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Altered functional connectivity and low-frequency signal fluctuations in early psychosis and genetic high risk

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ABSTRACT

Studying individuals at increased genetic risk for schizophrenia may generate important theories regarding the emergence of the illness. In this investigation, genetic high-risk individuals (GHR, $n = 37$) were assessed with functional magnetic resonance imaging and compared to individuals in the first episode of schizophrenia (FESZ, $n = 42$) and healthy comparison subjects (HCS, $n = 59$). Measures of functional connectivity and the amplitude of low-frequency fluctuation (ALFF) were obtained in a global, data-driven analysis. The functional connectivity measure, termed degree centrality, assessed each voxel's connectivity with all the other voxels in the brain. GHR and FESZ displayed increased degree centrality globally and locally. On ALFF measures, GHR were indistinguishable from HCS in the majority of areas but resembled FESZ in insula, basal ganglia and hippocampus. FESZ evidenced reduced amplitude of the global neural signal as compared to HCS and GHR. Results support the hypothesis that schizophrenia diathesis involves functional connectivity and ALFF abnormalities. In addition, they further an emerging theory suggesting that increased connectivity and metabolism may be involved in schizophrenia vulnerability and early stages of the illness.

1. Introduction

First-degree relatives of individuals with schizophrenia (genetic high risk, GHR) have approximately ten times greater risk for schizophrenia than the general population (Lichtenstein, 2009). GHR studies must be clearly distinguished from behavioral high-risk studies. In the latter case, individuals are selected for inclusion because of psychotic-like symptoms (Chapman et al., 1994; Fusar-Poli et al., 2016; Miller et al., 1999). Thus, observations confound current symptomatology with risk factors.

Studying young GHR compared to healthy comparison subjects (HCS) and individuals with schizophrenia in the first psychotic episode (FESZ) may distinguish risk from symptom mechanisms. Biomarkers shared by FESZ and GHR but not HCS may be risk indicators whereas those distinguishing FESZ from GHR and HCS may be psychosis indicators. Biomarkers that distinguish GHR from FESZ and HCS may be indicators of vulnerability specifically related to schizophrenia genes, as opposed to other types of risk, or may represent adaptions to the stress of earlier neurobiological abnormalities (Davis, 2006; Krystal et al., 2016; Turrigiano et al., 1994).

Biomarkers derived from functional magnetic resonance imaging (fMRI) data collected during rest have become a major focus in schizophrenia research. Resting data has been predominantly explored through functional connectivity, the study of the correlation between spatially distinct blood oxygen-level dependent (BOLD) timecourses. Functional connectivity measures provide information regarding the coordination of brain areas during spontaneous activity.

Studying functional connectivity in GHR may shed light on recent theories suggesting that hyperconnectivity in brain networks may be a hallmark of schizophrenia vulnerability. This increased excitation may be the result of GABA dysfunction, perhaps produced by reduced

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glutamatergic drive early in development (Krystal et al., 2016; Krystal et al., 2017). Hypoconnectivity, observed later in the illness, may be a consequence of increased neuronal excitation early in the course of the disorder (Krystal and Anticevic, 2015; Schobel et al., 2013; Sullivan and O'Donnell, 2012).

A finding of increased connectivity in GHR would importantly inform our theories regarding schizophrenia genesis, suggesting that hyperconnectivity may mediate between genetic vulnerability and development of the disorder. However, despite evidence of increased connectivity in the prefrontal cortex of GHR and FESZ (Anticevic et al., 2015a; Anticevic et al., 2015b), there has never been, to our knowledge, a data-driven, whole-brain functional connectivity analysis of GHR. To accomplish this, we use a well-established connectivity technique called "degree centrality" (DC; Buckner et al., 2009; Rubinov and Sporns, 2010) to evaluate the theory that the brains of GHR and FESZ are predominantly hyperconnected as compared to HCS. DC is viewed as a data-driven technique because each voxel in the brain is considered equally using the exact same techniques. This contrasts with theoretically-driven methods such as seed voxel connectivity (Biswal et al., 1995; Hampson et al., 2006) in which the investigator chooses to study the connectivity of voxels from a few specific areas.

DC provides critical information regarding the coordination of brain activity across regions in the brain. However, when connectivity between areas differs from the norm, connectivity metrics do not provide information indicating local abnormalities in spontaneous brain fluctuations that may lead to divergent connectivity. Measures of the amplitude of low-frequency fluctuations (ALFF), a regional measure of the integrity of spontaneous low-frequency fluctuations, can provide information regarding the integrity and magnitude of brain activity (Zou et al., 2008). Thus, we complemented our DC analysis with analysis of ALFF, a measure that has revealed significant regional abnormalities in cortical and subcortical areas in individuals with schizophrenia (SZS; Hoptman et al., 2010; Turner et al., 2013). We have previously reported ALFF abnormalities in young GHR (Tang et al., 2015).

In conclusion, we hypothesized that GHR and FESZ would have greater DC than HCS and would also exhibit divergent ALFF relative to HCS. In FESZ, medication is a major confound, so we compared medicated and unmedicated FESZ and performed chlorpromazine equivalent (a measure of anti-psychotic dose) analyses. To help test the functional significance of DC and ALFF abnormalities, we related them to available behavioral measures.

