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Original Article

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Working Memory Modulation of Frontoparietal Network Connectivity in First-Episode Schizophrenia

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Abstract

Working memory (WM) impairment is regarded as a core aspect of schizophrenia. However, the neural mechanisms behind this cognitive deficit remain unclear. The connectivity of a frontoparietal network is known to be important for subserving WM. Using functional magnetic resonance imaging, the current study investigated whether WM-dependent modulation of effective connectivity in this network is affected in a group of first-episode schizophrenia (FES) patients compared with similarly performing healthy participants during a verbal *n*-back task. Dynamic causal modeling (DCM) of the coupling between regions (left inferior frontal gyrus (IFG), left inferior parietal lobe (IPL), and primary visual area) identified in a psychophysiological interaction (PPI) analysis was performed to characterize effective connectivity during the *n*-back task. The PPI analysis revealed that the connectivity between the left IFG and left IPL was modulated by WM and that this modulation was reduced in FES patients. The subsequent DCM analysis confirmed this modulation by WM and found evidence that FES patients had reduced forward connectivity from IPL to IFG. These findings provide evidence for impaired WM modulation of frontoparietal effective connectivity in the early phase of schizophrenia, even with intact WM performance, suggesting a failure of context-sensitive coupling in the schizophrenic brain.

Key words: dynamic causal modeling, dysconnection hypothesis, functional magnetic resonance imaging, *n*-back

Introduction

Working memory (WM) impairment is a common cognitive deficit in schizophrenia (Lee and Park 2005; Piskulic et al. 2007; Forbes et al. 2008) and is viewed as an important aspect of schizophrenic thought disorder (Addington and Addington 2002;

Arnsten 2013), potentially underlying several of the cognitive impairments observed in schizophrenia (Goldman-Rakic 1994; Silver 2003).

Meta-analyses of neuroimaging studies have shown that frontoparietal regions are consistently activated during WM tasks

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irrespective of paradigms and modalities (Wager and Smith 2003; Owen et al. 2005), thus constituting a core component of the WM network (Rottschy et al. 2012). The lateral prefrontal cortex (PFC) is typically associated with processes such as encoding, manipulation, and response selection (D'Esposito et al. 2000), whereas the posterior parietal cortex (PPC) is attributed an important role in storing, maintaining, and retrieving information (Jonides et al. 1998; Guerin and Miller 2011). However, evidence also exists linking lateral PFC to maintenance (Cohen et al. 1997; Narayanan et al. 2005) and PPC to manipulation (Champos and Petrides 2010) of information in WM. Thus, the coupling (i.e. functional integration) of these areas appears crucial for WM performance. Evidence from functional magnetic resonance imaging in humans has shown increased coupling between PFC and PPC as WM load is increased (Ma et al. 2012; Dima et al. 2014) and this connection has been linked to performance (Shen et al. 2015). This transient change in coupling is enabled by the (short-term) plasticity of synapses and, according to the dysconnection hypothesis (Friston 1998), provides a mechanism through which pathology may arise in schizophrenia. More specifically, the dysconnection hypothesis suggests an aberrant modulation of synaptic efficacy, particularly in brain systems associated with learning and memory (Friston 1998). This modulation is thought to be mediated by the neuromodulatory regulation of glutamatergic N-methyl-D-aspartate receptor function (Stephan et al. 2006).

Currently, one of the most plausible ways of investigating (short-term) synaptic plasticity is dynamic causal modeling (DCM) (Friston et al. 2003). DCM enables estimation of effective connectivity among ensembles of neurons—as well as experimentally induced modulations of such connectivity—making it a powerful tool for investigating the dysconnection hypothesis (Stephan and Friston 2010). Thus, given the importance of the coupling between frontal and parietal areas in mediating WM and the dysconnection hypothesis, we used DCM to investigate functional integration within the frontoparietal network in a cohort of first-episode schizophrenia (FES) patients performing an *n*-back task.

A few studies have examined modulations within this frontoparietal network in healthy participants and in schizophrenia patients using DCM. One study using an *n*-back task found increased modulation of forward effective connectivity (from PPC to PFC) as WM load was increased in healthy subjects (Dima et al. 2014) and another study found this using immediate and delayed memory tasks (Ma et al. 2012). However, one study found evidence for load-dependent modulation of the backward connection of a frontoparietal network (i.e. from PFC to PPC) during an *n*-back task in healthy subjects and that this modulation was decreased in a group of chronic schizophrenia patients (Deserno et al. 2012), whereas another study found this aberrant modulation in subjects experiencing their first episode of psychosis (Schmidt et al. 2013). Using structural equation modeling, another study failed to find effective connectivity from PFC to PPC but instead found positive connectivity from left PPC to left PFC, as well as medication-specific changes in connectivity depending on the type of antipsychotic medication (Schlösser et al. 2003). Thus, findings are mixed regarding the primary direction of influence and modulation by WM load, both within the healthy population and schizophrenia patients. Although there may be several reasons for such diversity, the heterogeneity of schizophrenia patients (illness stage, medication status, etc.) and differences in WM performance may lead to additional inconsistencies. For example, a meta-analysis (Snellenberg et al. 2006) has demonstrated that group differences

in dorsolateral PFC activations between schizophrenia patients and healthy participants are dependent on differences in WM performance and it is possible that such differences may also influence connectivity and modulatory estimates in DCM.

