Published in final edited form as:

Neuroimage. 2009 May 1; 45(4): 1190–1198. doi:10.1016/j.neuroimage.2009.01.006.

How Well Does Structural Equation Modeling Reveal Abnormal Brain Anatomical Connections? An fMRI Simulation Study

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Abstract

Many brain disorders result from alterations in the strength of anatomical connectivity between different brain regions. This study investigates whether such alterations can be revealed by examining differences in interregional effective connectivity between patient and normal subjects. We applied one prominent effective connectivity method – Structural Equation Modeling (SEM) – to simulated functional MRI (fMRI) timeseries from a neurobiologically realistic network model in which the anatomical connectivity is known and can be manipulated. These timeseries were simulated for two task conditions, a delayed match-to-sample (DMS) task and passive-viewing, and for “normal subjects” and “patients” who had one weakened anatomical connection in the neural network model. SEM results were compared between task conditions as well as between groups. A significantly reduced effective connectivity corresponding to the weakened anatomical connection during the DMS task was found. We also obtained a significantly reduced set of effective connections in the patient networks for anatomical connections “downstream” from the weakened linkage. However, some “upstream” effective connections were significantly larger in the patient group relative to normals. Finally, we found that of the SEM model measures we examined, the total error variance was the best at distinguishing a patient network from a normal network. These results suggest that caution is necessary in applying effective connectivity methods to fMRI data obtained from non-normal populations, and emphasize that functional interactions among network elements can become abnormal even if only part of a network is damaged.

Introduction

Functional neuroimaging procedures such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have been applied to clinical populations for such purposes as identifying abnormal brain areas (Paulesu et al., 1996), early detection of disease (Azari et al., 1993a; Dickerson, 2006; Haxby et al., 1986), and assessing therapeutic treatment (Delfino et al., 2007; Goekoop et al., 2004). Because many brain disorders, such as Alzheimer dementia, Parkinson’s disease and autism, are thought to involve abnormal interregional anatomical connectivity (Bhat and Weiner, 2005; Courchesne and Pierce, 2005; Minshew and Williams, 2007; Morrison et al., 1990; Rogers and Morrison, 1985), a recent trend in functional neuroimaging has been to use network connectivity analysis methods to identify and investigate the damaged anatomical connections that might be responsible for the

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functional and behavioral abnormalities associated with specific disorders (e.g., Bokde et al., 2006; Grafton et al., 1994; Horwitz et al., 1988, 1995, 1998;; Just et al., 2007), or to assess the extent of neuroplasticity following various therapeutic/rehabilitative treatments (Azari et al., 1993b; Kelly and Garavan, 2005; Liu et al., 2007; van Eimeren and Siebner, 2006). Relatively newer methods in structural MRI, diffusion tensor imaging and specifically diffusion tractography, have also been used to explore these anatomical alterations (e.g., Catani et al., 2008; Head et al., 2004); for a review, see Johansen-Berg and Behrens (2006).

One popular method for ascertaining interregional connectivity using functional neuroimaging data is structural equation modeling (SEM). This technique was introduced into neuroimaging for brain effective connectivity analysis (McIntosh and Gonzalez-Lima, 1991; McIntosh et al., 1994), which determines task-dependent (Buchel and Friston, 1997; Honey et al., 2002; McIntosh et al., 1994) or group-dependent (Au Duong et al., 2005; Grafton et al., 1994; Horwitz et al., 1995; Rowe et al., 2002; Schlosser et al., 2003a) changes in a hypothesized causal structure (or path model). A path model is obtained by selecting a specified set of brain regions, and combining explicit data about their anatomical connections (often based on results from neuroanatomical studies in nonhuman primates) with their task-specific interregional functional covariances (obtained from PET or fMRI). Some type of computational optimization analysis is then used to determine the functional strengths (i.e. the effective connectivities) of each anatomical link between the regions that provide the closest match between the experimentally determined interregional functional covariances and those based on the computed functional strengths. The final set of computed effective connections defines the functional network corresponding to each task (or group) under study (Kim et al., 2007).

With respect to neurological and psychiatric disorders, an important application of effective connectivity analysis, as exemplified by the references listed above, has been to identify dysfunctional interregional connections in a patient group, and possibly use this as the basis for early detection of disease. Furthermore, effective connectivity analysis also can be used as an *in vivo* assessment of rehabilitation and/or therapeutic interventions. However, because we do not know in any given subject which neural pathways are abnormal, there is no empirical way to know that SEM analysis correctly reveals abnormal interregional anatomical connections. In general, one does not know if the functional networks obtained using SEM with real experimental data actually represent the underlying neural relationships.

One way to examine the adequacy of SEM to identify dysfunctional anatomical connections is by using a neurobiologically realistic computational model in which the interregional anatomical links are known and have connection strengths that can be altered. We have constructed such a model that performs a visual delayed match-to-sample (DMS) task for 2D object shape (Tagamets and Horwitz, 1998; Horwitz and Tagamets, 1999; Horwitz et al., 2005). This model allows us to simulate neuronal and fMRI BOLD activity that closely matches experimentally acquired data. Therefore, we can employ this model as a testing ground where fMRI data can be related to its underlying neural substrate, and where evaluation of brain functional and effective connectivity can be investigated (for some previous examples, see Horwitz et al., 2005; Kim and Horwitz, 2008; Lee et al., 2006).

In the current paper, we investigated how well SEM can be used to examine differences in effective connectivity in disorders of brain connectivity. Specifically, using simulated fMRI data, we examined the SEM-based effective connectivity changes generated by a damaged anatomical connection in the model. The main question we asked was: do the results of an SEM analysis on this network lead to conclusions that correctly reflect the actual nature of the underlying neural network?

Methods

Large-scale Neural Network Model

A large-scale neural computational network was used to simulate region-specific neuronal and fMRI data (Tagamets and Horwitz, 1998; Horwitz and Tagamets, 1999; Horwitz et al., 2005). The model contains four major brain regions; primary sensory cortex (V1/V2), secondary sensory cortex (V4), inferior temporal cortex (IT), and prefrontal cortex (PFC). The PFC consists of four sub-populations; FS (stimulus-sensitive units), D1 (units active during the delay between stimuli), D2 (units active during stimulus presentation and during the delay), and FR (units whose activity increases if there is a match between the first and second stimuli). These four PFC neuronal types have simulated neural activities based on those found by Funahashi et al. (1990) in monkey. Although the actual neurons are likely to co-exist in the same macroscopic brain location, we will treat them as if they comprise spatially separated brain regions because the anatomical connections among four submodules are complex and thus offer a good test for SEM (see Tagamets and Horwitz, 1998 and Horwitz et al., 2005) (see Fig. 1).

