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Disruptions in the Left Frontoparietal Network Underlie Resting State Endophenotypic Markers in Schizophrenia

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Abstract: Advances in functional brain imaging have improved the search for potential endophenotypic markers in schizophrenia. Here, we employed independent component analysis (ICA) and dynamic causal modeling (DCM) in resting state fMRI on a sample of 35 schizophrenia patients, 20 first-degree relatives and 35 control subjects. Analysis on ICA-derived networks revealed increased functional connectivity between the left frontoparietal network (FPN) and left temporal and parietal regions in schizophrenia patients ($P < 0.001$). First-degree relatives shared this hyperconnectivity, in particular in the supramarginal gyrus (SMG; $P = 0.008$). DCM analysis was employed to further explore underlying effective connectivity. Results showed increased inhibitory connections to the left angular gyrus (AG) in schizophrenia patients from all other nodes of the left FPN ($P < 0.001$), and in particular from the left SMG ($P = 0.001$). Relatives also showed a pattern of increased inhibitory connections to the left AG ($P = 0.008$). Furthermore, the patient group showed increased excitatory connectivity between the left fusiform gyrus and the left SMG ($P = 0.002$). This connection was negatively correlated to inhibitory afferents to the left AG ($P = 0.005$) and to the negative symptom score on the PANSS scale ($P = 0.001$, $r = -0.51$). Left frontoparietotemporal dysfunction in schizophrenia has been previously associated with a range of abnormalities, including formal thought disorder, working memory dysfunction and sensory hallucinations. Our analysis uncovered new potential endophenotypic markers of schizophrenia and shed light on the organization of the left FPN in patients and their first-degree relatives. *Hum Brain Mapp 38:1741–1750, 2017.*

Key words: neuroimaging; endophenotypes; schizophrenia; biomarker

INTRODUCTION

Schizophrenia is a severe neuropsychiatric disorder that manifests with a multitude of symptoms including delusions, hallucinations, social withdrawal, apathy and speech disorganization (DSM IV). It affects approximately 1% of the world population [Bhugra, 2005; Saha et al., 2005] with significant economic, social and humanistic burden on

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the individual affected and on broader society [Csoboth et al., 2015]. Genetics play a significant role in the disease with heritability estimated to be around 64%, with a concordance rate of 45% for homozygotic twins and 12% for dizygotic twins [Lichtenstein et al., 2009, Tsuang 2000]. Endophenotypic markers are defined as heritable and measurable components that mediate the path between the genotype and phenotypic expression and are more likely to be expressed in individuals at high genetic risk, particularly first-degree relatives [Gottesman and Gould, 2003]. They can range over a wide array of measurements and may be biochemical, anatomical, cognitive or neurophysiological in nature [Ferrarelli, 2013]. The search for endophenotypic markers in schizophrenia is an especially active area of research as it may prove critical in uncovering pathways and mechanisms that predispose to the disease as well as in identifying individuals at high risk.

Resting state functional magnetic resonance imaging (rs-fMRI) has emerged as a powerful tool in revealing intrinsic connection abnormalities in schizophrenia [Yu et al., 2012]. Studies involving rs-fMRI have shown widespread connection abnormalities in neural networks in the brain, that include the default mode, central executive and frontoparietal networks [Yu et al., 2012]. Nonetheless, results remain far from uniform and are complicated by the heterogeneity of the disorder, sample sizes as well as the medication history of the subjects. The default mode network (DMN), for example, is one of the most studied resting state networks and while some studies reveal hyperconnectivity, others show hypoconnectivity or altered connectivity with areas outside the DMN [Broyd et al., 2009; Karbasforoushan and Woodward, 2012; Ongür et al., 2010; Rotasrska-Jagiel et al., 2010; Tang et al., 2013; Whitfield-Gabrieli and Ford, 2012]. Repovš and Barch show that the frontoparietal network exhibits weaker connectivity with cerebellar networks and Unschuld et al. report that patients with schizophrenia tend to have stronger within network connectivity in the frontoparietal network [Repovš and Barch, 2012; Unschuld et al., 2014]. The latter finding was also correlated with reduced working memory ability [Unschuld et al., 2014]. Some studies have also looked for alterations that are more specific to particular symptoms. Wolf et al. showed increased connectivity of the speech related network with bilateral temporal regions and decreased connectivity with the cingulate cortex in 10 patients with auditory verbal hallucinations [Wolf et al., 2011]. These findings were also correlated with the strength of auditory hallucinations [Wolf et al., 2011]. Ford et al. reported hyperconnectivity of the visual network with the amygdala in patients with schizophrenia who experience visual hallucinations [Ford et al., 2015].

