included in the model are selected beforehand using either statistical criteria or a theoretical guide (see section on data-driven versus theory-driven modeling presented below). There was some indeterminacy in the simplistic models used in these simulations, so there will likely be even more in complicated neural-based models. In social science applications of structural equation modeling, one of the main concerns is the validity of data-driven modifications of models, in which it is unclear how much of the data-driven causal structure results from statistical noise [Freedman, 1987; MacCallum et al., 1992]. The uniqueness of neural structural equation models is less of a problem because the causal structure is established by neuroanatomy. However, if modifica-

tions to the anatomical model are made from the data, the simulation results presented here suggest that the same concerns as in social science applications should extend to the neural applications.

ANATOMICAL CONSTRAINTS

In the central nervous system there are numerous ways one area can have a functional impact on another. Many neural systems have a parallel anatomical organization by which connections between areas can be both direct (hierarchical) and indirect. Effects decomposition of anatomically based structural equation models allows for the evaluation of whether the influence of one region on another is through a direct effect or is mediated through one or more indirect routes. Moreover, when evaluating experimental differences, it is entirely possible for the total effects of two regions to be the same while direct and indirect effects differ, or for total effects to differ when direct effects do not.

An empirical example comes from a 2-DG study that examined the effects of footshock on visual system metabolic activity in patterned light and darkness [McIntosh et al., 1992; McIntosh and Gonzalez-Lima, 1992a]. A 2-by-2 design was employed having a patterned light–footshock condition, patterned light–no shock condition, darkness–footshock condition, and darkness–no shock condition. For full details of the study and results, the interested reader is referred to the primary papers. To illustrate the information obtained by constraining the expression of the covariances by the neuroanatomy, portions of the functional models from patterned light–no shock and darkness–no shock conditions will be presented.

Figure 6 shows the direct and total effects for the geniculocortical portion of the rat visual system structural equation models. The full model contained the lateral posterior thalamic nucleus and the superficial and intermediate layers of the superior colliculus. The geniculocortical portion was selected to illustrate the difference between total and direct effects and how the anatomical model helps to interpret these effects. The upper portion of the figure shows that the ascending thalamocortical direct effects from the dorsal lateral geniculate nucleus (LGNd) to primary visual cortex (VC1) were stronger in the patterned light model. Descending corticothalamic direct effects from secondary visual cortex (VC2) were weaker in the patterned light model, and all other direct effects were not statistically different between models. Evaluation of the total effects within this tri-nodal loop (bottom of Fig. 6) provided additional information about the influence of indirect effects. The darkness model showed strong corticofugal effects from both VC1 and VC2, but in the patterned light model, the corticofugal effects were zero and the thalamocortical effects were relatively stronger.

The differences between direct and total effects in Figure 6 suggested that the indirect effects through corticocortical connections and thalamocortical loops acted to change the nature of thalamocortical interactions. For example, the sign of the direct effect from LGNd to VC2 was negative for the patterned light model. The indirect effect of the LGNd would be through the positive ascending path to VC1 and the positive loop between VC1 and VC2. A positive loop tends to amplify effects transmitted through it and therefore the indirect effect of LGNd was large and positive (conversely, negative loops tend to dampen total effects). This, added to the relatively smaller negative direct effect of LGNd on VC2, resulted in a large positive total effects from LGNd. Corticocortical interactions may have acted to modify the ascending thalamic signal in the patterned light model. Cortical modulation of ascending signals has been documented in electrophysiological studies [Molotchnikoff et al., 1984; Wickelgreen and Sterling, 1969]. Though much of this modulation is likely from descending corticofugal influences, the functional models shown here suggest that corticocortical interactions, especially feedback from secondary cortices, may also play an important role. Reversible lesion experiments with cortical cooling have suggested that feedback effects are an important determinant of primary cortical responses [Sandell and Schiller, 1982]. Without the use of the anatomy as the foundation to express the interregional covariance relationships, it would not have been possible to determine if the differences in the ascending effects between patterned light and darkness models were simply because of direct thalamic influences or if they resulted from mediation through indirect effects. The ability to distinguish between direct and indirect effects is an important quality of structural equation modeling that sets it apart from other covariance-based methods.

The example presented above shows that the anatomical foundation is the key feature for neural structural equation models. An immediate concern with the use of the anatomical constraint is the degree to which the anatomical model reflects reality. Any system of equations in which there are unknowns to be solved benefit from constraints to possible solutions. Using the connective anatomy of the system helps to constrain solutions. However, if all major and minor paths were included, most models would con-

