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Spontaneous Brain Activity Alterations in First-Episode Psychosis: A Meta-analysis of Functional Magnetic Resonance Imaging Studies

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***Background and Hypothesis*: Several studies have shown that spontaneous brain activity, including the total and fractional amplitude of low-frequency fluctuations (LFF) and regional homogeneity (ReHo), is altered in psychosis. Nonetheless, neuroimaging results show a high heterogeneity. For this reason, we gathered the extant literature on spontaneous brain activity in first-episode psychosis (FEP), where the effects of long-term treatment and chronic disease are minimal. *Study Design*: A systematic research was conducted on PubMed, Scopus, and Web of Science to identify studies exploring spontaneous brain activity and local connectivity in FEP estimated using functional magnetic resonance imaging. 20 LFF and 15 ReHo studies were included. Coordinate-Based Activation Likelihood Estimation Meta-Analyses stratified by brain measures, age (adolescent vs adult), and drug-naïve status were performed to identify spatially-convergent alterations in spontaneous brain activity in FEP. *Study Results*: We found a significant increase in LFF in FEP compared to healthy controls (HC) in the right striatum and in ReHo in the left striatum. When pooling together all studies on LFF and ReHo, spontaneous brain activity was increased in the bilateral striatum and superior and middle frontal gyri and decreased in the right precentral gyrus and the right inferior frontal gyrus compared to HC. These results were also replicated in the adult and drug-naïve samples. *Conclusions*: Abnormalities in the frontostriatal circuit are present in early psychosis independently of treatment status. Our findings support the view that altered frontostriatal can represent a core neural alteration of the disorder and could be a target of treatment.**

Key words: resting-state functional connectivity/resting-state functional magnetic resonance imaging/amplitude of low-frequency fluctuations/fractional amplitude of low-frequency fluctuations/regional homogeneity/psychosis

Introduction

Psychosis is a severe psychiatric syndrome that often arises in late adolescence/early adulthood and has a large impact on patient's quality of life.[1,2] Among several pathophysiological theories, an intriguing hypothesis suggests that psychosis may derive from altered spontaneous brain activity in different areas of the brain.[3] Spontaneous brain activity refers to neuronal activity that occurs without external stimuli or specific task demands.[4] Importantly, in vitro studies have demonstrated that neurons have ionic conductances that are responsible for their excitability and provide them with autorhythmic electrical oscillatory properties that generate synchronous firing in large groups of neurons, referred to as networks.[5] It has been suggested that these autorhythmic properties of neurons form the basis for an intrinsic spontaneous functional brain system that provides internal context to sensory input and contributes to basic functional states, including consciousness and attention.[5]

Resting-state functional magnetic resonance imaging (rs-fMRI) has been widely used to explore intrinsic spontaneous brain activity and functional connectivity (FC) in patients with psychosis in different stages of illness, describing differences at the regional level as well as in large-scale networks.[6,7] In particular, rs-fMRI allows the estimation of several functional metrics of the brain, including the amplitude of low-frequency fluctuations (ALFF) and the fractional amplitude of low-frequency fluctuations (fALFF), measures that are capable of detecting the magnitude of spontaneous fluctuations in the blood oxygen level-dependent signal (BOLD) at the voxel-level, which reflects spontaneous neural activity.[8] To calculate the ALFF, the time series for each voxel is band-pass filtered to select the frequencies between 0.01 and 0.08 Hz. Then, a fast Fourier transform, which returns the power

spectrum in the frequency domain, is applied. Finally, ALFF is calculated as the average square root of the power spectral density of the low-frequency filtered time series.[9] Differently, fALFF represents the relative contribution of these fluctuations to the entire frequency band.[10,11] Interestingly, Biswal and colleagues[12] observed that LFFs in the resting brain were higher in gray matter than in white matter. Subsequent research showed that the fMRI BOLD signal was correlated with local field potentials (LFP), a measure that reflects the subthreshold signals generated from integrated electrical activity in pre- and post-synaptic terminals in the brain.[13–15] In particular, Logothetis and colleagues[14] pioneered the simultaneous study of LFP and fMRI data in primates, showing that LFPs were correlated with the BOLD response. Importantly, spontaneous fluctuations in the BOLD signal have been shown to correlate with LFP activity in the range of slow cortical potentials.[16] Converging evidence from investigations on brain intra- and extra-cellular calcium, potassium, and chlorine concentrations suggests that the dynamics of ion concentration mediated by neuronal and glial activity can produce very slow spontaneous fluctuations of the BOLD signal.[17] Moreover, studies in minimally conscious individuals have reported fMRI signal variations in primary sensory cortices in anesthetized children due to LFF at approximately 0.034 Hz using the power spectrum method, indicating that ALFF could be suggestive of regional spontaneous neuronal activity in this population.[18] Similarly, fMRI data from studies in squirrel monkeys at different dosages of anesthetic drugs displayed that increasing levels of anesthesia resulted in diminishing amplitudes of signal fluctuations and reduced power of fluctuations in the low-frequency band.[19] Furthermore, in recent years, several studies have demonstrated that ALFF and fALFF relate to large-scale neural synchronization and reflect cerebral physiological states.[20–22]