The purpose of the study is to uncover possible new endophenotypic markers of schizophrenia using rs-fMRI on a sample of healthy control subjects, patients with schizophrenia and healthy first-degree relatives. We hypothesized that abnormal connectivity in major resting state networks may be shared by healthy relatives of patients with the disorder and thus potentially serve as endophenotypic markers. For that aim, we used a novel combination of independent component analysis (ICA)-based approaches and dynamic causal modeling. In a first step, we employed ICA in a data-driven approach to uncover major neural networks in the resting brain and then looked for group differences in networks reliably identified in resting state studies and known to be involved in the disease [Narr and Leaver, 2015; Smith et al., 2009; van den Heuvel and Hulshoff, 2010]. In a second step, we used dynamic causal modeling (DCM) to elucidate the causal dynamics underlying functional connectivity abnormalities in affected networks. DCM utilizes a neural model to explain BOLD connectivity data and in the process estimates effective neural connectivity between different regions of the brain [Daunizeau et al., 2011]. Although DCM use has been mostly employed in task-based experiments, recent innovations have allowed its use in resting state data [Friston et al., 2014, Razi et. al 2015]. DCM allows for more neuronally and biologically plausible interpretations, giving more insight into the functional organization of resting state networks and increasing the likelihood of finding genetic correlates [Birnbaum and Weinberger, 2013].

METHODS

Subjects

Resting state fMRI data was acquired from healthy subjects, patients with schizophrenia (SZ) and first-degree relatives of schizophrenia patients (RL). Subjects gave written informed consent for participation after the study was approved by the Ethics Committee in Georg August University. Each subject underwent a diagnostic interview by at least one experienced psychiatrist. Patients were recruited from the Department of Psychiatry and Psychotherapy, University Medical Center Göttingen. They met the diagnostic criteria of schizophrenia according to DSM IV and their symptoms were assessed with the Positive and Negative Symptom Scale (PANSS). Exclusion criteria for the patient sample included substance abuse within the last month, cannabis abuse within the last 2 weeks, past or present substance dependency, somatic or mental disorders that would interfere with the protocol, acute suicidal tendency or an inability to give written consent. Exclusion criteria for subjects in the control group included any DSM IV diagnosis for the subject or a first-degree relative. Subjects in the relatives group had at least one first-degree relative diagnosed with schizophrenia and were never diagnosed with any DSM IV entity. They were also not relatives of subjects in the patient group. The final sample included 303 healthy subjects, 35 patients diagnosed with schizophrenia and 20 healthy first-degree relatives after one subject from the relatives group, three from

the patient group and 24 from the control group were excluded due to excessive motion (see Section Independent component analysis). From the total of 303 healthy subjects, 35 subjects were age and gender matched to the SZ and RL groups. We refer to this group as the matched-Healthy Control Group (mHC). The rest of the 303 healthy subjects that were not included in the matched sample are referred to as "HC."

fMRI Acquisition

Resting-state fMRI data was acquired in a Siemens Magnetom TRIO 3T scanner. Scanning parameters for the functional acquisition were: $3 \times 3 \times 3$ mm^3 voxel size, 33 slices, interscan interval of 2,000 ms, 64×64 matrix, 0.6 mm spacing, flip angle of 70 degrees, FOV 192 mm, TE 30 ms and a total of 160 volumes. Additionally, a high-resolution, T1-weighted 3D anatomical set (MPRAGE sequence, TE 4.42 ms, TR 11.9 ms, flip angle 15°, field of view 256×256 mm2, voxel size $1 \times 1 \times 1$ mm^3, 176 consecutive slices) was collected for each subject. Functional scanning time lasted approximately 5.2 min. During that time, subjects were instructed to keep their eyes open and fixated on a cross in the middle of the screen. Subjects were asked if they fell asleep during the recording process, and no subject reported doing so.

Statistical Analysis

Independent component analysis

Preprocessing was performed with SPM 8 and included the following steps: motion realignment, exclusion of subjects with maximal translational movement larger than 3 mm and maximal rotational movement larger than 3 degrees, co-registration with the anatomical T1, slice-time correction and normalization to the standard MNI space. In addition, the 6 motion parameters and their first temporal derivatives were inserted in a GLM model and regressed from the data. Regression of motion parameters before group ICA analysis has been shown to significantly improve signal-to-noise ration and sensitivity to group differences [Vergara et al., 2016].