The aim of the current study was to investigate how WM modulation of the connectivity within the frontoparietal network is affected in FES patients. The recruitment of FES patients decreases the risk of findings being confounded by factors such as long-term treatment or chronic illness and may therefore provide important insights into the underlying pathophysiology. The FES patients recruited in the current study were taken from one of our previous studies where we were unable to demonstrate a significant difference in performance between the FES patients and the healthy controls thus enabling us to discount effects due to differences in task performance. Although not a general characteristic of FES, a few other studies have also failed to find significant between-group differences in terms of performance (e.g. Tan et al. 2005; van Raalten et al. 2008; Jung et al. 2013).

In this study, the left and right inferior frontal gyri (IFG)/dorsolateral prefrontal cortex (dlPFC) (We consider the label IFG to most accurately reflect the anatomy of the VOI(s) in our study; however, we note that the majority of studies on WM refer to this (and nearby) region(s) using the label dlPFC. In the remainder of the manuscript, we refer to this VOI as IFG.) were chosen as volumes of interest (VOIs) due to their crucial role in WM (Owen et al. 2005; Rottschy et al. 2012) and their high degree of engagement by our task (see Results). Context-dependent functional connectivity of these regions was first established using psychophysiological interaction (PPI) analysis to identify regions showing load-dependent effects on coupling between groups. In particular, such effects were anticipated in the inferior parietal lobe (IPL) because previous research has revealed that schizophrenic patients show reduced load-dependent connectivity between the IFG and IPL (Deserno et al. 2012; Kyriakopoulos et al. 2012; Schmidt et al. 2013). Whole-brain PPI analysis on the voxel level allows the detection of all regions showing load-dependent effects with a seed VOI; however, the inferences which may be drawn (e.g. regarding the directionality of effects) are limited (Friston et al. 1997). Thus, guided by the PPI findings, we went on to perform a DCM analysis to test explicitly different patterns of directed connectivity and modulation.

Materials and Methods

The current work is based on data previously published by Zhou et al. (2014). For details on task design and data acquisition protocol please see the Supplementary Material.

Participants

Seventeen FES patients were recruited from the Department of Psychiatry, the Second Xiangya Hospital of Central South University, Changsha, Hunan province, People's Republic of China. Interviews were conducted using the Structured Clinical Interview for DSM-IV patient version. All patients received atypical antipsychotic medication at the time of scanning. Eighteen age-, gender-, and education-matched healthy controls were recruited from a community sample in Changsha City. Written informed consent was obtained from all participants. The study was approved by the ethics committee of Second Xiangya Hospital of Central South University (Zhou et al. 2014).

A power analysis was conducted to estimate the number of subjects needed to obtain a power of 80% and 90% on a 2-sampled t-test. Based on an effect size reported in Deserno et al. (2012) for modulation of the connection between prefrontal and parietal areas and using a pooled variance estimate, we estimated the number of subjects in the 2 groups to be 12 and 13 or 16 and 17 for 80% and 90% power, respectively. However, note that this power analysis is based on a between-group effect at a different connection than where we observe an effect.

Preprocessing

Initial image preprocessing was performed using Statistical Parametric Mapping (SPM12) (<http://www.fil.ion.ucl.ac.uk/spm/>) and included slice timing correction, motion correction, structural and functional image co-registration, segmentation, normalization (based on each participant's structural image) to the Montreal Neurological Institute (MNI) 152 template, and smoothing using a kernel with a full-width half maximum of $8 \times 8 \times 8$ mm. The normalized images were interpolated to a resolution of $3 \times 3 \times 3$ mm. Additionally, in order to reduce the influence of head motion, wavelet despiking, as implemented by the BrainWavelet Toolbox (<http://www.brainwavelet.org/>), was performed (Patel et al. 2014).

To further account for residual motion and physiological noise (e.g. of cardiac and respiratory origin), several nuisance regressors were included in all general linear models (GLMs) as covariates of no interest: 1) 24 parameters (6 head motion parameters, 6 head motion parameters one time point before, and the 12 corresponding squared variables) obtained by rigid body head motion correction (Friston et al. 1996; Lund et al. 2006; Yan et al. 2013) and 2) 5 principal components from an anatomically defined noise VOI (composed of white matter and cerebrospinal fluid), an approach which has been shown to accurately describe physiological noise in gray matter (Behzadi et al. 2007). Finally, a high-pass filter with a cutoff of 250 s (0.004 Hz) was implemented to remove low frequency drifts while retaining most task-related frequencies.

Statistical Analyses

To identify areas engaged by the task, an initial standard activation analysis was performed. This was used to identify VOIs used as seeds in the PPI analyses. Guided by the PPI results, a subsequent DCM analysis was performed to estimate effective connectivity and modulatory effect of WM within a frontoparietal network of interest.

Activation Analysis

Three variables capturing the task conditions (0-back, 2-back, and cue) were used as regressors of interest in a mass univariate approach based on the GLM. To identify areas activated by the task, a 2-back > 0-back contrast was used.