2. Materials and methods

2.1. Participants

The study was approved by the Ethics Committee of China Medical University. Forty-two FESZ, 37 GHR and 59 HCS participated in the study and were included in the final analysis. FESZ were currently or recently experiencing a first psychotic episode at the time of scanning and were subsequently diagnosed with schizophrenia. All GHR had a parent with schizophrenia. Potential subjects were excluded for major medical or neurologic illness or alcohol or substance abuse/dependence. GHR and HCS were excluded if diagnosed with an Axis I diagnosis or prescribed psychiatric medication. Some of the HCS and FESZ scans used in this study were previously analyzed in a study of connectivity in the prefrontal cortex (Anticevic et al., 2015a) or a study of ALFF (Tang et al., 2015; see Table 1).

All participants were independently assessed via structured psychiatric interview by two trained psychiatrists. Participants older than 18 were diagnosed using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-IV Axis I Disorders (SCID-IV; First et al., 1995) translated to Chinese (http://www.scid4.org/trans.html). Participants younger than 18 years were diagnosed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version (K-SADS-PL,Kaufman et al., 1997, local Chinese translation). Participants were assessed with the Modified Card Sorting Test (MCST; Nelson, 1976), a rule-based assessment of working memory, and rated on a Chinese language version (Zhang, 1984) of the Brief Psychiatric Rating Scale (BPRS; Overall et al., 1974). Descriptive information regarding the sample is supplied in Table 2. Details regarding subjects, image acquisition, data preprocessing and analysis software are in the Supplement.

Table 1
Sample overlap between this study and other studies from this group.

Group			PFC connectivity only (Anticevic et al., 2015a)		
			Yes	No	Total
HCS	ALFF only (Tang et al., 2015)	Yes	22	0	**22**
		No	0	37	**37**
	Total		**22**	**37**	**59**
FESZ	ALFF only (Tang et al., 2015)	Yes	42	0	**42**
		No	0	0	**0**
	Total		**42**	0	**42**
GHR	ALFF only (Tang et al., 2015)	Yes	10	0	**10**
		No	0	27	**27**
	Total		**10**	**27**	**37**

1. Anticevic, A., et al., NMDA Receptor Antagonist Effects on Prefrontal Cortical Connectivity Better Model Early Than Chronic Schizophrenia. Biol Psychiatry 77 (6), 2015a, 569–80.
2. Tang, Y., et al., Neural activity changes in unaffected children of patients with schizophrenia: A resting-state fMRI study. Schizophr Res, 2015. 168 (1–2): p. 360–5.

2.2. Degree centrality maps

DC, previously shown to be sensitive to functional dysconnectivity in schizophrenia (Lo et al., 2015; Palaniyappan and Liddle, 2014), is a well-established connectivity metric derived from graph theory that evaluates direct connections between one node and all other nodes in a network identifying areas that connect multiple brain areas, termed hubs (Buckner et al., 2009). To calculate DC, we regressed out six head motion parameters and the signal timecourse from white matter and cerebrospinal fluid using Statistical Parameter Mapping 8 masks (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/.) Then the images were detrended and filtered using a band-pass temporal filter (0.01–0.08 Hz). To control for micro-movements (Power et al., 2012; Power et al., 2014), we denoised the images with wavelet despiking (Patel et al., 2014). Voxel-based weighted DC, also known as node strength (Zuo et al., 2012), was then calculated on a per subject basis. Pearson correlation coefficients (r) between the timecourses of all voxel pairs within the grey matter mask were calculated, thresholding the resulting subject matrices at $r > 0.2$ to reduce noise (Dai et al., 2015). A Fisher's r-to-z transformation was applied to the surviving correlations and summed yielding the DC measure. Calculations are illustrated in the Supplement (Fig. S1). The resulting statistical maps were spatially smoothed with a Gaussian 6 mm^3 full-width-at-half-maximum (FWHM) filter.

The statistical removal of the timecourse of the entire brain, affects results and has been a controversial issue in the study of resting state functional connectivity leading to calls for explicit study of the global signal in psychopathological populations (Chai et al., 2012; Hahamy et al., 2014; Yang et al., 2014). Accordingly, we compared global signal across our groups. Calculations are described under ALFF.

2.3. ALFF maps

For the ALFF calculations, the normalized images were spatially smoothed with a Gaussian filter (6 mm^3 FWHM), and de-trended. To compute the ALFF of every voxel classified as grey matter, each voxel's time series was transformed into the frequency domain and its power spectrum obtained. Then the square root of each frequency of the power spectrum was calculated and the average square root was obtained across the 0.01–0.08 Hz band at each voxel. The resulting quantity was called ALFF and was normalized by dividing it by the

Table 2
– Participant Demographics and Descriptive Statistics.

