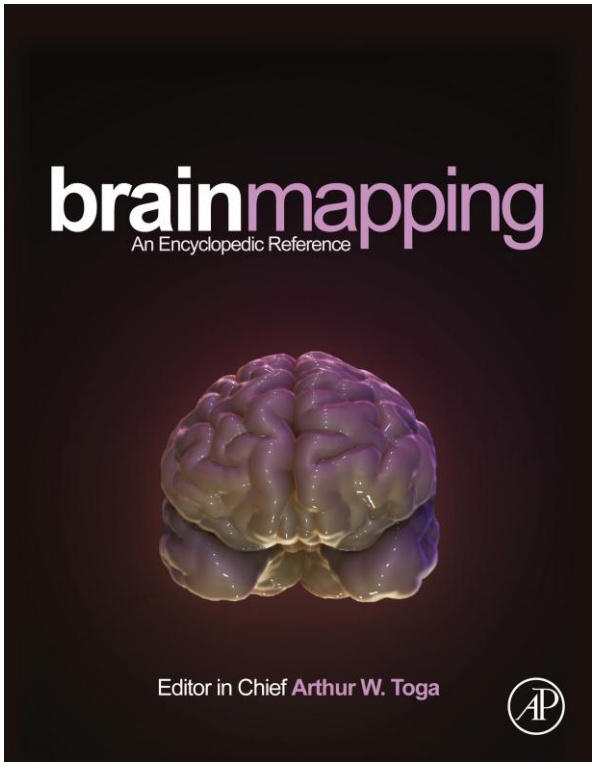

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Effective Connectivity

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Glossary

Autoregressive model (Granger) A model in which the present value of a time-varying process (e.g., the activity of a brain region) linearly depends on some number of its own previous values.

Bayesian model inversion (DCM) An optimization procedure in which the data are used to update the unknown parameters of the causal model, subject to the constraints imposed by the prior distribution, resulting in the posterior distribution.

Effective connectivity Direct influence of one neural element on another.

Forward model (DCM) A mapping from the underlying neural activity generated by the causal model to some observable data feature, such as BOLD, EEG, and MEG activity.

Functional connectivity A temporal association (e.g., correlation and covariance) between the time courses of two neural elements.

Modification index (SEM) The potential improvement in model fit if a parameter of the model (e.g., path coefficient) were allowed to freely vary.

Path coefficient (SEM) A regression weight (beta) that describes the strength of a particular effective connection.

Posterior distribution (DCM) An updated distribution for each parameter that reflects both prior beliefs and empirical knowledge.

Prior distribution (DCM) A distribution for each parameter (e.g., synaptic couplings) that reflects prior beliefs about that parameter and serves as a soft constraint in the ensuing optimization procedure.

Spectral Granger causality (Granger) Total power in one signal that can be attributed to another signal.

Stacked run (SEM) A framework for testing for group and condition differences, wherein several alternative models are simultaneously fitted.

Structural equations (SEM) A set of linear regression equations that describe how much of the variance in a target region is accounted for by the activity in other regions that project to it.

Transfer entropy (Granger) Total information in one signal that can be attributed to another signal.

Network Analysis and Effective Connectivity

A fundamental challenge in neuroscience is to understand how neural operations engender mental phenomena, from sensation to perception to higher cognition. Early clinical studies looking at cognitive deficits following lesions often attributed discrete mental operations to specific brain regions. Modern neuroimaging techniques, which can simultaneously measure activity in the whole brain during some mental function, have reinforced neurobiological theories that emphasize the distributed and integrative nature of neural operations. Brain regions do not operate in isolation, but as part of an interacting network, and the contribution of a particular region must depend on the status of the other elements of the network (neural context; Bressler & McIntosh, 2007; McIntosh, 2000).