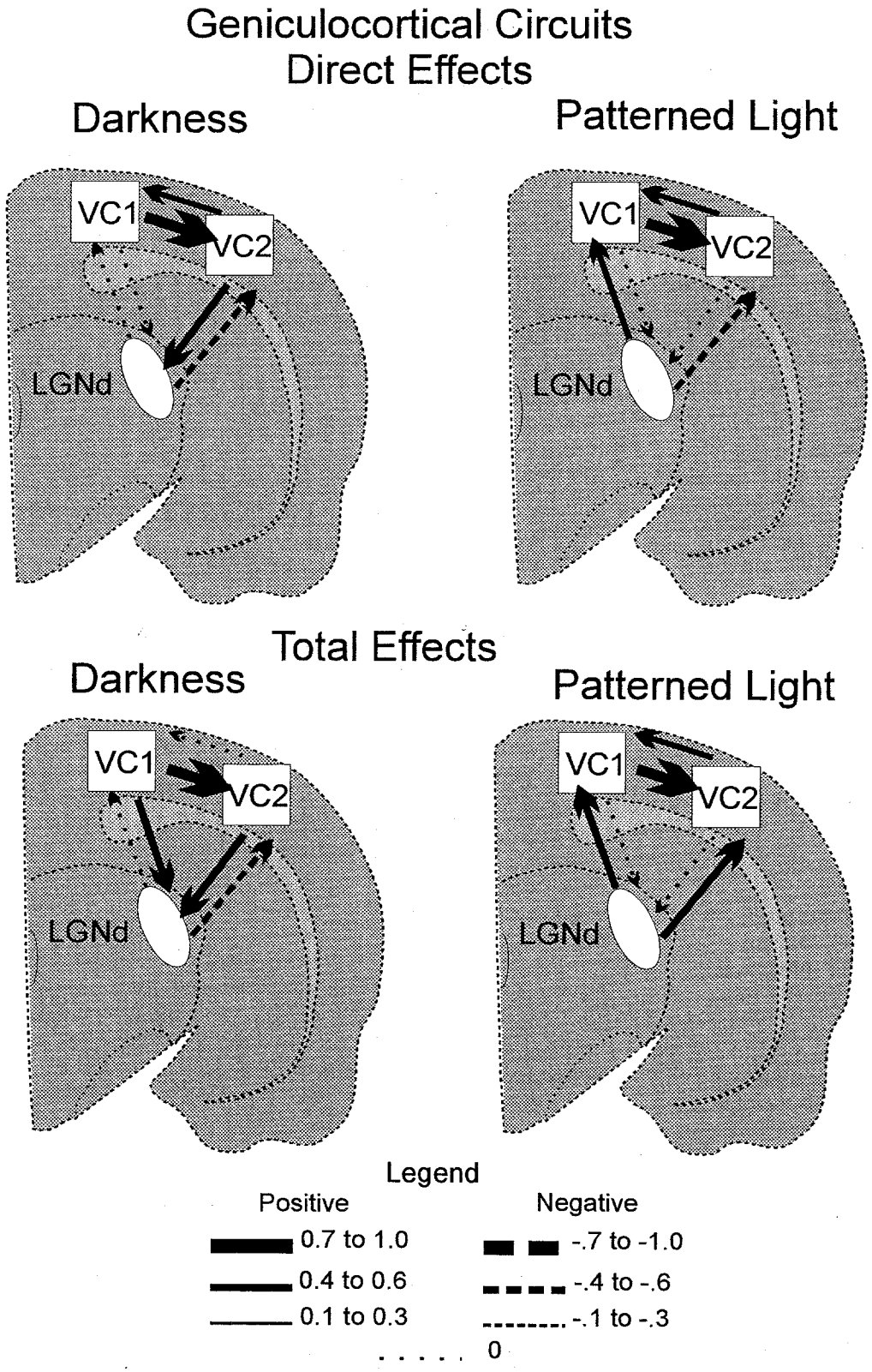


Figure 6.

Schematic of geniculocortical functional models obtained for rats presented with patterned light or darkness. Models are presented on a coronal section of the rat brain with the interacting regions shown in white (top is dorsal and right is lateral). The top two models represent the direct effects of the source region on the target region. The bottom two models represent the total effects, which are the sums of direct effects and indirect effects through other regions. The size of the direct or total effect is indicated by the relative width of the arrow. Values for the width gradient are given in the legend at the bottom of the figure. Positive influences are shown as solid arrows, whereas negative ones are shown as segmented arrows. LGNd, dorsal lateral geniculate nucleus; VC1, primary visual cortex; VC2, secondary visual cortex.

tain reciprocal loops at nearly every level, with some interconnections between levels, both feedforward and feedback. When all possible anatomical connections are included, it is likely that an underdetermined system of equations would result, in which there are either the same number of known and unknown elements or more unknown elements. In either case, unique solutions are not obtainable. A hierarchical model building strategy could be used whereby a smaller part of the model is estimated first, the parameters fixed at those estimates, and then more paths and regions added to complete the model [McIntosh and Gonzalez-Lima, 1992a]. In most cases, however, some compromise between anatomical accuracy and interpretability may be needed. Any modeling effort, whether based on simulations or data-fitting, is necessarily a simplifications and represents an approximation of reality. It is the degree of simplification that determines the utility of the model.