	HCS	FESZ	GHR	Significance
Gender (M/F)	27/32	21/21	23/14	ns
Age, mean (SD)	20.9 (4.0)	19.0 (4.0)	20.5 (4.8)	ns
Education, mean (SD)	$13.2\ (3.3)_a$	$10.4\ (2.7)_b$	$11.4\ (3.2)_b$	***
BPRS total, mean (SD, n)	$18.1(0.5,16)_a$	$38.7\ (11.5,42)_b$	$18.6\ (1.7,37)_c$	**
MCST categories complete, mean (SD, n)	$4.1\ (2.2,30)_a$	$1.7\ (1.9,29)_b$	$2.7\ (2.1,35)_c$	**
MCST total errors, mean (SD, n)	$17.23\ (12.3,30)_a$	$29.0\ (12.8,29)_b$	$23.4\ (12.5,35)_b$	*
MCST trials to complete first category, mean (SD, n)	$15.4\ (13.2,30)_a$	$30.6\ (17.8,29)_b$	$26.9\ (16.1,33)_b$	*
MCST % perseverative error, mean (SD, n)	0.35 (0.2,29)	0.39 (0.28,29)	0.36 (0.23.35)	ns
Medication, n (%)	0	23 (55)	0	
Antipsychotic (all atypical), n (%)	0	20 (48)	0	
Chlorpromazine equivalents, mean (SD)	0	237(217)	0	
Antidepressant/mood stabilizer/anti-Parkinsonian, n (%)	0	4(17)/2(5)/0	0	

Numbers with the same subscript in the same row, do not differ statistically. Post-hoc tests were completed with Tukey's HSD.
* $p < 0.01$.
** $p < 0.001$.
*** $p < 0.0001$.

individual's global mean ALFF within the mask at each voxel. This measure, termed standardized ALFF, has been shown to minimize noise (Zou et al., 2008). To obtain the average amplitude of the global signal for grey matter, we averaged per-voxel ALFF in the grey matter mask before standardization. The resulting global signal measure, termed "global ALFF" solely assessed low frequencies, those shown to be most sensitive to differences between SZS and HCS (Yang et al., 2014).

2.4. Statistical analysis

To test for group differences in DC and ALFF, voxel-wise one-way ANOVA was used with cluster correction. All maps were corrected for multiple comparisons with 3dClustSim using the new auto-correlation function (Cox et al., 2017), a cluster correction procedure available in AFNI. For both the DC and the ALFF analyses, the program determined a minimum cluster size using Monte Carlo simulations (10,000 iterations) so as to achieve a per-voxel threshold of $p < 0.01$ with a cluster-wise threshold of $p < 0.01$. For the clusters showing significant difference among the three groups, the mean DC or ALFF values were extracted inside the cluster for each subject, and post-hoc pairwise *t*-tests were performed. Tukey's Honest Significant Difference Test was employed to control for multiple group comparisons. Additional information on statistical analysis is provided in the Supplement.

3. Results

3.1. Subject characteristics

The three groups did not differ statistically in age or gender (Table 2). HCS were more highly educated than FESZ and GHR. FESZ attained average scores on the BPRS in the mild to moderate range (Leucht et al., 2005), whereas GHR did not differ from HCS. GHR and FESZ performed more poorly than HCS on a test of prefrontal function (MCST; Nelson, 1976), with GHR tending to score better than FESZ.

3.2. Degree centrality

The voxel-wise ANOVA indicated many clusters spanning the entire cortex in which DC differed in the three groups (Table 4, Fig. 1A, Fig. S2). No differences in motion as measured by frame displacement (Jenkinson et al., 2002) were observed between groups ($p = 0.49$, Table 3). In all but one cluster, GHR and FESZ were hyperconnected as compared to HCS and did not differ significantly from each other (Fig. 1B). However, in cluster 1 (anterior middle temporal gyrus), GHR displayed significantly elevated DC in comparison with HCS and FESZ with no difference between HCS and FESZ (Fig. 1C). The DC distribution (Fig. 1D) also indicated increased DC in FESZ and GHR. A follow-up

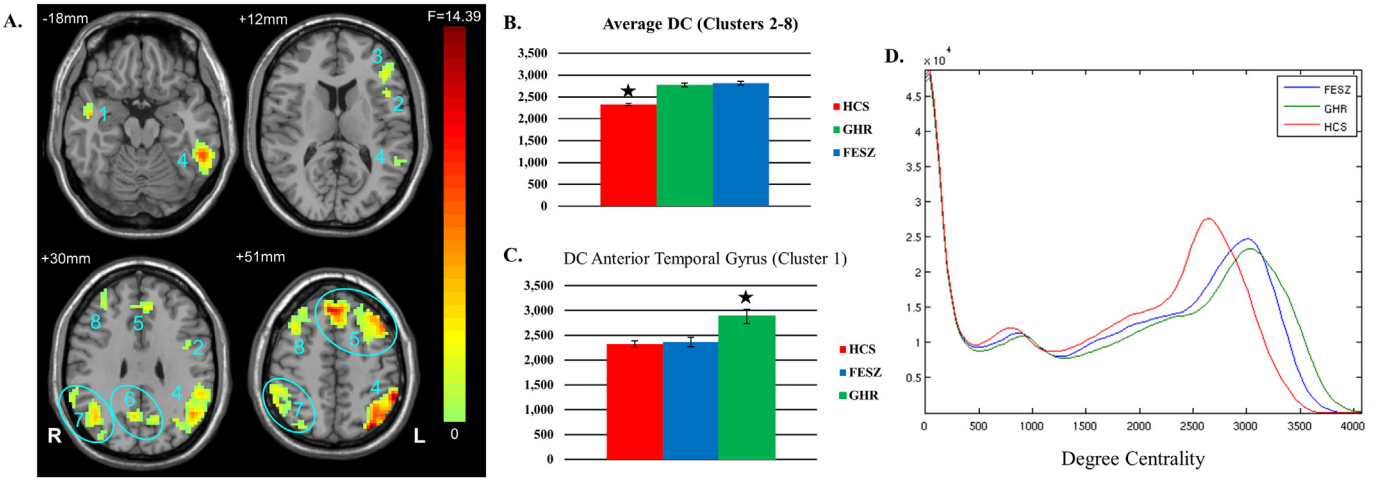

Fig. 1. Degree centrality. A) Clusters in which DC differs between HCS, FESZ, and GHR as determined by one-way ANOVA shown at $p < 0.01$ per-voxel and $p < 0.01$ cluster-wise. Blue rings are used enclose statistically significant voxels that are all in one cluster. B) Average DC by group, clusters 2–8, C) Average DC by group, Cluster 1 (Anterior Temporal Gyrus), D) DC distribution by group.