Group ICA analysis was performed with FSL on the 268 HC subjects that did not include the 35 healthy subjects that were matched to the SZ and RL groups. This approach allowed us to independently and unbiasedly obtain maps of major resting state networks and has been shown to be more reliable and sensitive to group differences [Griffanti et al., 2016]. Smoothing of 6 mm, high-pass filtering with a threshold of 0.01 Hz and brain extraction were additionally performed on all subjects with FSL. We specified "automatic dimensionality estimation" in FSL to estimate the number of components in the data. As a result, 12 components were outputted from the ICA analysis. The components were examined and those corresponding to the default mode network (DMN), the visual network (VN), the central executive network (CEN), the left frontoparietal network (FPN) and the right FPN were subsequently chosen for further analyses. Cross-examination with networks described in prior literature was done with visual inspection [Smith et al., 2009]. We chose those particular networks among the 12 outputted networks because they have been reliably identified in several major rsFMRI studies and because of extensive literature associating them with schizophrenia [Ford et al., 2015; Narr and Leaver, 2015; Smith et al., 2009; van den Heuvel and Hulshoff, 2010].

TABLE I. Peak voxel coordinates of the major nodes in the left frontoparietal networks involved in the DCM analysis

Region	Peak voxel coordinate (MNI space)	Brodmann area
Left inferior frontal gyrus	−50 22 28	BA 44
Left angular gyrus	−42 −62 48	BA 39
Left occipitotemporal **cortex**	−58 −54 −16	BA 37
Left anterior cingulate gyrus	−2 30 20	BA 24
Left supramarginal gyrus	−54 −18 16	BA 40

Next, dual regression on the SZ, RL and 35 matched HC group was ran utilizing FSL to generate subject-specific versions of the spatial maps and associated time series, using the set of spatial maps outputted from the group-average analysis [Beckmann et al., 2009; Filippini et al., 2009]. First, for each subject, the group-average set of spatial maps is regressed (as spatial regressors in a multiple regression) into the subject's 4D space-time dataset. This results in a set of subject-specific time series, one per group-level spatial map. Next, those time series are regressed (as temporal regressors, again in a multiple regression) into the same 4D dataset, resulting in a set of subject-specific spatial maps, one per group-level spatial map.

To determine group differences between the HC and SZ groups, subject-specific maps for the 5 selected components were used in a second-level analysis in SPM 12. Statistical significance was considered for $P = (0.05/5)/2 = 0.005$ (Family Wise Error [FWE], whole-brain cluster-extent correction). Cluster-level significance corresponds to the statistical significance of contiguous voxels whose voxel-wise statistical value is above a certain threshold [Friston et al., 1994]. We chose a conservative voxel-wise value of $P = 0.001$, uncorrected [Woo et al., 2014]. Another second-level analysis was performed using age, gender, laterality and smoking status as cofactors.

Clusters showing significant differences between the HC and SZ groups were then employed as masks in a second level analysis between HC and RL subjects, to determine any potential endophenotypic markers. Clusters were considered potential endophenotypic markers for $P = 0.05$ after correction for multiple comparisons across voxels within the mask, using cluster-extent FWE, with a voxel threshold of $P = 0.001$ uncorrected. A similar analysis was performed with gender, age, laterality and smoking status as cofactors.

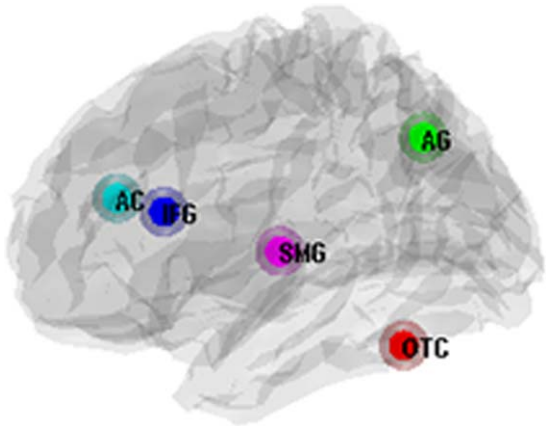

Figure 1.
Location of the nodes that are part of the DCM analysis. AC: anterior cingulate, IFG: inferior frontal gyrus, AG: angular gyrus, SMG: supramarginal gyrus and OTC: occipitotemporal cortex. [Color figure can be viewed at wileyonlinelibrary.com]