In addition, local FC can be explored with Regional Homogeneity (ReHo), which is considered to reflect the regulation and coordination of local neuronal activity (see below).[23] ReHo is defined as Kendall's coefficient concordance (KCC) between the time series of a voxel and its nearest neighbors. KCC is a statistic that accounts for the overall concordance of a group of time series, scoring from 0 (no concordance) to 1 (perfect concordance). This can be calculated between a voxel and his face-wise neighbors (7 voxels), his face- and edge-wise neighbors (19 voxels), or his face-, edge-, and node-wise neighbors (27 voxels).[23,24] Some more sophisticated applications of ReHo include: 2dReHo, a 2-dimensional variant in which preprocessed fMRI data are projected onto vertices of the cortical surface, then the KCC is calculated between a vertex and its nearest neighbors[25,26]; Cohe-ReHo, a technique which measures synchronization in the frequency domain and does not rely on KCC calculation.[27] Interestingly, ALFF and ReHo have been found to have a strong positive relationship, suggesting that spontaneous neural activity in a voxel is accompanied by an increase in synchronization with the neighboring voxels and amplitude fluctuations of the BOLD signal.[28,29] In addition, since a large body of research has shown that local measures of brain activity (ie, LFF and ReHo) have adequate test-retest reliability, as well as substantial reproducibility in the gray matter compared to global measures of brain connectivity,[30] independent of the physiological correction method and sampling rate, we decided to limit our meta-analysis to the former measures that can be considered reliable biomarkers to explore changes in brain intrinsic activity associated with brain disorders.[25,31–33]

Rs-FC in chronic psychosis was consistently found to be reduced within the prefrontal cortex (PFC) and between the thalamus and the PFC, while increased between the thalamus and the somatosensory areas.[34,35] Moreover, numerous studies have shown FC alterations in the executive network (EXE), a brain network with central hubs in the prefrontal and posterior parietal cortex associated with high-level cognitive functions, including attention control, working memory, and executive task performance.[35–38] Meta-analytic evidence on intrinsic regional brain activity in first-episode and chronic schizophrenia (SCZ) showed a decrease in ALFF in the default mode network (DMN), the sensorimotor network (SMN), and the visual network (VIS) regions, and an increase in the putamen, salience network (SAL), and frontotemporal regions.[39] Moreover, a meta-analysis on spontaneous brain activity in SCZ at different stages of the disorder, demonstrated a decrease in ALFF/fALFF and ReHo in SCZ in the somatosensory cortex, posterior parietal cortex, and occipital cortex, as well as increased ALFF/fALFF and ReHo in the bilateral striatum, medial temporal cortex, and medial PFC.[7]

These alterations in spontaneous neural activity in chronic psychosis could be associated with several factors, including abnormal neurodevelopmental pathways,[40,41] childhood trauma,[42] and dopamine dysfunction.[43] Moreover, abnormalities in FC appear to be also related to the neuromodulatory effects of drugs, particularly antipsychotic medications,[44,45] tobacco,[46] and substances.[47] Therefore, the study of neural activity in patients with first-episode psychosis (FEP) presents several advantages compared to chronic patients, since FEP manifest psychotic symptoms and are often drug-naïve or minimally exposed to medications.[48,49] Moreover, FEP is marginally affected by disease progression, which could also affect neural activity.[50,51] Notably, several studies investigating FC in FEP observed significant alterations.[6,52–57] Specifically, much evidence confirms a dysconnectivity between cortical and subcortical structures, the striatum, in particular,[6,36,52,56–59] which is consistent with the major biological hypotheses of the pathogenesis of psychosis, all including striatal dysfunction as a major feature.[60]

A recent meta-analysis of seed-based studies showed widespread resting-state FC abnormalities in FEP in regions including the dorsolateral prefrontal cortex, the

superior and middle frontal gyrus, the cerebellum, and the striatum.[61] Another meta-analysis investigated the ALFF in the cerebellum, describing a reduction in the subregions connected both with the motor/premotor cortex and with PFC in drug-naïve FEP,[62] consistently with other findings linking cerebellar structural and functional alterations to cognitive and motor dysfunction in SCZ.[63–65] Interestingly, the authors observed that patients with a longer duration of the disease showed decreased ALFF in the right cerebellar Crus I compared to patients with a shorter duration of the disease, and patients with higher PANSS negative scores presented attenuated ALFF in the right cerebellar Crus I and right cerebellar lobule in comparison with patients with lower PANSS negative scores.[62]

In this paper, we collected all available studies on spontaneous brain activity changes in FEP. On the one hand, ReHo is sensitive to regional variability in the time domain, whereas ALFF and fALFF measure voxel-wise changes in the frequency domain. Crucially, a growing number of studies in healthy and psychiatric individuals have shown that these measures are largely correlated and are complementary in measuring local spontaneous activity.[28,66–72] Importantly, a recent investigation has demonstrated that fALFF and ReHo are both capable of detecting BOLD signal changes in the low-frequency domain (0.01–0.1 Hz) with high correlation.[73] Thus, to gain a complete understanding of the pathophysiology of FEP, we decided to: first, perform a meta-analysis of ALFF/fALFF and ReHo studies separately to identify modality-specific changes; second, in accordance with previous meta-analyses,[74–76] to identify the overall changes of spontaneous neural activity, we combined these complementary measures,[28,29,70] and performed a meta-analysis of ALFF/fALFF and ReHo studies together. We hypothesized that abnormal spontaneous neural activity would be altered within large-scale networks spanning prefrontal and striatal regions involved in mediating higher cognitive and affective functions.

Materials and Methods

Article Selection and Classification

We conducted a systematic research on PubMed, Scopus, and Web of Science of the literature published before January 2022 without any language restriction, following the Meta-analysis of Observational Studies in Epidemiology guidelines (MOOSE).[77] A combination of the following keywords was used: (psychotic disorders OR psychotic OR psychosis OR schizophrenia) AND (first-episode OR first episode) AND (fMRI OR MRI, functional OR functional MRI OR functional MRIs OR MRIs, functional) AND (connectivity OR resting state OR resting-state OR ALFF OR fALFF OR ReHo). The reference lists of relevant reviews and meta-analyses were then checked for additional relevant studies. The initial search resulted in 802 articles. After removing duplicates and reviewing the abstracts and inclusion criteria of the participants of these articles, 53 papers were selected for full-text reading. When full-text articles were not available, direct contact was made with the authors.

