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ARTICLE

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Frontal lobe fALFF measured from resting-state fMRI as a prognostic biomarker in first-episode psychosis

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Clinical response to antipsychotic drug treatment is highly variable, yet prognostic biomarkers are lacking. The goal of the present study was to test whether the fractional amplitude of low-frequency fluctuations (fALFF), as measured from baseline resting-state fMRI data, can serve as a potential biomarker of treatment response to antipsychotics. Patients in the first episode of psychosis ($n = 126$) were enrolled in two prospective studies employing second-generation antipsychotics (risperidone or aripiprazole). Patients were scanned at the initiation of treatment on a 3T MRI scanner (Study 1, GE Signa HDx, $n = 74$; Study 2, Siemens Prisma, $n = 52$). Voxelwise fALFF derived from baseline resting-state fMRI scans served as the primary measure of interest, providing a hypothesis-free (as opposed to region-of-interest) search for regions of the brain that might be predictive of response. At baseline, patients who would later meet strict criteria for clinical response (defined as two consecutive ratings of much or very much improved on the CGI, as well as a rating of ≤3 on psychosis-related items of the BPRS-A) demonstrated significantly greater baseline fALFF in bilateral orbitofrontal cortex compared to non-responders. Thus, spontaneous activity in orbitofrontal cortex may serve as a prognostic biomarker of antipsychotic treatment.

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INTRODUCTION

Antipsychotic medications with activity at the dopamine D2 receptor remain the primary pharmacologic treatment for patients with psychotic disorders such as schizophrenia, despite highly variable response [1]. About one-third of patients with schizophrenia are ultimately resistant to treatment with antipsychotic medications [2], and more than half of these lack even minimal response (20% reduction of positive symptoms) in the first episode of illness [3, 4]. Moreover, a large number of patients demonstrate only partial response to antipsychotic treatment [5], and a substantial minority of first-episode patients fail to demonstrate robust response (defined either as a 50% reduction in positive symptoms [4] or as an absence of frank psychosis [6, 7]). The first episode of illness is especially important clinically for at least three reasons: (1) it is the phase of illness associated with the greatest risk of suicide [8, 9]; (2) it may be the best opportunity to mitigate long-term illness trajectory [10]; and (3) the onset period of late adolescence/early adulthood represents a critical period for attaining functional milestones in the transition to independence [11]. Thus, identification of individuals at risk for poor response is an important clinical goal, yet prognostic biomarkers are lacking [12].

Furthermore, from a research perspective, identification of biomarkers for poor response to antipsychotics may point toward novel treatment targets and mechanisms not addressed by existing pharmacologic agents [12, 13]. Biomarker studies conducted in first-episode patients may be advantageous, compared to studies in more chronic populations, due to the ability to obtain baseline measurements unconfounded by lengthy exposure to treatment and ongoing illness processes [14] and the availability of the full range of clinical outcomes, as compared to the abundance of partial and poor responders in samples of convenience [4].

Resting-state functional magnetic resonance imaging (rs-fMRI) has become an increasingly utilized tool in the quest for treatment biomarkers in schizophrenia [15]. Compared to task-based fMRI, rs-fMRI is more easily performed in acutely ill patients in their first psychotic episode, and may provide information congruent to that obtained with task-based fMRI [16]. Importantly, the large majority of the energy expenditure of the brain is accounted for by spontaneous fluctuations, whereas task-related activations represent <5% of this total [17].

Although many rs-fMRI studies of antipsychotic response have been limited to the cross-sectional comparison of treatment-responsive and non-responsive patients to each other and/or to controls [15], Table 1 displays key parameters of all *prospective* rs-fMRI studies in first-episode psychosis to date. Table 1 includes all studies in which baseline rs-fMRI measures were examined in relation to subsequent treatment response over a period of weeks or months (i.e., "prognostic biomarker" studies). In general, longitudinal sample sizes for previous studies were small (median

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Table 1. Previous first-episode studies examining baseline resting-state fMRI predictors of antipsychotic response.