Psychophysiological Interaction

To examine context-specific connectivity, a PPI analysis (Friston et al. 1997) was performed. This identifies contributions over and above those which can be explained by the shared main effect of task (related to mental activity) and nontask effects (mediated by connectivity with other regions) (O'Reilly et al. 2012). Although directional in nature, the PPI model is not uniquely specified in terms of effective connectivity and so the

term "contribution" has been proposed (Friston et al. 1997). In short, a PPI analysis is a way of investigating the contribution of the activity of one region in explaining the response of another.

Because the activation analysis did not show any between-group differences (see the Supplementary Material), VOIs were selected based on an effect across groups for the 2-back > 0-back contrast (see Supplementary Table S1 and Fig. S2). For the PPI analysis, the left IFG ($x = -42, y = 27, z = 27$) and the right IFG ($x = 42, y = 36, z = 27$) were chosen as VOIs and time series for both were extracted using SPM12. This was accomplished by extracting the first eigenvariate from a sphere with a radius of 6 mm, starting from the group-level peak coordinates and moving the center of the sphere to the nearest local maximum within 10 mm (alternatively, if this was not possible, to nearest suprathreshold voxel, likewise within 10 mm) masking by a 2-back > 0-back contrast thresholded at $P < 0.05$ (uncorrected) at the individual level. In one patient, no suprathreshold voxels were present and so the first eigenvariate was extracted from a 6-mm sphere centered at the group-level peak coordinates. Excluding this patient from the analysis did not affect the results reported below.

For each VOI, separate PPI analyses were conducted using SPM12. The interaction term was generated from the VOI time series and a psychological variable reflecting the context or task set, that is, WM, created using a 2-back > 0-back contrast. The interaction term was entered as a regressor of interest, whereas the physiological and psychological variables were entered as covariates of no interest. Subject-specific PPI regression coefficients were estimated at the within-subject level and then tested within and between groups at the between-subject level using the standard SPM random effects (RFX) summary statistic approach.

Because the VOI was identified with the same contrast used to define the psychological variable, our PPI analyses were low in statistical power (due to the large amount of shared variance between the regressors). We therefore used a cluster-level family-wise error (cFWE) correction with a voxel-level threshold of $P < 0.001$ (uncorrected) (Woo et al. 2014).

Dynamic Causal Modeling

Based on the group differences in the PPI analysis, we tried to determine the dominant (if any) direction of modulation using DCM (Friston et al. 2003). Because the PPI analysis only revealed changes in connectivity between the left IFG and the left IPL in the schizophrenia patients, we focused on these regions in the DCM analysis.

DCM was performed using DCM (rev. 5729) from SPM12 (rev. 6225). Our model (subgraph) consisted of 3 regions (nodes)—left IFG, left IPL, and primary visual cortex (V1) (see Supplementary Fig. S1). The signal from the left IPL was extracted using the same procedure as for the left IFG, except that the 2-back > 0-back contrast was masked with the cluster of the PPI effect (in IPL) (For one patient, the first eigenvariate was extracted from the entire mask of the PPI effect due to lack of task effect.). Admittedly, the 10-mm distance constraint is rather arbitrary, however, as is evident from Supplementary Figures S6 to S9, the DCM results are stable across different distances. The V1 VOI was specified functionally by the cue contrast (since it afforded a stable visual response that was minimally affected by other task-related activations) and the subject-specific location of each VOI was determined by masking the cue contrast with a mask of Brodmann area 17, moving to the global maximum, and extracting the first eigenvariate from voxels within 6 mm.

Since both IFG and IPL are engaged in processing visual information (Katsuki and Constantinidis 2012), endogenous (between-region) connectivity was assumed to exist bidirectionally between all nodes in the network. All stimulus functions from the first-level analysis coding for visual events (i.e. 0-back, 2-back, and cue) were used to drive V1, while the 2-back condition, reflecting the WM component of the experiment, was used to modulate the endogenous connectivity. The experimental inputs to the DCM were not mean centered.

The primary question of interest was whether WM modulated the connection IFG → IPL (backward modulation), IPL → IFG (forward modulation), or both, and if any group differences were apparent. This motivated a partition of the model space into backward, forward, bidirectional, and null (no modulation) subspaces each of which were augmented to include models where WM modulated the remaining connections (i.e. to and from V1). We included the latter models because 1) WM is likely to modulate the top-down influence of higher level cortex on primary visual areas (e.g. biasing attention toward goal-relevant features) and so the connections to and from V1 may be modulated by WM load (e.g. high load will leave fewer resources available for efficient target selection) (Soto et al. 2008), and 2) uncertainty about a model attribute of interest can be reduced by pooling information over subsets of models differing only in this particular attribute (Stephan et al. 2010). Thus, overall the model space comprised 64 models partitioned into 4 subgroups, each containing 16 models, representing modulation of forward, backward, bidirectional, and no (frontoparietal) connectivity. We assessed the evidence for the different models and estimated model parameters using a one-state, bilinear, deterministic DCM. See Figure 1 for an overview of the model space.