STRUCTURAL EQUATION MODELING IN HUMAN PET STUDIES

Structural equation modeling of animal 2-DG studies have provided important insights into brain operation. Recent extensions of structural equation modeling to PET rCBF studies in humans have also provided important information beyond what was concluded from examination of regional activity changes [McIntosh et al., 1994a]. The initial application was to a visual perception study comparing cortical interactions during match-to-sample tasks for object vision (face matching) versus spatial vision (dot-location matching). The object vision task showed relatively greater activity in ventral occipitotemporal brain areas while the spatial vision task showed relatively greater activity in dorsal occipital and parietal cortices [Haxby et al., 1991]. These results suggested a functional segregation of visual processing streams into dorsal and ventral pathways similar to that observed in nonhuman primates [Ungerleider and Mishkin, 1982]. Using a principal components analysis, we were able to identify temporal and prefrontal regions showing task-related covariance patterns. Structural equation models from anatomical models of dorsal and ventral processing streams were constructed for both object and spatial vision tasks. The brain regions included striate and extrastriate area 17 and 18, dorsal and ventral areas 19 (19d and 19v), occipitotemporal area 37, temporal area 21, parietal area 7, and frontal area 46. The ventral stream consisted of the connections from areas 17/18, through area 19v, then into area 37 and area 21, and terminated in area 46. The dorsal stream started in areas 17/18, then went through area 19d and parietal area 7 and ended in frontal area 46. Interactions between the two streams were included as the anatomical connections between areas 37 and 7, and areas 7 and 21. There was also a feedback path included from area 46 to area 19v. The functional models for the right hemisphere were consistent with the differences in mean rCBF. Areas along the ventral stream showed strong interactions in the object vision task, relative to spatial vision, while spatial vision functional models showed stronger interactions along the dorsal stream. Structural equation modeling extended the results by showing how processing followed into temporal and frontal cortices. The models added to the results by showing that these two streams were not functionally independent as there were strong interactions between them in both conditions. Also, the effects of frontal lobe feedback were task dependent, where feedback was present only in the spatial vision model.

Within the same anatomical model, the left hemisphere functional models did not show the separation of processing streams present in the right hemisphere. This seemed contrary to the activation results, which showed equal activation in both hemispheres. It was hypothesized that the bilateral activation may have arisen from transcallosal influences of the right hemisphere on the left [Horwitz et al., 1992a]. Interhemispheric structural equation models showed that this hypothesis was tenable. As illustrated schematically in Figure 7, ventral areas in the right hemisphere had stronger contralateral influences than did the left hemisphere areas. In the spatial vision models, dorsal areas showed similar asymmetric influences. These asymmetries could only have been deduced from the covariance analyses.

We have recently extended the object vision models to look at changes in this basic functional network in a delayed match-to-sample task in which the delay interval was parametrically increased. In this study, we were able to replicate the original object vision network, and we showed changes in both right hemisphere and left hemisphere interactions as a function of increasing delay [McIntosh et al., 1994b]. Across the delay interval, the functional models showed a decrease in the right hemisphere interactions along the ventral stream with stronger interactions among dorsal areas into cingulate cortex, and bilateral increased interactions among frontal, temporal, and cingulate areas. Collectively, the results from these studies show that the application of structural equation modeling to brain imaging in humans will greatly aid in the

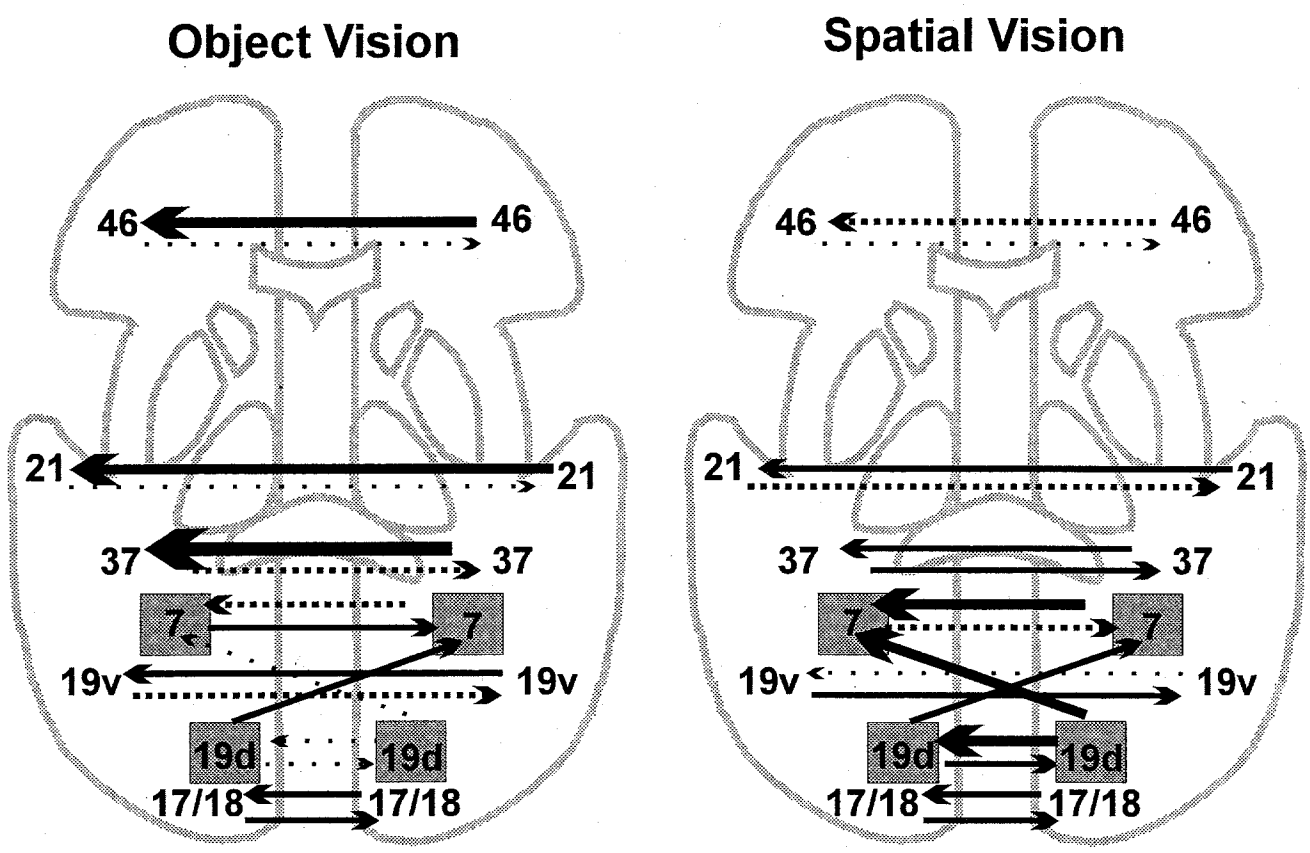


Figure 7.