In neuroimaging, neural interactions are conceptualized and estimated in terms of two distinct but related notions of connectivity. Functional connectivity refers to temporal associations between neural elements and may be estimated using correlation or covariance, as well as coherence and mutual information. Thus, two elements with statistical interdependency are said to be functionally connected. Yet a functional connection between two neural elements does not imply that they are communicating directly, as their covariation may be due to common inputs from another source. Effective connectivity is a logical progression from functional connectivity and refers to the direct influence of one neural element on another (Aertsen, Gerstein, Habib, & Palm, 1989; Friston, 1994).

The key distinction between functional and effective connectivity lies in the levels of inference they allow. Functional connectivity, estimated as statistical dependencies between neural elements, does not allow inference on the directionality of influence. Effective connectivity is estimated by formulating an explicit causal model of how neural elements influence one another, thereby allowing inference about directional influences. This is illustrated in Figure 1, wherein the two anatomical networks differ in one aspect: the presence of a direct projection from node A to node B (McIntosh & Korostil, 2008). Nodes A and B receive common inputs, and as a result, they would display functional connectivity in both networks. Thus, the two networks could not be differentiated in terms of functional connectivity, but could in terms of effective connectivity. The purpose of effective connectivity is to explicitly model directionality in the network.

In this article, we give an overview of three techniques for estimating effective connectivity. Two are confirmatory, in the sense that an explicit model of element interactions is formulated and tested to see whether it fits the observed data and/or whether it fits the observed data better than alternative models (structural equation modeling, (SEM) and dynamic causal modeling (DCM)). The third (Granger causality) is also used to estimate causal influence but is usually applied in an exploratory fashion to any pair of neural elements. Indeed, Granger causality can also be thought of as an assessment of directed functional connectivity, because it tests for dependencies over time.

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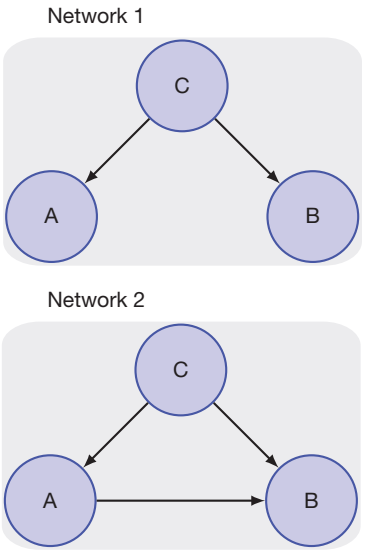

Figure 1 Two different network configurations. The networks have similar topologies, save for a projection from A to B, which is absent in network 1 and present in network 2. Because A and B receive common inputs from C, functional connectivity would not be able to distinguish between the two configurations. Effective connectivity, which explicitly models the directionality of influence, would be able to determine if there is any residual influence from A and B, once the intervening effects of C are accounted for. Adapted from McIntosh, A. R., & Korostil, M. (2008). Interpretation of neuroimaging data based on network concepts. *Brain Imaging and Behavior*, 2(4), 264–269.

Structural Equation Models

The goal of SEM is to test whether a hypothesized causal structure is consistent with the empirical data (Jöreskog, Sörbom, Magidson, & Cooley, 1979; Loehlin, 1987). In neuroimaging, SEM models are usually a subset of brain regions and the patterns of causal influence among them (McIntosh & Gonzalez-Lima, 1991; McIntosh et al., 1994; McIntosh & Gonzalez-Lima, 1994). Regions to be included in the model are typically selected based on prior hypotheses or analytic outcomes. Patterns of influence between regions are anatomically constrained, such that effective connectivity between two regions is possible only if there is a direct anatomical link (although indirect effects are possible).

