RESEARCH ARTICLE

Frequency specific resting state functional abnormalities in psychosis

Suril Gohel¹ | Juan A. Gallego^{2,3} | Delbert G. Robinson^{4,5,6} | Pamela DeRosse^{4,5,6} | Bharat Biswal^{7*} | Philip R. Szeszko^{8,9*}

¹Department of Health Informatics, School of Health Professions, Rutgers Biomedical and Health Sciences, Rutgers University, Newark, New Jersey

²Department of Psychiatry, Weill Cornell Medical College, New York, New York

³New York-Presbyterian Hospital - Westchester Division, White Plains, New York

⁴Center for Psychiatric Neuroscience, Feinstein Institute for Medical Research, Manhasset, New York

⁵Psychiatry Research, Zucker Hillside Hospital, Northwell Health System, New York

⁶Department of Psychiatry, The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York

⁷Department of Biomedical Engineering, New Jersey Institute of Technology, Newark, New Jersey

⁸Mental Illness Research Education Clinical Center and Mental Health Patient Care Center, James J. Peters Veterans Affairs Medical Center, Bronx, New York

⁹Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York

Correspondence

Philip R. Szeszko, Ph.D., James J. Peters Veterans Affairs Medical Center, Mental Illness Research, Education and Clinical Center (MIRECC) and Mental Health Patient Care Center, 130 West Kingsbridge Road, Bronx, NY 10468.
Email: philip.szeszko@va.gov or
Email: philip.szeszko@mssm.edu

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Abstract

Resting state functional magnetic resonance imaging studies of psychosis have focused primarily on the amplitude of low-frequency fluctuations in the blood oxygen level dependent (BOLD) signal ranging from .01 to 0.1 Hz. Few studies, however, have investigated the amplitude of frequency fluctuations within discrete frequency bands and higher than 0.1 Hz in patients with psychosis at different illness stages. We investigated BOLD signal within three frequency ranges including slow-4 (.027–.073 Hz), slow-3 (.074–0.198 Hz) and slow-2 (0.199–0.25 Hz) in 89 patients with either first-episode or chronic psychosis and 119 healthy volunteers. We investigated the amplitude of frequency fluctuations within three frequency bands using 47 regions-of-interest placed within 14 known resting state networks derived using group independent component analysis. There were significant group x frequency interactions for the visual and motor cortex networks, with the largest significant group differences (patients < healthy volunteers) evident in slow-4 and slow-3, respectively. Also, healthy volunteers had an overall higher amplitude of frequency fluctuations compared to patients across the three frequency ranges in the visual cortex, dorsal attention and motor cortex networks with the opposite effect (patients > healthy volunteers) evident within the salience and frontal gyrus networks. Subsequent analyses indicated that these effects were evident in both first-episode and chronic patients. Our study provides new data regarding the importance of BOLD signal fluctuations within different frequency bands in the neurobiology of psychosis.

KEYWORDS

first-episode, frequency bands, resting state fMRI, schizophrenia

1 | INTRODUCTION

In task-based functional magnetic resonance imaging (fMRI) studies, the low frequency blood oxygen level dependent (BOLD) signal

(ranging from .01 to 0.1 Hz) is filtered from the statistical analysis so that neural activity associated with a task can be identified. In 1995, however, Biswal, Zerrin, Haughton, and Hyde (1995) reported that these low frequency fluctuations are in coherence between bilateral precentral gyrus regions during the resting state in the absence of external stimuli. The correlations between BOLD signals have been

*Denotes joint senior authorship.

identified as resting state functional connectivity that represents neuronal fluctuations and functional integration among brain regions, which has been widely replicated. In addition, some brain regions have been demonstrated to have differences in resting state BOLD signal power, as defined by the amplitude of low-frequency fluctuations (ALFF) (Zang et al., 2007).

There is now considerable evidence from resting state functional magnetic resonance imaging (rsfMRI) studies that schizophrenia and associated psychotic disorders may be characterized by neurodevelopmental abnormalities involving loss of segregated systems (default mode, frontal parietal and visual attention) and increased coherence between these systems by young adulthood (Satterthwaite & Baker, 2015). Such abnormalities have also been observed among individuals at risk for psychosis (Anticevic et al., 2012; Bernard et al., 2014; Dandash et al., 2014; Fryer et al., 2013). Moreover, these abnormalities do not appear to be an artifact of antipsychotic medications (Argyelan et al., 2014; Guo et al., 2014) and may potentially serve as a biomarker for symptom improvement associated with antipsychotic treatment (Sarpal et al., 2015). Furthermore, disturbances in resting state networks have been linked to neuropsychological deficits (Argyelan et al., 2014), positive symptoms (Rotarska-Jagiela et al., 2010), negative symptoms (Sorg et al., 2013). There is also considerable evidence that such abnormalities may serve as an endophenotype in studies assessing genetic predisposition to psychosis (Khadka et al., 2014; Meda et al., 2014). Although converging evidence for disrupted neuronal integration at rest has been observed in these studies, they have focused primarily on functional integration at low-frequency BOLD fluctuations (i.e., <0.1 Hz).