Dynamic causal modeling

In order to further investigate the causal interactions underlying differences in functional connectivity in the affected networks, we employed dynamic causal modeling for the major nodes of the networks and regions showing group differences in connectivity. DCM employs a neuronally plausible model for the observed BOLD responses and allows the estimation of effective connectivity between the different nodes of the network. Effective connectivity quantifies the influence of one region over another, thus it is directed (from one region to another) and deterministic (establishing causal relationships) [Daunizeau et al., 2011]. We employed in this study spectral DCM utilizing SPM 12, as it is more computationally efficient than stochastic DCM and has shown better sensitivity to group differences for the estimation of effective connectivity parameters [Friston et al., 2014]. Instead of modeling the time series of neuronal fluctuations, spectral DCM models their cross correlation function (their second order statistics), and thus enables a more explicit and direct relationship to functional connectivity [Friston et al., 2014]. Our analysis consisted of the following steps: region of interest specification, extraction of time series and model specification, estimation of model parameters, post hoc model selection for the three groups and comparison of effective connectivity parameters if the same optimal model was selected for all three groups. We also tested for correlations among significant connections and between connections and clinical parameters on the PANSS. Regions of interest were based on spheres of 3 mm radii centered around voxels with peak connectivity parameters to the left FPN in each of the four major nodes of the left FPN (the inferior frontal gyrus, the angular gyrus, the occipitotemporal **cortex** and the anterior cingulate), in addition to the region showing differences between healthy subjects on one side and control and relatives on the other side. We restricted the analysis to the left hemisphere for simplicity, keeping the total number of nodes less than 6, and because the major group differences for the dual regression analysis were in the left hemisphere. For a more thorough description of the steps involved in the DCM analysis, please see our Supporting Information section.

The locations of the peak voxels and the respective regions are provided in Table I and Figure 1.

TABLE III. Clinical data for the patients group diagnosed with schizophrenia

Illness duration	7.3 ± 7.7 years
PANSS	53.22 ± 1.93
Psychotropic medications at time of investigation	Atypical antipsychotics: 33/35 Typical antipsychotics: 3/35 Mood stabilizer: 1/35 Lithium: 0/35 Antidepressants: 9/35 Benzodiazepines: 2/35 No medications: 1/35
CPZ equivalents:	564.8 ± 434.2 mg/day

RESULTS

Demographics

Table II provides an overview of the demographic information for each of the four groups. ANOVA analysis revealed no significant differences between mHC, SZ and RL groups ($P = 0.38$) for age. A Chi-square test for gender also showed no significant differences between the three

TABLE II. Overview of pertinent demographics information

	mHC	SZ	RL	*P*
n	35	35	20	—
Age	31.7 (±1.7)	32.3 (±1.7)	36 (±2.3)	0.38
Gender	28 males, 7 females	28 males, 7 females	11 males, 9 females	0.08
Smoking status	1 smoker, 34 nonsmokers	20 smokers, 15 nonsmokers	5 smokers, 15 nonsmokers	$P < 0.001$
Handedness	35 right handed	28 right handed, 7 left handed	19 right handed, 1 left handed	$P = 0.01$

P values correspond to ANOVA analyses for age and chi-square analysis for gender. mHC= matched healthy control group, SZ = schizophrenia patients, RL = first-degree relatives of schizophrenia patients.