Model Specification

The path diagram in Figure 2 (left) illustrates how a structural model is mathematically formulated (McIntosh and Mišić, 2013). The activity of each region is treated as a variable. Effective connectivity between elements is specified by a system of linear regression equations, termed *structural equations*, that define the sources of variance for each region. In the present example, x_i represents the variance of each region, which is partitioned into variance explained by other regions, as well as an error or residual term (ψ_{x_i}). Residual terms represent exogenous influences from other regions that could not be included in the model, as well as the influence of a region on itself. The regression weights p, q, r, s, and t (also known as *path coefficients*) represent the strength of each effective connection. The causal order of the network is given by the system of structural equations

$$\begin{aligned} x_1 &= \psi_{x_1} \\ x_2 &= px_1 + \psi_{x_2} \\ x_3 &= qx_1 + rx_2 + \psi_{x_3} \\ x_4 &= sx_2 + tx_3 + \psi_{x_4} \end{aligned} \quad [1]$$

This system of equations is used to generate a predicted or *implied* covariance matrix (McArdle & McDonald, 1984). The implied covariance matrix is a prediction of the variances of neural elements and their mutual covariances, parameterized by the path coefficients. For example, the pairwise correlations R_{x_i, x_j} predicted by eqn [1] are

$$\begin{aligned} R_{x_1,x_2} &= p \\ R_{x_1,x_3} &= q + pr \\ R_{x_1,x_3} &= ps + prt + qt \\ R_{x_2,x_3} &= r + pq \\ R_{x_2,x_3} &= s + rt + pqt \\ R_{x_3,x_4} &= t + sr + qps \end{aligned} \quad [2]$$

Model Estimation

Path coefficients and residual variances are estimated recursively by fitting the implied covariance matrix to the empirical covariance matrix. Thus, SEM uses patterns of functional connectivity (covariances) to estimate effective connectivity (path coefficients).

Path coefficients represent the proportion of activity in one area that is determined by the activity of other areas that project to it. For example, in Figure 2, the structural equation for any given connection (e.g., x_1–x_3) contains terms that represent the influence of other areas (e.g., the path coefficients for x_1–x_2 and x_2–x_3), in addition to the path coefficient for that connection. As a result, a path coefficient can be thought of as a semipartial correlation, because it reflects the influence of one area on another, with influences from other areas held constant.

Model Inference

The simplest question that can be addressed with SEM is whether the model fits the observed data. Here, the discrepancy between the implied and empirical covariance matrices is assessed using some goodness-of-fit statistic, such as the χ^2. A model that is not consistent with the data would yield a large χ^2 value, indicating a significant departure from the empirical (i.e., expected) covariance matrix.

A principal strength of SEM is that it can be extended to compare multiple models that represent competing hypotheses. For instance, if two regions are reciprocally connected, SEM can be used to test whether the effective connections between them are equal (i.e., symmetrical) or unequal (i.e., asymmetrical). The implied covariance matrices for the symmetrical and asymmetrical models are compared to the empirical covariance matrix, generating two separate statistics, $\chi^2_{\text{symmetric}}$ and $\chi^2_{\text{asymmetric}}$, for their respective goodness of fit. The model fits are then compared directly using the χ^2 difference test; the difference $\chi^2_{\text{asymmetric}} - \chi^2_{\text{symmetric}}$ is computed and assessed with respect to the difference in degrees of freedom for the two models. The test assesses whether the modification of