Table 3
Descriptive statistics for global ALFF and motion.

Measure	Mean (SD)		
	HCS	FESZ	GHR
Global ALFF[a]	4.0(1.2)	3.0(0.9)[a]	3.6(1.2)
Frame Displacement[b]	0.05(0.03)	0.06(0.04)	0.06(0.05)

[a] HCS vs. FESZ, $p < 0.0001$. HCS vs. GHR, ns. GHR vs FESZ, ns.
[b] Measured at each time point on a per-subject basis by a previously developed method (Jenkinson et al., 2002).

analysis on all correlations less than negative 0.02 indicated that there were no differences between groups in terms of negative correlations between nodes.

3.3. Signal amplitude

To reduce skewness, the log of the global ALFF was used for all analyses. The ANOVA results indicated that global ALFF differed between the three groups, $F(2,135) = 9.97$, $p < 0.0001$, Table 3. FESZ displayed lower global ALFF than HCS ($p < 0.0001$). GHR did not differ statistically from HCS or FESZ.

The voxel-wise F test revealed numerous clusters in which ALFF differed between the three groups (Fig. 2, Table 5). Though the DC clusters were predominantly in cortical areas, the ALFF clusters included limbic areas and basal ganglia as well as cortical areas. There were small areas of overlap between ALFF and DC clusters in bilateral superior frontal and paracingulate gyrus and in left operculum and supramarginal gyrus.

As a group, GHR resembled either HCS or FESZ depending on spatial location. In the majority of clusters, FESZ differed from HCS and GHR with no statistically significant difference between the latter two groups. In anterior areas, FESZ were higher than the other groups (Fig. 2B) and in posterior areas they were lower than the other groups (Fig. 2C). In a minority of areas, HCS displayed lower ALFF than GHR and FESZ with no difference between the latter groups (Fig. 2D). These areas included the basal ganglia, insula and left hippocampus (clusters 2, 6 and 8).

3.4. Medication status

Approximately half of the FESZ were receiving medications. Medicated FESZ and non-medicated FESZ did not differ in either DC or ALFF cluster scores. Moreover, chlorpromazine equivalents, a measurement of anti-psychotic dose (see Table 3 in Andreasen et al., 2010), did not correlate with ALFF or DC cluster scores. Medicated FESZ exhibited significantly lower global ALFF than unmedicated SZS, $t(40) = 2.56$, $p = 0.014$. There was no correlation between chlorpromazine equivalents and global ALFF.

3.5. Exploratory analysis of cluster scores

All the DC clusters correlated significantly with each other, $r = 0.40–0.90$, all p's < 0.0001. The DC clusters in which GHR and FESZ were significantly higher than HCS (DC clusters 2–13) correlated between −0.20 and 0.45 with the ALFF clusters in predominantly subcortical areas including basal ganglia and limbic lobe extending to hippocampus and in default areas (Table S4). In contrast, the DC cluster in which GHR were significantly elevated compared to HCS and FESZ (DC cluster 1, anterior temporal gyrus) correlated both positively and negatively with predominantly cortical non-default areas. The absolute value of the correlations ranged from 0.19 to 0.25.

We hypothesized that ALFF clusters in areas typically involved in working memory (ALFF clusters 9, 10, 11, and 13) would correlate with MCST errors. A weak overall correlation across the groups was found between the total cluster score in these areas and MCST error, $r = 0.25$, $p = 0.02$ (Fig. 3A). There was no interaction between group and total cluster scores in the working memory areas. DC cluster scores did not predict errors on the MCST. Global ALFF amplitude marginally predicted BPRS ratings in FESZ, $r(42) = 0.30$, $p = 0.06$. There was no interaction between the presence/absence of medication and global ALFF amplitude.

4. Discussion

This study combined DC and ALFF in one study to assess the correlation as well as the integrity and amplitude of brain activity in FESZ and GHR. As predicted, these groups, compared to HCS displayed increased connectivity in the whole brain and in most clusters. In measures of signal amplitude, FESZ differed markedly from HCS in the majority of clusters and displayed lower global ALFF. GHR were indistinguishable from HCS in global ALFF and in almost all ALFF clusters. The exceptions were clusters in basal ganglia, insula and hippocampus. In these areas, GHR and FESZ had reduced ALFF in comparison to HCS and did not differ from each other.

To our knowledge, this is the first report of whole brain global hyperconnectivity ascertained by a data-driven method in GHR or FESZ. It extends our earlier findings of increased intra-PFC connectivity in GHR and FESZ (Anticevic et al., 2015a) which were subsequently replicated in a separate sample of FESZ and matched controls (Anticevic et al., 2015b). However, the latter study reported clusters of reduced and increased connectivity in GHR compared to matched controls. This discrepancy may reflect differences in methods as our study considered positive and negative correlations separately whereas the Anticevic study combined them.