To compare models, an RFX Bayesian model selection (BMS) approach was used resulting in expected model probabilities and exceedance probabilities (EPs) for each model. The latter were used for determining the model (family) providing the best explanation of the data.

Subsequently, Bayesian model averaging (BMA) was used to obtain parameter estimates weighted by the evidence of each model for all subjects. Classical RFX analyses were used to explore (post hoc) the significance of parameters within and between groups using 1- and 2-sampled t-tests, respectively. The major interest of this study was the changes in the modulation effect in the FES patients, hence inference on group differences was restricted to the 6 modulatory parameters. Family-wise error rate was controlled using a Bonferroni corrected threshold correcting for 6 comparisons. Given that the Bonferroni correction is subjected Type II errors in this setting, results reaching $P < 0.05$ (uncorrected) are reported as trends. The group-level analyses (including the results on the endogenous connection strengths) are provided in the Supplementary Material.

Brain–Behavior Analysis

Linear regression was used to explore brain–behavior relationships. The DCM parameter showing significant group differences, that is, the modulation of IPL → IFG (see Results), was used to predict behavioral metrics (the sensitivity index, d' , and the response bias, c , from signal detection theory; Stanislaw and Todorov 1999; Zhou et al. 2014) of the 2-back condition while controlling for age, gender, and education. Separate analyses were conducted for each group. In addition, we also explored

the relationship between the DCM parameter showing significant group differences and the symptom severity.

Results

Behavioral Performance and Brain Activation

Results of the analysis of behavioral performance and brain activation are provided in the Supplementary Material. In general, there were no group differences in task performance or brain activation during the n -back task, however, the FES patients did show a larger response bias (see Supplementary Fig. S2 and Table S1). Additionally, including the (demeaned) medication dose in the second-level SPM contrast (2-back vs. 0-back) showed no significant effect of medication status, nor did including this effect change the results of the second-level contrasts.

Psychophysiological Interaction

Using left IFG as a seed region showed that the connectivity with left IPL, supplementary motor area (SMA), and several cerebellar regions were modulated by WM in the control group, whereas the FES patients showed this effect only in the SMA ($P < 0.05$, FWE corrected) (see Supplementary Figs S3 and S4, and Table S2). A cluster in the left IPL also can be found in the FES patients using a less stringent threshold ($P < 0.001$ uncorrected) (Supplementary Fig. S4). Testing for group differences revealed significantly higher modulation of connectivity in the control group in the left IPL ($x = -30$, $y = -57$, $z = 48$, $t = 4.62$, $P = 0.02$, cFWE corrected) and right cerebellum ($x = 6$, $y = -72$, $z = -33$, $t = 4.92$, $P = 0.02$, cFWE corrected) (see Fig. 2 and Supplementary Table S2). FES patients did not exhibit stronger WM modulation of any connections. Using right IFG as a seed region did not show any within-group effects nor any group differences (all P s > 0.05 , cFWE corrected).

Dynamic Causal Modeling

The bidirectional partition of models seemed to outperform the others in the control group with an EP of 0.66. In the patient group, however, the forward family explained the data the best (EP of 0.49) (see Fig. 3; see Supplementary Fig. S5 for information on which (subspace) models were driving the effects at family level). Due to the indefinite results of the BMS over the 2 groups, inference on parameters proceeded using BMA by averaging over all 64 models, thus preventing bias due to model selection.

The modulation of WM on the bidirectional connections between left IPL and left IFG was significant ($P < 0.05$, Bonferroni corrected) and positive in both groups. In the control group, the modulation of the connections from V1 to left IFG and left IPL was also significant ($P < 0.05$, Bonferroni corrected) and negative. No other modulations were significant in the schizophrenia group (Supplementary Table S3).

Two-sampled t-tests were used to test between-group differences on the 6 modulatory parameters. The modulation of the left IPL to the left IFG showed a significant between-group difference ($P < 0.05$, Bonferroni corrected) in that it was significantly larger in the control group than the FES group. See Figure 4, Supplementary Tables S3 and S4 for an overview of the BMA results.

Brain–Behavior Analysis

Using linear regression, in which the modulation strength of IPL → IFG was used to predict the (absolute) c score, we found significant, negative correlation in the schizophrenia group ($\beta = -0.49$, $P = 0.02$) suggesting that increased modulation was associated