Neuronal oscillations are distributed linearly on a logarithmic scale and have unique characteristics and inter-relationships among different frequency bands (Buzsaki & Draguhn, 2004), which appear to be preserved in the mammalian order (Buzsaki & Watson, 2012). Specifically, neuronal oscillations can be decomposed into distinct frequency bands including: slow-1 (0.5–1.2 Hz); slow-2 (0.198–0.5 Hz); slow-3 (.073–0.198 Hz); slow-4 (.027–.073 Hz); and slow-5 (.01–.027 Hz). Oscillations within specific frequencies have been linked to particular cells and associated circuits, presumably maximizing the integration of information across neural networks in the context of behavioral demands (Friston, Bastos, Pinotsis, & Litvak, 2014; Gregoriou, Paneri, & Sapountzis, 2015). For example, it has been demonstrated that interneurons play a unique role in oscillations within hippocampal networks (Allen & Monyer, 2014). Moreover, neural oscillations, which have been implicated in memory encoding, change in association with memory retrieval (Watrous & Ekstrom, 2014) and have implications for the emergence of language (Maguire et al., 2013). Although neural oscillations in brain activity have primarily been investigated using electroencephalography, recent technological advancements have prompted studies of specific frequency bands using rsfMRI (Gohel & Biswal, 2014).

Despite the implications of the prior work highlighting the relevance of frequency bands, few studies to date have investigated different frequencies within the low-frequency band of .01 to 0.1 Hz using rsfMRI in psychosis and no study has investigated BOLD

frequency bands >0.1 Hz. Hoptman et al. (2010) reported that 29 patients with schizophrenia demonstrated lower ALFF compared to healthy volunteers in the lingual gyrus, cuneus and precuneus and greater ALFF in the left parahippocampal gyrus within the slow-4 band. Similarly, Turner et al. (2013) observed lower ALFF in posterior brain regions in psychosis and higher ALFF in the frontal cortex compared to healthy volunteers in a large multisite study. In contrast, Huang et al. (2010) reported that compared to healthy volunteers, antipsychotic drug-naïve first-episode schizophrenia patients demonstrated significantly lower ALFF within the range of .01–.08 Hz in the medial prefrontal cortex with concomitant increases within the right and left putamen.

More recently, using data derived from the Bipolar-Schizophrenia Network on Intermediate Phenotypes Consortium, Meda et al. (2015) reported that compared to controls, patients with schizophrenia demonstrated consistent hypoactivation in precuneus/cuneus within the slow-5 and slow-4 frequency bands assessed using both absolute and fractional power. Similarly, Yu et al. (2014) examined resting state fMRI activity in slow-5, slow-4 and the standard band of .01–.08 Hz in 69 patients with schizophrenia and 62 healthy controls. They reported that low frequency fluctuations in slow-4 were higher overall in the basal ganglia, cingulate cortex and fusiform gyrus, but lower overall in the middle temporal gyrus, lingual gyrus, inferior frontal gyrus and ventromedial frontal gyrus within slow-5. Moreover, these authors noted that several brain regions (including the inferior occipital gyrus, precuneus and thalamus) demonstrated significant frequency band $\times$ group interactions suggesting that spontaneous neural activity may be frequency dependent among patients with schizophrenia.

A potential limitation of prior rsfMRI studies investigating different frequency bands is that they have focused on the traditional low-frequency band (.01–0.1 Hz). Recent studies, however, have demonstrated the presence of resting state functional connectivity patterns at frequency bands higher than 0.1 Hz (Boubella et al., 2013; Gohel & Biswal, 2014). The goal of the current study was to compare patients with psychosis with healthy volunteers to assess group differences in BOLD signal amplitude in three distinct frequency bands, including slow-2 (0.199–0.25 Hz), slow-3 (.072–0.198 Hz) and slow-4 (.027–.073 Hz) consistent with our prior work (Gohel & Biswal, 2014) as well as the overall BOLD frequency band of .01–0.25 Hz. We hypothesized that abnormalities in the power of BOLD signal fluctuations associated with psychosis would be frequency dependent and extend to frequency bands higher than 0.1 Hz.

2 | METHODS

2.1 | Subjects

A total of 208 subjects participated in this study including 119 healthy volunteers and 89 patients with psychosis who met a prior motion criterion for study inclusion (described below; see Gohel & Biswal, 2014). Study participants were recruited from two different sources: (1) Zucker Hillside Hospital (ZHH) and (2) the COBRE online data

repository (The Center for Biomedical Research Excellence -http://fcon_1000.projects.nitrc.org/indi/retro/cobre.html).