Table 4
Significant degree connectivity clusters.

Cluster	Voxels	PV_X	PV_Y	PV_Z	Hemisphere	Brain Regions	BA	F	P (Corrected)
1	105	51	0	−27	R	Temporal Pole	21	9.332	1.60E-04
2	72	−39	0	27	L	Inferior Frontal Operculum, Insula, Precentral gyrus	9/44/6	8.576	3.12E-04
3	53	−45	33	12	L	Triangular Inferior Frontal Gyrus	46	6.977	1.31E-03
4	1332	−33	−75	51	L	Superior Parietal Lobule, Inferior Parietal Lobule, Angular Gyrus, Superior Temporal Gyrus, Middle Temporal Gyrus, Inferior Temporal Gyrus, Supramarginal Gyrus, Middle Occipital Gyrus	40/39/7/19/20/37/21	11.339	2.81E-05
5	836	3	33	51	R/L	Middle Frontal Gyrus, DLPFC, MPFC, ACC, Supplementary Motor Area	8/6/9/32	10.328	6.70E-05
6	105	6	−63	30	R/L	Precuneus	31/7	7.785	6.31E-04
7	573	45	−57	33	R	Inferior Parietal Lobule, Angular Gyrus, Supramarginal Gyrus, Middle Occipital Gyrus, Superior Parietal Gyrus	40/39/7	9.427	1.47E-04
8	233	36	39	45	R	Middle Frontal Gyrus, DLPFC	8/9/6/10	8.586	3.09E-04

All degree connectivity clusters included in this table.

Table 5
Significant ALFF clusters.

Group	Cluster	Voxels	MNI coordinates	Hemisphere	Brain regions
HCS<FESZ>GHR	1	96	24,−18,−12	R	Amygdala, Hippocampus, Parahippocampal Gyrus
	4	141	33,42,−9	R	Frontal Pole
	9	181	12,54,30	R	Anterior Cingulate, Medial Prefrontal Cortex, Superior Frontal Gyrus
	10	128	−12,51,33	L	Superior Frontal Gyrus
	11	66	−60,−48,30	L	Supramarginal Gyrus
	13	91	−6,36,48	R/L	Superior Frontal Gyrus
HCS > FESZ<GHR	5	50	51,−75,−3	R	Lateral Occipital Gyrus
	7	198	6,−93,18	R/L	Cuneus, Superior and Middle Occipital Gyrus
	12	148	9,−75,57	R/L	Precuneus, Cuneus
FESZ<HCS	3	385	−15,−60,−6	L	Lingual Gyrus, Cuneus, Fusiform Gyrus
FESZ>HCS < GHR	2	403	−18,3,−15	L	Amygdala, Hippocampus, Parahippocampal Gyrus, Caudate, Temporal Pole
	6	94	12,12,9	R/L	Caudate
	8	76	−42,6,9	L	Insula, Frontal Inferior Operculum

All ALFF clusters included in this table.

GHR and FESZ evidenced equal amounts of hyperconnectivity, a finding that suggests that it may be an aspect of schizophrenia diathesis. This observation adds fuel to an emerging theory regarding excitation-inhibition imbalance in schizophrenia that draws on parallels between findings in schizophrenia and healthy subjects administered the *N*-Methyl-D-aspartate (NMDA) receptor glutamate receptor antagonist, ketamine (Krystal et al., 2016). Ketamine increases cortical functional connectivity (Driesen et al., 2013) and other signs of cortical activation including elevations in glucose metabolism (Lahti et al., 1995; Vollenweider et al., 1997), cortical firing rate (Jackson et al., 2004) and extracellular glutamate levels (Moghaddam et al., 1997). Acknowledging that the relationship between connectivity and glucose metabolism is complex and not fully understood (Thompson et al., 2016), we have advanced the theory that PFC hyperconnectivity observed in GHR and FESZ is related to increased excitation as compared to inhibition (Anticevic et al., 2015a; Anticevic et al., 2015b; Krystal and Anticevic, 2015). This has been strengthened by the finding that schizophrenia symptoms in a large FESZ sample were weakly correlated with intra-PFC hyperconnectivity and may normalize after treatment (Anticevic et al., 2015b). We were not able to replicate the cross-sectional results in the current study, perhaps due to insufficient statistical power.

4.1. Signal amplitude

Though functional connectivity seemed most sensitive to schizophrenia vulnerability, low-frequency BOLD signal amplitude both globally and on a per-voxel basis (ALFF) seemed most sensitive to the disease itself. FESZ, as a group, showed lower global ALFF than HCS and GHR who were indistinguishable statistically from each other. Unmedicated FESZ showed less reduction in global ALFF than medicated FESZ with no relationship to antipsychotic dose in chlorpromazine equivalents. Thus, since only the most ill patients were medicated, the reduced global ALFF may have been related to illness severity rather than medication per se.

