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Abnormal Resting State fMRI Activity Predicts Processing Speed Deficits in First-Episode Psychosis

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Little is known regarding the neuropsychological significance of resting state functional magnetic resonance imaging (rs-fMRI) activity early in the course of psychosis. Moreover, no studies have used different approaches for analysis of rs-fMRI activity and examined gray matter thickness in the same cohort. In this study, 41 patients experiencing a first-episode of psychosis (including $N = 17$ who were antipsychotic drug-naive at the time of scanning) and 41 individually age- and sex-matched healthy volunteers completed rs-fMRI and structural MRI exams and neuropsychological assessments. We computed correlation matrices for 266 regions-of-interest across the brain to assess global connectivity. In addition, independent component analysis (ICA) was used to assess group differences in the expression of rs-fMRI activity within 20 predefined publicly available templates. Patients demonstrated lower overall rs-fMRI global connectivity compared with healthy volunteers without associated group differences in gray matter thickness assessed within the same regions-of-interest used in this analysis. Similarly, ICA revealed worse rs-fMRI expression scores across all 20 networks in patients compared with healthy volunteers, with *posthoc* analyses revealing significant ($p < 0.05$; corrected) abnormalities within the caudate nucleus and planum temporale. Worse processing speed correlated significantly with overall lower global connectivity using the region-of-interest approach and lower expression scores within the planum temporale using ICA. Our findings implicate dysfunction in rs-fMRI activity in first-episode psychosis prior to extensive antipsychotic treatment using different analytic approaches (in the absence of concomitant gray matter structural differences) that predict processing speed.
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INTRODUCTION

Brain dysconnectivity has been hypothesized to have a central role in the neurobiology of schizophrenia (Friston and Frith, 1995; Pettersson-Yeo *et al*, 2011), with resting state functional magnetic resonance imaging (rs-fMRI) being used increasingly to characterize these abnormal networks. Several prior rs-fMRI studies conducted in patients with chronic schizophrenia reported lower overall activity (Alonso-Solís *et al*, 2012; Argyelan *et al*, 2014; Liang *et al*, 2006; Liu *et al*, 2006) as well as aberrant activity within language (Liemburg *et al*, 2012) and default mode/executive control networks (Hoptman *et al*, 2010; Woodward *et al*, 2012), disrupted connectivity between cortical and subcortical regions (Anticevic *et al*, 2014; Zhang *et al*, 2012; Zhou *et al*, 2007) and interhemispheric dysconnectivity (Hoptman *et al*, 2012). It is widely acknowledged, however, that there are multiple ways to analyze rs-fMRI data. The use of different methods may contribute to inconsistent findings, and thus studies incorporating multiple approaches for rs-fMRI data analysis may shed light on abnormal circuits in the neurobiology of psychosis. Moreover, given that antipsychotics may potentially influence rs-fMRI measures (Lui *et al*, 2010), studies conducted early in the course of illness prior to extensive pharmacological intervention are of critical importance to the field, but findings have thus far been inconsistent (eg, Guo *et al*, 2014a,b; He *et al*, 2013; Lui *et al*, 2009, 2010; Ren *et al*, 2013).

Despite the widespread use of rs-fMRI studies in schizophrenia, there is still a paucity of work investigating the relationship between these deficits and neuropsychological functioning (Brennan *et al*, 2013). Bassett *et al*, (2012) reported that functional connectivity and topological metrics were correlated with verbal fluency performance and that network organization, which contained mainly weak connections, was correlated strongly with attention and memory in patients. In addition, variability within

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prefrontal and nonprefrontal connectivity (Cole *et al*, 2011) and altered connectivity between the frontal–parietal and cerebellar regions (Repovs *et al*, 2011) predicted severity of cognitive deficits in patients. He *et al*, (2012) reported that rs-fMRI abnormalities within the bilateral orbital frontal cortex were associated with cognitive processing speed in schizophrenia patients. These findings converge with prior work indicating that abnormal rs-fMRI connectivity was associated with worse processing speed in patients with chronic schizophrenia (Argyelan *et al*, 2014; Wang *et al*, 2014).