2.2 | Zucker Hillside Hospital cohort

A total of 58 patients with psychosis (mean age = 28.6 years, $SD = 11.8$; 37M/21F) were recruited from the Zucker Hillside Hospital in Glen Oaks, NY including 38 patients experiencing a first-episode of psychosis and 20 with chronic psychosis who met the motion criteria described below. All patient diagnoses were based on the SCID for Axis I DSM-IV Disorders supplemented by information from clinicians and, when available, family members. Patients met DSM-IV criteria for schizophrenia ($n = 35$), schizoaffective disorder ($n = 5$), schizophreniform disorder ($n = 12$) or psychotic disorder, not Otherwise specified (NOS) ($n = 6$).

Sixty-nine healthy volunteers (mean age = 30.1; $SD = 13.7$; 40M/29F) from the Zucker Hillside Hospital site who met the motion criteria described below were recruited from advertisements posted on websites and by word of mouth to match the demographic distributions of patients. All healthy volunteers were assessed using the SCID for DSM-IV disorders Non-Patient Edition (First, Spitzer, Gibbon, & Williams, 2002). Exclusion criteria for healthy subjects included the denial of any lifetime history of a major mood or psychotic disorder as determined by clinical interview using the SCID-NP.

Exclusion criteria for all participants at the ZHH site included: (a) MRI contraindications; (b) significant medical illness; (c) prior psychosurgery; (d) DSM-IV diagnosis of Tourette's syndrome, developmental disorders, autism and neurological conditions; (e) DSM-IV mental retardation; (f) stroke; and (g) pregnancy. All procedures were approved by the Northwell Health Institutional Review Board. Written informed consent was obtained from all individuals, and from a parent or legal guardian in the case of minors. Written assent was obtained from all minors.

2.3 | COBRE cohort

A total of 31 patients (mean age = 36.0; $SD = 14.1$; 24M/7F) with schizophrenia and 50 healthy controls (mean age = 33.8; $SD = 11.4$; 34M/16F) obtained from the online COBRE data repository were included in the study. Anatomical and rsfMRI images were downloaded for each of the subjects. All individuals were screened and excluded if they had a history of neurological disorder, mental retardation, history of severe head trauma with more than 5 min loss of consciousness, history of substance abuse or dependence within the last twelve months. Diagnostic information was obtained using the SCID.

2.4 | Image acquisition

The scanning parameters for the rsfMRI scan at ZHH were: TR = 2 s, TE = 30 ms, matrix size = $64 \times 64 \times 40$ slices, voxel size = $3.7 \times 3.7 \times 3.0$ mm³ and for the anatomical SPGR were: matrix size: $256 \times 256 \times 216$ slices, voxel size = $0.938 \times 0.938 \times 1$ mm³. Individuals were told to keep their eyes closed during the scan and to "not think of anything in particular." For the COBRE data set, resting state fMRI data was obtained using the following scanning parameters: TR = 2.0 s,

TE = 29 ms, matrix size = 64×64 , 32 slices, voxel size = $3 \times 3 \times 4$ mm³ and an anatomical MPRAGE scan was obtained with TR/TE/TI = 2,530/[1.64, 3.5, 5.36, 7.22, 9.08]/900 ms, matrix = $256 \times 256 \times 176$, voxel size = 1 mm³. Individuals were instructed to keep their eyes open during the scan. Further information about the specific scanning paradigm for the COBRE data set can be obtained from http://fcon_1000.projects.nitrc.org/indi/retro/cobre.html.

2.5 | Motion

Head motion related fMRI signal changes has received considerable attention in the literature with prior empirical work demonstrating that long-distance correlations are reduced in association with motion, whereas short-distance correlations may be increased (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; Van Dijk, Sabuncu, & Buckner, 2012). An important goal of the current study was to examine changes in BOLD signal power at frequencies higher than 0.1 Hz, which imply faster signal changes. Although no studies to date have examined the relationship between motion and BOLD signal power higher than 0.1 Hz, it is conceivable that motion could affect BOLD signal power > 0.1 Hz to a greater extent compared to the lower frequency ranges (Power et al., 2012). We, therefore, only included individuals in the current study who met a stringent previously defined motion criterion based on our published study examining these frequency bands (Gohel & Biswal, 2014). Specifically, we excluded individuals who had greater than one voxel maximum motion in any direction. In addition, we computed frame-wise displacement as defined by Jenkinson, Beckmann, Behrens, Woolrich, and Smith (2012) for all subjects and implemented a threshold by excluding individuals demonstrating mean framewise displacement greater than 0.5 mm from analysis (Gohel & Biswal, 2014).