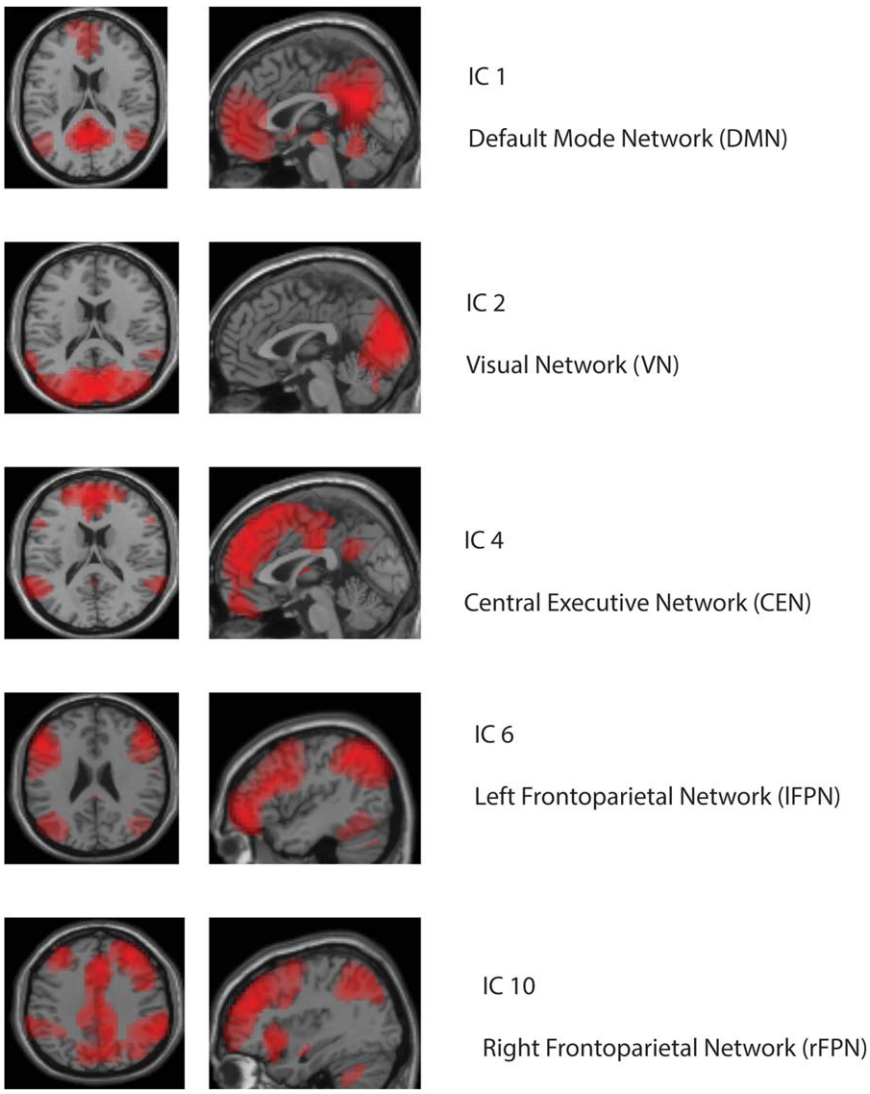

Figure 2.

Profiles of networks chosen for subsequent analyses. IC corresponds to "independent component" followed by a number indicating the position of the network in regards to its capacity to explain variance in the data. Areas in red correspond to thresholded z values outputted from the independent component analysis. [Color figure can be viewed at wileyonlinelibrary.com]

groups ($P = 0.08$). The nonmatched HC group showed significant differences for age in comparison to all other groups ($P < 0.001$ for all comparisons, Wilcoxon rank sum test) and for gender in comparison to mHC and SZ ($P < 0.001$, chi-square). The three matched groups also differed in regards to smoking and handedness ($P < 0.001$ and P −0.01, respectively). Clinical information regarding the patient group is shown in Table III.

Independent Component Analysis

Group-ICA yielded 12 independent components, from which five networks corresponding to the DMN, the CEN, the VN, the left FPN and right FPN were chosen for further analyses because of their strong association with schizophrenia as well as reliable identification in major rs-fMRI studies [Ford et al., 2015; Narr and Leaver, 2015; van den Heuvel and Hulshoff, 2010]. Figure 2 shows the profiles of those networks. Only the left FPN showed significant differences between the mHC group and the SZ group after implementing dual regression and correcting for multiple comparisons. SZ subjects showed significantly increased connectivity with the left FPN in a cluster that stretches from the Heschl gyri medially to the middle and superior temporal gyri and Brodmann Area 40 in the supramarginal gyrus ($P < 0.001$, FWE cluster-corrected),