The investigation of gray matter structural abnormalities, which have been identified early in the course of illness (Shepherd *et al*, 2012), and rs-fMRI activity in the same cohort of patients is of critical importance to the interpretation of rs-fMRI studies, but little work has addressed this topic. Ren *et al*, (2013) reported group differences in gray matter volume mainly in thalamo-cortical networks, while alterations in the amplitude of low-frequency fluctuations were observed in fronto-parietal and default mode networks. In contrast, using voxel-based morphometry and rs-fMRI Lui *et al*, (2009) reported no rs-fMRI connectivity abnormalities within brain regions with less gray matter in patients compared with healthy volunteers, including the superior temporal gyrus, middle temporal gyrus, and anterior cingulate gyrus. Although voxel-based morphometry and voxel-based cortical thickness can provide similar results, the former may be influenced by cortical surface folding, and prior work has attributed greater sensitivity to voxel-based cortical thickness measures (Hutton *et al*, 2009), which we thus used in the current study.

The goals of the current study were (1) to examine rs-fMRI activity in patients experiencing a first-episode of psychosis with minimal or no prior antipsychotic treatment compared with healthy volunteers using region-of-interest analyses encompassing 266 cortical and subcortical regions and ICA using 20 predefined templates of brain network activity; (2) to examine the functional correlates of these rs-fMRI patterns; and (3) to investigate the relationship between rs-fMRI activity and cortical thickness within the same regions-of-interest. We hypothesized that patients would demonstrate global abnormalities in rs-fMRI activity using both region-of-interest and ICA approaches and that these functional abnormalities would be associated with worse processing speed and greater clinical impairment consistent with our prior study in chronic schizophrenia.

MATERIALS AND METHODS

Subjects

Forty-one patients experiencing a first-episode of psychosis were recruited from admissions to the Zucker Hillside Hospital as part of their participation in an NIMH-sponsored, 52-week, double-blind, randomized, controlled trial (ClinicalTrials.gov ID: NCT00320671). Patients received a physical exam and laboratory screening to rule out medical causes for their psychotic episode. Patient diagnoses were based on the Structured Clinical Interview for Axis I DSM-IV Disorders (SCID) supplemented by information from clinicians and family members. First-episode patients met DSM-IV criteria for schizophrenia (undifferentiated = 17 and paranoid = 10), schizophreniform disorder ($n = 8$), schizoaffective disorder ($N = 1$), or psychosis not otherwise specified ($N = 5$). Seventeen patients met DSM criteria for substance use/dependence diagnoses, including (numbers in parentheses): cannabis abuse/dependence ($N = 16$), alcohol abuse/dependence ($N = 6$), cocaine dependence ($N = 2$), amphetamine dependence ($N = 1$), and polysubstance dependence ($N = 1$). On average, patients had a total lifetime exposure of 5.1 (median = 4.0; range = 0–21) days of antipsychotic treatment prior to the scan. The minimally treated patients were (1) treated briefly in the clinical trial prior to the baseline scan; (2) untreated at the time of the baseline scan, but had prior exposure to antipsychotics previously; or (3) both. Seventeen patients were antipsychotic drug-naive at the time of the scan. Mean age of patients were 21.5 years (SD = 5.5). Mean age at first psychotic symptoms was 19.0 years (SD = 5.6); data were unavailable for three patients.

We recruited 41 healthy volunteers from advertisements posted on websites and by word of mouth. Exclusion criteria for healthy volunteers included the lifetime history of a major mood or psychotic disorder as determined by clinical interview using the SCID-NP. Exclusion criteria for all study participants included MRI contraindications, serious medical conditions, or mental retardation. This study was approved by the NSLIJ IRB, and written informed consent was obtained from all study participants or their parents in the case of minors. All minors provided written informed assent to participate in the study.

Image Acquisition

MRI exams were conducted at NSUH on a 3T GE HDx scanner. For image registration, we acquired anatomical scans in the coronal plane using a 3D spoiled gradient (SPGR) sequence (TR = 7.5 ms, TE = 3 ms, matrix = 256 × 256, FOV = 240 mm) producing 216 contiguous images (slice thickness = 1 mm) through the whole head. We acquired rs-fMRI scans comprising a total of 150 echo-planner imaging volumes with the following parameters: TR = 2000 ms, TE = 30 ms, matrix = 64*64, FOV = 240 mm, slice thickness = 3 mm, and 40 continuous axial oblique slices (one voxel = $3.75 \times 3.75 \times 3\ mm^3$). During the acquisition, all subjects were instructed to 'close their eyes and not think of anything in particular.'