The computational details associated with the model are given in Tagamets and Horwitz (1998). In brief, every region is composed of multiple excitatory-inhibitory units each of which represents a cortical column. Regions are linked by both feedforward and feedback connections. The majority of these connections are excitatory (an excitatory element in one region synapsing onto excitatory units in another region), but some are inhibitory (an excitatory unit in one region synapsing onto inhibitory elements in another region); see Fig. 1. There are different scales of spatial integration in the first three stages, with the primary sensory region having the smallest spatial window and IT the largest. The time-step used in the models corresponds to a time of approximately 5 ms.

The region-specific neural activities were generated by the model performing a visual DMS task. The task design consisted 10 blocks and each block contained 6 DMS task trials and 6 'passive-viewing' (PV) trials in which scrambled visual objects are presented. Each trial consisted of presentation of the first stimulus for 1 sec, a 1.5 sec delay, presentation of the second stimulus for 1 sec, and 1 sec for the response (and the inter-trial interval) period.

We note that half the units in each region were assigned as non-specific neurons to which noise patterns were presented asynchronously and randomly relative to the presentation times of the stimuli. This effect provides the trial-to-trial variability that may arise, in part, from the interactions between neuronal network elements responding to the task of interest and brain regions not specifically involved in the task, which are likely to occur in real subjects (for a discussion of the sources of variability in fMRI data, see Horwitz et al., 2005).

Block-to-block variability was modeled by modulating the value of a parameter that we have named the attention parameter, which informs the model as to which task (DMS or PV) to perform. This parameter modulates how D2 units respond to a given stimulus; e.g., the higher the attention, the better the representation that is maintained during the delay period. The attention parameter also influences activity in posterior brain regions (e.g., V4) via feedback connections from D2. The attention values of the DMS task ranged from 0.22 to 0.31 (in arbitrary units) in steps of 0.01 for each block. The attention parameter for all passive-viewing (PV) task trials was fixed at 0.05.

Subject-to-subject variability was obtained by varying the interregional anatomical connection weights (see Horwitz et al., 2005 for details). This allows us to generate a sufficient number of datasets for group analysis, and also to simulate data representing healthy controls who have normal anatomical connections as well as patients who have damaged anatomical connections.

An example of assigning connection weights can be found in Table 1 of (Horwitz et al., 2005). In terms of percentage of the connection weight values used in the Tagamets-Horwitz model (1998), the weights ranged from 0.7 to 0.98 with a mean of 0.84. To investigate how well SEM reflects the underlying neuronal relationships, we evaluated the differences of the effective connectivities (i.e., the path coefficients) between normal controls and patients. Patients were specifically generated by reducing one anatomical connection from inferior temporal cortex (IT) to prefrontal cortex (PFC) to an average of 20% of its normal values (range: 15–25%). Additionally, we included another patient group that has exactly the same anatomical connection weights as the normal controls for all connections except the one from IT to PFC, which was set to the same reduced weight values as that of the patient group. We called this additional patient group the ‘clone’ group because each subject was a replicate of a normal control subject except for the one weakened anatomical path. Any group differences between controls and clones are attributable only to the one weakened anatomical link, and not to differences in other anatomical connections.

We simulated three groups of fMRI datasets: 20 normal controls, 20 clone patients, and 20 patients. Following the procedure we have used before (e.g., Horwitz et al., 2005; Husain et al., 2004), for each subject, the absolute value of the simulated integrated synaptic activity (ISA) in each region was integrated over 10 timesteps (50msec), and convolved with a gamma function representing the hemodynamic response function (Boynton et al., 1996) to produce a temporally smoothed fMRI BOLD signal, which was then down-sampled every 2 sec (TR=2sec) to give the final fMRI time series data. Each regional fMRI time series was divided into separate time series for the DMS and PV conditions (160 time points for each), and standardized to zero mean and unit variance.

Structural Equation Modeling (SEM)

There are several components of an SEM analysis: (a) identification of the nodes of the proposed neurofunctional network; (b) determining how the nodes are causally connected to each other; (c) evaluating the interregional effective connectivities (i.e., the path coefficients); and (d) estimating how well the structural equation model fits the experimental data.

Concerning the first two of these components, the issue in SEM of determining the underlying neurofunctional model nodes and their connections can be addressed by using prior neuroanatomical information (e.g., McIntosh et al., 1994) or by a data-driven model selection approach such as partial least squares (McIntosh et al., 1996). Although the choice of the regions comprising the model and their interregional connections is a difficult issue, we will not deal with it here. Rather, because we know the true underlying anatomical model in our simulation model, we will use it as the path model (see Figure 1).

For each subject, model fitting and path parameter estimations were performed for each condition (DMS and PV) using LISREL software (Scientific Software International, Inc, Lincolnwood, IL). LISREL estimates path coefficients by minimizing the discrepancy between a correlation (or covariance) matrix obtained from the observed fMRI data and a correlation matrix implied by the model. The discrepancy function is called the fit function, which is a form of the log maximum-likelihood (ML) function, $F_{ML} = \log|\Sigma(\theta)| + tr(S\Sigma^{-1}(\theta)) - \log|S| - k$, where k is the number of variables (or brain regions). This function approaches zero if the sample correlation matrix S equals the implied correlation matrix (Σ) given a certain parameter vector (θ) (Joreskog and Sorbom, 1986; Schlosser et al., 2006). The estimated path coefficients represent the expected change in the activity of one region given a unit change in the activity of the region influencing it (Bollen, 1989). Also associated with each node is an error variance, which indicates the proportion of total variance in each region that is not accounted for by the effects of regions in the model. Such error variances are usually either fixed or estimated *a priori* to reduce the number of free parameters, thereby allowing greater freedom in

specification of the connections between regions (Bullmore et al., 2000; McIntosh et al., 1994). In our study, we adopted a simple way of fixing the values of the error variances. We first allowed the error variances and path coefficients to be free to be estimated in LISREL. Then we entered the initially estimated error variances as fixed values into LISREL, and fitted the model again to obtain the estimated path coefficients and goodness-of-fit measures used for our investigation.

To determine the goodness-of-fit of the model to the simulated fMRI data, we used the Goodness-of-fit index (GFI) which is a relatively stable indicator of model fit (Joreskog and Sorbom, 1986). GFI is a form of one minus the ratio of the minimum of the fit function after the model has been fitted ($F(S, \Sigma(\hat{\theta}))$) to the fit function of null model ($F(S, \Sigma(0))$). Therefore, a GFI value close to 1 indicates a good fit, and $GFI > .85$ is considered as an adequate fit of the network model (Schlosser et al., 2003a, 2006).

We next compared estimated path parameters between the two task conditions for each group, and between the three groups for each task condition. Also, the GFI values and the total estimated error variances were analyzed and compared between normal subjects and patients.