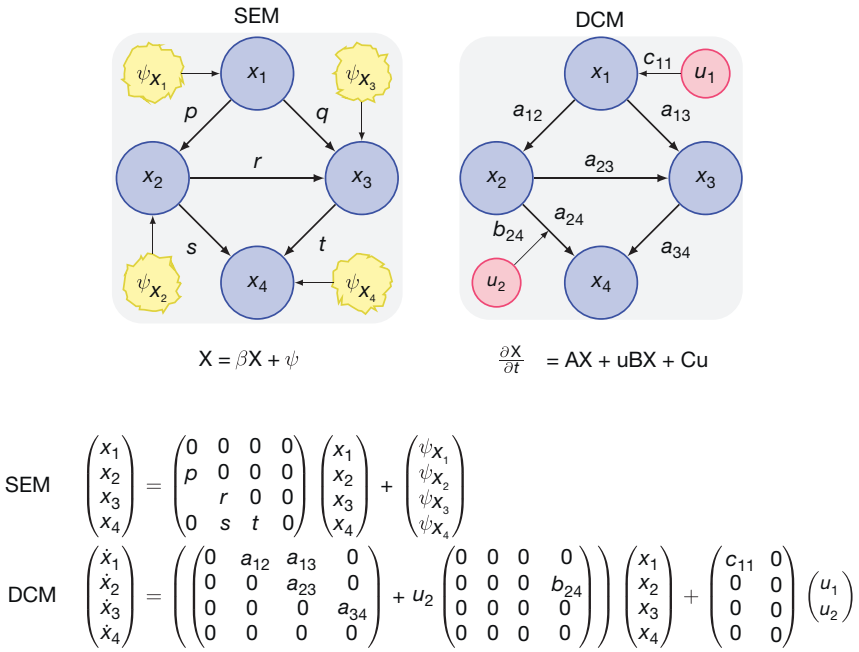

Figure 2 Similarities and differences between SEM and DCM. In SEM (left), causal order is specified by a system of linear regression equations with one set of path coefficients (β) and error terms (ψ). In DCM (right), causal order is specified by a system of differential equations parameterized in terms of synaptic couplings (A), as well as exogenous inputs (u) that may influence either the synaptic couplings between regions (B) or intrinsic activity in individual regions (C). Adapted from McIntosh, A., & Mišić, B. (2013). Multivariate statistical analyses for neuroimaging data. *Annual Review of Psychology*, 64, 499–525.

allowing asymmetrical effects for reciprocal connections significantly improves model fit. A significant difference would imply that the additional path coefficient improved the overall model fit, providing evidence that the path coefficients are different for the two connections. Functional connectivity, which is symmetrical by definition, could not be used to make inferences on these competing hypotheses (McIntosh & Gonzalez-Lima, 1994).

The hierarchical approach we have just described can also be used to test whether effective connections differ between conditions or groups. To test for group differences for specific connections, several models can be nested in a single multigroup (stacked) run (McIntosh, Cabeza, & Lobaugh, 1998). In a null model, path coefficients are constrained to be the same for all groups, yielding the same implied covariance matrix for each group. The alternative model allows path coefficients for those connections to vary, yielding a separate implied covariance matrix for each group. If the fit is significantly improved by allowing path coefficients to vary, then there is a significant difference in those effective connections between conditions.

So far, we have described how SEM can be used in a confirmatory manner, where the causal structure is predefined based on known anatomy and the inferential focus is on whether specific effective connections change between tasks. Bullmore et al. (2000) proposed a more relativistic approach to model selection, where only the nodes of the network are specified a priori, while the connectivity of the model is filled out in a data-driven manner. The procedure starts with a null model, in which all path coefficients are set to zero. At each iteration, the path coefficient with the largest *modification index* (the improvement in model fit if that path coefficient were allowed to freely vary) is temporarily unconstrained and added to the model. Since the addition of any path will improve the χ^2 value, the modification is evaluated using a parsimonious fit index, which is high for models that have both a well-fitting implied covariance matrix and the fewest paths (Bollen, 1986). A path is added permanently only if it improves the fit index; otherwise, the path with the next highest modification index is unconstrained and evaluated. The procedure continues until the fit index cannot be increased further by adding paths, resulting in a model that optimally fits the observed data. There is a distinct possibility of capitalization on chance with such an iterative fitting procedure, however, cross-validation either within the sample or on a new sample is necessary.

Dynamic Causal Modeling

DCM is a Bayesian framework for estimating experimentally induced changes in effective connectivity. Unlike SEM and Granger causality, it seeks to estimate causal influence at the level of the underlying neuronal dynamics, rather than at the level of the observations (e.g., fMRI BOLD signal or EEG/MEG) (Friston, Harrison, & Penny, 2003).