Motion Analyses

We investigated the potential effects of motion on functional connectivity by examining both relative and absolute motion displacement during the rs-fMRI exam (see Supplementary Material)

Image Processing

We used FSL (http://www.fmrib.ox.ac.uk) and AFNI (http://afni.nimh.nih.gov/afni) based script libraries from the 1000 Functional Connectomes Project (http://www.nitrc.org/projects/fcon_1000 (Biswal *et al*, 2010) for preprocessing and a lab-developed script in the R statistical language for additional analysis as described below. All resting-state scans were preprocessed using the scripts from the 1000

Functional Connectomes Project ('fcon scripts'). Standard preprocessing included removal of the first four 'dummy' scans, motion correction, and spatial smoothing (6-mm FWHM Gaussian kernel). Standard registration and normalization to MNI152 space was employed with the resulting transformation applied to each individual's functional data set (12 parameter affine transformation). The time series were then high- and low-pass filtered (cutoff frequencies were 0.005 and 0.1 Hz, respectively). Each individual's 4D time series data were regressed on eight predictors: white matter (WM), cerebrospinal fluid, and six motion parameters. Consistent with our prior work (Argyelan *et al*, 2014) and others (Yang *et al*, 2014), we did not regress out global signal, because it would have interfered with the connectivity strength (CS) calculation.

Image Processing Using Regional CS

We computed regional mean time series for all individuals' rs-fMRI data by using a set of predefined regions (Power *et al*, 2011) used in chronic psychosis patients previously (Argyelan *et al*, 2014). In their prior study, Power *et al*, (2011) demonstrated that their 264 regions are not only functionally relevant but can eliminate artificial low distance correlations. We also added caudate nucleus regions-of-interest bilaterally. After obtaining 266 time series per subject, we decomposed these signals with maximal overlap discrete wavelet transform (Percival and Walden, 2000) similar to the method described by Lynall *et al*, (2010). We used the Daubechies wavelet transform filter of length 4 and used the 0.060–0.125 Hz (due to the preprocessing cutoff frequency at 0.1 Hz; in our case, this covers the range of 0.06–0.10 Hz) scale wavelet coefficients for further analysis. We used the R wavelet package to implement these calculations (Aldrich, 2013). We then estimated the correlation of these wavelet transformed signals (wavelet coefficients) between each possible pair of regions. For each *i* region, we then averaged the correlation coefficients that *i* region had with all the other *j* regions (ie, we averaged each row of the correlation matrix), and according to its usual name in the connectivity literature, we called this metric CS. This measure reflects how strongly one region is connected to other regions in general and is called regional-based CS. Global connectivity was defined as the first principal component of the variance across these measures (Argyelan *et al*, 2014). Repeated-measures analysis of variance was used to examine whether regions-of-interest were significantly different between groups in the global connectivity analysis. The within-subject factor was region-of-interest ($n = 266$), and the between-subject factor was the group (patient *vs* control).

Image Processing Using Independent Component Analysis (ICA)

To further support our analysis with regional-based connectivity measures, we also conducted ICA. In 2010, Biswal *et al*, (2010) reported evidence for 20 independent rs-fMRI components within the brain making it feasible to examine patterns of resting state activation using publicly available templates and facilitate cross-study comparisons. In the current study, the dual-regression approach was used to identify within-subjects' fMRI data, subject-specific temporal dynamics and associated spatial maps to compute 'expression scores' within these 20 predefined networks (Biswal *et al*, 2010). This involved using the full set of predefined group-ICA spatial maps in a linear model (ie, spatial regression) against our rs-fMRI data sets, resulting in matrices describing temporal dynamics for each component and individual. This was then followed by using the time course matrices in a linear model (ie, temporal regression) against the rs-fMRI data set to estimate subject-specific spatial maps. Individual spatial maps were correlated with the predefined healthy group ICA spatial templates to estimate the degree of 'expression' within 20 individual brain networks acquired in a large cohort of healthy volunteers (Biswal *et al*, 2010). Thus these individual network 'expression scores' were higher if that particular network's intra-network correlations conformed better to the standard network (which was determined using a large healthy data set). We used repeated-measures ANCOVA to determine how well the resting state data from our study were expressed within these 20 predefined networks. Network served as a within-subjects factor, whereas sex and group served as between-subjects factors. Age and intracranial volume served as statistical covariates. Independent components identified as significantly different between patients and healthy volunteers were subsequently examined using voxelwise analysis in SPM5 ($p < 0.05$, FWE corrected) to identify regional differences within networks.