SEM procedures estimate several types of parameters including the interregional effective connectivities, error variances, as well as various model goodness-of-fit measures. For the practical use of SEM in clinical studies, it is crucial to determine which SEM measures would be useful to discriminate the networks of patients from those of healthy subjects. To address this issue, we first compared estimated path coefficients between the three subject groups. We also evaluated estimated error variances and the goodness-of-fit index (GFI). Moreover, we obtained the “standard normal path model” by fitting the time series data characterizing an average pattern of fMRI data for the normal group. We compared this standard model to the model for individual subjects by a stacked model approach (McIntosh and Gonzalez-Lima, 1991, 1994). Specifically, the time series representing a group of normal subjects can be characterized by the first eigenvariate obtained by principal component analysis (PCA) (Bullmore et al., 2000; Honey et al., 2002). Those regional eigentimeseries were fitted to the model as the “standard normal path model”. The model differences between the ‘normal path model’ and the model for individual subjects of the normal and patient groups were then evaluated by a stacked model approach as the chi-square differences between the null and alternative models. The null model represents a model in which path coefficients are constrained to be equal between the two models being “stacked”, while the alternative model is such that path coefficients are allowed to differ. A large chi-square difference indicates a significant difference between the “standard normal path model” and the individual path model. Finally, we compared the chi-square differences between normal and patient groups.

Results

Path model fitting

The simulated fMRI dataset for each condition for each subject was fitted to the path model. Measured GFI values ranged between 0.82 and 0.92 for all subjects, indicating a relatively good fit. The mean and standard deviation of the estimated path coefficients (corresponding to the interregional effective connectivities) for each group are summarized in Table 1 for (a) the DMS task condition and (b) the PV condition. The statistical significance of the connection strength for each path coefficient was tested using a one sample t-test and its 95% confidence interval and is displayed in Table 1.

For the DMS task condition, all excitatory connections for all groups had strong effective connections. Some of the inhibitory connections were not significantly different from zero (see Table 1a). This result is not unexpected, given the fact that the anatomical strengths of all

inhibitory connections were relatively lower than those of the excitatory connections. Similarly, for the passive-viewing condition, two paths, from D1 to IT and from FR to D2, were not significant for normal group, which correspond to inhibitory connections. The paths from FS to D2 and FR to D2 were not significant for both clone and patient groups (see Table 1b).

DMS task condition versus Passive-viewing (PV) condition

To examine changes in effective connectivity between the DMS and PV conditions, single path coefficients were compared using paired t-tests for each group (Table 2)¹ and the results are depicted in Figure 2(a). For the normal group, the forward connection from IT to PFC (FS) and two feedback connections from PFC (D2) to V4 and IT were significantly stronger for the DMS task than for the PV condition. Significantly stronger effective connections were obtained between the D1 (whose units are active during the delay between stimuli) and D2 (whose units are active during stimulus presentation and delay) modules and from D1 to FR (which contains units that are active when the stimuli match). There also were several negative connectivity changes for the condition comparison (e.g., V1 to V4).

For the patient and clone groups, almost all of the DMS-PV effective connectivity differences were not significantly different from zero, including the IT-FS connection. For both abnormal groups, the effective connection from PFC (D2) to IT was reduced during the task versus passive-viewing.

Normal Controls versus Patients

We next analyzed group differences in effective connectivity. A one-way ANOVA was used for comparing the three groups (normals, patients, clones). Table 3 gives F-test statistics with probability values for the individual path coefficients. The paths showing a significant group difference with $P < 0.05$ were further examined by a pairwise group comparison test as a post hoc analysis to identify groups showing significant differences.

We found that there were no significant differences for any path coefficient between clones and patients at a 95% confidence level.

There were, however, noticeable differences between controls and patients. All significantly different paths between controls and patients were consistent with those between controls and clones (Table 3 and Figure 2b). As a result, we shall henceforth restrict our discussion to only the normal and patient groups. Figure 2b shows that the effective connection from IT to PFC (FS) and feedback connections from PFC (D2) to V4 and IT were significantly stronger for controls than patients for the task condition. Also, all excitatory connections within PFC had stronger effective connections for controls relative to patients. For the PV condition, the path from IT to PFC (FS) and some interactions within PFC were stronger for controls than patients. However, feedback connections were not different between groups.

There were a few path coefficients (e.g., V1 to V4) that were significantly larger in the patient group than in the controls in the DMS condition, and one in the PV condition.

¹Because we are interested in how well SEM can perform, we did not correct our statistical tests for multiple comparisons, as might be done on actual experimental data. In this way, our results represent the “best” that SEM can do. Thus, any limitations we find can be attributed to SEM and not some ancillary aspect of the analysis such as performing multiple statistical tests. If we had employed a Bonferroni correction, the only path coefficients in Fig. 2 that would no longer be significantly different are D2-IT for all three groups in Fig. 2a and D1–D2 for the normal group in Fig. 2a.

Identification of a non-normal network

For many years an important medical application of functional neuroimaging has been its utilization for the purpose of early detection of disease (e.g., Drzezga, 2008; Haxby et al., 1986; Ries et al., 2008). It had been suggested that SEM (Horwitz et al., 1995) or other multivariate methods (Clark et al., 1991, Azari et al, 1993a), because they examine multiple (and interacting) brain regions, may be more sensitive than focusing on single brain regions for detecting functional brain abnormalities prior to their clinical manifestations. We can use the results of our simulation analysis to explore which of various measures of the SEM network for each individual “patient” might be better at differentiating the normal subject networks from the patient networks. The measures examined were GFI, total error variance and a statistical measure of how different a single subject’s model is from a model representing the normal subjects.

Goodness-of-fit index (GFI) and error variance—We examined the GFI values and estimated error variances of the normal and patient groups for the DMS task condition. The GFI values of normal controls ranged between 0.83 and 0.92, and those of patients were between 0.9 and 0.99. We also compared the estimated error variances between the two groups. The total error variances for normal controls were significantly smaller (mean= 0.76) than those for patients (mean=3.02). Specifically, error variances in the four sub-modules constituting the PFC were increased dramatically for the simulated patients. Figure 3 shows the GFI values and total error variances for normal subjects and patients. Although the high GFI values indicate a better fit for patients, the significantly larger error variances of patients indicate that the better GFI values were obtained by the unexplained error variance on each node rather than by the values of the inter-regional linkages. In other words, the high GFI values of models for patients might be induced by the fact that brain regional activations were affected mostly by the noise inputs. A discussion of the relation between error variance and the fit function can be found in Bullmore et al. (2000).