Causal Model

As with SEM, an initial model of causal influence is defined by specifying a set of regions, which may be chosen based on hypotheses or analyses. Each region in the model is composed of neuronal subpopulations intrinsically coupled to each

other. Neuronal populations at each region are extrinsically coupled to each other, forming a network. The activity of each neuronal population is governed by a set of coupled stochastic or ordinary differential equations that relate the rate of change of activity $\left(\frac{\partial x}{\partial t}\right)$ to current activity (x):

$$\frac{\partial x}{\partial t} = f(x, u, \theta^c) \quad [3]$$

Synaptic coupling between populations is mathematically represented by introducing terms for the state of one population into the equation for the state of another population, thereby allowing the former to influence the latter. The speed with which one population influences another is described by a set of coupling parameters (θ^c). The coupling parameters θ^c are unknown, and the purpose of DCM is to infer them, analogous to path coefficients in SEM but focusing on the observed time series. Exogenous influences (u), representing experimental manipulations, manifest as external inputs that induce changes in an individual population or in the coupling between populations.

Forward Model

The underlying causal model describes the temporal evolution of neuronal activity. To allow comparison between the causal model and the observed data, a forward model is used to translate this neural activity into predicted neuroimaging measurements, analogous to the implied covariance matrices in SEM. The forward model is a mapping (g) from the underlying neuronal activity (x) to some feature of the data (y):

$$y = g\left(x, \theta^f\right) \quad [4]$$

The forward model is chosen according to the imaging modality used in the experiment. If the data are evoked responses, such as event-related potentials or fields, the forward model g is the lead field matrix, modeling the propagation of electric current or magnetic fields though the brain, cerebrospinal fluid, skull, and scalp. The location and orientation of the source dipole are parameterized by θ^f (Kiebel, David, & Friston, 2006). If the data are BOLD contrast, g models the hemodynamic response by mapping local neuronal activity to changes in blood flow, blood volume, and deoxygenated hemoglobin (Buxton, Wong, & Frank, 1998). In that case, parameters θ^f represent rate constants of vasodilatory signal decay and autoregulatory feedback by blood flow (Stephan, Weiskopf, Drysdale, Robinson, & Friston, 2007).

Figure 2 demonstrates that SEM and DCM have much in common (McIntosh and Mišić, 2013). From the perspective of SEM, the extrinsic synaptic couplings implemented in DCM can be thought of as the grand average effective connectivity across all conditions and the modulatory effects as the changes in extrinsic connectivity due to experimental manipulation. From the perspective of DCM, SEM can be thought of as a special case in which the system is driven by noise rather than systematic exogenous inputs (Figure 2), while the interactions are linear and take place at the level of the observations, rather than at the neural level (McIntosh and Mišić, 2013).

Model Inversion

Once the causal model has been translated from neuronal activity to predicted data (e.g., ERPs and BOLD signal), it can be compared to the observed data to estimate the unknown parameters of the model, including the synaptic couplings. In DCM, the comparison between predicted and observed data is done within a Bayesian framework. Unknown model parameters are assumed to be random variables. Before the experiment is performed, these parameters have a prior distribution, which reflects a priori knowledge about their values. A prior distribution constrains the unknown parameters to an interval or to a fixed value. For instance, if two regions share no known anatomical connection, their synaptic coupling may be assumed to be zero. Likewise, prior empirical knowledge may be used to set the likely range of values of some hemodynamic parameters.

Following the experiment, the data are used to update the model (i.e., estimate the parameters), resulting in a posterior distribution for each parameter, which reflects both prior beliefs and empirical knowledge. This updating procedure (Bayesian model inversion) seeks to maximize the *model evidence*, defined as the probability of the data given the present model. Model evidence is highest for models that explain the data accurately and have the fewest parameters.