Cortical Thickness Analysis

We used FreeSurfer (v5.1) to conduct cortical reconstruction of our 3D MRI data set (http://surfer.nmr.mgh.harvard.edu). Using well-documented steps described previously (Dale *et al*, 1999; Fischl and Dale, 2000), a pial surface and a gray–WM interface was created and stored with a triangular tessellation representation. The distance between these surfaces, which is the cortical thickness, is calculated for each vertex of the triangular representation. Using a freesurfer script (mri_surf2vol), we projected our 266 nodes so that vertices were assigned with node numbers, and thus we were able to calculate the thickness scores associated with the individual nodes. This approach is illustrated in Figure 1. Repeated-measures analysis of variance was used to examine whether groups differed in cortical thickness with the within-subjects factor being region-of-interest. In addition, we used principal component analysis to determine whether this method could separate the groups from each other.

Clinical, Neuropsychological, and Handedness Assessments

Patients completed the 18-item Brief Psychiatric Rating Scale Anchored-version (Overall and Gorham, 1962), and we derived a total score by summing all the items. We also administered the MCCB to patients with our *apriori* hypothesis focused on processing speed. The neuropsychological domains and total BPRS score were investigated in relationship to the overall global connectivity metric and regions that distinguished patients from healthy volunteers in the voxelwise results from the IC analysis using Pearson

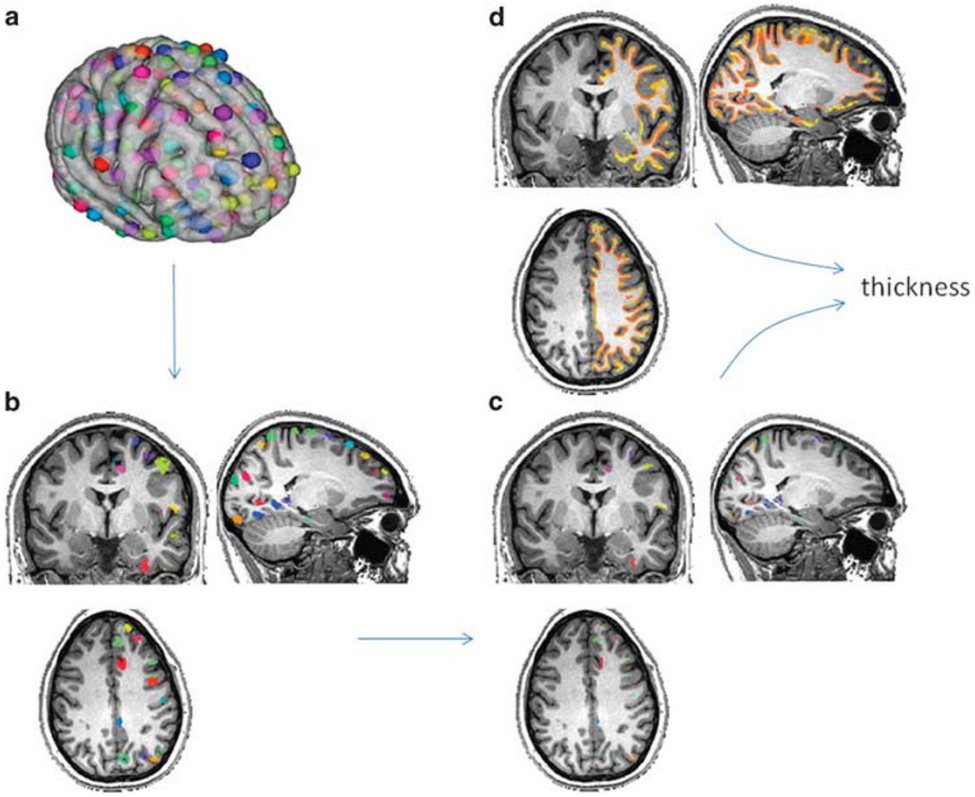

Figure 1 Region-based cortical thickness approach. The 266 nodes that were used as resting state functional magnetic resonance imaging seeds are illustrated in panel a. The nodes were then projected into Freesurfer space aligning them with vertices from the gray–white interface. The vertices with the corresponding gray matter ribbon are illustrated in the left hemisphere in panel b. Regions-of-interest and their corresponding gray–white matter interface are provided in panel c. The gray–white matter interface, color-coded with corresponding thickness is illustrated in panel d. Lighter colors denote thicker gray matter regions above that area such that gray matter is defined as the distance between the interface and the pial surface. The region-level calculation of thickness is an average of the regions in panel c over the values in panel d. This is illustrated in the left hemisphere but was done similarly in the right hemisphere.