Interhemispheric functional models for object vision and spatial vision tasks (see text). Brodmann areas are shown on a schematic of a horizontal section of the human brain (top is anterior, and left is left within each section). More dorsally located areas 7 and 19d are separated by gray boxes. The figure illustrates the asymmetric interhemispheric interactions in both tasks. The magnitude of the direct effect is indicated by the relative width of the arrow. The values for the width gradient are as shown in Figure 6. Positive influences are shown as solid arrows, whereas negative ones are shown as segmented arrows.

interpretation of the distributed activity changes underlying cognitive operations.

DATA-DRIVEN VERSUS THEORY-DRIVEN MODELING

A concern with image-based analyses is whether an objective- or data-driven method is superior to a purely theoretical approach. This has been an issue in the analysis of PET data and is demonstrated by the difference in pixel-based (objective) versus region-of-interest based (theoretical) approaches [e.g., Fox et al., 1988 versus Petit et al., 1993]. A similar distinction can be made in covariance analysis and is often distinguished as exploratory (objective) versus confirmatory (theoretical) analyses. Principal components analysis (PCA) and factor analysis are essentially exploratory techniques since no constraints are placed upon how the variance in the system is expressed. Structural equation modeling is typically thought of as a confirmatory approach (confirmatory factor analysis) since a causal model is usually being confirmed or disconfirmed [Loehlin, 1987].

A purely data-driven approach requires additional statistical methods to construct a structural model. These methods are used to select regions that appear to be operating as a functional unit. Some examples include the use of univariate analyses of regional activity between conditions (e.g., *t*-tests, ANOVA), or other multivariate methods such as PCA (and derivatives) and discriminant analysis. Univariate differences in regional activity can provide clues for some regions that need to be included in a structural equation model. PCA based on the covariances between brain areas summarize the potentially large covariance matrices from the common patterns of relationships among brain regions and suggest regions that may be part of different functional systems.

This approach has been used in PET rCBF studies of visual perception to select regions for a structural equation model [McIntosh et al., 1994a,b]. A further extension of this, discriminant analysis, selects weighted combinations of regions that differentiate experimental conditions and serves as an indication of the functional systems that distinguish conditions. Discriminant analysis has been used for the selection of relevant regions for inclusion in a model in a brain mapping study of associative learning [McIntosh and Gonzalez-Lima, 1994]. Other groups have also used principal components analyses, but not in the context of building structural equation models [Goldenberg et al., 1989; Lagrèze et al., 1993; Moeller and Strother, 1991; see also papers by Friston and Alexander and Moeller in this issue].

Data-driven approaches can be confounded by sample-specific conditions that limit the generalizability of the results. For example, heterogeneous samples, outlier observations, and measurement error can all influence covariances within a sample. All analysis algorithms cannot distinguish these sources of variance and therefore they may be expressed in what appears to be strong changes in covariance. Principal components analysis may be especially vulnerable since it simply summarizes the covariance matrix and therefore if some of the observed covariance patterns are a result of noise, they will be reflected in the principal components [Widaman, 1993].

Theory-driven approaches usually entail the selection of a "system of interest" before the experiment. This was the approach used in our initial application of structural equation modeling to functional neuroimaging studies of the rat auditory and visual systems [McIntosh and Gonzalez-Lima, 1991, 1992a]. The theory-driven approach is used when specific hypotheses are being tested about the nature of a particular neural system. For example, the choice of the auditory system was driven by the hypothesis that functional interactions in the auditory system could code for the behavioral significance of acoustic stimuli as well as the pure physical characteristics [McIntosh and Gonzalez-Lima, 1991, 1993]. While the same potential statistical problems with sample-specific characteristics can affect theory-driven models, a major concern with theory-driven approaches is whether the actual functional models for a given task are identified. It is possible that the system of interest does not show a change in the experiment and that the functional model is actually composed of another set of regions.

As with most dichotomies, distinctions such as data-driven versus theory-driven are useful in discussing seemingly opposing views or approaches but are seldom useful in practice. Therefore, rather than assuming a posture at either end of the continuum, it is more productive to amalgamate qualities of both objective and theoretical approaches into covariance-based modeling efforts. This represents a *data-driven but hypothesis-constrained approach* to modeling. For experimental conditions in which the functional systems involved are not obvious, a data-driven approach can be adopted to select brain areas using such methods as a PCA or discriminant analysis along with univariate regional analyses. Structural equation modeling can provide clues as to possible functional influences (i.e., paths) that should be added to the model to improve explanatory power. The data-driven approach should be constrained by whether the functional influence can theoretically exist—whether there is an anatomical connection between regions. For example, suppose in modeling the cortical visual system there is a large modification index for a connection from striate cortex to prefrontal cortex. Since there have been no reports of direct striatofrontal connections, this path would not be included. This may be taken as a case in which the influence is mediated by indirect connections (e.g., occipito-temporal-frontal) and suggests that another region should be added to the model. Examples of the data-driven theory-constrained approach are in FDG experiments dealing with Pavlovian conditioning in rats [McIntosh and Gonzalez-Lima, 1994] and in human PET rCBF studies of visual perception and memory [McIntosh et al., 1994a,b].