We included the papers that met the following criteria: (a) original peer-reviewed papers; (b) patients met standardized diagnostic criteria (DSM, ICD) for schizophrenia spectrum psychoses (schizophrenia, schizoaffective, and schizophreniform disorders) and affective psychoses (bipolar disorder and major depression with psychotic features); (c) it was explicitly reported that patients had a duration of illness ≤5 years; (d) Talairach (TAL) or Montreal Neurological Institute (MNI) peak effect coordinates of significant differences between FEP and HC were reported. Studies were excluded if: (a) they did not investigate spontaneous brain activity using ALFF, fALFF, or ReHo techniques; (b) they used ROI analyses; (c) peak coordinates were not available even after contacting the authors. A total of 35 studies were selected (see figure 1 for the selection process).

Since the articles by Jiang et al,[26] Cui et al,[59] Li et al,[78] and Fang et al[79] reported data from two or more cohorts, they were treated as independent studies for meta-analytic purposes; furthermore, the articles reporting multiple measures were considered as two different studies for ReHo and for ALFF/fALFF analyses, respectively.[59,79–81]

We also stratified the meta-analysis for age: if both samples in a study had a mean age ≤ 18 years, the population was classified as adolescent FEP, otherwise it was classified as adult FEP. None of the studies reported details of the familiar psychiatric history.

All studies were evaluated with the Imaging Methodology Quality Assessment Checklist (adapted from Strakowski et al[82]) (see Supplementary Material).

Data Extraction

Information including the peak coordinates of each significant effect between groups, as well as additional study-specific information, was extracted from each study.

Coordinate-Based Meta-Analyses (CBMA)

First, we performed a meta-analysis for the ALFF/fALFF and ReHo studies separately. Then, we performed a global meta-analysis merging all rs-fMRI studies. Third, to reduce heterogeneity, we rerun global CBMAs focusing on a specific age group (Adult FEP ALFF/fALFF n = 12, Adolescent FEP ALFF/fALFF n = 3; Adult FEP ReHo n = 10, Adolescent FEP ReHo n = 5). In addition, to unravel the effects of antipsychotics on spontaneous brain activity, we repeated the meta-analyses including only those studies that explored ALFF/fALFF and ReHo in antipsychotic-naïve FEP.

CBMA analyses were computed with the revised Activation Likelihood Estimation (ALE) algorithm[83,84] using GingerALE software (GingerALE 3.0.2, http://www.brainmap.org/ale/). The coordinates of all significant peaks for each eligible contrast (FEP > HC and/or FEP < HC)

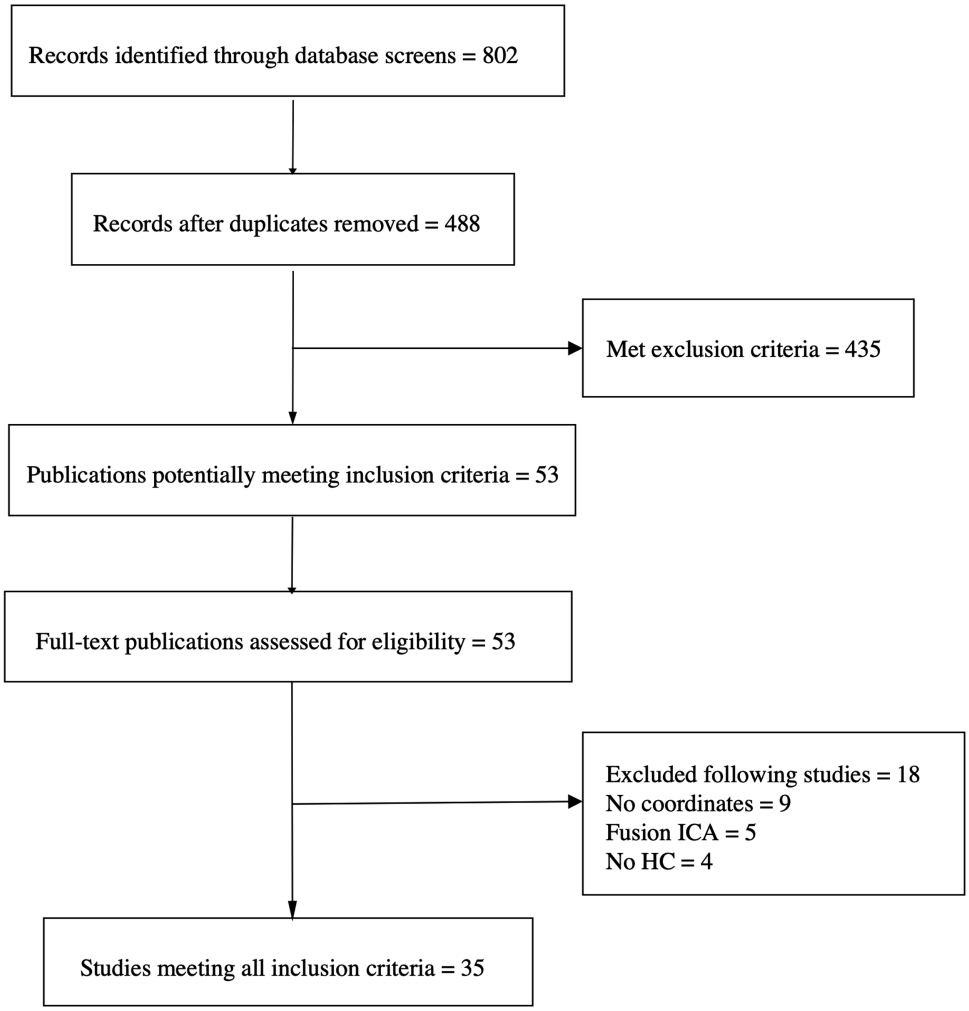

Fig. 1. PRISMA flowchart for the meta-analysis of imaging articles in FEP. Each selected article could include multiple volumetric measures that were considered individual studies. Therefore, the sum of the studies is greater than the selected articles.