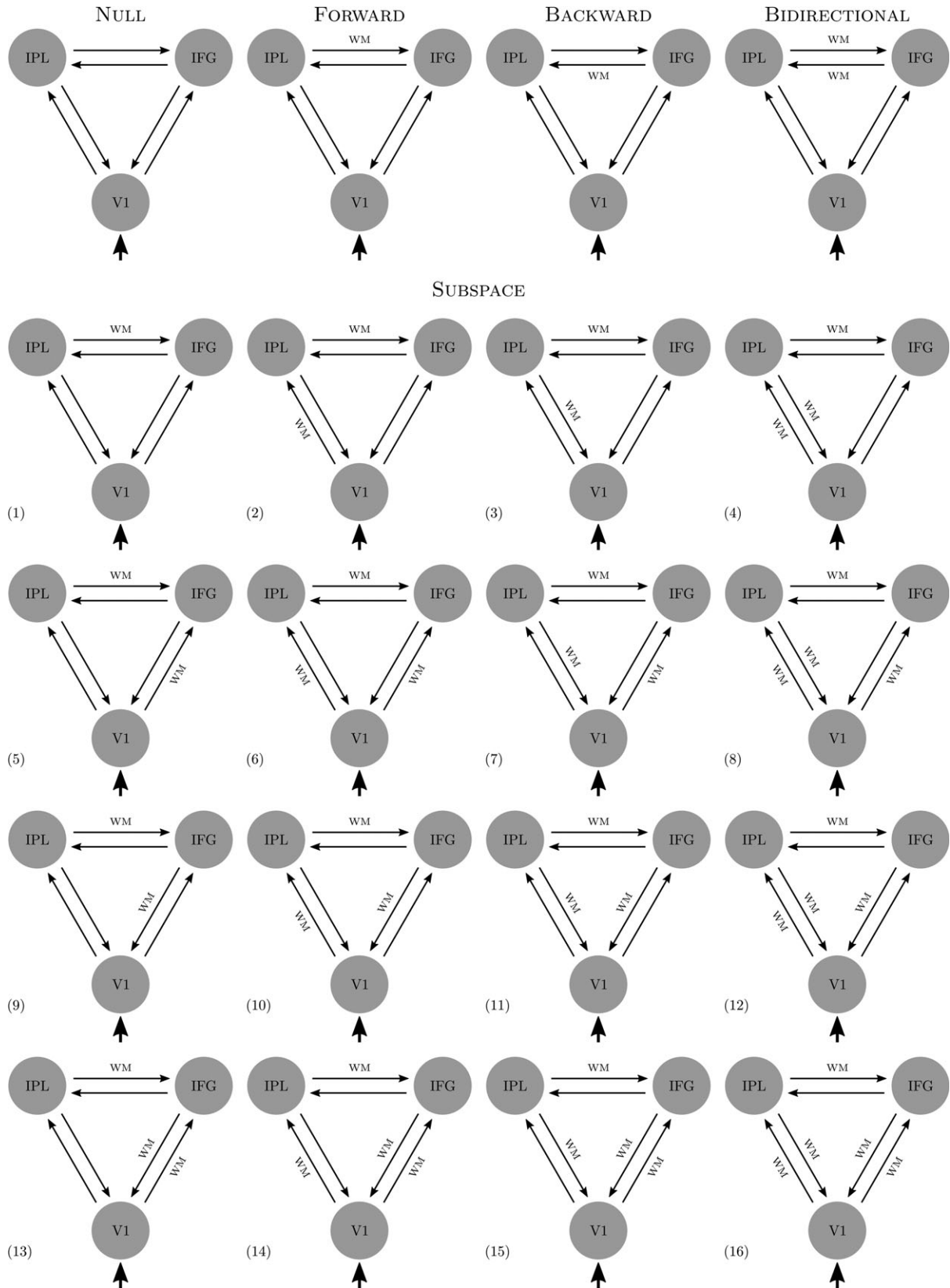


Figure 1. Model space of the DCM analysis. Top row shows the modulatory parameters defining the partitions of the model space. Bottom 4 rows show the model subspace generated by including all possible modulations (here shown for the forward model). The bottom arrow denotes visual input.

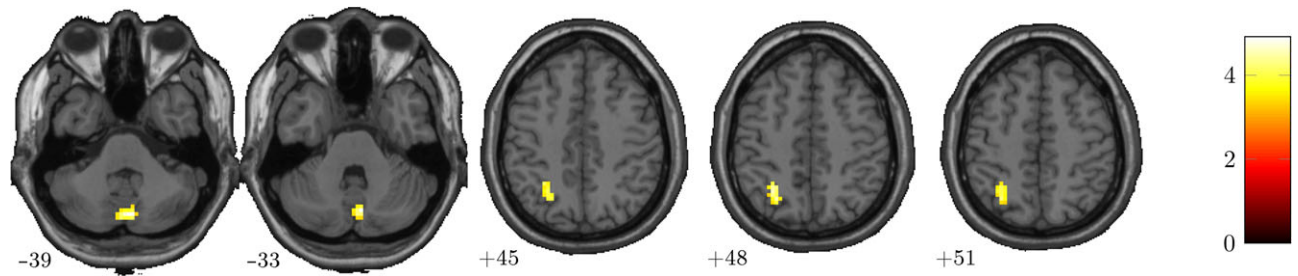


Figure 2. Between-group differences (healthy controls > FES patients) in PPIs (using the left IFG as seed) at $P < 0.05$ (FWE corrected at cluster level) with a voxel-level threshold of $P < 0.001$ (uncorrected). Colorbar indicates t-statistic.