Product Moment correlations. We minimized type-I error in structure-function analyses by adjusting alpha to 0.01 (two-tailed). All individuals were classified as either right- or left-handed based on a modified version of the Edinburgh Inventory.

RESULTS

The first-episode patient and healthy comparison groups were well matched on relevant demographic factors. Specifically, the groups did not differ significantly ($p<0.05$) in distributions of age, sex, handedness, education, height, or weight (Table 1). In patients, the mean total BPRS score at baseline was 43.7 ± 8.2. A greater proportion of patients were smokers compared with healthy volunteers ($p=0.013$, OR = 6.99, Fisher's Exact Test). BPRS scores for antipsychotic drug-naive patients was 43.9 (SD = 9.7) and for minimally treated patients was 43.5 (SD = 7.2). There were no significant ($p<0.05$) group differences in the distributions of average FD or DVARS values between groups as illustrated in Supplementary Figures S1 and S2.

Analysis of the global CS measure revealed a significant main effect of group ($F=36.09$, $df=1$, $p<0.001$) such that global connectivity was significantly lower in patients compared with healthy volunteers overall (Figure 2), but there was no significant group × region interaction ($p>0.05$). There was no significant ($p>0.05$) difference in the global CS between antipsychotic drug-naive patients and those patients who had received minimal treatment. Patients who were smokers had greater connectivity compared with non-smoking patients ($F=42.49$, $df=1$, $p<0.001$, Supplementary Figure S3). Substance use did not have any significant effect on functional connectivity among patients (Supplementary Figure S3). Greater global dysconnectivity correlated significantly with slower processing speed among patients ($r=-0.45$, $df=37$, $p=0.005$) but not with any of the other neuropsychological domains or BPRS total score.

The individual expression scores from the ICA for patients and healthy volunteers are provided in Figure 3. The results of this analysis revealed a significant main effect of group ($F=16.68$, $df=76$, $p<0.001$), as well as a group-by-IC interaction ($F=1.79$, $df=76$, $p=0.049$). Follow-up univariate ANCOVAs revealed that patients had significantly lower expression scores compared with healthy volunteers within the medial visual (IC1; $F=15.03$, $df=1,76$, $p<0.001$), lateral visual (IC3; $F=7.59$, $df=1,76$, $p=0.007$), posterior cingulate default mode (IC6; $F=3.99$, $df=1,76$, $p=0.049$), ventral default mode (IC14; $F=9.53$, $df=1,76$, $p=0.003$), salience (IC16; $F=6.08$, $df=1,76$, $p=0.016$),

Table 1 Sample Characteristics

	First-episode patients ($N=41$)	Healthy volunteers ($N=41$)	df	Test statistic	*p*-Value
Age	21.5 (5.5)	21.5 (5.1)	80	$t=0.05$	NS
Sex (M/F)	29M/12F	29M/12F	1	$\chi^2=0$	NS
Laterality quotient	0.77 (0.33)	0.69 (0.49)	80	$t=-0.89$	NS
Education (years)	12.2 (2.1)	13.3 (3.3)	80	$t=1.84$	NS
Height (inches)	67.4 (3.6)	68.2 (4.1)	79	$t=0.85$	NS
Weight (pounds)	154.3 (29.4)	159.4 (29.8)	79	$t=0.78$	NS

Data are presented as mean ± SD in parentheses, unless otherwise indicated. Height and weight were unavailable for one patient.

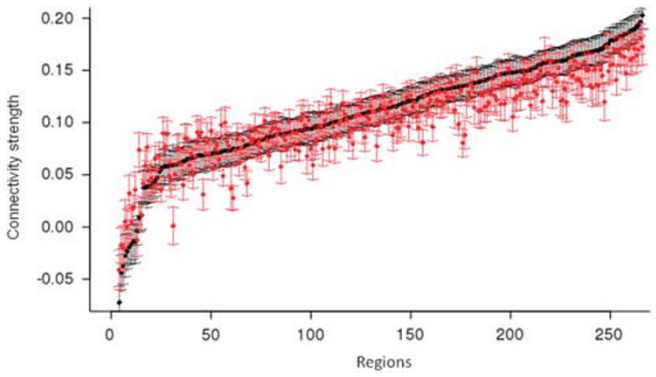

Figure 2 Average connectivity strength in patients and healthy volunteers. Red lines denote patients, and black lines denote healthy volunteers. SEMs are provided for each node. Regions are presented based on their connectivity strength rank order in healthy volunteers.