2.6 | Image processing

Image processing methods were the same for all individuals and used SPM 8 (<http://www.fil.ion.ucl.ac.uk/spm/>), FSL version 5.0 (Jenkinson et al., 2012, <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>) and AFNI (Cox, Jesmanowicz, & Hyde, 1995) (<http://afni.nimh.nih.gov/afni/>). In the first step the first 5 time-points (10 s) were removed from the rsfMRI data to eliminate T1-relaxation effects. In the second step, we performed motion correction using SPM's realign function to align each individual's BOLD fMRI data to the mean of the images. During motion correction, head movement was recorded in six directions and used to exclude individuals with significant motion (as defined above) and to regress out the effects of motion on BOLD signal. Following motion correction, individuals' rsfMRI data were coregistered to the anatomical image. Each anatomical image was segmented into gray matter, white matter and cerebrospinal fluid probability maps using the "New Segment" function in SPM8 while deriving a deformation field. Following segmentation individuals' rsfMRI data were transformed to MNI standard space using the deformation field derived during the segmentation step. For all individuals, probability maps for cerebrospinal fluid and white matter were thresholded at $p > 0.95$ to create CSF and WM masks, respectively. Using these masks the BOLD time series was extracted from the resting state data set and

FIGURE 1 Regions-of-interest comprising the 14 independent components in this study. (a) Visual cortex; (b) salience network (c) left-frontal parietal network; (d) insular cortex; (e) right frontal-parietal network; (f) basal ganglia network; (g) default-mode network (posterior part); (h) default mode network; (i) fusiform gyrus; (j) higher visual network; (k) dorsal attention network; (l) frontal gyrus; (m) motor network; and (n) inferior frontal gyrus [Color figure can be viewed at wileyonlinelibrary.com]

the first five principal components were derived. A COMPCORR and Friston-24-based GLM model was implemented to reduce the effect of physiological noise and motion timeseries from the BOLD fMRI data using FSL. The GLM model thus included a total of 34 regressor time-series (five principal components of white matter, five principal components of cerebrospinal fluid, six motion parameters, six autoregressive motion parameters and twelve quadratic models of the motion parameters) (Bharat et al., 2015). Residual time-series were extracted for each voxel following regression and used in subsequent analyses.

2.7 | Group ICA analysis

Following regression, each individual's BOLD time-series was temporally band-pass filtered in low-frequency bands (.01–0.1 Hz) using AFNI's 3dBandPass program. Following temporal filtering, group independent component analysis was performed using a temporal concatenation approach available in FSL melodic and 20 independent components were extracted. Each of the 20 independent components was compared with the independent components derived from FCP-1000 maps (Biswal et al., 2010) using software developed in-house (Taylor & Saad, 2013) and 14 known resting state networks were identified for this data set.

Because the spatial extent of resting state networks derived through ICA can be heterogeneous across subjects and groups we attempted to minimize this bias by implementing a region-of-interest

approach (with a standard size sphere). Thus, each of the 14 resting state networks in this study was formed by taking the average of 1 to 7 noncontiguous clusters (regions-of-interest) using the AFNI program 3dClustSim (see Figure 1 for MNI coordinates). For each cluster peak voxel coordinates were derived. A 6 mm sphere was placed around the peak coordinates to create the 47 regions-of-interest (see Table 1) that were averaged for each ICA, respectively. For each region-of-interest we extracted power in the BOLD signal for each individual in each of the three frequency bands as described below.

2.8 | Frequency-specific amplitude of BOLD signal fluctuations

We segmented the overall BOLD frequency band from .0 to 0.25 Hz (TR=2 s, sampling frequency=0.5 Hz) into three distinct frequency bands including slow-2 (0.199–0.25 Hz), slow-3 (.074–0.198 Hz) and slow-4 (.027–.073 Hz) based on earlier studies (Gohel & Biswal, 2014; Zuo et al., 2010). For each of these three distinct frequency bands, we computed power of the BOLD signal based on methods defined by Zhang et al. (2007) using the “3dRSFC” AFNI command (Taylor & Saad, 2013). Briefly, we computed voxel-level fast Fourier transformations for individuals' BOLD fMRI time-series across the whole frequency band to derive power at each frequency. The square-root of power at each frequency band was obtained to derive frequency specific amplitude measures. This frequency specific amplitude was

TABLE 1 MNI coordinates for the 47 regions-of-interest derived from independent component analysis and corresponding names derived from the Talairach atlas