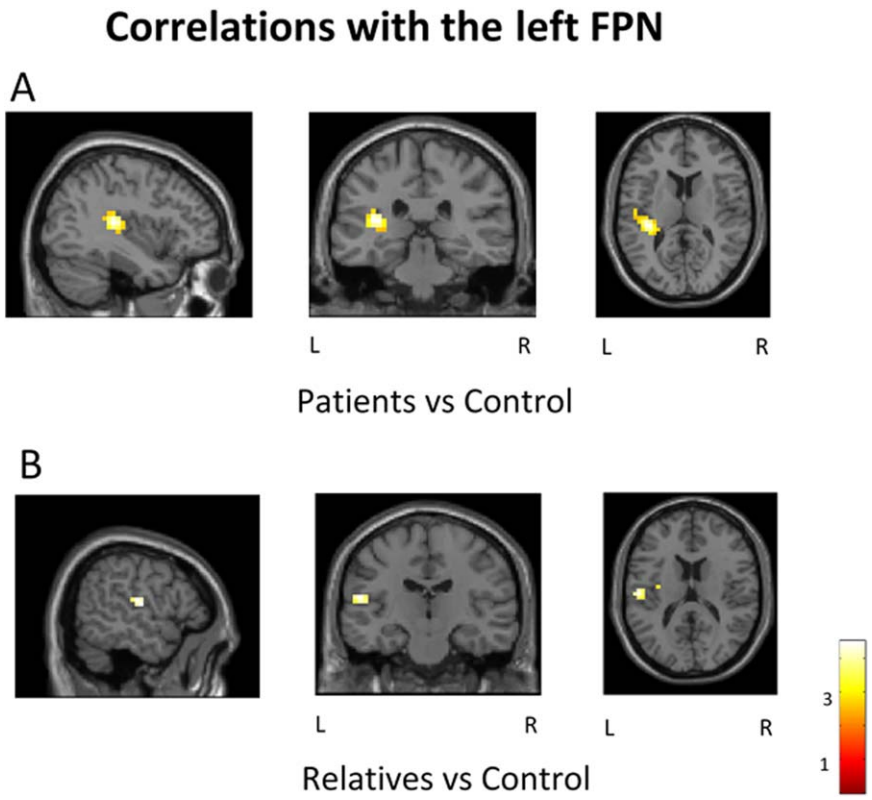

Figure 3.
Clusters showing significant differences in connectivity with the LFP between A) the SZ and hMC groups and B) the RL and mHC groups. Both patients and relatives showed higher connectivity with the LFP in comparison to control in a similar region. Shown are voxels with $P < 0.001$ uncorrected. The colorbar corresponds to t values. [Color figure can be viewed at wileyonlinelibrary.com]

with peak activation in the Heschl Gyri (Fig. 3a). Small-volume correction for this cluster on the contrast comparing relatives with mHC also showed significantly increased correlation with the left FPN, although correlation was strongest for the supramarginal gyrus ($P = 0.008$, FWE cluster-corrected) (Fig. 3b). Second-level analysis after controlling for age, gender, smoking and handedness also revealed similar extent and P values for the correlations.

Dynamic Causal Modeling

Post hoc model selection revealed the fully connected model to be the best fitting model in the three groups (Supporting Information Fig. 1), allowing us to directly compare effective connectivity parameters between the groups. Heat maps shown in Figure 4 display effective connectivity mean values for all connections in the three groups. There were two connections involving the left SMG that showed significant differences between the patient group and the control group after controlling for multiple comparisons. The first was a connection from the left SMG to the left angular gyrus (AG) and was significantly more inhibitory in the patient group ($P = 0.001$). The second was a connection from the left occipitotemporal **cortex** to the left SMG and was significantly more excitatory in the patient group ($P = 0.002$). In addition, the three other afferents to the left AG were also significantly more inhibitory in the patient group, although two of them not after correcting for multiple comparisons (see Fig. 5). Because results showed a clear pattern of more inhibitory connections to the left AG from all other nodes, we ran an ANOVA analysis to assess for such an effect between the two groups (see Methods) and found it to be highly significant ($P < 0.001$).

To assess for possible endophenotypic markers, we compared effective connectivity parameters between healthy subjects and first-degree relatives for the connections that showed significant differences between healthy subjects and patients. Relatives also showed a pattern of inhibitory afferents to the left AG and the ANOVA analysis was also highly significant ($P = 0.008$). Figure 5 shows all incoming connections to the left AG in the three groups.

Finally, correlation analysis showed that mean inhibitory afferent connection to the left AG was negatively correlated to the OTC→SMG connection ($P = 0.005$). Correlations

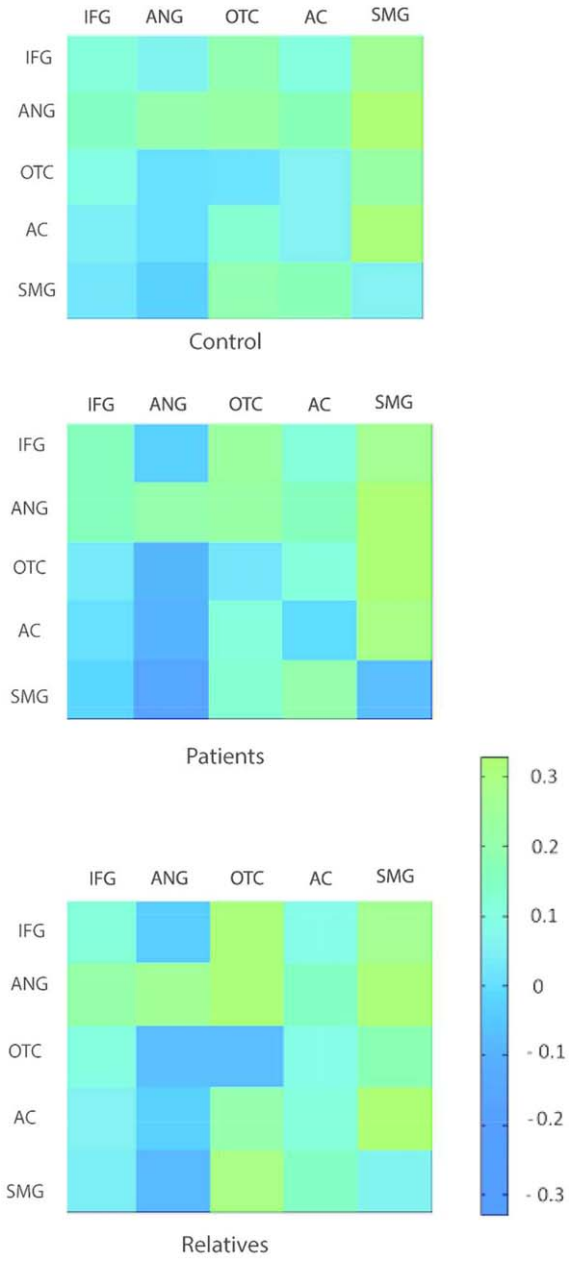

Figure 4.