Inference

DCMs allow statistical inference on models and on parameters (Stephan et al., 2007, 2010). Two models can be compared directly by taking either the ratio of their respective evidence (Kass & Raftery, 1995) or the difference in their respective log evidence. A model with evidence more than 20 times greater than another model is considered stronger. This procedure (Bayesian model selection) can be used to make a wide variety of comparisons, such as DCMs with different inputs, different anatomical connections, and different priors. Models with different numbers of parameters can be compared directly because evidence takes into account model complexity. Once the optimal model is selected, specific parameters can be statistically assessed with respect to their posterior densities.

Note that the relative log evidence (or log Bayesian factor) plays exactly the same role as the difference in χ^2 goodness-of-fit statistics in SEM. As we will see in the next section, in Granger causality, the implicit likelihood of two models is indexed by the F-statistic. Thus, all of these statistics can be regarded as comparing the likelihood of models with and without particular connections or dependencies.

Granger Causality

Autoregressive Models

If the past of signal x_1 contains information that can help to predict the future of another signal x_2 above and beyond information contained in the past of x_2 itself, then x_1 is said to have causal influence on x_2 (Wiener, 1956). Assuming that it is purely linear, this causal relationship can be mathematically represented as a linear regression, where the past values of x_1 are used to predict the present value of x_2 (Granger, 1969). In

other words, if the prediction error for present values of x_2 is reduced by inclusion of past values of x_1, x_1 exerts causal influence on x_2 (Ding, Chen, & Bressler, 2006; Seth, 2007). Notice that time is important in making inferences about effective connectivity, similar to DCM with time delays, but unlike SEM, which focuses on zero-order covariances. For any given pair of signals, causal influence can be assessed in both directions by reversing their roles, allowing causal effects (i.e., effective connectivity) to be either reciprocal or unidirectional.

In the context of neuroimaging, where the focus is on causal relationships within a network of brain regions, this definition can be extended to the multivariate case, such that the present activity of all regions is predicted by the past activity of all other regions. Maintaining the assumption that they are linear, these causal relationships can be mathematically represented as a multivariate linear regression, also known as a multivariate vector autoregressive (MVAR) model (Goebel, Roebroeck, Kim, & Formisano, 2003). At the outset, the model will contain terms for every possible connection in the network, with each connection tested individually to determine if it is significantly different from zero. In this manner, a directed subnetwork depicting causal flow can be extracted without an a priori hypothesis about precise pattern of effective connectivity among regions, analogous to the relativistic SEM approach (Bullmore et al., 2000).

An MVAR model of order m seeks to predict the present (tth) values of p variables (e.g., brain regions) as a linear combination of their m previous values. The tth sample from the multivariate time series is represented as a p-dimensional vector $\mathbf{X}(t)$:

$$\mathbf{X}(t) = \sum_{i=1}^{m} \mathbf{A}(i)\mathbf{X}(t-i) + \mathbf{E}(t) \qquad [5]$$

The ith matrix $\mathbf{A}(i)$ has dimensions $p \times p$ and contains autoregressive coefficients for time lag i, which can be estimated by ordinary least squares. $\mathbf{E}(t)$ is a vector of residuals. The present value of the jth region $x_j(n)$ is a linear combination of m past values of all other regions, weighted by the elements of the jth column of matrix $\mathbf{A}(i)$. Thus, for an individual effective connection, the influence of all other regions in the network is accounted for and partialled out. Since the effective connections are formulated as regression equations, their significance is typically assessed via the F-test. Alternatively, a confidence interval on the autoregressive coefficients can be constructed by bootstrapping (Roebroeck, Formisano, & Goebel, 2005).

Spectral and Nonlinear Extensions

The Granger framework has been further developed and adapted for specific types of signals and causal relationships, two of which we outline here. The first innovation concerns signals that naturally contain strong oscillatory components in specific bands, such as electromagnetic neural activity. The Granger framework can be extended to the frequency domain, allowing a spectral representation of causal influence (Ding et al., 2006; Geweke, 1982; Kaminski, Ding, Truccolo, & Bressler, 2001). Spectral Granger causality is applied to signals that have been transformed to the frequency domain; it is calculated for each frequency and interpreted as the total power in some signal x_1 that can be attributed to another signal x_2. Spectral Granger causality is closely related to the directed transfer function (Kaminski et al., 2001) and partial directed coherence (Baccalá & Sameshima, 2001).