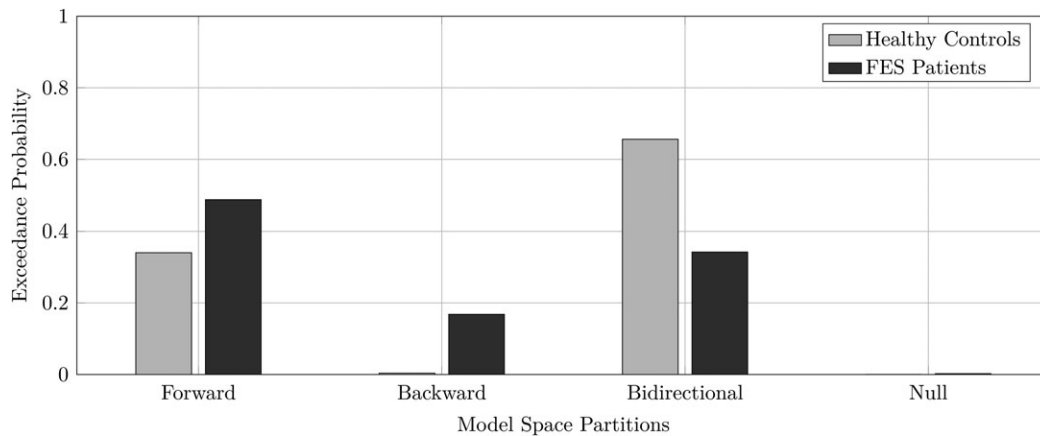


Figure 3. BMS showing EPs for each partition of the model space.

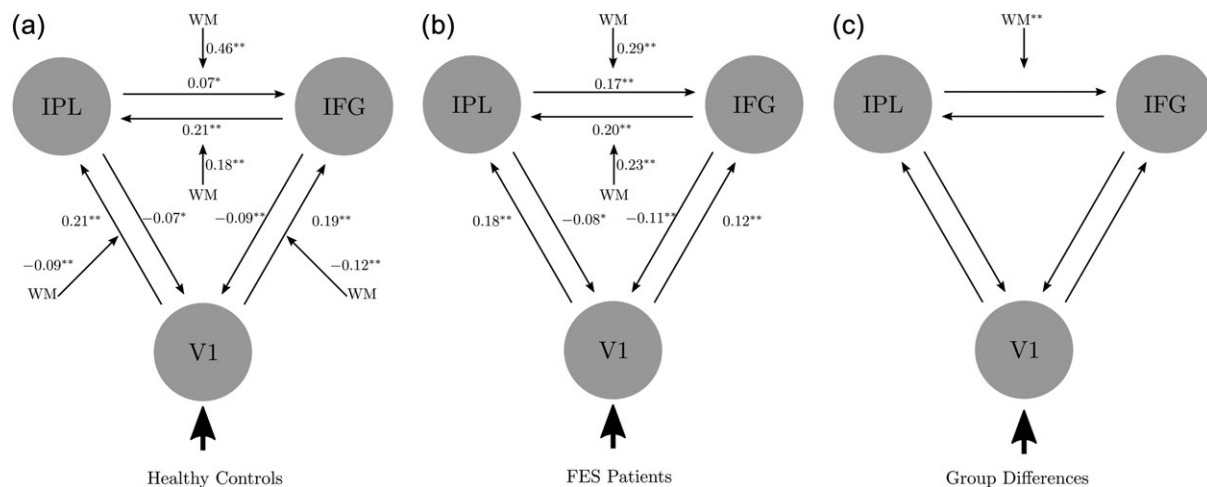


Figure 4. Parameter estimates from BMA averaging over the entire model space (i.e. all 64 models). (a) and (b) show within-group results (modulatory parameters with $P > 0.05$ are omitted). (c) shows between-group differences (modulatory parameters with $P > 0.05$ are omitted). In all cases, the bottom arrow denotes visual inputs. * Trend at $P < 0.05$ (uncorrected for multiple comparisons). ** Significant at $P < 0.05$ (Bonferroni corrected for multiple comparisons).

with lower response bias. A similar analysis using d' as dependent variable did not reveal any significant within-group relationships.

With respect to the clinical correlates of brain activity and connectivity, we found no correlations between symptom severity (as measured by the Scale for the Assessment of Positive (or Negative) Symptoms (SAPS and SANS, respectively), and the summed score, i.e. SAPS + SANS) and brain activity (2-back vs. 0-back). We found a negative correlation ($\beta = -0.49$,

$P = 0.05$) between SANS and the WM-induced modulation of the connection from IPL to IFG (i.e. our main result from the DCM analysis) suggesting that negative symptoms were associated with lower modulation of this connection.

Additionally, we found a correlation between SAPS and the response bias from the 0-back condition ($\beta = -0.62$, $P = 0.03$) such that a low SAPS score was associated with one type of bias, whereas a high SAPS score was associated with the

opposite bias. We report these results as trends, however, since none survived a correction for multiple comparisons.

Discussion

The current study supports the notion of abnormal WM modulation of frontoparietal connectivity in schizophrenia and extends our knowledge on how such connectivity may be altered in the early phase of schizophrenia. The PPI analysis showed that the connectivity between left IFG and left IPL was modulated by WM and that this modulation was reduced in FES patients. A subsequent DCM analysis confirmed this modulation by WM and found evidence that FES patients had reduced forward connectivity from left IPL to left IFG. These findings suggest that in the early phase of schizophrenia, even with intact WM performance, the functional interaction within the frontoparietal network is less sensitive to context or cognitive set. This may be related to different strategies used to perform the WM task.