were used as input for the CBMAs. Analyses were performed in the Montreal Neurological Institute (MNI) reference space; when coordinated were expressed in Talairach space, they were converted to MNI.[85] Significance was assessed using a cluster-level P(FWE) = .05 thresholding with a cluster forming threshold of $P = .001$ for $n \geq 17$ studies and a voxel-level P(FWE) = .05 thresholding for $8 \leq n < 17$ studies, respectively[86,87] (see Supplementary Material). To assess the effect of negative studies, we simulated the effects of including them in our meta-analyses by adding randomly created noise studies as in Acar et al[88] (see Supplementary Material). MRIcron was used to display brain images.

Results

Characteristics of the Studies

Overall, 20 studies reporting differences in ALFF/fALFF (15 ALFF, 5 fALFF) between FEP and HC, and 15 studies showing a difference in ReHo values were included. Of these studies, three ALFF and five ReHo studies were performed in adolescent FEP. The mean age was 21.1 (4.7) years for FEP and 21.9 (4.5) years for HC, respectively.

The mean duration of psychosis was 9.41 (8.8) months. Within the 15 ReHo studies, 13 were performed in a drug-naïve sample. In the study by Yang et al,[89] at the recruitment, 21 of 22 patients were receiving medications, which they stopped 72 hours before the scan, whereas Zhao et al[80] included patients with a cumulative duration of antipsychotic treatment shorter than 12 weeks and medications were stopped 24 hours before the scan. A total of 18 ALFF/fALFF investigations focused on drug-naïve FEP, while Tang et al[90] and Zhao et al[80] included medicated subjects. Sociodemographic details of the participants of the included studies are reported in tables 1 and 2.

CBMA in the Overall Sample

ALFF/fALFF. We found a significant increase in ALFF/fALFF in FEP compared to HC in the right striatum [peak coordinates (x,y,z) = 20,12,4].

Table 1. ALFF/fALFF Studies of FEP: Study Characteristics

Study (First author)	Year	Antipsychotic treatment	Patients			Healthy controls			Quality score
			n	% *F*	Age (ys) m (SD)	*n*	% *F*	Age (ys) m (SD)	
Children									
Li	2020	Naïve	72	66.67	14.7 (1.78)	79	58.23	14.3 (2.17)	7
Liang	2019	Naïve	30	63.33	13.0 (1.4)	30	53.33	12.9 (1.4)	8
Zheng	2016	Naïve	35	42.86	15.50 (1.76)	30	56.67	15.43 (1.54)	9
Adults									
Cui	2016	Naïve	17	41.18	21.24 (3.85)	19	47.37	23.79 (3.75)	9
Cui	2016	Naïve	15	46.67	22.53 (4.07)	19	47.37	23.79 (3.75)	9
Fang	2021	Naïve	35	40.00	22.26 (5.25)	34	32.35	21.35 (2.94)	10
Fang	2021	Naïve	34	14.71	22.68 (4.66)	34	32.35	21.35 (2.94)	10
He	2013	Naïve	115	53.91	25.36 (8.26)	113	49.56	26.61 (8.90)	10
Hu	2016	Naïve	42	35.71	24.86 (4.80)	38	34.21	24.76 (4.56)	10
Huang	2010	Naïve	66	54.55	24.2 (8.4)	66	54.55	24.5 (8.6)	9
Lei	2015	Naïve	124	50.81	24.47 (6.67)	102	50.98	24.75 (6.83)	10
Li	2017	Naïve	41	43.90	23.32 (6.94)	42	42.86	23.29 (7.33)	9
Li	2017	Naïve	42	40.48	22.86 (6.70)	42	42.86	23.29 (7.33)	9
Li	2016	Naïve	20	70.00	22.9 (8.5)	16	56.25	22.4 (4.4)	9.5
Lian	2018	Naïve	18	55.56	20.44 (2.99)	30	46.67	20.53 (2.10)	8
Lui	2010	Naïve	34	61.76	24.6 (8.5)	34	61.76	25.0 (8.0)	9
Ren	2013	Naïve	100	59.00	24.30 (7.45)	100	59.00	24.39 (7.58)	9.5
Tang	2019	23/42 medicated	42	50.00	19.0 (4.0)	59	54.24	20.9 (4.0)	9
Yin	2021	Naïve	30	56.67	19.8 (3.1)	30	56.67	20.8 (2.7)	9.5
Zhao	2018	< 12 weeks, stop ≥ 24 h	58	53.45	20.4 (3.3)	39	51.28	22.2 (4.6)	9.5

Note: The quality score was assessed using the Imaging Methodology Quality Assessment Checklist.
FEP, first-episode psychosis; F, female; M, mean; SD, standard deviation; ys, years; NR, not reported.