This combined approach has an additional benefit in developing theories of brain operation. Because each structural equation model combines empirical data with researcher intuition it forces the models to be explicitly described. Each anatomical connection needs to be confirmed. Any connections that are included without specific reference to neuroanatomy (e.g., effective connections) need concrete theoretical explanation as to whether the effective connection is mediated through brain areas not included in the structural equation model. Neural structural equation models add a degree of exactness that is not often present in brain imaging studies. With the ability of brain imaging to measure activity through the entire brain it is often the case that numerous areas show increases or decreases in activity in an experiment. Brain imaging researchers will often discuss the results in terms of "functional networks" without specific references to how these networks are formed. By requiring that the networks be expressed in a covariance-based model, the assumptions of the researcher as to the organization of the network are more easily seen.

The relative exactness of neural structural equation models also allows for the generation of testable hypotheses. The functional models obtained from structural equation models of the human cortical visual system showed that feedback from prefrontal cortex was present in a match-to-sample task involving spatial location, but not in the matching of faces [McIntosh et al., 1994a]. This led to the hypothesis that the involvement of feedback from the prefrontal cortex depends on the task difficulty. Moreover, in the face-matching task there was a stronger influence of the right hemisphere on left hemisphere than the left hemisphere on the right. This led to the hypothesis that the right hemisphere was engaged in most of the task and that left hemisphere involvement was through callosal influences. Our research on associative learning involving Pavlovian conditioning of auditory stimuli in the rat [McIntosh and Gonzalez-Lima, 1994] has suggested that the sign (positive versus negative) of the influences within a basal forebrain loop involving the septal regions and the nucleus accumbens may reflect the motivational or affective property of the acoustic stimulus. The associative value, on the other hand, may have been reflected by interactions within a limbic thalamocortical circuit of retrosplenial, perirhinal, and insular cortices and the anterior thalamus.

The value of structural equation modeling as a data analytic tool for brain imaging, and as a hypothesis-generating hypothesis-testing tool has been discussed. There is another potential role for neural structural equation models as a bridge between experimental data and neural network modeling both at the systems and neuronal level [see Horwitz and Sporns, 1994, for a full discussion of these issues]. Here, the functional models can act as constraints for computational models based on regional interactions [Otto et al., 1992] or neuronal interactions [Tononi et al., 1992]. This potential will greatly expand the theoretical utility of structural equation modeling in neuroscience.

WHAT IS THE BENEFIT OF ANALYTIC APPROACHES TOWARD THE STUDY OF NEURAL INTERACTIONS IN NEUROSCIENCE?

Many contemporary cognitive neuroscience theories are based mainly on evidence obtained concerning the role a particular structure plays in a particular behavior. For example, research on memory has differentiated between those memory processes that are "hippocampal dependent" and "hippocampal independent" [Eichenbaum et al., 1992; Squire et al., 1993]. These theories incorporate data from animal lesion studies, human clinical studies, and studies that monitor regional activity during tasks of interest (e.g., electrophysiology). On the other hand, if the covariance among neural elements is critical to brain operation, the role of any given region in a particular behavior must be viewed in the context of its interactions with other regions. Network analytic approaches have supported the idea that brain function involves the cooperative interaction among many neural regions, and though it may be that a particular area is critical for a certain function, the performance of any task is a result of the functional interactions of many regions [John and Schwartz, 1978; Gonzalez-Lima, 1992; McIntosh and Gonzalez-Lima, 1993].

The study of neural interactions will be important for relating cognitive theories with brain operations. It is highly unlikely that the functional organization of the brain follows the independent modular organization of psychological constructs. Therefore, it is also unlikely that a single brain region has only one cognitive function. Instead, functionally specialized anatomical networks within the brain may be more easily related to cognitive constructs. There may not be a single brain area that represents "attention" for instance, but there are more likely numerous brain areas whose interactions represent attention operations. The important point is that it may be possible for parts of the same anatomical network to be involved in another function when the interactions change. For example, numerous behavioral brain studies have suggested that primary auditory areas show activity related both to the perceptual components of a stimulus and its learned behavioral relevance [Gonzalez-Lima, 1992, McIntosh and Gonzalez-Lima, 1993; Scheich et al., 1992; Weinberger et al., 1990]. Thus, the same anatomical network can code, in parallel, the perceptual and behavioral properties of stimuli depending on the nature of the interactions between the parts of the network. The hippocampus has a well-established role in declarative memory processes [Squire et al., 1993], but its activity has also been related to voluntary motor behavior and sensory processing in high states of arousal [Bland, 1986; Sainsbury et al., 1987] and habituation or motivation [Gray and McNaughton, 1983; Jarrard, 1993]. These examples suggest that different brain areas can play important roles in multiple functions beyond their classical distinctions, and this may be a general property of the central nervous system rather than specific to only a few brain regions. Indeed, these views are consistent with the adaptive characteristics of the central nervous system, in which functional organiza-