Mean effective connectivity parameters for all connections and for each of the three groups in Hz. Rows correspond to sources and columns to destinations. Nonself connections were predominantly excitatory on average, with the exception of afferent connections to the left AG which were inhibitory in the patient and relative groups. [Color figure can be viewed at wileyonlinelibrary.com]

between connections with significant different between healthy subjects and patients and clinical measures showed a strong negative correlation between the OTC→SMG connection and the negative score on the PANSS scale ($r = -0.51$, $P = 0.001$).

DISCUSSION

We used resting state analyses to derive possible endophenotypic markers in schizophrenia. Analysis on ICA-derived networks revealed increased connectivity of the left FPN with an area that stretches from the left Heschl Gyri to the middle and superior temporal gyri and the supramarginal gyrus (SMG) in patients with schizophrenia. First-degree relatives also shared this increased connectivity although it was more limited to the supramarginal gyrus (SMG). We further employed DCM analysis to better characterize the nature of the increased connectivity as well as the pattern of causal interactions between the major nodes of the left FPN. DCM revealed two major connection abnormalities: increased inhibitory connection to the left angular gyrus (AG) and increased excitatory connection from the left occipitotemporal cortex (OTC) to the SMG. Only the negative afferent connectivity to the AG was shared by the relatives, although there was a strong inverse correlation in the patient sample between negative afferent connectivity to the AG and the OTC→SMG connection. Furthermore, we found the OTC→SMG connection to be anti-correlated with the negative score on the PANSS scale.

Previous studies have looked for potential inherited imaging markers of schizophrenia [Chang et al., 2014; Collin et al., 2011; Meda et al., 2014; Tian et al., 2011] but, to our knowledge, this is the first study that shows that increased connectivity in the left FPN with auditory and language areas and increased inhibitory connections to the left AG in the resting state are potential endophenotypic markers. Abnormalities within the primary auditory cortex (PAC), the superior and middle temporal gyri and language-related regions have been extensively documented

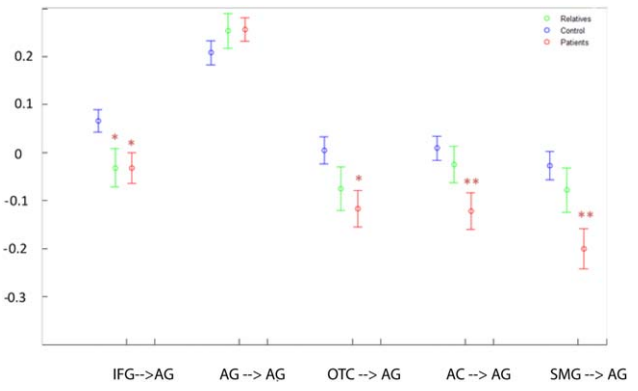

Figure 5.

Mean effective connectivity in Hz for afferent connections to the left AG. Error bars represent standard errors of the mean. Single stars correspond to $P < 0.05$ and double stars to $P < 0.006$ after correction for multiple comparisons. A two way ANOVA with afferent connection to the left AG (with exception of self-connection) and group as factors was significant in comparison to control for both patients ($P < 0.001$) and relatives ($P = 0.008$). [Color figure can be viewed at wileyonlinelibrary.com]

in schizophrenia and perhaps not surprisingly were mostly linked to positive symptoms [Alderson-Day et al., 2015]. Connectivity between the frontoparietal network and the auditory network was shown to covary with the severity of positive symptoms [Rotarska-Jagiela et al., 2010]. Using the bilateral primary auditory cortex as a seed region, increased connectivity within the auditory cortex and with language-related regions such as the left superior parietal lobule was reported [Shinn et al., 2013] although Gavrilescu et al. also report decreased connectivity within the auditory cortex [Gavrilescu et al., 2010]. Increased connectivity between the superior temporal gyrus and the left inferior frontal gyrus, the seat of Broca's area, has also been extensively documented [Clos et al., 2014; Diederen et al., 2013; Hoffman et al., 2011; Wolf et al., 2011] although decreases in connectivity were also reported [Sommer et al., 2012]. The SMG has been also specifically linked previously with positive symptomatology [Bhojraj et al., 2009, 2011; Jeong and Kubicki, 2010; Kubota et al., 2011; Zhang et al., 2008].