Table 2. ReHo Studies of FEP: Study Characteristics

Study (First author)	Year	Antipsychotic treatment	FEP patients			Healthy controls			Quality score
			n	% *F*	Age (ys) m (SD)	*n*	% *F*	Age (ys) m (SD)	/10
Children									
Jiang	2015	Naïve	26	50.00	14.51 (1.94)	25	52.00	14.37 (2.97)	9.5
Liu	2018	Naïve	48	56.25	15.79 (1.64)	31	54.84	15.42 (1.52)	9.5
Lyu	2021	Naïve	32	53.13	16.75 (1.22)	27	62.96	16.40 (2.12)	9
Wang	2018	Naïve	48	56.25	15.79 (1.64)	31	54.84	15.42 (1.52)	9.5
Xia	2019	Naïve	32	62.50	13.72 (2.20)	33	60.61	13.15 (2.02)	9
Adults									
Cui	2016	Naïve	17	41.18	21.24 (3.85)	19	47.37	23.79 (3.75)	9
Cui	2016	Naïve	15	46.67	22.53 (4.07)	19	47.37	23.79 (3.75)	9
Fang	2021	Naïve	35	40.00	22.26 (5.25)	34	32.35	21.35 (2.94)	10
Fang	2021	Naïve	34	14.71	22.68 (4.66)	34	32.35	21.35 (2.94)	10
Jiang	2015	Naïve	20	55.00	26.40 (8.01)	17	52.94	30.29(11.01)	9
Yan	2020	Naïve	69	27.54	24.22 (7.08)	74	39.19	26.27 (6.97)	9
Yang	2021	Stop ≥ 72 h	17	17.65	31.07 (8.98)	30	20.00	34.60(10.05)	9.5
Yin	2021	Naive	30	56.67	19.8 (3.1)	30	56.67	20.8 (2.7)	9.5
Zhao	2018	< 12 weeks, stop ≥ 24 h	58	53.45	20.4 (3.3)	39	51.28	22.2 (4.6)	9.5
Zhao	2018	Naïve	44	29.55	23.7 (5.3)	26	34.62	22.6 (3.7)	9

Note: The quality score was assessed using the Imaging Methodology Quality Assessment Checklist.
FEP, first-episode psychosis; F, female; M, mean; SD, standard deviation; ys, years; NR, not reported.

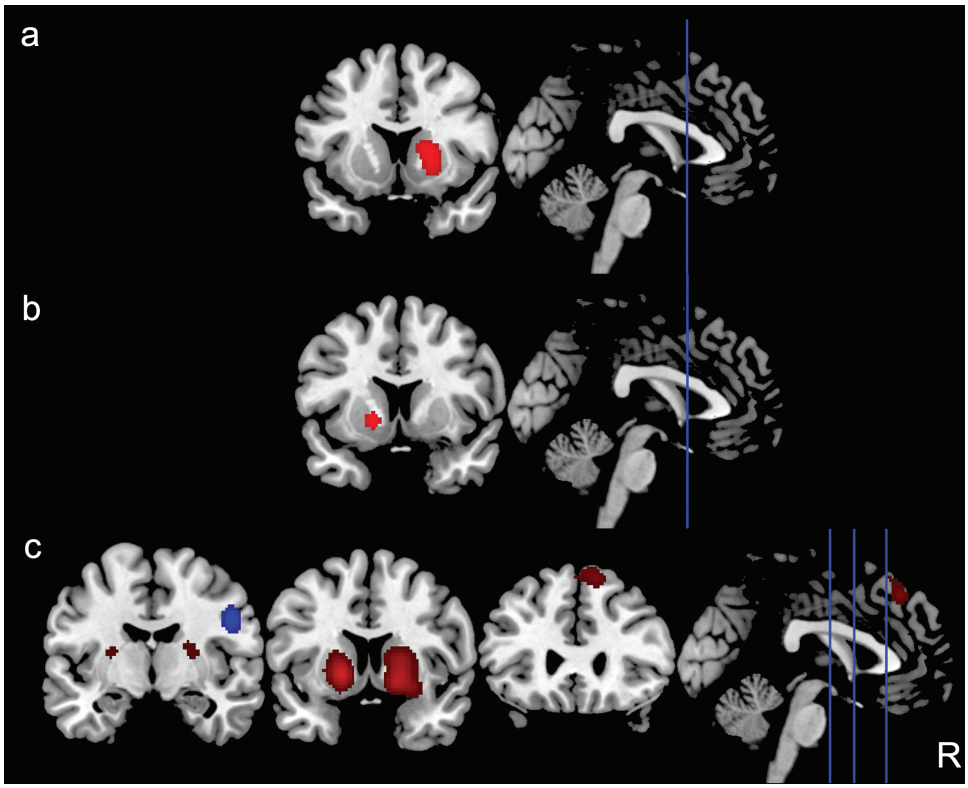

Fig. 2. CBMA of intrinsic activity alterations in FEP compared to HC. (a) ALFF/fALFF; (b) ReHo; (c) all measures. Increased intrinsic activity in FEP compared to HC is shown in red and blue (light grey and dark grey in black and white printed copy), respectively. All images are thresholded with $P < .005$, and a spatial extent of 10 voxels. R, right.

ReHo. FEP compared to HC presented higher ReHo in the left striatum [peak coordinates $(x,y,z) = -16,10,-4$].

All Measures. A significant increase in ALFF/fALFF and ReHo was observed in FEP compared to HC in the right striatum [peak coordinates $(x,y,z) = 18,14,0$], in the left striatum [peak coordinates $(x,y,z) = -16,10,-2$], and bilateral superior frontal gyrus/middle frontal gyrus (SFG/MFG) [peak coordinates $(x,y,z) = -4,36,46$]. We also observed a decrease in spontaneous brain activity in the right precentral gyrus and the right inferior frontal gyrus (IFG) [peak coordinates $(x,y,z) = 50,-4,30$] (figure 2, Supplementary tables S.4–S.6). These results did not change when only one measure per study was included in those articles reporting multiple measures for the same sample and when we included only the studies that used a correction for multiple comparisons.

CBMA in Adult FEP

ALFF/fALFF. FEP had higher ALFF/fALFF compared to HC in the right striatum [peak coordinates $(x,y,z) = 22,12,-6$].

ReHo. We observed a significant increase in ReHo in FEP compared to HC in the left striatum [peak coordinates $(x,y,z) = -16,10,-4$].