tion is viewed as dynamically related to the particular environmental demands rather than a static property [John and Schwartz, 1978; McIntosh and Gonzalez-Lima, 1993, 1994; Merzenich and Sameshima, 1993; Pascaul-Leone et al., 1994; Recanzone et al., 1992; Scheich et al., 1992; Wolpaw and Lee, 1989; Zohary et al., 1994]. Brain imaging techniques will make an important contribution to the understanding of this property, given their ability to assess activity across many neural regions. Covariance analyses like structural equation modeling will contribute to this understanding by determining the functional relations among these areas and showing how they are modified depending on the behavioral/cognitive requirements.

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REFERENCES

Aertsen A, Bonhoeffer T, Krüger J (1987): Coherent activity in neuronal populations: Analysis and interpretation. In: Caianiello ER (ed): Physics of Cognitive Processes. Singapore: World Scientific Publishing, pp. 1–34.

Aertsen AMH, Gerstein GL, Habib MK, Palm G (1989): Dynamics of neuronal firing correlation: Modulation of "effective connectivity." J Neurophysiol 61:900–917.

Ahissar E, Vaadia E, Ahissar M, Bergman H, Arieli A, Abeles M (1992): Dependence of cortical plasticity on correlated activity of single neurons and on behavioral context. Science 257:1412–1415.

Arbuckle J (1992): AMOS 3.1 Documentation Package. Philadelphia: Temple University.

Batini C, Bernard JF, Buissert-Delmas C, Horcholle-Bossavit G (1983): Cerebellar output response to afferent stimulation: Energy consumption and unit activity in the cat fastigial nucleus. Exp Brain Res 52:400–410.

Bentler PM (1985): Theory and Implementation of EQS, A Structural Equations Program. Los Angeles: BMDP Statistical Software.

Bentler PM, Weeks DG (1980): Linear structural equations with latent variables. Psychometry 45:289–308.

Berry WD (1984): Nonrecursive Causal Models. Sage University Paper Series on Quantitative Applications in the Social Sciences. Beverly Hills: Sage Publications.

Bland BH (1986): The physiology and pharmacology of hippocampal formation theta rhythms. Prog Neurobiol 26:1–54.

Bollen KA (1989): Structural Equations with Latent Variables. New York: Wiley.

Boomsma A (1985): Nonconvergence, improper solutions, and starting values in LISREL maximum likelihood estimation. Psychometry 50:229–242.

Cohen J, Cohen P (1983): Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences. Hillsdale, NJ: Lawrence Erlbaum Associates.

Damasio AR (1989): The brain binds entities and events by multiregional activation from convergence zones. Neural Comp 1:123–132.

Davidon WC (1959): Variable Metric Method for Minimization. AEC Research and Development Report, ANL5990. Argonne, IL: Argonne National Laboratory.

Eichenbaum H, Otto T, Cohen NJ (1992): The hippocampus: What does it do? Behav Neural Biol 57:2–36.

Fletcher R, Powell MJD (1963): A rapidly convergent decent method for minimization. Comput J 6:163–168.

Fox PT, Mintun MA, Reiman EM, Raichle ME (1988): Enhanced detection of focal brain responses using intersubject averaging and change distribution analysis of subtracted PET images. J Cereb Blood Flow Metab 8:642–653.

Freedman DA (1987): As others see us: A case study in path analysis. J Educ Stat 12:101–128.

Friston KJ, Frith CD, Liddle PF, Frackowiak RSJ (1991): Comparing functional (PET) images: The assessment of significant change. J Cereb Blood Flow Metab 11:690–699.

Friston KJ, Frith CD, Liddle PF, Frackowiak RSJ (1992): Motor practice and neurophysiological adaptation in the cerebellum: A positron emission tomography study. Proc R Soc Lond [Biol] 248:223–228.

Friston KJ, Frith CD, Liddle PF, Frackowiak RSJ (1993a): Functional connectivity: The principal-component analysis of large (PET) data sets. J Cereb Blood Flow Metab 13:5–14.

Friston KJ, Frith CD, Frackowiak RSJ (1993b): Time-dependent changes in effective connectivity measure with PET. Hum Brain Mapp 1:69–79.

Gerstein GL, Perkel DH, Subramanian KN (1978): Identification of functionally related neural assemblies. Brain Res 140:43–62.

Gevins A, Cutillo B (1993): Spatiotemporal dynamics of component processes in human working memory. Electroencephalogr Clin Neurophysiol 87:128–143.

Gevins AS, Doyle JC, Cutillo BA, Schaffer RE, Tannehill RS, Bressler SL (1985): Neurocognitive pattern analysis of a visuospatial task: Rapidly-shifting foci of evoked correlations between electrodes. Psychophysiology 22:32–43.

Goldenberg G, Poderka I, Steiner M, Willimes K, Suess E, Deecke L (1989): Regional cerebral blood flow pattern in visual imagery. Neuropsychologia 27:641–664.