The observed reduced global ALFF in FESZ may be related to pervasive low-level neural noise. Potentially, low level noise would reduce coherence locally thus diminishing ALFF (Cortes-Briones et al., 2015; Robbe et al., 2006). The increased noise could also lead to the increased

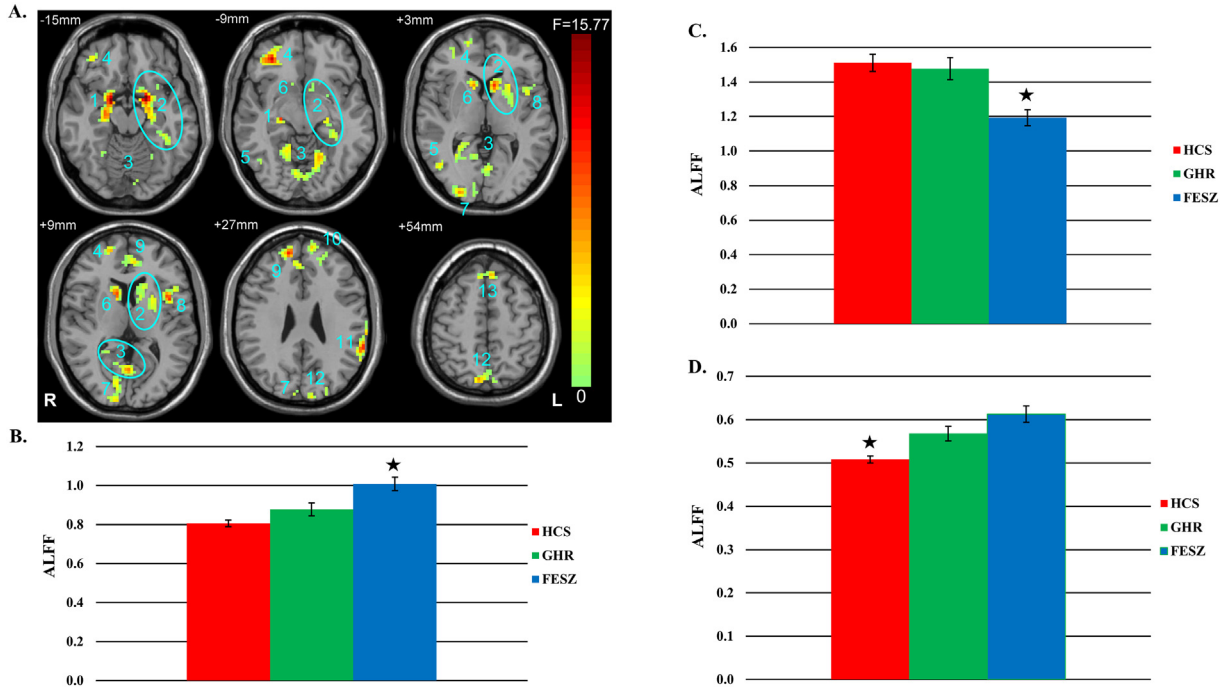

Fig. 2. ALFF. A) Clusters in which ALFF differs between HCS, FESZ and GHR as determined by one-way ANOVA shown at $p < 0.01$ voxel-wise and $p < 0.01$ cluster-wise. B) ALFF in Cluster 4 illustrating increased ALFF in FESZ found in anterior clusters. C) ALFF in Cluster 7 illustrating decreased ALFF in FESZ found in posterior clusters. D) ALFF in Cluster 2 illustrating reduced ALFF in HCS.

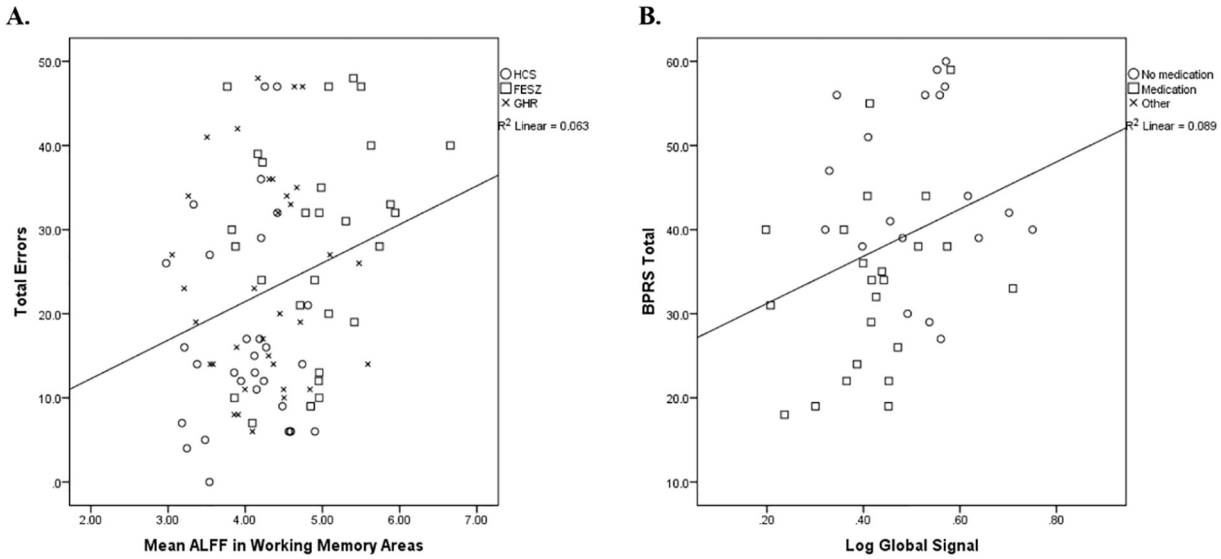

Fig. 3. Relationship between brain measures and clinical variables. A) Correlation between total ALFF in working memory areas and total errors on the MCST, a working memory task. B) Correlation between log global ALFF and BPRS total controlling for medication status, FESZ only.