First author	Institution	PMID	Year	*N*	All FE?	Predictor	ROI	Method	Meds	Duration
Hengyi Cao [63]	Sichuan Univ	34525195	2022	62	Yes	CTC hyper-conn	CTC network	FC	Variable	12 months
Chenyang Yao [30]	Sichuan Univ	34925087	2021	55	Yes	Postcentral gyrus ReHo	N/A	fALFF/ReHo	Variable	12 months
Jose Maximo [64]	UAB	34414373	2021	43	Yes	DMN connectivity	DMN	FC	RISP	16 weeks
Yingchan Wang [65]	Shanghai	34365083	2021	64	Yes	DMN-CEN	Triple-network	Dynamic FC	Variable	12 weeks
Yingchan Wang [20]	Shanghai	34079256	2021	127	Yes	Degree centrality	Left I/MTG	Graph theory	Variable	12 weeks
Sugai Liang [66]	Sichuan Univ	33408329	2021	49	Yes	Null	Triple-network	FC	Variable	6 weeks
Akhil Kottaram [67]	Melbourne, Aus	32469448	2020	30	No	Within-DMN FC	DMN	FC	NR	12 months
Ang Li [18]	CAS Beijing	32251404	2020	95	No	Striatal	Striatum	fALFF/ReHo + FC	Variable	6 weeks
Gosa Tarcijonas [22]	UPMC	31150557	2020	43	Yes	GP/insula/ACC	Globus pallidus	FC	Variable	6 months
Shaoqiang Han [23]	Chengdu	31759811	2020	38	Yes	Striatal-Salience	Striatum	FC	RISP	8 weeks
Bo Cao [24]	CAS Beijing	29921920	2020	38	Yes	STG	STG	FC/mutual info	RISP	10 weeks
Daniel Bergé [68]	UC Davis	33323140	2020	43	"Recent"	Null	Thalamus	FC	Variable	12 months
Liu-Xian Wang [29]	Xijing Hospital	30967317	2019	36	Yes	Null	N/A	Graph theory	Variable	16 weeks
Long-Biao Cui [19]	Xijing Hospital	30701701	2019	123	No	Parietal	N/A	ALFF	Variable	Variable
Huabing Li [25]	Changsa, Hunan	31307956	2019	76	Yes	Putamen	Striatum	fALFF	OLZ	8 weeks
Renrong Wu [26]	Changsa, Hunan	31649567	2019	32	Yes	Putamen	Striatum	fALFF	OLZ	8 weeks
Yiwen Zhang [69]	Shanghai	31171498	2019	23	Yes	SM subnetworks	Sensorimotor ctx	FC	Variable	8 weeks
Esther Blessing [70]	NKI/Shanghai	31433843	2019	27	Yes	Anterior Hc	Hippocampus	FC	Variable	8 weeks
Deepak Sarpal [21]	ZHH	26315980	2016	41	Yes	Striatal	Striatum	FC	RISP/ARI	12 weeks
Nina Kraguljac [71]	UAB	26873890	2016	28	No	Hc/ACC/caudate	Hippocampus	FC	RISP	6 weeks
Alan Anticevic [72]	Chengdu	25568120	2015	25	Yes	PFC hyper-conn	PFC	FC	Variable	12 months
Nina Kraguljac [73]	UAB	26793436	2015	28	No	DAN	4 Yeo networks	FC	RISP	6 weeks
Jennifer Hadley [74]	UAB	24165885	2014	21	No	VTA/dACC	VTA	FC	RISP	6 weeks

UAB University of Alabama at Birmingham, *CAS* Chinese Academy of Sciences, *UPMC* University of Pittsburgh Medical Center, *UC* University of California, *NKI* Nathan Kline Institute, *ZHH* Zucker Hillside Hospital, *CTC* Cerebello-Thalamo-Cortical, *hyper-conn* hyper-connectivity, *DMN* Default Mode Network, *CEN* Central Executive Network, *I/MTG* Inferior/Middle Temporal Gyrus, *STG* Superior Temporal Gyrus, *ACC* Anterior Cingulate Cortex, *GP* Globus Pallidus, *SM* sensorimotor, *Hc* hippocampus, *PFC* Prefrontal Cortex, *DAN* Dorsal Attention Network, *VTA* Ventral Tegmental Area, *dACC* dorsal Anterior Cingulate Cortex, *FC* functional connectivity, *ReHo* Regional Homogeneity, *RISP* risperidone, *OLZ* olanzapine, *ARI* aripiprazole, *NR* Not Reported.

$N = 41$ in Table 1). Notably, two of the three studies with relatively large sample sizes in Table 1 included a mix of first-episode and multi-episode patients in their longitudinal studies [18, 19]; only one study comprised exclusively of patients in the first episode of illness was comparable in size to the present report [20].