All measures. A significant increase in ALFF/fALFF and ReHo in FEP compared to HC was observed in the right striatum [peak coordinates $(x,y,z) = 18,14,-2$], the left striatum [peak coordinates $(x,y,z) = -18,12,-2$], and the left SFG/MFG [peak coordinates $(x,y,z) = -4,36,46$]. In addition, we observed a decrease of the spontaneous brain activity in the right inferior and superior parietal lobule (IPL/SPL) [peak coordinates $(x,y,z) = 46,-54,48$] and in a cluster including the left SFG, MFG, orbitofrontal gyrus, and anterior cingulate (ACC) [peak coordinates $(x,y,z) = -8,52,-26$] (figure 3, Supplementary tables S.4–S.6).

CBMA in Drug-naïve FEP

ALFF/fALFF. The ALFF/fALFF values were higher in FEP compared to HC in the right striatum [peak coordinates $(x,y,z) = 22,12,2$].

ReHo. Exploratory analyses on seven studies revealed a significant reduction in ReHo in FEP compared to HC in the right precentral gyrus and IFG [peak coordinates $(x,y,z) = 50,-4,30$], in the right supramarginal gyrus [peak coordinates $(x,y,z) = 33,-39,42$], and in the left precentral gyrus [peak coordinates $(x,y,z) = -14,-24,72$].

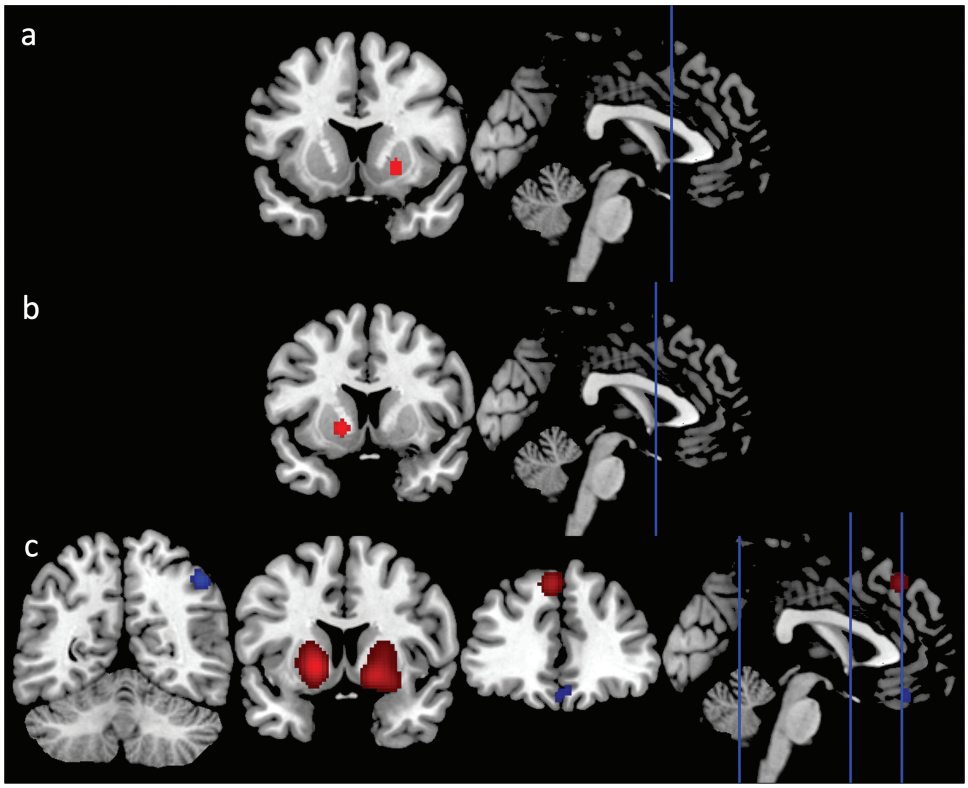

Fig. 3. CBMA of intrinsic activity alterations in adult FEP compared to HC. (a) ALFF/fALFF; (b) ReHo; (c) all measures. Increased intrinsic activity in adult FEP compared to HC is shown in red and blue (light grey and dark grey in black and white printed copy), respectively. All images are thresholded with $P < .005$, and a spatial extent of 10 voxels. R, right.

All Measures. We found a significant increase in ALFF/fALFF and ReHo in FEP compared to HC in the right striatum [peak coordinates $(x,y,z) = 18,14,-2$], in the left striatum [peak coordinates $(x,y,z) = -18,12,-2$], and bilateral SFG/MFG [peak coordinates $(x,y,z) = 12,26,58$]. Moreover, we observed a decrease in ALFF/fALFF and ReHo in the right precentral gyrus and IFG [peak coordinates $(x,y,z) = 50,-4,30$] (figure 4, Supplementary tables S.4–S.6).

Discussion

In this meta-analysis, we collected all available evidence on altered spontaneous brain activity in FEP measured using ALFF, fALFF, and ReHo measures. Two main results emerged: (a) FEP presented increased spontaneous neural activity in the striatum and specifically increased ALFF/fALFF in the left and ReHo in the right striatum, respectively; when combining complementary information from all measures of spontaneous neural activity, this was increased in FEP in the bilateral striatum, bilateral SFG/MFG and decreased in the right precentral gyrus and IFG, respectively; (b) the results were replicated in the sample of drug-naïve patients.