The standard normal path model versus individual path models—Principal component analysis (PCA) was used to identify an average pattern of response over all normal subjects in each region. PCA was applied to the ($m=20$ normal subjects $\times$ $n=160$ time points) data matrix for each region for the DMS task condition to obtain the first eigenvector (Bullmore et al., 2000; Honey et al., 2002). The interregional correlation matrix was constructed using the pairwise correlations between the first eigenvectors, and the path model fitting was performed using this correlation matrix. We considered this path model as the standard normal model, and it was compared to the path model of each subject of both the normal and patient groups using a stacked model approach. A stacked model approach compares the chi-square values of the null and alternative models to analyze the statistical difference between two path models. The null model requires that the path coefficients are constrained to be equal between two models comprising the ‘stack’, and the alternative model allows the path coefficients to differ. However, we note that the significance of chi-square differences was not estimable because the relatively large sample size (in our study, $n=160$ time points) inflated the chi-square values, which could lead to rejection of a relatively good model. Therefore we did not focus on the statistical significance of the stacked model results, but, rather, analyzed how these values differed between normal subjects and patients. The result is shown in Figure 4(a). We notice that two “normal subjects” appeared as significant outliers from others in the normal group. Therefore, the standard path model was re-evaluated without these two subjects, and the re-evaluated chi-square differences from a stacked model approach are presented in Figure 4(b). This figure shows a better separation of path models of the patients from the standard normal model compared to the normal subjects, although there is some overlap of the results between the two groups.

Discussion

In the last several years, we have used large-scale, biologically realistic neural modeling to attempt to understand the neurobiological basis of different measures of functional and effective connectivity (Horwitz et al., 2005; Kim and Horwitz, 2008; Lee et al., 2006; Marrelec et al., 2007). In the present study, this type of modeling was employed to examine one of the most widely used techniques for evaluating effective connectivity – structural equation modeling. Specifically, we investigated how well a damaged anatomical connection can be revealed by SEM using realistically simulated fMRI data. The chi-square goodness-of-fit results showed that the SEM model provided a good fit to the DMS task for all three groups. We compared SEM models between groups and found that the SEM model for normals was significantly different from that for patients. In particular, the weakened anatomical link between IT and the prefrontal submodule FS had a significantly reduced effective connection for the simulated patients compared to the simulated normal subjects, as did a number of “downstream” connections involving the prefrontal submodules. However, we also found that some “upstream” effective connections were significantly larger in the patient group than in the normals. Our third major finding was that of the SEM model measures we examined, the total error variance was the best at distinguishing a patient network from a normal network. We will comment on each of these findings in the following paragraphs.

Condition and group comparison results

We generated normal control, clone and patient groups consisting of twenty fMRI datasets each. Brain regional signals were generated by a large scale neural model developed by Tagamets and Horwitz (Tagamets and Horwitz, 1998; Horwitz and Tagamets, 1999). The model performed both a visual delayed match-to-sample (DMS) task and a passive viewing (PV) control task during which simulated fMRI time series were generated. Because the fMRI data were produced by a large scale neural network, this network was defined as the path model for SEM analysis. Each fMRI dataset from each individual subject was then fitted to the path model to estimate path coefficients (i.e., effective connections) and error variances, as well as model goodness-of-fit indices (GFI). GFI values higher than 0.82 for all subjects indicated relatively good fits. The functional strengths of paths corresponding to the excitatory-to-excitatory anatomical connections were significantly different from zero at $p < 0.05$ for all three groups, except for the FS → D2 connection during the PV condition for the clone and patient groups. As found in previous studies (e.g., Marrelec et al., in press), the effective connections corresponding to many of the inhibitory pathways were not statistically different from zero. The reason is that the dynamics of the neuronal units in the model are such that activation of the inhibitory units tends to reduce a module's activity, which, in turn, results in the module becoming uncorrelated with the input module. In a block-type design, for a significant fMRI effective connection, the neural activity along the structural link needs to be more sustained than transient. Whether this is due to the computational architecture of our model, or is the case in real brains requires further investigation.

We found few differences in either the DMS or PV conditions between the patient networks and the clone networks. Because there was only one anatomical connection that differed between the clone and normal subject networks (i.e., IT → FS), we can say that the functional differences between patient and normal SEM networks are caused by this single connection, and not by the other small differences in the anatomical weights that characterize each normal and patient network.

The differences in the effective connections between the DMS and PV conditions for the controls and for the patients were displayed in Fig. 2a. As one would have hoped, the IT → PFC was significantly larger in the control subjects, as were a number of other connections. Interestingly, the connection between V1 and V4 in the normal group showed a significant

decline in the DMS task relative to PV (we will return to this). In the patient and clone groups, however, no significant effective connectivity differences between conditions were detected, except for one connection: a prefrontal to inferior temporal connection that was reduced in value during the DMS task compared to passive viewing. In particular, the effective connectivity of the damaged anatomical connection between IT and PFC did not differ between conditions. This is the result one would prefer, since it supports the notion that a damaged anatomical connection conveys less “information” (using this word rather loosely) than does an undamaged one; the conveyed signal essentially becomes noise, which does not differ between conditions. This result also points to the importance of networks in mediating behavior. Once we have a damaged connection that plays a crucial role in the circuit mediating a behavior, the network no longer operates normally, and in this particular case, that means that the effective connections in many parts of the circuit do not show a task dependent change in value.

We also tested group-specific functional changes of effective connectivity by comparing the normal to the damaged networks (with the weakened IT-PFC anatomical connection). For the DMS task condition, the anatomically weakened IT→PFC connection of the damaged brain network had an effective connectivity that was significantly reduced compared to the normal subjects’ network. Moreover, not only was the damaged connection aberrant, downstream connections within the PFC and two feedback connections from PFC to IT and V4 were also functionally suppressed for the damaged network relative to the normal network, although the underlying anatomical connections were intact. This important finding indicates that the presence of a significantly suppressed functional pathways in a damaged brain network does not always mean that the underlying anatomical connection is abnormal.

Another important finding from our simulation analysis concerned connections such as V1→V4 and V4→IT that were significantly larger in the patients than in the normal subjects during the DMS task. When results like these are found in actual experimental data, it is often said that the increased connectivity seen in the patients relative to the normal subjects may represent some type of compensatory mechanism (e.g., increased or better early visual processing is an attempt to adapt to the pathology occurring downstream). However, there was no plasticity in our model of the patients (i.e., the anatomical weights of all pathways, except the IT→FS connection, were not altered); indeed, nothing has changed with respect to the bottom-up processing of the visual stimuli between V1 and IT. The reason the V1→V4 and V4→IT are larger in the patients relative to normals is that there is a reduction in the strength of the effective connections of the feedback links from PFC to the posterior areas. Because of this, the activity in V4, for example, is more tightly coupled to the activity in V1 (this can even be seen in the correlation coefficients: in normals the mean V1–V4 correlation for the DMS task is 0.702, whereas in patients it is 0.796).