DC noted in the FESZ and to a lesser extent GHR. Such noise would critically affect information processing and has been hypothesized to be a paradigmatic aspect of schizophrenia (Spencer, 2011; Uhlhaas and Singer, 2013; Yang et al., 2014). Interestingly, this pattern of increased connectivity and decreased global signal as measured by ALFF may be reversed in chronic schizophrenia (Yang et al., 2014). These patterns may be related to increases in connectivity and excitability in the early course followed by decreases in the later course of the disorder, perhaps attendant on homeostatic mechanisms (Krystal et al., 2017).

FESZ displayed divergent ALFF in clusters throughout the brain both cortically and subcortically. In anterior clusters, FESZ had greater ALFF than HCS and in posterior clusters they had reduced ALFF. This pattern, as well as the particular areas of divergent ALFF, parallel studies in chronic SZS (Turner et al., 2013). In almost all clusters, differences between HCS and GHR did not reach statistical significance but were in the same direction as those between HCS and FESZ. However, there were a group of three subcortical clusters (Anticevic et al., 2015a; Buckner et al., 2009; Chapman et al., 1994) in which GHR and FESZ exhibited increased ALFF as compared to HCS while not differing from each other. These clusters were previously noted to be divergent in chronic SZS as compared to HCS (Andreasen et al., 2010; Hoptman et al., 2010; Lui et al., 2015). In addition, two of them (clusters 2 and 6) encompassed caudate, hippocampus and surrounding cortex, in accord with our previous results in a smaller, partially overlapping GHR sample (Tang et al., 2015). These results must be viewed cautiously and need replication in an entirely independent sample, since a recent very large study (Bipolar-Schizophrenia Network on Intermediate Phenotypes, or B-SNIP) found that differences between SZS and HCS did not generalize to GHR (Meda et al., 2015).

The risk and illness-related alterations in DC and ALFF showed preliminary evidence of clinical significance, i.e., correlation with cognitive function and symptoms. Complementing an earlier report (Fryer et al., 2015), we found that ALFF in anatomical areas previously shown to be activated in working memory (D'Esposito et al., 1998; Driesen et al., 2008; Leung et al., 2002) was positively correlated with working memory performance. In FESZ, global ALFF was marginally positively correlated with BPRS total score.

DC and ALFF were interrelated in this study, suggesting that ALFF disturbances in hippocampus, default areas, and basal ganglia were related to hyperconnectivity. DC clusters fell into two camps: a large, inter-correlated group (clusters 2–10) in which GHR and FESZ were hyperconnected compared to HCS, and a single cluster in middle temporal gyrus (cluster 1) in which GHR were hyperconnected compared to FESZ and HCS. Higher DC in the large group of clusters was correlated with higher ALFF in the basal ganglia and medial temporal lobe structures including hippocampus. Hippocampus and basal ganglia are generators of neural rhythms that coordinate cortical and subcortical activity (Helie and Fleischer, 2016; Sirota, 2008).

Increased DC in anterior middle temporal gyrus was the only DC finding unique to GHR, This region, the location of cluster 1, is involved with language, semantic memory, visual perception and multimodal sensory integration (Onitsuka et al., 2004). Grey matter decreases in this area have been noted in early and later course SZS (Hu et al., 2013; Onitsuka et al., 2004). Interestingly, hypermetabolism and, potentially hyperconnectivity, have been linked with grey matter loss (Schobel et al., 2013). DC in the middle temporal gyrus was correlated with ALFF clusters in PFC cognitive control areas along with surrounding temporal and occipital cortex. Thus, as with the large group of DC clusters, increased ALFF in areas that control or regulate other brain areas, i.e., PFC, seemed to correlate with connectivity in downstream areas.

This study was unusual in combining functional connectivity and ALFF in the same study. These biomarkers uniquely differentiated the groups and had different clinical correlates. The findings support including both resting state biomarkers in future studies. In healthy subjects, ALFF and functional connectivity are usually highly related when measured across the timecourse (Di et al., 2013; Tomasi et al., 2013) or when temporal fluctuations in functional connectivity are correlated with ALFF fluctuations (Tomasi et al., 2016). These relationships are influenced by network properties and external versus internal inputs (Tomasi et al., 2017). Our paper raises the possibility that these relationships are disordered in the schizophrenia spectrum, a contention borne out by a recently published study (Fu et al., 2018). Further investigation in terms of neural energetics and local versus long-distance connectivity may be helpful in elucidating the causes of these alterations and their relationship to genetic predisposition and psychosis onset.