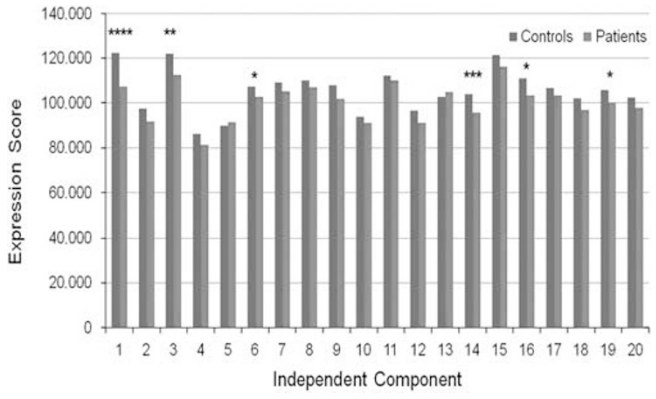

Figure 3 Independent component analysis expression scores in patients and healthy volunteers. *$p<0.05$; **$p<0.01$; ***$p<0.005$; ****$p<0.001$.

and somatosensory (IC19; $F=6.07$, $df=1,76$, $p=0.016$) networks. Between-group voxelwise analyses of these six ICs revealed significantly ($p<0.05$, FWE corrected) lower rs-fMRI activity within the left planum temporale (MNI space, $x=-44$, $y=-32$, $z=10$; Figure 4a and b) within the salience network (IC16) and the basal ganglia (MNI space, $x=-44$, $y=12$, $z=56$; Figure 4c and d) within the somatosensory network (IC19) in patients compared with healthy volunteers. An illustration of the four additional networks (ie, IC1, IC3, IC6, IC14) that differed between groups but did not yield significant voxelwise differences is provided in Supplementary Figure S4. Investigation of the neuropsychological correlates of IC16 and IC19 revealed that slower processing speed correlated with lower rs-fMRI activity within the left planum temporale ($r=0.44$, $df=37$, $p=0.007$) but not with any of the other neuropsychological domains or total BPRS score. There was no significant ($p>0.05$) difference in the above discussed measures (CS, planum temporale, or basal ganglia rs-fMRI measures) between antipsychotic drug-naive patients and those patients who had received minimal treatment.

Cortical Thickness Measures

Analysis of the cortical thickness measures did not reveal either a significant group main effect or significant group × region interaction. Additional principal component analysis could not significantly differentiate the groups from each other. Moreover, cortical thickness did not correlate with CS assessed by the rs-fMRI measures.

DISCUSSION

In this study, we used complementary approaches for analysis of rs-fMRI data in patients experiencing a first episode of psychosis. We observed significantly lower overall rs-fMRI activity using a region-of-interest-based global CS metric as well as overall worse expression scores across 20 predefined templates using ICA in patients compared with healthy volunteers. Moreover, both analytic approaches provide evidence for a relationship between abnormal rs-fMRI activity and processing speed deficits. Resting state fMRI abnormalities in our first-episode patients were observed in the absence of overall or regionally specific gray matter thickness differences between groups. Strengths of our study include the use of a well-characterized clinical cohort of first-episode psychosis patients studied early in the course of psychosis prior to extensive pharmacological intervention, use of healthy volunteers individually age- and sex-matched to patients, different analytic approaches of the rs-fMRI data, investigation of neuropsychological functions in relationship to rs-fMRI activity in patients and use of the same regions-of-interest to investigate cortical thickness and rs-fMRI measures.

The results of the region-of-interest global connectivity analysis replicate our prior findings in chronic schizophrenia (Argyelan *et al*, 2014) using a different cohort of individuals with the same methods and sequence parameters