Most of the prognostic biomarker studies listed in Table 1 limit the investigation to functional connectivity (FC) of pre-defined regions of interest. For example, we [21] and others [18, 22–26] have focused on the corpus striatum, given the enrichment of this structure in dopamine D2 receptors, the target of all effective antipsychotics [27, 28]. Only three prognostic biomarker studies examined the whole brain in a hypothesis-free manner, and one of these [29] was underpowered ($n = 36$) and reported null results. A second study [19] identified parietal lobe abnormalities as predicting antipsychotic non-response; however, this study included a large sub-cohort of patients with chronic illness mixed together with first-episode patients, treated with a wide range of different antipsychotic medications (including clozapine), with outcome measured after variable treatment durations. A third study [30], comprising 55 first-episode patients also studied on variable medications over a long duration (12 months), reported differences between responders and non-responders on a measure of regional homogeneity of signal in the postcentral gyrus; however, this finding only emerged in the context of a multimodal "fusion" analysis of structural, functional, and diffusion measures and represented loadings ("mixing coefficients") on an independent component derived from the fusion analysis. Thus, there is a substantial gap in the first-episode literature of hypothesis-free, brain-wide analyses of resting-state fMRI data.

While most of the studies in Table 1 examined resting-state FC across brain regions, intrinsic resting activity within brain regions has been less well studied as a potential biomarker. Specifically, the fractional amplitude of low-frequency fluctuations (fALFF [31]) is a measure thought to capture spontaneous neural activity, and has been shown to correlate with local brain glucose metabolism [32–35]. Importantly, regions with greater fALFF also demonstrate a greater degree of centrality [36, 37], a measure of connectedness derived from graph theory, suggesting that fALFF underpins (to some extent) FC of brain networks. However, relative to FC, fALFF has the advantage of being relatively less susceptible to movement artifacts [38], and fALFF has been shown to be less impacted by physiologic noise compared to an older measure of local activity, ALFF [31, 39]. Moreover, fALFF has been demonstrated to be stable over the course of an fMRI session [40], as well as reliable over time (measured in hours, weeks, or months) [39, 41], a necessary attribute for a potential biomarker [42].

One very early study [43] suggested that treatment-related increases in ALFF across several cortical regions (prefrontal, dorsal parietal, and superior temporal), as well as the caudate, were correlated with symptom improvement over 6 weeks. However, this study focused on change in ALFF over time, and did not examine baseline ALFF as a prognostic biomarker. As shown in Table 1, there have been no studies of fALFF alone as a prognostic biomarker in exclusively first-episode cohorts. The goal of the present study was to test whether the measurement of fALFF can provide a baseline prognostic biomarker and/or change-biomarker of acute (12-week) positive symptom response to antipsychotic medication in a large cohort of patients experiencing a first episode of psychosis. To allow hypothesis-free biomarker discovery, we utilized voxelwise measures of fALFF across the whole brain.

METHODS AND MATERIALS

Subjects

Subjects included 126 patients (33.3% female, mean age = 22.6, SD = 5.7) with first-episode psychotic disorders and minimal exposure to APs (median exposure = 5 days; all patients <2 years). All subjects underwent scanning while entering 12 weeks of prospective treatment with second-generation APs (risperidone or aripiprazole). Consistent with our prior studies [6, 7], stringent treatment response criteria were applied for ratings obtained on weeks 1, 2, 3, 4, 6, 8, 10, and 12: response required two consecutive ratings of much or very much improved on the CGI, as well as a rating of ≤3 on four psychosis-related items of the BPRS-A [44]. By these criteria, 83 patients were classified as responders; these subjects did not differ from 43 non-responders in age, sex, scanner type (GE or Siemens), or movement during the scan (framewise displacement, FD), as displayed in Table 2. In addition, as shown in Table 2, responders and non-responders did not differ in level of symptoms at baseline, as measured by the four psychosis items of the BPRS-A and by total BPRS-A scores. There were also no significant differences between responders and non-responders on any of the demographic or baseline clinical variables when divided by scanner type. All subjects provided written, informed consent under a protocol approved by the Institutional Review Board of the Feinstein Institutes for Medical Research at Northwell Health.