Gonzalez-Lima F (1992): Brain imaging of auditory learning functions in rats: Studies with fluorodeoxyglucose autoradiography and cytochrome oxidase histochemistry. In: Gonzalez-Lima F, Finkenstädt T, Scheich H (eds): Advances in Metabolic Mapping Techniques for Brain Imaging of Behavioral and Learning Functions. NATO ASI Series D: Vol 68. Dordrecht: Kluwer Academic Publishers, pp 39–109.

Gonzalez-Lima F, Finkenstädt T, Scheich H (eds) (1992): Advances in Metabolic Mapping Techniques for Brain Imaging of Behavioral and Learning Functions. NATO ASI Series D: Vol 68. Dordrecht: Kluwer Academic Publishers.

Gray JA, McNaughton N (1983): Comparison between the behavioural effects of septal and hippocampal lesions: A review. Neurosci Biobehav Rev 7:119–183.

Harris RJ (1975): A Primer of Multivariate Statistics. New York: Academic Press.

Haxby JV, Grady CL, Horwitz B, Ungerleider LG, Mishkin M, Carson RE, Herscovitch P, Schapiro MB, Rapoport SI (1991): Dissociation of object and spatial visual processing pathways in human extrastriate cortex. Proc Natl Acad Sci USA 88:1621–1625.

Hayduk LA (1987): Structural Equation Modeling with LISREL: Essentials and Advances. Baltimore, MD: John Hopkins University Press.

Heil P, Scheich H (1986): Effects of unilateral and bilateral cochlea removal on 2-deoxyglucose patterns in the chick auditory system. J Comp Neurol 252:279–301.

Horwitz B, Sporns O (1994): Neural modeling and functional neuroimaging. Hum Brain Mapp 1:269–283.

Horwitz B, Grady CL, Haxby JV, Schapiro MB, Rapoport SI, Ungerleider LG, Mishkin M (1992a): Functional associations among human posterior extrastriate brain regions during object and spatial vision. J Cognit Neurosci 4:311–322.

Horwitz B, Soncrant TT, Haxby JV (1992b): Covariance analysis of functional interactions in the brain using metabolic and blood flow data. In: Gonzalez-Lima F, Finkenstädt T, Scheich H (eds): Advances in Metabolic Mapping Techniques for Brain Imaging of Behavioral and Learning Functions. NATO ASI Series. Dordrecht, The Netherlands: Kluwer Academic Publishers, pp 189–218.

Jarrard LE (1993): On the role of the hippocampus in learning and memory in the rat. Behav Neural Biol 60:9–26.

John ER, Schwartz EL (1978): The neurophysiology of information processing and cognition. Annu Rev Psychol 29:1–29.

Jöreskog KG (1973): A general method for estimating a linear structural equation system. In: Goldberger AS, Duncan OD (eds): Structural Equation Models in the Social Sciences. New York: Seminar Press, pp 85–112.

Jöreskog K, Sörbom D (1979): Advances in Factor Analysis and Structural Equation Models. Cambridge: Abt Books.

Jöreskog KG, Sörbom D (1989): LISREL 7 User's Reference Guide. Mooresville, IN: Scientific Software, Inc.

Kenny DA, Judd CM (1984): Estimating nonlinear and interactive effects of latent variables. Psychol Bull 96:201–210.

Lagrèze HL, Hartmann A, Anzinger G, Schaub A, Deister A (1993): Functional cortical interaction patterns in visual perception and visuospatial problem solving. J Neurol Sci 114:25–35.

Loehlin JC (1987): Latent Variable Models: An Introduction to Factor, Path and Structural Analysis. Hillsdale, NJ: Lawrence Erlbaum Associates.

Luria AR (1973): The Working Brain. New York: Basic Books.

MacCallum RC, Roznowski M, Necowitz LB (1992): Model modifications in covariance structure analysis: The problem of capitalization on chance. Psychol Bull 111:490–504.

McArdle JJ, McDonald RP (1984): Some algebraic principles of the Reticular Action Model for moment structures. Br J Math Stat Psychol 37:234–251.

McIntosh AR, Gonzalez-Lima F (1991): Structural modeling of functional neural pathways mapped with 2-deoxyglucose: Effects of acoustic startle habituation on the auditory system. Brain Res 547:295–302.

McIntosh AR, Gonzalez-Lima F (1992a): Structural modeling of functional visual pathways mapped with 2-deoxyglucose: Effects of patterned light and footshock. Brain Res 578:75–86.

McIntosh AR, Gonzalez-Lima F (1992b): The application of structural modeling to metabolic mapping of functional neural systems. In: Gonzalez-Lima F, Finkenstädt T, Scheich H, (eds): Advances in Metabolic Mapping Techniques for Brain Imaging of Behavioral and Learning Functions. NATO ASI Series. Dordrecht, The Netherlands: Kluwer Academic Publishers, pp 219–258.

McIntosh AR, Gonzalez-Lima F (1993): Network analysis of functional auditory pathways mapped with fluorodeoxyglucose: Associative effects of a tone conditioned as a pavlovian excitor or inhibitor. Brain Res 627:129–140.

McIntosh AR, Gonzalez-Lima F (1994): Network interactions among limbic cortices, basal forebrain and cerebellum differentiate a tone conditioned as a Pavlovian excitor or inhibitor: Fluorodeoxyglucose mapping and covariance structural modeling. J Neurophysiol 72:1717–1733.

McIntosh AR, Cooper RM, Gonzalez-Lima F (1991): Metabolic activation of the rat visual system by patterned light and footshock. Neurosci Lett 133:311–314.