In addition, no study has yet utilized DCM in the resting state to uncover potential endophenotypic markers. The use of DCM in such studies is important, as it is likely to elucidate the neuronal connectivity abnormalities underlying BOLD functional correlations, yielding more insight into the organization of the network and increasing the probability of finding genetic correlates [Birnbaum and Weinberger, 2013]. Although relatives did not share the stronger excitatory connections, they did share the overall negative afferent connections to the left AG, suggesting that such negative interaction is a potential endophenotypic marker of the disease. The left AG plays a critical role in the semantic and language network [Binder and Desai, 2011], but it is also part of a larger region in the inferior parietal lobule that is considered a "supramodal convergence zone" [Binder and Desai, 2011; Binder et al., 2009; Jamadar et al., 2013] and is involved in the heteromodal association network and in information integration from several sensory modalities, ascribing meaning and context [Pearlson et al., 1996]. Abnormalities within the IPL have been linked to working memory dysfunction in schizophrenia [Torrey, 2007] as well as impairments in reality perception and cognitive insight [Bedford et al., 2012; Guo et al., 2014; Lee et al., 2015]. Bzdok et al. conducted connectivity-based parcellation of the left inferior parietal lobule and found that the region commonly thought of as the angular gyrus is connected to areas more strongly engaged in higher level social cognitive and language processes, as opposed to more rostro-ventral areas of the IPL which are appear to be correlated to lower level functionality [Bzdok et al., 2016]. Our results suggest that abnormalities within the AG more specifically and the IPL more generally may be mediated by inhibitory interactions from other regions of the left FPN.

Furthermore, correlation analyses in the patient sample revealed two major findings: a strong negative correlation between inhibitory afferents to the left AG and the left OTC→ left SMG connection and a strong negative correlation between the left OTC→left SMG connection and the negative score on the PANSS scale. The clinical correlation we report here is important for several reasons. First, because it is relatively strong and highly statistically significant, on the order of $P = 0.001$, it provides additional external validation of resting state DCM analysis. Second, the correlation analysis grounds our endophenotypic marker finding regarding the left AG with a clinical phenotype. It suggests that negative inhibitory afferents to the left AG predispose to excitatory activity between the left OTC and the left SMG, which in turn is directly associated with a phenotypic form of the disease with low negative symptomatology. This potentially has important clinical consequences for screening and prognostic purposes, if further validated in an independent sample.

There are several limitations to our study. First, our analysis does not allow us to conclusively determine the functional significance of these correlations. Our patient sample was medicated and displayed low average positive symptomatology (average of 12 over 7 items) which possibly precluded from finding additional correlations and, more importantly, our resting state experiments were not accompanied with working memory, executive functioning or language-related behavioral paradigms so that we could obtain more functionally specific correlations. Second, the three groups in our study differed significantly in regards to smoking and handedness. Subsequent analysis showed that these factors could not explain the differences we report in this study. Our study, however did not take in consideration differences in IQ levels, education or parental socioeconomic status. Third, our patient sample was relatively small and medicated. Nonetheless, because we report shared differences between healthy unmedicated relatives and patients, medication status cannot explain the results we obtain here. Fourth, we found differences only in the left FPN after correcting for multiple comparisons. The ICA findings in the left FPN would survive even after correcting for all 12 outputted networks so that the significance of our results is independent of the choice of selected networks. Other studies have found differences in the DMN, the CEN, the right FPN and other networks [Fornito et al., 2012; Yu et al., 2012]. These differences however have been very variable from study to study [Narr and Leaver, 2015]. For example, while Woodward et al. fail to find any differences within the salience network [Karbasforoushan et al., 2012], Orliac et al. and Kraguljac et al. do [Kraguljac et al., 2016; Orliac et al., 2013]. Furthermore, Kraguljac et al. do not report any significant differences within the DMN [Kraguljac et al., 2015]. Several factors are likely to explain the variability in these findings. These include medication status of the patients, low sensitivity due to relatively small patient samples, patient selection and resting state paradigms. It will be important to replicate findings on unmedicated, large, multicentric samples, with a consistent resting state experimental

paradigm and with matching of samples in regards to IQ, handedness, education and socioeconomic statuses. Furthermore, analyses on patient populations with more distinctive phenotypes are likely to result in more consistent findings.

In summary, utilizing ICA and DCM in the resting state, we have uncovered novel potential endophenotypic markers in schizophrenia: increased functional connectivity of the left supramarginal gyrus to the left frontoparietal network as well as increased inhibitory connections from nodes of the network to the left angular gyrus. Our analysis additionally revealed the neural connective abnormalities that may underlie left frontoparietal dysfunction in schizophrenia.

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