Network name	ROI #	X	Y	Z	Region-of-interest name
Visual	01	-12	67	7	Right Cuneus
Salience	02	-6	-23	31	Right cingulate Gyrus
	03	30	-41	31	Left superior frontal Gyrus
	04	-30	-44	28	Right superior frontal Gyrus
	05	-33	-17	4	Right insula
	06	33	-17	1	Left insula/left BA 47
Left frontal parietal	07	45	-20	34	Left Precentral Gyrus/left BA 9
	08	36	67	49	Left superior parietal lobule
	09	39	-50	-2	Left middle frontal Gyrus
	10	9	-29	46	Left superior frontal Gyrus
Insular cortex	11	36	19	1	Left Claustrum
	12	-45	10	1	Right insula
Right frontal parietal	13	-39	-17	52	Right superior frontal Gyrus/right BA 8
	14	-51	49	46	Right inferior parietal lobule
	15	-39	-53	-5	Right middle frontal Gyrus
	16	-6	-29	46	Right medial frontal Gyrus/right BA 8
	17	48	55	46	Left inferior parietal lobule/left BA 40
Basal ganglia	18	-15	-5	7	Right Lentiform nucleus
	19	18	-2	7	Left Lentiform nucleus/left putamen
Default mode (posterior)	20	6	64	34	Left Precuneus/left BA 7
	21	36	64	46	Left superior parietal lobule/left BA 7
Default mode (anterior)	22	-57	49	16	Right superior temporal Gyrus
	23	54	55	22	Left superior temporal Gyrus
	24	6	52	40	Left Precuneus
	25	3	-53	28	Left superior frontal Gyrus/left BA 9
	26	-54	-26	7	Right inferior frontal Gyrus/right BA 45
	27	-9	-29	61	Right superior frontal Gyrus
	28	51	-23	10	Left inferior frontal Gyrus/left BA 45
Fusiform Gyrus	29	33	61	-14	Left Declive
	30	-33	58	-14	Right Declive
	31	24	-5	-14	Left Subcallosal Gyrus /left BA 34
	32	-24	-8	-17	Right inferior frontal Gyrus/left BA 47
Higher visual cortex	33	-21	94	1	Right Cuneus
	34	21	94	1	Left Cuneus
Dorsal attention	35	-39	37	64	Right Postcentral Gyrus
	36	48	28	40	Left Postcentral Gyrus/left BA 2
	37	48	64	-2	Left inferior temporal Gyrus
Middle frontal Gyrus	38	6	-47	10	Left medial frontal Gyrus/left BA 10
	39	9	-29	58	Left superior frontal Gyrus
Motor cortex	40	-57	4	28	Right Precentral Gyrus
	41	57	4	25	Left Precentral Gyrus
Inferior frontal Gyrus	42	-48	-17	25	Right inferior frontal Gyrus/right BA 9
	43	-33	-26	-8	Right inferior frontal Gyrus
	44	45	-17	25	Left inferior frontal Gyrus/left BA 46
	45	33	-26	-11	Left inferior frontal Gyrus
	46	-33	55	49	Right superior parietal lobule
	47	-3	-20	55	Right superior frontal Gyrus/right BA 6

averaged across the frequency bands slow-2, slow-3 and slow-4 to derive voxel-level frequency band specific amplitude measures. For each individual, the amplitude at each voxel was normalized by mean

amplitude across the whole brain to derive a measure similar to mALFF (Amplitude of Low-frequency Fluctuation) for each frequency band. These measures are similar to the ones used in earlier studies

describing frequency-based amplitude differences in schizophrenia (Hoptman et al., 2010; Yu et al., 2014).

In contrast to earlier studies that focused on BOLD fluctuations in traditional low-frequency bands (<0.1 Hz), we also investigated the power of BOLD fluctuations in higher frequency bands. As the term ALFF traditionally applies to the power of BOLD fluctuations in only low-frequency bands (<0.1 Hz) here we define AFF as a general term to describe the amplitude of BOLD frequency fluctuations. Additionally, we did not utilize fractional measures in the current study given that fALFF (fractional Amplitude of Low-Frequency Fluctuations) measures traditionally calculate the ratio of power in low-frequency bands to the power in the whole BOLD frequency band (Zou et al., 2015). Thus, to calculate a fractional measure for the amplitude of frequency fluctuation similar to fALFF, one needs to divide AFF in any given frequency band with the combination of the other frequency bands. This implies that lower fAFF could be due to either lower AFF of the numerator frequency band or higher AFF in either one or both of the denominator frequency bands. Similarly, higher fAFF could be attributed to either higher AFF of the numerator or lower AFF in either one or both of the denominator frequency bands. For example, higher fAFF in slow-4 frequency band can be attributed to either increased power in slow-4 frequency band or decreased BOLD signal power in slow-3 and slow-2 frequency bands or the combinations of both. Thus, the interpretation of study results would be confounded if there were group $\times$ network $\times$ frequency interactions in combination with the caveats listed above.

2.9 | Region-of-interest analyses

For each of the 14 networks, we computed average AFF by taking the mean of the respective ROIs comprising a given network (see Table 1) in each of the three frequency bands (i.e., mAFF). Scores for the 14 networks were imported into SPSS (version 16) and we used repeated measures ANCOVA to specifically test the group $\times$ region $\times$ frequency interaction with alpha set to < .05. The between subjects factors included group (patient and healthy volunteer) and sex. The within subjects factor was network score (14 networks) and mAFF within the three frequency bands (slow-2, slow-3 and slow-4). Age and site were included as group level statistical covariates. Given the assumption of sphericity was violated we used Greenhouse–Geisser correction to adjust degrees of freedom. Post hoc investigation of specific frequency ranges that were significant between groups were conducted using alpha set at .05.