Some aspects of the study design and execution affected conclusions that might be derived from this sample. First, the GHR sample was restricted to individuals with little psychopathology. This may facilitate dissociating genetic risk from psychopathology. However, they were less likely to develop schizophrenia and other psychiatric problems than non-symptomatic GHR (Mirsky et al., 1995). Second, approximately half the FESZ were too ill to maintain off medication and received antipsychotic medication, potentially affecting network metrics and ALFF (Bolding et al., 2012; Hadley et al., 2014). However, there

was little evidence that group differences were strongly moderated by medication. The possible exception would be global ALFF which was lower in medicated than unmedicated FESZ but unrelated to a measure of antipsychotic potency. Third, the fact that some individuals were not assessed with the MCST and BPRS could limit and bias findings regarding functional significance. Fourth, our sample was exclusively Han Chinese. This racial homogeneity may reduce sources of variance and thus make it easier to identify schizophrenia-related alterations in ALFF and DC. Alternatively, results may not generalize to other racial groups because of racially specific differences in the expression of schizophrenia genes and/or their interaction with the environment. Finally, because the study is cross-sectional, any hypotheses about schizophrenia development generated by our findings require testing in a longitudinal study.

Overall, the results suggest that hyperconnectivity and ALFF abnormalities may be aspects of schizophrenia development. GHR and FESZ show comparable levels of hyperconnectivity in whole-brain, data-driven degree centrality analysis as compared to HCS. The observation that hyperconnectivity is present in the earliest phases of illness accords with the hypothesis that deficits in GABA signaling, an early neurodevelopmental feature of schizophrenia, might precede the emergence of the full spectrum of schizophrenia symptoms (Hoftman et al., 2015; Krystal et al., 2016; Lewis et al., 2008). In contrast, global ALFF and ALFF deficits were predominantly associated with FESZ and not GHR, suggesting that this neural signal reflects hypothesized neural changes associated with disease progression, such as progressive synaptic loss (Krystal et al., 2016), rather than genetic risk. The only finding specific to the GHR group in this study was high DC in anterior temporal lobe. Because we do not have longitudinal data in the GHR group, it is not yet clear whether this signal reflects psychiatric vulnerability or resilience. In summary, the resting fMRI signal contains a great deal of information that might inform our understanding of risk and disease mechanisms. These biomarkers may be increasingly important as we understand their neurobiological and clinical implications.

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Conflict of interest

Dr. Krystal consults for the following companies for less than $5000 per year: AMGEN, AstraZeneca Pharmaceuticals, Biogen (Idec, MA), Biomedisyn Corporation, Forum Pharmaceuticals, Janssen Research & Development, Otsuka America Pharmaceutical, Inc., Sunovion Pharmaceuticals, Inc., Takeda Industries, and Taisho Pharmaceutical Co., Ltd. He serves on the advisory board of Biohaven Pharmaceuticals, Blackthorn Therapeutics, Inc., Lohocla Research Corporation, Luc Therapeutics, Inc., Pfizer Pharmaceuticals, TRImaran Pharma. Dr. Krystal has stock in ArRETT Neuroscience, Inc. and Biohaven Pharmaceuticals Medical Sciences and stock options in Blackthorn Therapeutics, Inc. & Luc Therapeutics, Inc. Astra Zeneca and Pfizer Pharmaceuticals provide investigational drugs for research studies. He has the following patents: 1) Seibyl JP, Krystal JH, Charney DS. Dopamine and noradrenergic reuptake inhibitors in treatment of schizophrenia. US Patent #:5,447,948.September 5, 1995, 2) Vladimir, Coric, Krystal, John H, Sanacora, Gerard – Glutamate Modulating Agents in the Treatment of Mental Disorders US Patent No. 8,778,979 B2 Patent Issue Date: July 15, 2014, 3) Charney D, Krystal JH, Manji H, Matthew S, Zarate C., — Intranasal Administration of Ketamine to Treat Depression United States Application No. 14/197,767 filed on March 5, 2014; United States application or PCT International application No. 14/306,382 filed on June 17, 2014, 4) Arias A, Petrakis I, Krystal JH. – Composition and methods to treat addiction. Provisional Use Patent Application no.61/973/961. April 2, 2014. Filed by Yale University Office of Cooperative Research and 5): Chekroud, A., Gueorguieva, R., & Krystal, JH. "Treatment Selection for Major Depressive Disorder" [filing date 3rd June 2016, USPTO docket number Y0087.70116US00]. Provisional patent submission by Yale University. He is the editor of Biological Psychiatry and is employed by the Yale University School of Medicine and VA CT Healthcare System. All other authors have no conflict to declare.

CRediT authorship contribution statement

Yanqing Tang: Conceptualization, Investigation, Writing - review & editing. **Qian Zhou:** . **Miao Chang:** Data curation, Investigation, Methodology, Writing - review & editing. **Adam Chekroud:** Formal analysis, Investigation, Methodology, Writing - review & editing. **Ralitza Gueorguieva:** Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Writing - review & editing. **Xiaowei Jiang:** Data curation, Writing - review & editing. **Yifang Zhou:** Data curation, Writing - review & editing. **George He:** Formal analysis, Writing - review & editing. **Margaret Rowland:** Formal analysis, Visualization, Writing - review & editing. **Dahai Wang:** Data curation, Writing - review & editing. **Shinan Fu:** Data curation, Writing - review & editing. **Zhiyang Yin:** Data curation, Writing - review & editing. **Haixia Leng:** Data curation, Writing - review & editing. **Shengnan Wei:** Writing - review & editing. **Ke Xu:** Writing - review & editing. **Fei Wang:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing - original draft, Writing - review & editing. **John H. Krystal:** Conceptualization, Investigation, Methodology, Writing - review & editing. **Naomi R. Driesen:** Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Visualization, Writing - original draft, Writing - review & editing.

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Appendix A. Supplementary data

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