There are two important conclusions that can be drawn from the above discussion. First, one must interpret with caution the functional (in the sense of clinical) importance of patient-control differences in effective (or functional) connectivity. It might be possible to resolve some of the ambiguity concerning an altered connectivity measure by determining if the connectivity measure correlates with some measure of performance on the task under study. Second, our simulation results emphasize the importance of thinking in terms of network behavior when trying to understand how the brain implements a task. Even though our network only had one abnormality (the IT→PFC reduced anatomical connectivity), its functional consequences are found both downstream, but also upstream, with the upstream alterations being due to abnormal feedback connections.

It is worth remarking that the results discussed in the previous paragraph could be expressed differently in another commonly used effective connectivity method – Dynamic Causal

Modeling (DCM) (Friston et al., 2003). For situations like that studied in our paper, an important output of a DCM analysis would be the group difference in a task-specific modulation of an interregional connection. Often, such modulations are modeled individually (e.g., a separate DCM model is evaluated for each modulated connection, and a Bayesian model comparison would be used to determine which one yields the best fit; e.g., Lee et al., 2006). If this were done, one would only determine how a single connection is affected by the disorder, not how the entire network is disrupted during task performance in the affected group (although one could use a statistical procedure to compare connectivity parameters beyond the modulated connection). However, DCM also can be performed with modulating influences applied simultaneously to all connections [e.g., Sonty et al.'s study of primary progressive aphasia (Sonty et al., 2007)]. These differences between how SEM and DCM studies are conducted are worth noting when comparing the results of effective connectivity analyses between different investigators.

Comparison of networks was further investigated in our study by evaluating error variance estimates and GFI values. An interesting finding was that the measured GFI values tended to be higher values for the patients than for normal controls [See Figure 3 (a)]. This might lead one to conclude, incorrectly, that the path model fits the damaged anatomical network better than does the intact network. However, as shown in Figure 3 (b), there were remarkably higher error variances of the regions for the damaged anatomical network, indicating that the damaged networks fit better than the intact ones because their error variances (representing activity outside the network) accounted for a much larger fraction of the variability. Therefore, to identify the functional damage of patients' brain networks, it is important to take into account the error variances of each node and as well as the estimated interregional effective connectivities, and to determine how both affect model goodness-of-fit.

A potentially important use of SEM in clinical studies would be to help locate abnormal interregional connections by comparing patients' path models to those of healthy subjects (Au Duong et al., 2005; Grafton et al., 1994; Horwitz et al., 1995; Rowe et al., 2002; Schlosser et al., 2003b). If this could be applied on an individual basis, this approach might be useful for diagnostic and/or therapeutic evaluation (e.g., early detection of a brain disorder; determining the efficacy of a particular therapeutic treatment). A key ingredient to this approach would be the availability of a normal subject data base against which to compare an individual's data. To partially address this issue, we obtained a "standard normal path model" from simulated normal subjects and compared this model to individual normal subjects and patients by a stacked model approach (two of the simulated normal datasets were excluded because their path models showed significant deviation from the standard normal path model). Fig. 4b shows that there was a substantial difference between simulated patients and controls, although some overlap was present. Nonetheless, our results suggest that this approach to using SEM (or another effective connectivity method) has potential for becoming a useful clinical tool for disease diagnosis and/or evaluation of therapeutic treatments.

In conclusion, our results using neurobiologically realistic simulated fMRI data show that a weakened anatomical connection in a network mediating a task can be revealed using SEM, but abnormal effective connections may also occur for normal anatomical links.

Supplementary Material

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Acknowledgements

The work was supported by the NIDCD/NIH Intramural Research Program. We wish to thank Dr. Ajay Pillai for a critical reading of the manuscript.

References

- Au Duong MV, Boulanouar K, Audoin B, Treseras S, Ibarrola D, Malikova I, Confort-Gouny S, Celsis P, Pelletier J, Cozzzone PJ, Ranjeva JP. Modulation of effective connectivity inside the working memory network in patients at the earliest stage of multiple sclerosis. *Neuroimage* 2005;24:533–538. [PubMed: 15627595]
- Azari NP, Pettigrew KD, Schapiro MB, Haxby JV, Grady CL, Pietrini P, Salerno JA, Rapoport SI, Horwitz B. Early detection of Alzheimer's disease: a statistical approach using positron emission tomographic data. *J Cereb Blood Flow Metabol* 1993a;13:438–447.
- Azari NP, Pietrini P, Horwitz B, Pettigrew KD, Leonard HL, Rapoport JL, Schapiro MB, Swedo SE. Individual differences in cerebral metabolic patterns during pharmacotherapy in Obsessive-Compulsive disorder: A multiple regression/discriminant analysis of positron emission tomographic data. *Biol Psychiat* 1993b;34:798–809. [PubMed: 8292684]
- Bhat V, Weiner WJ. Parkinson's disease. Diagnosis and the initiation of therapy. *Minerva Med* 2005;96:145–154. [PubMed: 16175158]
- Bokde AL, Lopez-Bayo P, Meindl T, Pechler S, Born C, Faltraco F, Teipel SJ, Moller HJ, Hampel H. Functional connectivity of the fusiform gyrus during a face-matching task in subjects with mild cognitive impairment. *Brain* 2006;129:1113–24. [PubMed: 16520329]
- Bollen, KA. *Structural Equations with latent variables*. Wiley-Interscience; 1989.
- Boynton GM, Engel SA, Glover GH, Heeger DJ. Linear systems analysis of functional magnetic resonance imaging in human V1. *J Neurosci* 1996;16:4207–21. [PubMed: 8753882]
- Buchel C, Friston KJ. Modulation of connectivity in visual pathways by attention: cortical interactions evaluated with structural equation modelling and fMRI. *Cereb Cortex* 1997;7:768–78. [PubMed: 9408041]
- Bullmore E, Horwitz B, Honey G, Brammer M, Williams S, Sharma T. How good is good enough in path analysis of fMRI data? *Neuroimage* 2000;11:289–301. [PubMed: 10725185]
- Catani M, Jones DK, Daly E, Embiricos N, Deeley Q, Pugliese L, Curran S, Robertson D, Murphy DG. Altered cerebellar feedback projections in Asperger syndrome. *Neuroimage* 2008;41:1184–1191. [PubMed: 18495494]
- Clark CM, Ammann W, Martin WRW, Ty P, Hayden MR. The FDG/PET methodology for early detection of disease: A statistical model. *J Cereb Blood Flow Metabol* 1991;11:A96–A102.
- Courchesne E, Pierce K. Why the frontal cortex in autism might be talking only to itself: local over-connectivity but long-distance disconnection. *Curr Opin Neurobiol* 2005;15:225–230. [PubMed: 15831407]
- Delfino M, Kalisch R, Czisch M, Larramendy C, Ricatti J, Taravini IR, Trenkwalder C, Murer MG, Auer DP, Gershanik OS. Mapping the effects of three dopamine agonists with different dyskinesogenic potential and receptor selectivity using pharmacological functional magnetic resonance imaging. *Neuropsychopharm* 2007;32:1911–21.
- Dickerson BC. Functional MRI in the early detection of dementias. *Rev Neurol (Paris)* 2006;162:941–944. [PubMed: 17028561]
- Drzezga A. Concept of functional imaging of memory decline in Alzheimer's disease. *Methods* 2008;44:304–314. [PubMed: 18374274]
- Friston KJ, Harrison L, Penny W. Dynamic causal modelling. *Neuroimage* 2003;19:1273–302. [PubMed: 12948688]
- Funahashi S, Bruce C, Goldman-Rakic PS. Visuospatial coding in primate prefrontal neurons revealed by oculomotor paradigms. *J Neurophysiol* 1990;63:814–831. [PubMed: 2341879]
- Goekoop R, Rombouts SA, Jonker C, Hibbel A, Knol DL, Truyen L, Barkhof F, Scheltens P. Challenging the cholinergic system in mild cognitive impairment: a pharmacological fMRI study. *Neuroimage* 2004;23:1450–9. [PubMed: 15589109]
- Grafton ST, Sutton J, Couldwell W, Lew M, Waterman C. Network analysis of motor system connectivity in Parkinson's Disease: Modulation of thalamocortical interactions after pallidotomy. *Human Brain Mapp* 1994;2:45–55.