The studies included in this meta-analysis consistently showed an increase in bilateral striatal spontaneous neural activity in FEP. As consistently reported by the literature, the striatum plays a central role in several high-order functions, including reward anticipation,[91] cognitive and emotion processing, goal-directed behaviors,[92] sensorimotor function, habitual behaviors, and regulation of impulsivity.[77,78] In both SCZ and in FEP, abnormalities have been commonly described in the ventral and dorsal striatum.[59,79–81] In FEP, altered FC was observed between the dorsal caudate and the primary motor cortex, as well as between the ventral rostral putamen and the right temporal occipital fusiform cortex, and the dorsal rostral putamen and the anterior cingulate cortex. Notably, these abnormalities were found to predict an improvement in negative symptoms and general functioning.[56] Additionally, a recent study employing the independent component analysis to explore FC between brain networks revealed significant abnormalities within the caudate nucleus in FEP compared to HC.[93] Another investigation implicated altered ALFF within the caudate nucleus in FEP and reported that an increase in LFF in this area may be associated with successful antipsychotic treatment.[94] Increased striatal activity and local connectivity at rest can reflect endogenous overactivity of the striatal dopamine system (see below).[95,96] Interestingly, the increase in spontaneous striatal activity in FEP was also replicated in the drug-naïve sample, suggesting that resting-state activity of the brain was not influenced by antipsychotic treatment.

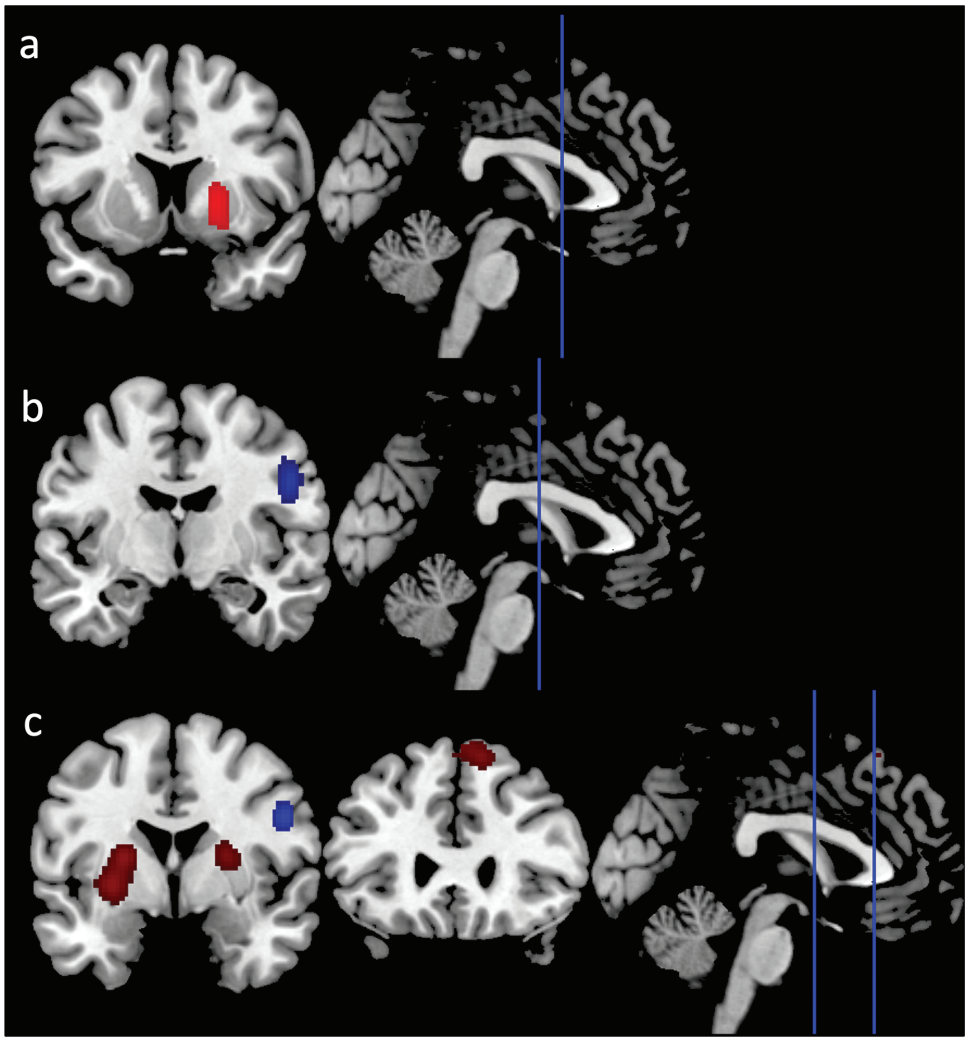

Fig. 4. CBMA of intrinsic activity alterations in drug-naïve FEP compared with HC. (a) ALFF/fALFF; (b) ReHo; (c) all measures. Increased and intrinsic activity in drug-naïve FEP compared to HC is shown in red and blue (light grey and dark grey in printed copy), respectively. All images are thresholded with $P < .005$, and a spatial extent of 10 voxels. R, right.

We also observed greater spontaneous neural activity in FEP in bilateral SFG and MFG, along with a reduction in the right precentral gyrus and IFG. Functional dysconnectivity of the frontostriatal network has long been implicated in the pathophysiology of psychosis.[97–99] Alterations in the frontostriatal circuit have been observed not only in SCZ[100] and in FEP,[101] but also in unaffected first-degree relatives of psychotic patients[101,102] and individuals at high risk for psychosis.[103] In addition, in FEP, the frontostriatal circuit appears to be affected by the duration of untreated psychosis[104] and it may be a biomarker for symptomatologic improvement associated with antipsychotic treatment.[105] Overall, our results support a dysfunction within the regions of the frontostriatal circuit that is intrinsic, not associated with drug treatment, and may contribute to the brain dysconnectivity that has been postulated in the pathophysiology of psychosis.