2.10 | Voxelwise analysis

We also used voxelwise analysis to complement the region-of-interest analyses using age, sex, motion and site as covariates. We initially compared all patients versus healthy volunteers to investigate frequency specific group level differences. Primary analyses compared all patients to healthy volunteers with subsequent analyses focused on the comparison of first-episode and chronic patients with healthy volunteers and group comparisons by site. To reduce any residual effect of motion on mAFF differences we included individuals' mean frame-wise displacement in the group level analysis as a covariate (Power

et al., 2012; Van Dijk et al., 2012; Yan et al., 2013). Group level statistics maps were thresholded at $p < .001$ with correction for multiple comparisons performed using "3dClustSim" in AFNI. We estimated the smoothness of the fMRI data using the updated method of calculating spatial autocorrelation using the 3dFWHMx program within AFNI. These acf values were further used as input into the 3dClustSim program, to derive a cluster size corresponding to a voxelwise p value of .001. This resulted in a cluster size of 22 voxels. These group level differences were overlaid onto the surface level maps using BrainNet-viewer (Xia, Wang, & He, 2013, <http://www.nitrc.org/projects/bnv>). In addition, we have also provided unbiased (i.e., unthresholded) Tstat maps of group level differences in Supporting Information Figure 1.

3 | RESULTS

There were no overall significant differences between patients and healthy volunteers in distributions of age, sex and motion. Based on comparison with the FCON-1000 ICA maps, we identified 14 independent components for investigation. Figure 1 displays the group level independent component maps and the corresponding regions-of-interest derived for this study are illustrated by the dark circle overlaid on independent component maps. The resting state networks in this study included: (A) visual cortex; (B) salience network; (C) left-frontal parietal network; (D) insular cortex; (E) right frontal-parietal network; (F) basal ganglia network; (G) default-mode network (posterior section); (H) default mode network (anterior section); (I) fusiform gyrus; (J) higher visual network; (K) dorsal attention network; (L) frontal gyrus; (M) motor network; and (N) inferior frontal gyrus. Table 1 provides the MNI coordinates for all regions-of-interest and the corresponding resting state networks to which they were assigned.

The group $\times$ IC $\times$ frequency interaction was significant ($F = 1.75$, $df = 13.53$, 2,733; $p = .042$) implying that the group level differences in BOLD signal power among the ICs were frequency dependent. Thus, we investigated group $\times$ frequency interactions for each of the ICs in posthoc analyses. There was a significant group $\times$ frequency interaction for visual cortex ($F = 3.57$, $df = 1.72$, 346; $p = .038$) with significant group differences evident in slow-2 ($F = 6.05$, $df = 1$, 202, $p = .015$; partial eta-squared = .029) and slow-3 ($F = 5.54$, $df = 1$, 202; $p = .020$; partial eta-squared = .027), but with the greatest effect size in slow-4 ($F = 11.41$, $df = 1$, 202, $p = .001$; partial eta-squared = .053). In addition, the group $\times$ frequency interaction was significant for the motor cortex ($F = 4.10$, $df = 1.63$, 330; $p = .025$) with the largest effect size evident in slow-3 ($F = 13.67$, $df = 1$, 202; $p = .001$; partial eta-squared = .063) and to a lesser extent slow-4 ($F = 7.37$, $df = 1$, 202, $p = .018$; partial eta-squared = .035). Bar-plots illustrating mAFF for these 2 resting state networks within each frequency band are provided in Figure 2.

In addition, there was a significant interaction of group by IC ($F = 4.98$, $df = 6.39$, 1,290; $p < .001$). Posthoc analyses revealed significant main effects of group for visual cortex ($F = 9.11$, $df = 1$, 202, $p = .003$), dorsal attention ($F = 7.76$, $df = 1$, 202; $p = .006$) and motor cortex ($F = 8.89$, $df = 1$, 202, $p = .003$) such that healthy volunteers had higher mAFF values compared to patients across the three frequency ranges. Significant main effects of group were also evident

FIGURE 2 Average mAFF in the different frequency bands. Bars represent 95% confidence interval of standard errors [Color figure can be viewed at wileyonlinelibrary.com]

for the salience ($F = 4.03$, $df = 1$, 202, $p = .046$) and frontal gyrus ($F = 5.75$, $df = 1$, 202, $p = .017$) networks such that patients had higher mAFF scores compared to healthy volunteers across the three frequency ranges. Bar-plots illustrating mAFF for each of these five resting state networks within each frequency band are provided in Figure 2.

There were also significant main effects of frequency for the dorsal attention ($F = 23.17$, $df = 1.52$, 306; $p < .001$) and motor ($F = 6.63$, $df = 1.63$, 330; $p = .003$) networks such that slow 4 was significantly higher than slow 3, which, in turn, was significantly higher than slow 2. Neither the main effect of sex nor interactions with sex were statistically significant.