- Haxby JV, Grady CL, Duara R, Schlageter NL, Berg G, Rapoport SI. Neocortical metabolic abnormalities precede non-memory cognitive deficits in early Alzheimer-type dementia. *Arch Neurol* 1986;43:882–885. [PubMed: 3488728]
- Head D, Buckner RL, Shimony JS, Williams LE, Akbudak E, Conturo TE, McAvoy M, Morris JC, Snyder AZ. Differential vulnerability of anterior white matter in nondemented aging with minimal acceleration in dementia of the Alzheimer type: evidence from diffusion tensor imaging. *Cereb Cortex* 2004;14:410–423. [PubMed: 15028645]
- Honey GD, Fu CH, Kim J, Brammer MJ, Croudace TJ, Suckling J, Pich EM, Williams SC, Bullmore ET. Effects of verbal working memory load on corticocortical connectivity modeled by path analysis of functional magnetic resonance imaging data. *Neuroimage* 2002;17:573–82. [PubMed: 12377135]
- Horwitz B, McIntosh AR, Haxby JV, Furey M, Salerno JA, Schapiro MB, Rapoport SI, Grady CL. Network analysis of PET-mapped visual pathways in Alzheimer type dementia. *NeuroReport* 1995;6:2287–2292. [PubMed: 8747138]
- Horwitz B, Rumsey J, Grady C, Rapoport SI. The cerebral metabolic landscape in autism: Intercorrelations of regional glucose utilization. *Arch Neurol* 1988;45:749–755. [PubMed: 3260481]
- Horwitz B, Rumsey JM, Donohue BC. Functional connectivity of the angular gyrus in normal reading and dyslexia. *Proc Natl Acad Sci USA* 1998;95:8939–8944. [PubMed: 9671783]
- Horwitz B, Tagamets MA. Predicting human functional maps with neural net modeling. *Hum Brain Mapp* 1999;8:137–42. [PubMed: 10524605]
- Horwitz B, Warner B, Fitzer J, Tagamets MA, Husain FT, Long TW. Investigating the neural basis for functional and effective connectivity. Application to fMRI. *Philos Trans R Soc Lond B Biol Sci* 2005;360:1093–1108. [PubMed: 16087450]
- Husain FT, Tagamets MA, Fromm SJ, Braun AR, Horwitz B. Relating neuronal dynamics for auditory object processing to neuroimaging activity: a computational modeling and an fMRI study. *Neuroimage* 2004;21:1701–20. [PubMed: 15050592]
- Johansen-Berg H, Behrens TE. Just pretty pictures? What diffusion tractography can add in clinical neuroscience. *Curr Opin Neurol* 2006;19:379–385. [PubMed: 16914977]
- Joreskog, KG.; Sorbom, D. Analysis of linear structural relationships by the method of maximum likelihood. Scientific software; Mooresville, IN: 1986.
- Just MA, Cherkassky VL, Keller TA, Kana RK, Minshew NJ. Functional and anatomical cortical underconnectivity in autism: evidence from an fMRI study of an executive function task and corpus callosum morphometry. *Cereb Cortex* 2007;17:951–961. [PubMed: 16772313]
- Kelly AM, Garavan H. Human functional neuroimaging of brain changes associated with practice. *Cereb Cortex* 2005;15:1089–1102. [PubMed: 15616134]
- Kim J, Horwitz B. Investigating the neural basis for fMRI-based functional connectivity in a blocked design: application to interregional correlations and psycho-physiological interactions. *Magn Reson Imaging* 2008;26:583–593. [PubMed: 18191524]
- Kim J, Zhu W, Chang L, Bentler PM, Ernst T. Unified structural equation modeling approach for the analysis of multisubject, multivariate functional MRI data. *Hum Brain Mapp* 2007;28:85–93. [PubMed: 16718669]
- Lee L, Friston KJ, Horwitz B. Large-scale neural models and dynamic causal modelling. *Neuroimage* 2006;30:1243–1254. [PubMed: 16387513]
- Liu Y, Yu C, Liang M, Li J, Tian L, Zhou Y, Qin W, Li K, Jiang T. Whole brain functional connectivity in the early blind. *Brain* 2007;130:2085–2096. [PubMed: 17533167]
- Marrelec G, Horwitz B, Kim J, Pelegrini-Issac M, Benali H, Doyon J. Using partial correlation to enhance structural equation modeling of functional MRI data. *Magn Reson Imaging* 2007;25:1181–1189. [PubMed: 17475433]
- Marrelec G, Kim J, Doyon J, Horwitz B. Large-scale neural model validation of partial correlation analysis for effective connectivity investigation in functional MRI. *Hum Brain Mapp*. (in press)
- McIntosh AR, Bookstein FL, Haxby JV, Grady CL. Spatial pattern analysis of functional brain images using partial least squares. *Neuroimage* 1996;3:143–57. [PubMed: 9345485]
- McIntosh AR, Gonzalez-Lima F. Structural modeling of functional neural pathways mapped with 2-deoxyglucose: effects of acoustic startle habituation on the auditory system. *Brain Res* 1991;547:295–302. [PubMed: 1884204]