McIntosh AR, Grady CL, Ungerleider LG, Haxby JV, Rapoport SI, Horwitz B (1994a): Network analysis of cortical visual pathways mapped with PET. J Neurosci 14:655–666.

McIntosh AR, Horwitz B, Haxby JV, Ungerleider LG, Grady CL (1994b): Functional cortical networks during short-term recognition memory for faces. Soc. Neurosci. Abstr 20:362.

Merzenich MM, Sameshima K (1993): Cortical plasticity and memory. Curr Opin Neurobiol 3:187–196.

Moeller JR, Strother SC (1991): A regional covariance approach to the analysis of functional patterns in positron emission tomographic data. J Cereb Blood Flow Metab 11:A121–A135.

Molotchnikoff S, Tremblay F, Lepore F (1984): The role of the visual cortex in response properties of the lateral geniculate nucleus in rats. Exp Brain Res 53:223–232.

Nobrega JN, Coscina DV (1983): Central injections of the GABA-transaminase inhibitor ethanolamine-O-sulfate (EOS): Effects on brain ^{14}C-2-deoxyglucose uptake and behavior in rats. Brain Res 262:243–252.

Nudo RJ, Masterton RB (1986): Stimulation-induced [^{14}C]2-deoxyglucose labeling of synaptic activity in the central auditory system. J Comp Neurol 245:533–565.

Opticon LM, Richmond BJ (1987). Temporal encoding of two-dimensional patterns by single units in primate inferior temporal cortex. III. Information theoretical analysis. J Neurophysiol 57:162–178.

Otto I, Grandguillaume P, Boutkhil L, Burnod Y, Guigon E (1992): Direct and indirect cooperation between temporal and parietal networks for invariant visual recognition. J Cognit Neurosci 4:35–57.

Pascaul-Leone A, Grafman J, Hallett M (1994): Modulation of cortical motor output maps during development of implicit and explicit knowledge. Science 263:1287–1289.

Pedhazur EJ (1982): Multiple Regression in Behavioral Research: Explanation and Prediction. 2nd Ed. New York: Holt, Reinhart and Winston.

Petit L, Orssaud C, Tzourio N, Salamon G, Mazoyer B, Berthoz A (1993): PET study of voluntary saccadic eye movements in humans: Basal ganglia-thalamocortical system and cingulate cortex involvement. J Neurophysiol 69:1009–1017.

Poline J-B, Mazoyer BM (1993): Analysis of individual positron emission tomography activation maps by detection of high signal-to-noise-ratio pixel clusters. J Cereb Blood Flow Metab 13:425–437.

Recanzone GH, Schreiner CE, Merzenich MM (1992): Plasticity in the frequency representation of primary auditory cortex following discrimination training in adult owl monkeys. J Neurosci 13:87–103.

Roland PE, Levin B, Kawashima R, Åkerman S (1993): Three-dimensional analysis of clustered voxels in ^{15}O-butanol brain activation images. Hum Brain Mapp 1:3–19.

Sandell JH, Schiller PH (1982): Effect of cooling area 18 on striate cortex cells in the squirrel monkey. J Neurophysiol 48:38–48.

Sainsbury RS, Heynen A, Montoya CP (1987): Behavioral correlates of hippocampal type 2 theta in the rat. Physiol Behav 39:513–519.

Scheich H, Simonis C, Ohl F, Thomas H, Tillen J (1992): Learning-related plasticity of gerbil auditory cortex: Feature maps versus meaning maps. In: Gonzalez-Lima F, Finkenstädt T, Scheich H (eds): Advances in Metabolic Mapping Techniques for Brain Imaging of Behavioral and Learning Functions. NATO ASI Series, Vol 68. Dordrecht, The Netherlands: Kluwer Academic Publishers, pp 447–475.

Squire LR, Knowlton B, Musen G (1993): The structure and organization of memory. Annu Rev Psychol 22:453–495.

Tononi G, Sporns O, Edelman GM (1992): Reentry and the problem of integrating multiple cortical areas: Simulation of dynamic integration in the visual system. Cereb Cortex 2:310–335.

Ungerleider LG, Mishkin M (1982): Two cortical visual systems. In: Ingle DJ, Goodale MA, Mansfield RJW (eds): Analysis of Visual Behavior, Cambridge MA: MIT Press, pp 549–586.

Weinberger NM, Ashe JH, Metherate R, McKenna TM, Diamond DM, Bakin J (1990): Retuning of auditory cortex by learning: A preliminary model of receptive field plasticity. Concepts Neurosci 1:91–132.

Wickelgreen BG, Sterling P (1969): Influence of visual cortex on receptive fields in the superior colliculus of the cat. J Comp Neurol 231:281–309.

Widaman KF (1993): Common factor analysis versus principal components analysis: Differential bias in representing model parameters? Multi Behav Res 28:263–312.

Wright S (1920): The relative importance of heredity and environment in determining piebald pattern of guinea pigs. Proc Natl Acad Sci USA 6:320–332.

Wolpaw JR, Lee CL (1989): Memory traces in primate spinal cord produced by operant conditioning of H-reflex. J Neurophysiol 61:563–572.

Zohary E, Celebrini S, Britten KH, Newsome WT (1994): Neuronal plasticity that underlies improvement in perceptual performance. Science 263:1289–1292.