Figure 3 provides the group level comparisons for voxelwise analyses in each of the frequency bands ($p < .001$, corrected for multiple comparisons using 3dClustSim). Consistent with the significant interaction effects from the region-of-interest analyses we observed lower mAFF in the slow-3 and slow-4 frequency bands within the bilateral motor cortex in all patients compared to healthy volunteers with the most robust effects observed in slow-3. We also observed significantly lower mAFF in the visual cortex in all patients compared to healthy volunteers within the slow-3 and slow-4 frequency bands that were most robust in slow-4 again consistent with the region-of-interest analyses. Moreover, Figure 3 demonstrates that these effects were also significant in first-episode and chronic patients when analyses were conducted separately by site. Based on the unthresholded T-stat maps, we also observed significant group differences in BOLD signal power. Specifically, patients demonstrate higher BOLD signal power in the anterior cortex in contrast to healthy volunteers who demonstrate higher BOLD signal power in the posterior cortex

Specifically, we assessed power in three distinct frequency bands including slow-4 (.027–.073 Hz), slow-3 (.074–0.198 Hz) and slow-2 (0.199–0.25 Hz), between patients with psychosis and healthy volunteers within 14 resting state networks. We observed a significant group $\times$ frequency interaction for the visual and motor cortical networks, with the most robust group differences (patients < healthy volunteers) as assessed from effect size measures in slow-4 and slow-3, respectively. Moreover, healthy volunteers and patients were significantly different in the visual cortex, dorsal attention and motor cortex networks such that healthy volunteers had higher mAFF compared to patients across the three frequency bands with opposite effects (patients > controls) observed within the salience and frontal gyrus networks. Our findings also support the hypothesis that the interaction and main effects observed across the total sample are evident in both first-episode and chronic patients with psychosis and expand prior findings to the investigation of higher frequency bands. Strengths of the current study include the use of large cohorts, stringent motion criteria and investigation of higher frequency BOLD fluctuations not examined in prior work.

We identified lower rsfMRI power across the three frequency bands in visual cortex, dorsal attention and motor cortex networks in patients compared to healthy volunteers, but the opposite pattern (patients > controls) in the salience and frontal gyrus networks. The identification of lower visual cortex activity and higher frontal cortex activity across frequency bands was particularly robust in the current study and in both first-episode and chronic patients as well as across sites. Our findings converge strongly with prior work. Specifically, Hoptman et al. (2010) and Meda et al. (2015) both reported lower ALFF in patients with psychosis compared to healthy volunteers in occipital regions within slow-4 and/or slow-5. In addition, Turner et al. (2013) reported that patients demonstrated higher rsfMRI low frequency power in frontal cortical regions, but less power in posterior regions than healthy volunteers, albeit in narrower frequency bands (.01–.08 Hz) compared to the current study. Our results are partly consistent with those from Huang et al. (2010) who reported lower

4 | DISCUSSION

The results of this study provide new evidence regarding the differential role of frequency band in rsfMRI abnormalities in psychosis.

FIGURE 3 Significant differences in mAFF across frequency bands using Voxelwise analysis [Color figure can be viewed at wileyonlinelibrary.com]

power of bold signal fluctuations in the low-frequency range in patients with schizophrenia compared to healthy controls in posterior brain regions. Conversely, our results also contradict some of the findings of Huang et al. (2010) who reported, lower ALFF within the range of .01–.08 Hz in the medial prefrontal region and Lui et al. (2010) who reported lower ALFF in ventral medial frontal regions in antipsychotic drug-naïve patients with first-episode schizophrenia. These observed differences may be due, in part, to different data processing methods. For example, in the current study we implemented a linear regression model to better characterize and reduce effects of physiological noise from the data whereas both Lui et al. (2010) and Huang et al. (2010) did not utilize approaches such as CompCorr (Behzadi et al., 2005).

In contrast to the current findings, He et al. (2013) reported lower fALFF in the medial prefrontal and orbital frontal cortex in patients compared to healthy volunteers. It should be acknowledged, however, that the current study analyzed the amplitude of frequency fluctuations in three distinct frequency bands, while the fALFF measure used by He et al. was derived by taking ratios of power in the low-frequency band (.01–.08 ~slow4 [.028–.073]) to the overall frequency band (slow-2, slow-3 and slow-4). Thus, lower fALFF in psychosis observed by He et al. could be attributed to either lower amplitude in low-frequency bands (.01–0.1 Hz ~slow-4) or higher amplitude in the high frequency bands (>0.1 Hz ~slow-2 + slow-3). In our prior work,

we have shown that various frequency bands contribute differing amounts of power to known resting state networks (Gohel & Biswal, 2014). Specifically, the combination of slow-2 and slow-3 frequency bands represents a similar amount of power as slow-4 in the default mode network, salience network and visual network. Thus, a direct comparison between higher mAFF observed in the frontal cortex of the brain in the current study and decreased fALFF observed by He et al. is not possible. Further studies that cover the whole frequency band of slow fluctuations (0–1.2 Hz) are required to study how greater mAFF in one frequency band can affect fAFF values across the brain.