- McIntosh AR, Gonzalez-Lima F. Structural equation modeling and its application to network analysis in functional brain imaging. *Hum Brain Mapp* 1994;2:2–22.
- McIntosh AR, Grady CL, Ungerleider LG, Haxby JV, Rapoport SI, Horwitz B. Network analysis of cortical visual pathways mapped with PET. *J Neurosci* 1994;14:655–66. [PubMed: 8301356]
- Minshew NJ, Williams DL. The new neurobiology of autism. *Arch Neurol* 2007;64:945–950. [PubMed: 17620483]
- Morrison, JH.; Hof, PR.; Campbell, MJ.; DeLima, AD.; Voigt, T.; Bouras, C.; Cox, K.; Young, WG. Cellular pathology in Alzheimer's disease: Implications for corticocortical disconnection and differential vulnerability. In: Rapoport, SI.; Petit, H.; Leys, D.; Christen, Y., editors. *Imaging, Cerebral Topography, and Alzheimer's Disease*. Springer Verlag; Berlin: 1990. p. 19–40.
- Paulesu E, Frith U, Snowling M, Gallagher A, Morton J, Frackowiak RSJ, Frith CD. Is developmental dyslexia a disconnection syndrome? Evidence from PET scanning. *Brain* 1996;119:143–157. [PubMed: 8624677]
- Ries ML, Carlsson CM, Rowley HA, Sager MA, Gleason CE, Asthana S, Johnson SC. Magnetic resonance imaging characterization of brain structure and function in mild cognitive impairment: a review. *J Am Geriatr Soc* 2008;56:920–934. [PubMed: 18410325]
- Rogers J, Morrison JH. Quantitative morphology and regional and laminar distributions of senile plaques in Alzheimer's disease. *J Neurosci* 1985;5:2801–2808. [PubMed: 4045553]
- Rowe J, Stephan KE, Friston K, Frackowiak R, Lees A, Passingham R. Attention to action in Parkinson's disease: impaired effective connectivity among frontal cortical regions. *Brain* 2002;125:276–289. [PubMed: 11844728]
- Schlosser R, Gesierich T, Kaufmann B, Vucurevic G, Hunsche S, Gawehn J, Stoeter P. Altered effective connectivity during working memory performance in schizophrenia: a study with fMRI and structural equation modeling. *Neuroimage* 2003a;19:751–63. [PubMed: 12880804]
- Schlosser R, Gesierich T, Kaufmann B, Vucurevic G, Stoeter P. Altered effective connectivity in drug free schizophrenic patients. *Neuroreport* 2003b;14:2233–7. [PubMed: 14625454]
- Schlosser RG, Wagner G, Sauer H. Assessing the working memory network: studies with functional magnetic resonance imaging and structural equation modeling. *Neuroscience* 2006;139:91–103. [PubMed: 16324797]
- Sonty SP, Mesulam MM, Weintraub S, Johnson NA, Parrish TB, Gitelman DR. Altered effective connectivity within the language network in primary progressive aphasia. *J Neurosci* 2007;27:1334–1345. [PubMed: 17287508]
- Tagamets MA, Horwitz B. Integrating electrophysiological and anatomical experimental data to create a large-scale model that simulates a delayed match-to-sample human brain imaging study. *Cereb Cortex* 1998;8:310–20. [PubMed: 9651128]
- van Eimeren T, Siebner HR. An update on functional neuroimaging of parkinsonism and dystonia. *Curr Opin Neurol* 2006;19:412–419. [PubMed: 16914982]

Large-Scale Neural Network

Figure 1.

The path diagram for SEM analysis. The path model, defined by the large-scale visual neural network of Tagamets and Horwitz (1998), includes seven modules and sixteen (excitatory and inhibitory) anatomical connections. Excitatory connections (E) are represented as solid arrows and inhibitory connections (I) as dashed arrows. All anatomical connections were included in the SEM path model, and the strengths of their functional linkages were compared between conditions and between groups. The modules of the network, defined in the text, include 4 modules (FS, D1, D2, FR) that comprise a prefrontal region and 3 visual processing regions (v1, v4 and IT). The attentional modulation, which controls whether the network performs the DMS task or passive viewing, is also shown.

(a) DMS task vs. Passive-viewing **(b) Normal vs. patient (clone) group** **Figure 2.**

(a) Path diagrams for the condition comparison for each group described in Table 2. To simplify the diagram, we only display the significant path coefficients that are common between the clone and patient groups. Red indicates positive significance (e.g., DMS > PV) and green means negative significance at the $p=0.05$ level (uncorrected); a dashed arrow means that the path coefficient is not significantly different between conditions.

(b) Path diagrams for the group comparison for both conditions described in Table 3. There were no statistical differences of the path coefficients between clone and patient groups, so that this comparison is not displayed. Red indicates positive significance (e.g., normals > patients) and green means negative significance at the $p=0.05$ level (uncorrected); a dashed arrow means that the path coefficient is not significantly different between groups.

Abbreviations: DMS – delayed match-to sample task; PV- passive viewing; abbreviations for each module same as in Fig. 1.

Figure 3.

Goodness-of-fit (GFI) values and total error variances of the SEM model of the DMS task condition for 20 simulated normal controls and 20 simulated patients. The plot on the left shows the GFI values for each subject in the two groups, and the plot on the right shows total estimated error variances for each subject in the two groups. Normal controls have considerably lower GFIs and error variances (average GFI= 0.88, average error variance = 0.76) compared to that of patients (average GFI= 0.95, average error variance = 3.02). Note that because some values overlap, it appears as if there are fewer than 20 data points.

Figure 4.

Chi-square differences between the standard normal SEM model and individual SEM models using a stacked model approach. Specifically, the standard normal path model was compared against each individual subject's path model in the normal and patient groups for the DMS task condition. (a) The standard normal path model was obtained using the first eigenvectors from all twenty normal subjects, and compared to each subject. (b) The standard normal path model using the first eigenvectors without two normal subjects that were outliers in (a) was used for the stacked model approach.

Table 1

Mean (standard deviation) values for the estimated path coefficients for each group (uncorrected for multiple comparisons). Inhibitory anatomical connections are indicated by (i). Path coefficients significantly different from zero are in bold.