The second innovation extends Granger causality to include nonlinear causal influences between signals. Here, the extent to which past values of one signal predict the present value of another is assessed by conditional mutual information, rather than linear regression known as transfer entropy (TE). This formulation defines causal influence as a directed exchange of information (Schreiber, 2000; Vicente, Wibral, Lindner, & Pipa, 2011). Specifically, TE from x_1 to x_2 is the decrease of uncertainty in future values of x_2 due to knowledge of past values of x_1, given past values of x_2. The advantage of this approach is that it does not assume any particular causal order (TE is computed for all pairwise connections) nor any particular type of causal influence (TE is sensitive to linear and nonlinear effects). Although TE was a bivariate measure in its initial formulation, it has been extended to the multivariate case such that confounding influences from intervening regions (i.e., indirect coupling) are accounted for and 'partialled' out (Vakorin, Krakovska, & McIntosh, 2009).

Summary

Effective connectivity describes the distributed network interactions that give rise to mental operations. A diverse repertoire of techniques has been developed to accommodate different assumptions, imaging modalities, and experimental questions. The techniques we have outlined often differ mathematically and sometimes philosophically, but they all represent specific and complementary models of how patterns of influence are established within a network of neural elements and how these patterns support mental function.

See also: **INTRODUCTION TO METHODS AND MODELING**: Bayesian Model Inversion; Bayesian Model Inference; Distributed Bayesian Inversion of MEG/EEG Models; Dynamic Causal Models for fMRI; Dynamic Causal Models for Human Electrophysiology: EEG, MEG, and LFPs; Forward Models for EEG/MEG; Granger Causality; Models of fMRI Signal Changes; Neural Mass Models; Resting-State Functional Connectivity.

References

Aertsen, A., Gerstein, G., Habib, M., & Palm, G. (1989). Dynamics of neuronal firing correlation: modulation of 'effective connectivity'. *Journal of Neurophysiology*, *61*(5), 900–917.

Baccalá, L., & Sameshima, K. (2001). Partial directed coherence: A new concept in neural structure determination. *Biological Cybernetics*, *84*(6), 463–474.

Bollen, K. (1986). Sample size and bentler and bonett's nonnormed fit index. *Psychometrika*, *51*(3), 375–377.

Bressler, S., & McIntosh, A. (2007). The role of neural context in large-scale neurocognitive network operations. In V. Jirsa & A. McIntosh (Eds.), *Handbook of brain connectivity* (pp. 403–419). Berlin: Springer.

Bullmore, E., Horwitz, B., Honey, G., Brammer, M., Williams, S., & Sharma, T. (2000). How good is good enough in path analysis of fmri data? *NeuroImage*, *11*(4), 289–301.

Buxton, R., Wong, E., & Frank, L. (1998). Dynamics of blood flow and oxygenation changes during brain activation: The balloon model. *Magnetic Resonance in Medicine*, *39*(6), 855–864.

Ding, M., Chen, Y., & Bressler, S. (2006). Granger causality: Basic theory and application to neuroscience. In S. Schelter, N. Winterhalder & J. Timmer (Eds.), *Handbook of time series analysis* (p. 437). Wiley-VCH.

Friston, K. J. (1994). Functional and effective connectivity in neuroimaging: A synthesis. *Human Brain Mapping*, *2*(1–2), 56–78.

Friston, K., Harrison, L., & Penny, W. (2003). Dynamic causal modelling. *NeuroImage*, *19*(4), 1273–1302.

Geweke, J. (1982). Measurement of linear dependence and feedback between multiple time series. *Journal of the American Statistical Association*, *77*(378), 304–313.