Scan parameters

All fMRI exams were conducted on a 3T scanner (GE Signa HDx, $n = 74$; Siemens PRISMA, $n = 52$; the present study represents first-episode patients ascertained over a period of 10 years, during which time a scanner replacement occurred). On the Signa, the resting-state scan lasted 5 min, during which 150 EPI volumes were obtained (TR = 2000 ms, TE = 30 ms, matrix = 64 × 64, FOV = 240 mm, voxel = 3.75 × 3.75 × 3 mm, 40 contiguous 3 mm oblique axial slices). On the PRISMA, two 7-min 17-s resting-state runs were obtained, one each with anterior-posterior and posterior-anterior phase encoding directions. Resting scans contained 594 whole-brain volumes, each with 72 contiguous axial/oblique slices in the AC-PC orientation (TR = 720 ms, TE = 33.1 ms, matrix = 104 × 90, FOV = 208 mm, voxel = 2 × 2 × 2 mm, 72 contiguous 2-mm oblique axial slices, multi-band acceleration factor = 8). Resting-state scans were collected with eyes closed. Wakefulness was verified by the research technician accompanying the patient in the scanner room. Subjects who could not maintain wakefulness during the scanning session were not included in the MRI study.

Calculation of fALFF and statistical analysis

Raw resting-state data, after removal of the first four scans, were preprocessed using standard pipelines including registration, normalization to the MNI template, linear trend removal, spatial smoothing (6 mm^3 kernel FWHM), and grand mean scaling. Utilizing Fourier Transformation at every voxel, we calculated the power of BOLD signal in the low-frequency range of 0.01–0.10 Hz and divided it by the power of BOLD signal across the entire frequency range (0–0.25 Hz) to calculate fALFF [31]. Voxelwise fALFF was compared between responders and non-responders using *t*-tests implemented in SPM with age, sex, scanner, and movement (FD) as nuisance covariates, and applying a height threshold of $p < 0.005$ and family-wise error (FWE)-corrected cluster size $p < 0.05$. As a conservative control for signal drop-out in ventral brain regions due susceptibility artifact in resting-state T2*-weighted scans, a whole-brain mask was applied such that any voxel with missing values in any subject's normalized data was removed.

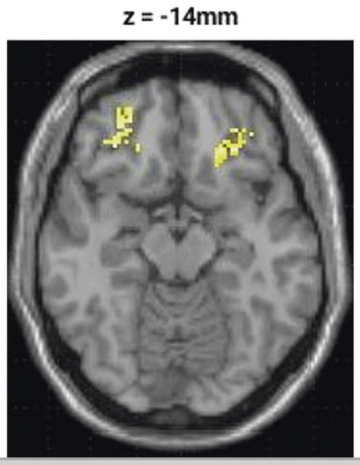
Individual values of fALFF, corrected for the nuisance covariates, were extracted for each subject at the peak voxels of significant regions in order to perform post hoc correlational analyses with clinical variables. For purposes of these post hoc analyses, magnitude of symptom response was computed by regressing symptom values at the study endpoint against baseline values; the residual score for each subject was utilized as the measure of response magnitude. Demographics and baseline clinical variables were compared between responders and non-responders using χ^2 tests for categorical variables, and *t*-tests for quantitative variables. For *t*-tests, Levene's test for equality of variances was performed, but for all analyses presented in Table 2, variances did not significantly differ from equal.

RESULTS

Compared to non-responders, patients who later met strict criteria for clinical response demonstrated significantly greater baseline fALFF in bilateral orbitofrontal cortex (OFC). As shown in Fig. 1, each cluster was statistically significant at a FWE corrected $p < 0.05$; together, these two clusters were significant at the set level ($p = 0.038$). By contrast, no significant clusters were identified

Table 2. Comparison of antipsychotic responders and non-responders on baseline demographic and clinical variables, across scanners.