(a) DMS task			
Paths	Normal group Mean (sd)	Clone group Mean (sd)	Patient group Mean (sd)
IT→V4	0.41 (.13)	0.41 (.14)	0.45 (.13)
D2→V4	0.26 (.09)	0.14 (.06)	0.13 (.06)
V1→V4	0.43 (.10)	0.57 (.11)	0.52 (.11)
V4→IT	0.68 (.06)	0.82 (.08)	0.83 (.05)
D1→IT (i)	-0.07 (.16)	-0.06 (.10)	-0.02 (.07)
D2→IT	0.32 (.17)	0.07 (.08)	0.07 (.08)
IT→FS	0.98 (.04)	0.77 (.14)	0.78 (.12)
D1→FS (i)	-0.01 (.06)	-0.12 (.23)	-0.16 (.21)
FS→D1 (i)	-0.02 (.25)	0.39 (.17)	0.41 (.22)
D2→D1	0.64 (.24)	0.27 (.07)	0.23 (.09)
FR→D1 (i)	0.12 (.28)	0.05 (.09)	0.08 (.06)
FS→D2	0.18 (.18)	-0.09 (.16)	-0.11 (.13)
D1→D2	0.49 (.14)	0.35 (.10)	0.36 (.10)
FR→D2 (i)	0.11 (.16)	0.00 (.16)	-0.02 (.16)
FS→FR	0.53 (.15)	0.34 (.16)	0.31 (.14)
D1→FR	0.42 (.19)	0.14 (.12)	0.16 (.12)
(b) Passive-Viewing task			
Paths	Normal group Mean (sd)	Clone group Mean (sd)	Patient group Mean (sd)
IT→V4	0.34 (.11)	0.36 (.13)	0.37 (.21)
D2→V4	0.15 (.06)	0.15 (.18)	0.12 (.07)
V1→V4	0.58 (.08)	0.60 (.10)	0.58 (.15)
V4→IT	0.70 (.08)	0.79 (.06)	0.81 (.07)
D1→IT (i)	0.03 (.13)	-0.07 (.09)	-0.05 (.09)
D2→IT	0.20 (.09)	0.14 (.08)	0.11 (.11)
IT→FS	0.92 (.06)	0.79 (.15)	0.77 (.14)
D1→FS (i)	0.04 (.07)	-0.24 (.19)	-0.24 (.16)
FS→D1 (i)	0.37 (.19)	0.50 (.17)	0.50 (.17)
D2→D1	0.30 (.12)	0.18 (.09)	0.18 (.10)
FR→D1 (i)	0.11 (.12)	0.09 (.09)	0.08 (.06)
FS→D2	0.17 (.10)	-0.05 (.15)	-0.06 (.14)
D1→D2	0.39 (.10)	0.33 (.08)	0.34 (.10)
FR→D2 (i)	0.01 (.19)	0.03 (.12)	-0.02 (.13)
FS→FR	0.62 (.15)	0.33 (.18)	0.34 (.14)
D1→FR	0.18 (.08)	0.10 (.13)	0.11 (.12)

Table 2

Comparison of path coefficient values between DMS and PV conditions (paired t-test) for each group. Bold indicates that the effective connectivity is significantly different between conditions at $P < 0.05$ (uncorrected). A negative T indicates that the effective connectivity was smaller in the DMS task compared to the PV condition. As above, (i) denotes an inhibitory connection.

	DMS task vs. Passive-viewing					
	Normal group			Clone group		
	T stat	P		T stat	P	Patient group
IT→V4	1.88	0.083		1.35	0.203	2.19
D2→V4	4.10	0.001		-0.20	0.845	0.41
V1→V4	-7.04	0.000		-0.95	0.365	-2.33
V4→IT	-1.49	0.162		2.01	0.065	1.49
D1→IT (i)	-2.07	0.058		0.32	0.758	1.07
D2→IT	3.07	0.008		-2.73	0.015	-2.65
IT→FS	3.49	0.003		-0.44	0.673	0.12
D1→FS (i)	-1.94	0.073		1.61	0.133	1.78
FS→D1 (i)	-6.91	0.000		-2.11	0.053	-1.92
D2→D1	8.00	0.000		4.05	0.001	1.79
FR→D1 (i)	0.27	0.797		-1.87	0.083	0.57
FS→D2	0.27	0.793		-0.73	0.484	-1.89
D1→D2	2.89	0.011		0.72	0.489	1.67
FR→D2 (i)	1.79	0.098		-0.78	0.455	0.22
FS→FR	-3.59	0.002		0.04	0.973	-0.79
D1→FR	5.99	0.000		0.87	0.407	1.79

Table 3

Path comparison among three groups for each condition. The F-test statistics (P values) from analysis of variance (ANOVA) are displayed. Significant p-values (<0.05) indicate that there are significant group differences. They are followed by the 95% confidence intervals identifying group differences that are significant. Because there were no significant differences in the path values between patient and clone groups, their statistic results are not presented in this table.

	DMS task			Passive-viewing		
	F _{2,57} (P)	Normal vs. Clone 95% CI	Normal vs. Patient 95% CI	F _{2,57} (P)	Normal vs. Clone 95% CI	Normal vs. Patient 95% CI
IT→V4	0.71 (0.5)	--	--	0.17 (0.85)	--	--
D2→V4	19.9 (<0.001)	0.06, 0.17	0.08, 0.18	0.35 (0.7)	--	--
V1→V4	9.26 (<0.001)	-0.22, -0.06	-0.17, -0.01	0.2 (0.82)	--	--
V4→IT	35.2 (<0.001)	-0.19, -0.09	-0.2, -0.1	13.27 (<0.001)	-0.09, -0.04	-0.16, -0.05
D1→IT	0.99 (0.38)	--	--	5.26 (0.008)	0.02, 0.18	0.001, 0.16
D2→IT	30.7 (<0.001)	0.16, 0.34	0.16, 0.34	4.26 (0.02)	--	0.01, 0.16
IT→FS	24.8 (<0.001)	0.13, 0.29	0.12, 0.29	7.93 (0.001)	0.13, 0.22	0.14, 0.24
D1→FS	3.83 (0.03)	--	0.01, 0.29	21.7 (<0.001)	0.16, 0.39	0.16, 0.38
FS→D1	25.5 (<0.001)	-0.57, -0.24	-0.6, -0.27	3.44 (0.04)	--	--
D2→D1	43.1 (<0.001)	0.25, 0.49	0.29, 0.53	8.51 (0.001)	0.12, 0.2	0.04, 0.2
FR→D1	0.88 (0.42)	--	--	0.45 (0.64)	--	--
FS→D2	20.1 (<0.001)	0.14, 0.38	0.17, 0.41	19.7 (<0.001)	0.12, 0.31	0.13, 0.33
D1→D2	9.08 (<0.001)	0.05, 0.22	0.04, 0.22	2.34 (0.11)	--	--
FR→D2	3.45 (0.04)	--	--	0.58 (0.56)	--	--
FS→FR	12.3 (<0.001)	0.07, 0.3	0.1, 0.33	21 (<0.001)	0.16, 0.41	0.16, 0.4
D1→FR	22.8 (<0.001)	0.07, 0.3	0.1, 0.33	2.52 (0.09)	--	--