Modulation of IPL → IFG by WM

We found increased connectivity from the left IPL to the left IFG during the 2-back condition in the healthy controls. This result is in line with studies showing load-dependent modulation of this connection during a delayed-matching-to-sample (Ma et al. 2012) and a verbal *n*-back (Dima et al. 2014) task as well as load-dependent modulation of the activity in these regions (Woodward et al. 2006). It should be noted, however, that other studies using DCM have found modulation in the opposite direction (i.e. from PFC to IPL) (Deserno et al. 2012; Schmidt et al. 2013). One of these studies (Schmidt et al. 2013) employed a task design similar to that of the current study (verbal *n*-back), however, they observed an effect only in the right hemisphere and only in untreated patients. The other study (Deserno et al. 2012) used a model space similar to that in our study but employed a numerical *n*-back task. Numbers may inadvertently activate nonverbal semantics (e.g. numerical magnitude) even in tasks where this is not explicitly required (Fischer et al. 2003) suggesting that even though numbers are often considered verbal material they may differ in subtle, yet significant, ways (Knops et al. 2006). This may in turn have an effect on how they are encoded, stored, and rehearsed in WM, perhaps accounting for some of the observed differences in modulation.

There is evidence supporting left hemispheric lateralization of verbal WM (Wager and Smith 2003; Nagel et al. 2013) and so it is possible that the connection from left IPL to left IFG is somehow related to the processing of verbal information (Ma et al. 2012). Specifically, since left IPL and left IFG are both assumed to be critical anatomical substrates of the phonological loop (Baddeley 2003)—being responsible for storage and rehearsal, respectively (Baddeley 2010)—this connection may be important for maintenance of verbal information in WM. The need to verbally encode stimuli during the 0-back condition may be minimal due to the limited WM requirements of this condition and so the positive modulation of the forward connection observed in the current study may reflect the increased flow of verbally coded information.

In the FES group, the modulation of IPL → IFG by WM was significantly lower compared with the healthy controls, suggesting an inability of the patients to modulate the synaptic efficacy of this network in accordance with the dysconnection hypothesis. Previous studies also support the notion of altered WM modulation of frontoparietal effective connectivity in schizophrenia (Deserno et al. 2012; Schmidt et al. 2013). In these

studies, however, the patients were performing worse than the controls, whereas in our study patients and controls were performing similarly, yet we still found decreased WM modulation of frontoparietal connectivity. Thus, it would appear that reduced (short-term) synaptic plasticity is indeed an intrinsic feature of schizophrenia as postulated by the dysconnection hypothesis (Friston et al. 1997) and not simply a correlate of bad performance (which may arise due to a multitude of reasons [Brown and Thompson 2010]).

We failed to find any within-group relationship between the modulation of IPL → IFG and 2-back performance (*d'*); however, we did find a (negative) correlation with the response bias (*c* score) in the schizophrenia group, a parameter on which the groups differed significantly in that the FES patients showed a larger response bias compared with the healthy controls. A response bias reflects the general tendency of a subject to respond in a particular manner (Stanislaw and Todorov 1999). Thus, it is related to the particular way in which a task is being performed (rather than how well it is being performed) and so would seem to somehow reflect the strategy adopted by the participant. Therefore, we speculate that the patients, compared with controls, might have been performing the task differently in terms of strategy. Specifically, since there is evidence linking the connection IPL → IFG to the processing of verbal material (see above), healthy subjects may have relied more on verbal processing during the 2-back condition, whereas this may not have been the case in the FES patients, suggesting a strategic difference in how they performed the 2-back task.

The Dysconnection Hypothesis and Frontoparietal Connectivity

Physiologically, our results suggest that the PFC fails to modulate its sensitivity to parietal afferents in response to changes in the WM task set. This is consistent with the findings of a previous (stochastic) DCM study of FES that “revealed reduced effective connectivity to the AF [anterior frontal] node of the DMN—reflecting a reduced postsynaptic efficacy of prefrontal afferents—in patients with first-episode schizophrenia” (Bastos-Leite et al. 2015). However, the foregoing study focused on resting state or endogenous activity, whereas our results speak to a failure to adjust prefrontal sensitivity to ascending (forward) inputs. This failure to contextualize or adjust synaptic efficacy or gain with task set has also been reported in DCM studies of electrophysiological responses. For example, Fogelson et al. studied schizophrenic patients during the visual processing of predictable and unpredictable stimulus sequences. They concluded that the patients “fail to adjust or optimize [this] connectivity when events can be predicted. Thus, the differential intrinsic recurrent connectivity observed during processing of predictable versus unpredictable targets was markedly attenuated in schizophrenia patients compared with controls, suggesting a failure to modulate the sensitivity of neurons responsible for passing sensory information or prediction errors up the visual cortical hierarchy” (Fogelson et al. 2014). These previous DCM studies appealed to predictive coding to interpret the failure to modulate the postsynaptic sensitivity to ascending afferents. In this refinement of the dysconnection hypothesis, the symptoms of schizophrenia are generally construed as false inference (e.g. hallucinations and delusions) that reflects an aberrant encoding of salience or precision at various levels in cortical hierarchies (Fletcher and Frith 2008; Corlett et al. 2010; Adams et al. 2013). Crucially, the encoding of salience or precision in predictive coding is thought to be

mediated by the postsynaptic sensitivity or gain of (superficial pyramidal) cells encoding prediction errors, which has been associated with attentional processing (Feldman and Friston 2010; Brown and Friston 2012). In this theoretical framework, our results suggest that the failure to increase the sensitivity of prefrontal neurons to ascending parietal afferents during increased WM load could be construed as a selective failure of attention to the attributes (or mnemonic representations) that would normally be engaged by our task.