	Responders ($N = 83$)	Non-responders ($N = 43$)	Statistical test (p value)
Scanner type (GE/Siemens)	53/30	21/22	$X^2(1) = 2.64$ ($p = 0.10$)
Sex (M/F)			
Both scanners	26/57	16/27	$X^2(1) = 0.44$ ($p = 0.55$)
GE scanner	15/38	3/18	$X^2(1) = 1.60$ ($p = 0.21$)
Siemens scanner	11/19	13/9	$X^2(1) = 2.57$ ($p = 0.11$)
Medication (RISP/ARI)			
Both scanners	61/22	29/14	$X^2(1) = 0.51$ ($p = 0.48$)
GE scanner	38/15	16/5	$X^2(1) = 0.15$ ($p = 0.70$)
Siemens scanner	23/7	13/9	$X^2(1) = 1.84$ ($p = 0.17$)
Mean age (SD)			
Both scanners	22.49 (5.58)	22.89 (5.94)	$t_{124} = 0.38$ ($p = 0.70$)
GE scanner	22.07 (6.23)	20.78 (3.84)	$t_{72} = -0.88$ ($p = 0.38$)
Siemens scanner	23.23 (4.20)	24.91 (6.92)	$t_{32*} = 1.01$ ($p = 0.32$)
Mean FD (SD)			
Both scanners	0.142 (0.106)	0.156 (0.137)	$t_{124} = 0.63$ ($p = 0.53$)
GE scanner	0.153 (0.128)	0.183 (0.188)	$t_{72} = 0.80$ ($p = 0.42$)
Siemens scanner	0.124 (0.040)	0.130 (0.051)	$t_{50} = 0.52$ ($p = 0.60$)
BPRS-A Psychosis Score (SD)			
Both scanners	13.80 (3.120)	14.51 (3.215)	$t_{124} = 1.20$ ($p = 0.56$)
GE scanner	14.04 (3.035)	14.24 (3.239)	$t_{72} = 0.28$ ($p = 0.78$)
Siemens scanner	13.40 (3.529)	14.77 (3.054)	$t_{50} = 1.46$ ($p = 0.15$)
Total BPRS-A Score (SD)			
Both scanners	43.35 (7.458)	44.19 (7.666)	$t_{124} = 0.59$ ($p = 0.23$)
GE scanner	42.62 (7.694)	41.52 (7.332)	$t_{72} = 0.56$ ($p = 0.58$)
Siemens scanner	44.63 (6.960)	46.73 (3.054)	$t_{50} = 1.05$ ($p = 0.30$)



			MNI		
p_{FWE}	Cluster size	Peak T	X	Y	Z
0.022	95	3.79	22	54	-18
0.002	131	4.16	-20	32	-14

Fig. 1 Significant clusters of greater baseline fALFF in responders relative to non-responders, displayed on an MNI-registered T1-weighted image. Statistical properties and MNI coordinates are listed below image.

in which non-responders showed greater baseline fALFF compared to responders.

As expected, extracted OFC fALFF values (especially in the left hemisphere) were significantly correlated with psychotic symptomatology at study endpoint as measured by raw values ($r = -0.275$, $p = 0.002$ and $r = -0.176$, $p = 0.049$, for left and right OFC, respectively), or values residualized against baseline symptoms ($r = -0.296$, $p < 0.001$ and $r = -0.167$, $p = 0.06$, respectively). Left OFC values were also significantly correlated with total symptomatology scores at study endpoint ($r = -0.287$, $p = 0.001$ and $r = -0.277$, $p = 0.002$, for raw and residualized scores, respectively), but correlations with right OFC were not significant ($r = -0.098$, $p = 0.27$ and $r = -0.087$, $p = 0.333$, for raw and residualized total scores, respectively). Importantly, individual fALFF values extracted from the left and right OFC were not significantly correlated with level of psychotic symptoms at baseline ($r = 0.068$, $p = 0.45$ and $r = -0.060$, $p = 0.50$, respectively). In addition, left and right OFC fALFF values were not significantly correlated with baseline total symptomatology on the BPRS-A ($r = -0.079$, $p = 0.38$ and $r = -0.065$, $p = 0.47$, respectively).

DISCUSSION

The present study examined fALFF derived from rs-fMRI to search the whole brain, in a hypothesis-free manner, for regions that might predict response to 12 weeks of treatments with standard antipsychotic medications (risperidone or aripiprazole). In the largest hypothesis-free prospective study to date in first-episode psychosis, we report that fALFF in bilateral OFC at baseline may serve as a prognostic biomarker. Specifically, patients who later demonstrated robust positive symptom response to risperidone or aripiprazole had greater orbitofrontal fALFF at baseline, compared to patients who failed to respond in their initial 12-week trial of these antipsychotic agents.

The present study complements and extends prior findings of prospective research on the first episode of psychosis as

summarized in Table 1. Most notably, the OFC demonstrates strong FC to the striatum [45], which has been the primary focus of most prior studies listed in Table 1. For example, in our own previous work [21], reduced baseline striatal connectivity at seven OFC loci formed part of the biomarker (termed the "striatal connectivity index"), which was significantly predictive of antipsychotic treatment response. Like most of the prognostic biomarker studies summarized in Table 1, our prior study [21] employed FC analysis based on a hypothesis-driven striatal region-of-interest. By contrast, the current study was not constrained by prior hypotheses. Only a few prior studies employed fALFF or related techniques, and several of these also limited their analysis to the striatum, such that only two prior studies listed in Table 1 [19, 30] employed a voxelwise design directly comparable to ours. While both of these studies identified abnormalities of the parietal lobe as predictive of treatment response, several key methodological differences to the present study make direct comparisons challenging. For example, one study [19] mixed first-episode and non-FE patients in the analysis and utilized widely variable durations of outcome as observed naturalistically; that study also examined ALFF, which is considered potentially confounded by global differences and physiological noise, as compared to fALFF [31]. The second study [30] examined a multimodal combination of structural and functional measures and did not report results for fALFF independently.