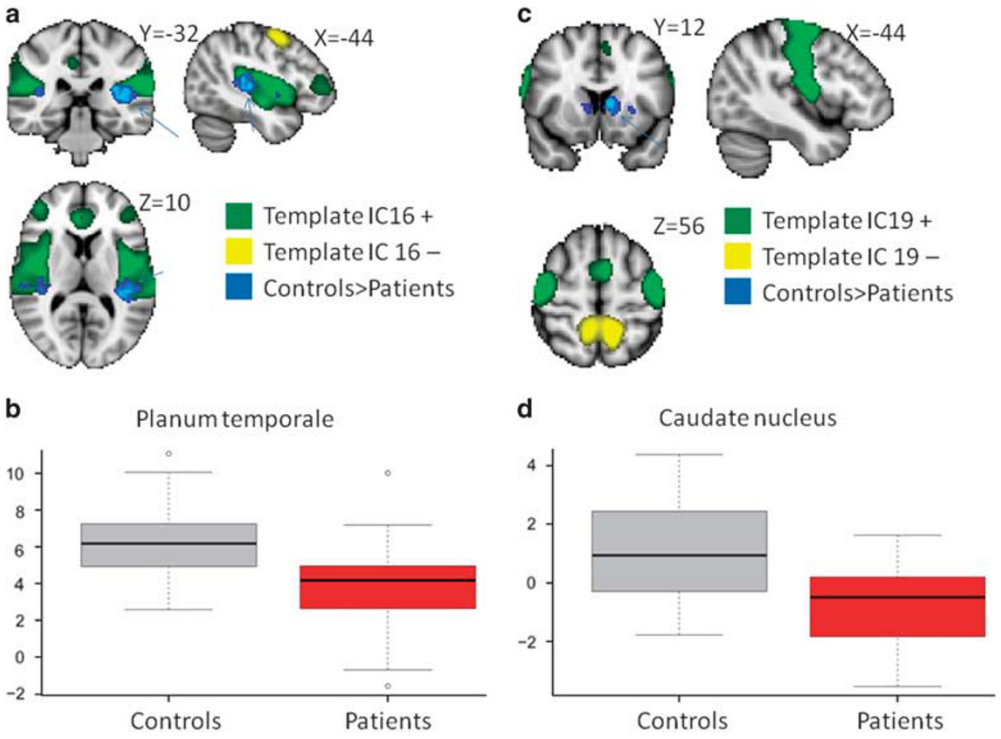

Figure 4 Illustration of significant ($p<0.05$; FWE-corrected) voxelwise analyses of independent components 16 and 19. Green and yellow indicate strongly correlating and anti-correlating regions respectively. (a) Salience network, blue indicates group differences in planum temporale, (c) Somatosensory network, blue indicates group differences in caudate nucleus, (b) and (d) are *post hoc* analyses in the corresponding blue region.

as the current study. In contrast to our prior study, however, we did not observe rs-fMRI connectivity abnormalities within specific regions-of-interest in patients compared with healthy volunteers. Coupled together, these studies are consistent with the possibility that although global dysconnectivity may be evident in both first-episode and chronic patients, there may be regionally specific changes in function over time that may involve striatal and/or thalamic regions (as observed in our prior study of chronic patients) that could conceivably be related to illness and/or medication factors. Moreover, consistent with our prior study in chronic patients (Argyelan *et al*, 2014) we also observed significant abnormalities in first-episode patients compared with healthy volunteers in sensory networks (both visual, auditory, and somatosensory). This may be particularly noteworthy because both prior empirical and theoretical work implicate a disruption in perceptual processes in schizophrenia (Butler *et al*, 2001; Grillon *et al*, 1992; Javitt *et al*, 1996; Notredame *et al*, 2014; Patterson *et al*, 2008; Umbricht and Krljes, 2005).

Consistent with the global connectivity analysis, we identified lower expression scores in first-episode patients overall compared with healthy volunteers using ICA. In contrast to the global connectivity analysis, however, the ICA implicated dysfunction within regions comprising the salience network, and in particular, the planum temporal. Brain regions comprising the salience network, including the temporal lobe, are critical for recruiting other networks to process environmental and sensory stimuli, have a role in self-monitoring and agency and have been strongly implicated in the neurobiology of psychosis (White *et al*, 2013). Specifically, increasing evidence suggests that abnormal salience contributes to the emergence of psychotic symptoms through dopamine dysregulation leading individuals to attribute environmental significance to stimuli that are otherwise considered irrelevant (Howes and Kapur, 2009). Aberrant salience processing may underlie psychotic symptoms and involve functional alterations in the striatum, hippocampus, and other subcortical dopamine regions in association with temporal regions (Orliac *et al*, 2013; Roiser *et al*, 2013). Other investigators (Heinz and Schlagenhauf, 2010) highlight that dopamine dysregulation in patients with psychosis could lead to aberrant attribution of incentive salience, thus leading to the emergence of psychotic behavior. Although we did not observe functional differences between antipsychotic drug-naive and minimally treated patients in this study, it is important to acknowledge that antipsychotic treatment often requires weeks to demonstrate efficacy, and thus our findings are not inconsistent with the salience network serving as either a state- or trait-related phenomenon associated with the emergence of psychotic symptoms.