V1 and Frontoparietal Connectivity

As to the remaining DCM parameters, the BMA analysis revealed that in the control group, the connectivity from V1 to IPL and IFG was negatively modulated by WM suggesting decreased flow of information between the primary visual system and frontoparietal areas as memory load was increased. This may be due to the limited capacity of the visual system (Rissman et al. 2008), thus prompting a shift in mnemonic strategy, perhaps toward verbal encoding and maintenance. This account is supported by evidence showing that verbal (and semantic) code makes an important contribution to the maintenance of objects in WM (Postle et al. 2005) as well as the main effect of task on reaction time (in the current study), the latter being consistent with the fact that encoding a letter verbally (or semantically) is more time consuming than simply encoding it as an object (Mottaghy et al. 2003). Furthermore, the involvement of verbal processing is supported by the left hemispheric dominance observed in the current study and others (Nagel et al. 2013), as well as the load-dependent involvement of such areas in maintenance processes (Woodward et al. 2006). Thus, the decreased coupling of the primary visual system with frontoparietal areas seems consistent with the interpretation that healthy controls depend on verbally coded information as memory load increases.

On the other hand, schizophrenia patients did not show significant decoupling of V1 and frontoparietal regions during the 2-back condition perhaps suggesting that they rely more on the visual system, whereas the controls may do so in the 0-back condition but in the more difficult 2-back condition, they start engaging the verbal system to a larger extent (simultaneously disengaging the visual system). However, this shift from visual to verbal processing may not be possible for the patients due to the “rigidity” and context-insensitivity of the schizophrenic brain (i.e. the inability to modulate synaptic efficacy) and so they continue to rely on the visual system during the 2-back task. Thus, though reflecting an abnormality, in effect it may act to compensate for the segregation within the frontoparietal network, hence offering a plausible explanation for the absence of any performance difference between the groups. We did not, however, find any significant group differences in the modulation of these parameters and so this account is somewhat speculative.

Limitations

This study had several limitations. First of all, though we suggested that our results reflect compromised verbal processing in the FES patients, this interpretation is somewhat speculative in that the experiment was not specifically designed to address this issue. Likewise, we were not able to distinguish different subprocesses of WM and so it is difficult to know exactly which processes are related to the observed modulations. Second, only a modest sample size was used making it difficult to detect all but large effects. Also, despite being a FES cohort, all

clinical subjects received antipsychotic medicine at the time of scanning, something which has been shown to influence estimates of functional (Lui et al. 2010; Jiang 2013), effective (Schmidt et al. 2013), and possibly structural (Shepherd et al. 2012a, 2012b) connectivity. WM modulation of the connection between IFG and IPL in the right hemisphere has been found to be modulated by antipsychotic medicine, such that nontreated patients—but not patients receiving antipsychotic medication—differed significantly from healthy controls on this DCM parameter (Schmidt et al. 2013). This suggests that medication may serve to modulate and normalize frontoparietal connectivity in patients experiencing first-episode psychosis (Lui et al. 2010). Third, in relation to the DCM analysis—on top of the usual sources of interstudy differences such as variations in clinical subpopulations and experimental design (Brown and Thompson 2010)—differences in model space and DCM priors may also contribute to discrepancies among studies (Dauvermann et al. 2014). Besides, evidence exists suggesting that some effects in schizophrenia may be nonlinear (Dauvermann et al. 2013) and so future studies may explore possible nonlinearities within this frontoparietal network. In the current study, the DCM model space was rather simple enabling us to focus on the connection(s) of interest and facilitate interstudy comparability. However, it might be interesting to extend the model space to include bilateral frontal and parietal regions as well as other areas known to be important for WM such as the SMA and anterior insula (Rottschy et al. 2012), areas which have also been implicated in schizophrenia in resting state (Manoliu et al. 2013; Moran et al. 2013) and executive tasks (Míndenbergl et al. 2009; Pujol et al. 2013).

Conclusion

Our study provides further evidence for impaired WM modulation of frontoparietal connectivity in schizophrenia. Positive modulation of forward connectivity in the left hemisphere may be related to increased reliance on verbal representations of stimuli and so this result may speak to the relative failure of the schizophrenic brain to contextualize its connectivity since FES patients showed a reduced modulation of coupling between these regions—2 of the main hubs in the executive network. Given that these patients were experiencing their first episode of schizophrenia, our findings suggests that such deficits are present at an early stage in this disorder.

Supplementary Material

Supplementary data are available at *Cerebral Cortex* online.

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Notes

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