The identification of lower rsfMRI activity in the visual cortex and higher rsfMRI activity in the frontal cortex has now been reported in multiple studies and across different frequency ranges (Hoptman et al., 2010; Turner et al., 2013) and, thus, appears to be a relatively robust finding in the literature. Similarly, Anticevic et al. (2012) reported higher rsfMRI activity in the prefrontal cortex in early course schizophrenia, which predicted symptom severity. In addition, using the amplitude of low-frequency fluctuation Zou et al. (2015) reported that frontal regions predicted working memory task activation and deactivation, which was most pronounced at the highest working memory loads suggesting that intrinsic prefrontal rsfMRI activity can predict “efficiency” of brain functioning. The identification of rsfMRI

abnormalities in occipital regions in patients with schizophrenia is consistent with reports of visual processing deficits regarding impaired contrast sensitivity (Butler et al., 2005) identification of visual contours (Feigenson, Keane, Roché, & Silverstein, 2014), motion perception (Jahshan, Wynn, Mathis, & Green, 2015), smooth pursuit eye movements (Franco, de Pablo, Gaviria, Sepulveda, & Vilella, 2014) as well as early stage visual-processing deficits that are linked to higher level cognitive disruptions (Butler et al., 2005). Moreover, abnormalities in occipital regions were observed using voxel-mirrored homotopic connectivity rsfMRI analysis in patients with schizophrenia compared to healthy volunteers (Hoptman et al., 2012) and disturbances in rsfMRI activity within primary sensory areas could have potential downstream effects including visual hallucinations (Ford et al., 2015). Similarly, Butler et al. (2006) have also reported significant effects of subcortical visual dysfunction in relationship to other cognitive impairments in schizophrenia. It should also be noted that integrated dysfunction between frontal and occipital pathways has been reported in the neurobiology of psychosis (Calderone et al., 2013; Khadka et al., 2014), which have also been linked to positive symptoms among individuals with nonclinical psychosis (Orr, Turner, & Mittal, 2014).

Few studies to date have investigated possible interaction effects between frequency bands in the range of .01 to .1 Hz using rsfMRI in psychosis and thus, it is difficult to compare our findings with prior work. In the study by Yu et al. (2014) rsfMRI activity was assessed in three different frequency bands including slow-5 (.01–.027 Hz), slow-4 (.027–.08 Hz) and the standard band of .01–.08 Hz with significant interactions of region-by-frequency band. Specifically, these authors reported significantly higher ALFF in the slow 4 band compared to the slow 5 band in the cingulate cortex, fusiform gyrus, basal ganglia and midbrain regions. In contrast, they observed higher ALFF in slow 5 (compared to slow 4) in the lingual gyrus, middle temporal gyrus, inferior frontal gyrus and ventromedial frontal gyrus. It is also noteworthy that in the current study, we also identified significant main effects of frequency for the dorsal attention and motor networks such that slow 4 was significantly higher than slow 3, which, in turn, was significantly higher than slow 2. To our knowledge such a “gradient effect” of decreased power from lower to higher frequencies has not been reported previously in the literature. Higher power in lower bands compared to higher bands could conceivably be related to differential energy consumption among brain regions, although further studies using a higher sampling rate are required to study a wider frequency distribution.

There were a number of study limitations that should be acknowledged that preclude firm conclusions. We did not examine functional integration among brain regions across frequency bands. Differential patterns of the amplitude of frequency fluctuations across brain regions imply differences in the frequency of neuronal fluctuations across regions that may give rise to disruptions in functional integration among brain regions. In addition, we combined data across two sites and thus vendor differences as well as task instructions (Zou et al., 2015) could conceivably affect study findings. We did, however, include site as a covariate in the analyses and additionally conducted analyses separately by site. It should also be acknowledged that in the current study we did not include the frequency bands slow-1 (0.5–1.2 Hz) and slow-5 (.01–.027 Hz), given our inability to examine frequencies higher than 0.25 HZ (TR-2 s, sampling frequency-0.5 Hz)

and to effectively remove slow scanner drift that may resemble slow-5 frequency band fluctuations. In addition, there is the possibility that antipsychotic medications may have influenced the observed findings; however, it should be acknowledged that results were comparable in both first-episode and chronic patients.

In sum, our study highlights the importance of considering BOLD signal fluctuations within different frequency ranges in neuroimaging studies of psychosis. Moreover, findings of differential rsfMRI effects within frontal and occipital regions in patients with psychosis versus healthy volunteers converge with prior findings and appear to be a replicable finding in the literature that warrants further investigation.

ORCID

Suril Gohel <http://orcid.org/0000-0003-2387-5021>

Bharat Biswal <http://orcid.org/0000-0002-3710-3500>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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