To the extent that fALFF indexes underlying neural activity [32, 35], our results suggest that first-episode patients with reduced baseline OFC activity are less likely to respond to conventional dopamine D2 agents. While a variety of clinical and preclinical studies have implicated OFC dysfunction in schizophrenia [16, 46], potentially indexing abnormal reward prediction [47] and/or reversal learning [48], the present study suggests that these abnormalities may especially be marked in treatment non-responsive patients. These results are consistent with several recent longitudinal studies demonstrating that structural MRI changes in OFC are associated with treatment non-responsive schizophrenia [49–51].

It is also noteworthy that activity and connectivity of the OFC is especially sensitive to dopaminergic modulation [52, 53]. Although the OFC is not a primary component of the most well-studied canonical networks (e.g., default mode, central executive, and salience networks) in schizophrenia [54], it is broadly interconnected with most other areas of cortex in a subregion-specific fashion [45]. In a study of healthy individuals [55], administration of an antipsychotic (amisulpride) altered widespread cortico-cortical connectivity patterns of the OFC, increasing its connectivity with dorsolateral prefrontal cortex (dlPFC), anterior cingulate cortex, and limbic cortex, while decreasing its connectivity to posterior sensory cortex. Notably, these patterns of altered OFC connectivity were analogous to changes in striatal connectivity that we have previously observed to be associated with antipsychotic efficacy in schizophrenia [56]. Moreover, the greatest effects of amisulpride on OFC connectivity were observed in the specific subregion (central OFC) identified as the prognostic biomarker in the present study. Related evidence suggests that dopamine receptor blockade by antipsychotic medication stabilizes representations of reward in OFC [52], which would allow enhanced guidance of adaptive plans for action in the dorsal prefrontal cortex [57, 58]. Results of the present study are consistent with the notion that patients with schizophrenia with insufficient baseline activity in the OFC may not benefit from the antipsychotic-driven enhancement of OFC-dlPFC connectivity and consequent stabilization of task representations. However, additional experimental work in both human and animal models would be required to test this hypothesis.

At the same time, it is important to acknowledge that the OFC is impacted by the activity of multiple neurotransmitters [59], including the 5-HT_{2A} receptor that is a significant target of most second-generation antipsychotics [60]. Moreover, activity and connectivity of the OFC is also impacted by modulation of metabotropic glutamate receptors [61], suggesting a possible target for future treatment development. Non-pharmacologic neuromodulatory techniques such as theta burst stimulation, recently shown to alter OFC activity in patients with compulsive behavior disorders [62], could also be trialed in patients with treatment-resistant schizophrenia.

Limitations

There are several limitations to the present study. First, imaging data were collected across two different scanners and scanning protocols. While this factor was included in all statistical models, scanner effects may contribute to both Type 1 and Type 2 errors. In addition, while the present study is the largest of its kind, it is still too small to reliably determine the potential sensitivity and specificity of OFC fALFF as a prognostic biomarker.

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AUTHOR CONTRIBUTIONS

TL and AKM conceived the idea and designed this analysis of the data. AKM, DGR, PRS, and TL designed the overall longitudinal study. MLB and JAG supervised the longitudinal study and clinical phenotypes. TL ran the primary analyses, with assistance from AM, MA, ADB, MJ, and JC. TL drafted the manuscript. All authors read and provided scientific feedback, and participated in finalizing the draft of the manuscript.

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COMPETING INTERESTS

DGR has been a consultant to Acadia, Advocates for Human Potential, Amalyx, American Psychiatric Association, C4 Innovations, Costello Medical Consulting, Health Analytics, Innovative Science Solutions, Janssen, Lundbeck, Neurocrine, Neuronix, Otsuka, Teva, and US World Meds and has received research support from Otsuka. DGR also provides training and consultation about implementing NAVIGATE treatment that can include compensation. AKM has been a consultant to Genomind, InformedDNA, and Janssen. MLB is a consultant for HearMe and Northshore Therapeutics. JAG has served as a consultant to Alkermes. No other authors report competing interests.

ADDITIONAL INFORMATION

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