Similar to what we observed in the overall sample, adult FEP presented increased low-frequency oscillations and local connectivity in the striatum and in the SFG and MFG. Additionally, they also had a decrease in global spontaneous neural activity in the IPL/SPL and in a cluster that included the left SFG, MFG, orbitofrontal gyrus, and ACC. Our result of altered intrinsic activity within the SFG/MFG and the SPL is consistent with reports of reduced FC in fronto-parietal regions in patients with SCZ, in FEP, and in individuals with at-risk mental state during working-memory tasks[106,107] and at rest.[108] Notably, these abnormalities appear to be normalized by treatment with antipsychotic treatment.[106] In addition, a seed-based study in FEP showed altered FC between the frontal, parietal, and striatal regions, which was correlated with the duration of untreated psychosis.[109] Taken together, this evidence shows altered resting-state alterations in adult FEP in the fronto-parietal-striatal circuit.

Unfortunately, the studies conducted on adolescents were sparse, so we could only perform exploratory analyses. Overall, alterations in the striatum were also observed in the sample of adolescent FEP, suggesting that striatal abnormalities are present throughout the age spectrum in FEP. As Weinberger first postulated, the pathophysiological changes associated with SCZ can occur during early brain development, and subsequent brain maturation is involved in the clinical expression of the disorder.[110] In line with this theory, a large body of evidence has shown that SCZ is characterized by abnormal plastic processes within late-maturing association cortices subserving cognitive, emotive, and social functioning.[111–113] Consistently with these data, the results of our exploratory analyses in adolescent FEP suggest that changes in brain function that can be seen as early as in the first phases of adolescence could be involved in the development of the disorder, while alterations in higher-order late-maturing cortices, including the prefrontal cortex, could be implicated in the pathophysiology of clinical manifestations that appear later in life.

In general, our results can also be interpreted in light of the neurotransmitter hypothesis of psychosis. Early studies advanced the dopamine hypothesis of SCZ, suggesting that SCZ was characterized by an excess of dopamine levels in the striatum as a consequence of increased release from the ventral tegmental area (VTA).[97] To confirm this theory, numerous investigations have detected increased dopamine in the striatum in patients with SCZ,[98] FEP,[99] and in individuals at-risk for psychosis.[103] Interestingly, our findings of increased spontaneous brain activity in the bilateral striatum are in line with these studies.[95,96] Similarly, the PFC dysfunction was initially interpreted as a consequence of a reduction of dopamine levels arising from the brainstem, but many other explanations have been proposed since the relationship between cortical and striatal dysfunction remains unclear.[114] Notably, the striatum has been suggested to have an indirect effect on cortical activity via VTA, substantia nigra, and thalamus.[114,115] On the other hand, a reconceptualization of the dopamine hypothesis in the 1990s proposed that striatal hyperdopaminergia could be secondary to cortical hypodopaminergia.[116,117] More recently, the glutamatergic hypothesis suggested that striatal hyperdopaminergia could be secondary to cortical glutamate dysfunction. In particular, neurodevelopmental abnormalities could cause a hypofunction of NMDA receptors (NMDAR) in cortical GABAergic parvalbumin-positive interneurons.[118,119] Consequently, the glutamate release from a cortico-cortical pyramidal neuron is unable to efficiently stimulate these GABAergic neurons, which in turn fails to inhibit downstream cortico-brainstem pyramidal neurons, leading to excessive release of glutamate in VTA and consequently increased dopamine in the striatum.[116,119] A relative state of glutamatergic excess has been frequently reported in cortical and subcortical areas in psychosis, in particular in the medial PFC and the striatum, and appears to be specific to the early stages of the disorder and to predict greater symptom severity and poorer functioning at baseline.[120–123] Consistently, elevated glutamate concentrations in the ACC were found to be inversely correlated with striatal dopamine synthesis in FEP.[124] Notably, we observed an increase in ALFF/fALFF in FEP relative to HC in the right striatum, whereas ReHo was higher in the left striatum. Positron emission tomography studies have reported an asymmetry in cerebral dopamine neurotransmission, which was observed both in healthy individuals[125,126] and in antipsychotic-naïve SCZ patients.[127] Therefore, our results suggest that ALFF/fALFF and ReHo, which are distinct albeit complementary measures, could be differentially sensitive to dopamine neurotransmission, thus reflecting the underlying the lateralization of the dopamine system.

The results of this meta-analysis must be interpreted in light of some limitations. First, the fMRI studies presented significant methodological differences, including diagnostic criteria for FEP and different imaging acquisition and analysis pipelines, which limit the generalizability of our findings. However, we included only studies that compared FEP with HC so that the effects of these differences on the estimation of brain activity would be subtracted before entering the meta-analysis. Second, some of the patients were not treatment-naïve, and therefore previous drug treatments may have affected their neural activity. For this reason, we stratified by treatment and confirmed the main findings. Third, some studies presented a limited sample size, which could have led to publication or outcome reporting biases. Lastly, none of the included studies provided estimates of test–retest reliability of the fMRI measures, thus not allowing the calculation measurement errors. However, previous investigations showed that ALFF, fALFF, and ReHo presented good/excellent between-subject test-retest reliability and excellent within-subject between-region reliability.[30]

Conclusions

Our study provides robust evidence for spontaneous neural activity alterations in FEP.

To increase the transparency, traceability, and replicability of our results, we followed the current guidelines for conducting neuroimaging meta-analysis.[86,88] Abnormalities in the frontostriatal circuit seem to characterize early psychosis, both in medicated and antipsychotic-naïve subjects. The discovery of frontostriatal dysconnectivity in early psychosis is consistent with the view that this represents a core neural deficit of the illness. Future longitudinal studies aimed at identifying the prognostic meaning of changes in spontaneous neural activity will be important to predict the progression of FEP to full-blown psychiatric disorders to carry out personalized preventive treatments.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

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