Using ICA, we also observed lower rs-fMRI activity within the caudate nucleus in first-episode patients compared with healthy volunteers. These findings suggest that functional connectivity between the caudate nucleus and cortical networks is impaired in schizophrenia. Indeed, other studies (Hoptman *et al*, 2010; Turner *et al*, 2013) implicated rs-fMRI abnormalities within the caudate nucleus and reported that an increase in the low frequency fluctuations in these areas may be associated with successful antipsychotic treatment (Lui *et al*, 2010). It should be acknowledged that while the caudate demonstrated lower connectivity in the ICA analysis in patients, it was outside

the network investigated. This therefore indicates that, contrary to IC 16 where intra-network changes were associated with group differences, in this network (IC 19) the source of group difference was mainly due to inter-network disruption. Given that inter-network correlations tend to be much weaker compared with intra-network correlations, these results indicate that these correlations could nonetheless result in significant group differences.

The finding that lower rs-fMRI global connectivity was associated with worse processing speed replicates our prior work in chronic patients (Argyelan *et al*, 2014) and thus extends this relationship to first-episode psychosis. Only processing speed correlated with aberrant rs-fMRI activity within the salience network (including the planum temporale) using ICA. This finding converges with increasing evidence that visuomotor coordination and motor representation are modulated by neurons within the temporal region (Tankus and Fried, 2012) and that cognitive processing speed is associated with temporal cortical structural integrity (Turken *et al*, 2008). Moreover, some data suggest that higher stages of language processing operate at a fixed speed and could theoretically impose a 'temporal bottleneck' on language functions (Vagharchakian *et al*, 2012). In this regard, Takeuchi *et al*, (2011) demonstrated that processing speed training was associated with both structural and functional changes in temporal regions.

It may be noteworthy that processing speed deficits were associated with rs-fMRI abnormalities as these neuropsychological deficits are often the most pronounced in first-episode schizophrenia as observed in meta-analytic studies (Mesholam-Gately *et al*, 2009). Thus processing speed may be particularly good in capturing generalized dysfunction contributing to widespread cognitive failures in schizophrenia (Rodríguez-Sánchez *et al*, 2007). In addition, processing speed deficits have been observed in high-risk samples compared with healthy individuals (Seidman *et al*, 2010), at-risk subjects who converted to psychosis (Lin *et al*, 2011), and adolescents in the community who are prodromal for psychosis (Kelleher *et al*, 2013). There are also data indicating that poor social outcome can be predicted by reduced processing speed in a clinical high-risk sample for psychosis (Carrión *et al*, 2013; Faber *et al*, 2011). Given that processing speed deficits are present in first-degree relatives of patients with schizophrenia (Ma *et al*, 2007), such measures could represent a valuable endophenotype, in combination with rs-fMRI studies, for molecular genetic studies of schizophrenia.

There are several limitations to our study that should be acknowledged. Although we did not observe group differences in cortical thickness measures assessed using the same regions-of-interest as the rsfMRI analysis, this does not preclude the possibility that group differences would be evident using larger regions-of-interest or even volumetric (manual or semi-automated) approaches. In addition, the use of global connectivity measures with 266 nodes could miss more focused abnormalities. An additional limitation may be the instructions provided to the subjects in that 'eyes open' *vs* 'eyes closed' have yielded different findings in the literature (Xu *et al*, 2014; Patriat *et al*, 2013), although in this study all subjects were provided with the same instructions. An additional limitation is that our findings may be influenced by factors such as substance use or smoking history. Ancillary analyses, however, indicated that functional connectivity was not significantly different among patients with and without a substance use history (Supplementary Figure S3). Moreover, in the case of smoking, the observed influence was in the opposite direction (ie, smoking history was associated with greater functional connectivity; Supplementary Figure S3). We also acknowledge that even a very short duration of antipsychotic treatment can have a significant effect on functional connectivity (Cole *et al*, 2013); however, our ancillary analyses did not indicate any differences between drug-naive and minimally treated patients.

In sum, our findings suggest that rs-fMRI abnormalities are evident in patients experiencing a first episode of psychosis prior to extensive pharmacological intervention assessed using both a global connectivity metric and ICA in the absence of concomitant gray matter structural alterations and that these rs-fMRI abnormalities predict processing speed deficits.

FUNDING AND DISCLOSURE

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