Goebel, R., Roebroeck, A., Kim, D., & Formisano, E. (2003). Investigating directed cortical interactions in time-resolved fmri data using vector autoregressive modeling and granger causality mapping. *Magnetic Resonance Imaging*, *21*(10), 1251–1261.

Granger, C. (1969). Investigating causal relations by econometric models and cross-spectral methods. *Econometrica*, *37*, 424–438.

Jöreskog, K., Sörbom, D., Magidson, J., & Cooley, W. (1979). *Advances in factor analysis and structural equation models*. Cambridge, MA: Abt Books.

Kaminski, M., Ding, M., Truccolo, W., & Bressler, S. (2001). Evaluating causal relations in neural systems: Granger causality, directed transfer function and statistical assessment of significance. *Biological Cybernetics*, *85*(2), 145–157.

Kass, R., & Raftery, A. (1995). Bayes factors. *Journal of the American Statistical Association*, *90*(430), 773–795.

Kiebel, S., David, O., & Friston, K. (2006). Dynamic causal modelling of evoked responses in eeg/meg with lead field parameterization. *NeuroImage*, *30*(4), 1273–1284.

Loehlin, J. (1987). *Latent variable models: An introduction to factor, path, and structural equation analysis*. Hillsdale, NJ: Lawrence Erlbaum.

McArdle, J., & McDonald, R. (1984). Some algebraic properties of the reticular action model for moment structures. *British Journal of Mathematical and Statistical Psychology*, *37*(2), 234–251.

McIntosh, A. (2000). Towards a network theory of cognition. *Neural Networks*, *13*(8–9), 861–870.

McIntosh, A., Cabeza, R., & Lobaugh, N. (1998). Analysis of neural interactions explains the activation of occipital cortex by an auditory stimulus. *Journal of Neurophysiology*, *80*(5), 2790–2796.

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

McIntosh, A., Grady, C., Ungerleider, L., Haxby, J., Rapoport, S., & Horwitz, B. (1994). Network analysis of cortical visual pathways mapped with pet. *Journal of Neuroscience*, *14*(2), 655–666.

McIntosh, A. R., & Korostil, M. (2008). Interpretation of neuroimaging data based on network concepts. *Brain Imaging and Behavior*, *2*(4), 264–269.

McIntosh, A., & Mišić, B. (2013). Multivariate statistical analyses for neuroimaging data. *Annual Review of Psychology*, *64*, 499–525.

McIntosh, A., & Gonzalez-Lima, F. (1994). Structural equation modeling and its application to network analysis in functional brain imaging. *Human Brain Mapping*, *2*(1–2), 2–22.

Roebroeck, A., Formisano, E., & Goebel, R. (2005). Mapping directed influence over the brain using granger causality and fmri. *NeuroImage*, *25*(1), 230–242.

Schreiber, T. (2000). Measuring information transfer. *Physical Reviews Letters*, *85*(2), 461–464.

Seth, A. (2007). Granger causality. *Scholarpedia*, *2*(7), 1667.

Stephan, K., Penny, W., Moran, R., den Ouden, H., Daunizeau, J., & Friston, K. (2010). Ten simple rules for dynamic causal modeling. *NeuroImage*, *49*(4), 3099–3109.

Stephan, K., Weiskopf, N., Drysdale, P., Robinson, P., & Friston, K. (2007). Comparing hemodynamic models with dcm. *NeuroImage*, *38*(3), 387–401.

Vakorin, V., Krakovska, O., & McIntosh, A. (2009). Confounding effects of indirect connections on causality estimation. *Journal of Neuroscience*, *184*(1), 152–160.

Vicente, R., Wibral, M., Lindner, M., & Pipa, G. (2011). Transfer entropy–A model-free measure of effective connectivity for the neurosciences. *Journal of Computational Neuroscience*, *30*(1), 45–67.

Wiener, N. (1956). The theory of prediction. In E. Beckenbach (Ed.), *Modern mathematics for engineers* (pp. 165–190). New York: McGraw-Hill.