TRAJECTORIES OF BRAIN ABNORMALITIES IN EARLY SCHIZOPHRENIA

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TRAJECTORIES OF BRAIN ABNORMALITIES IN EARLY SCHIZOPHRENIA

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EDITORIAL
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Editorial: Trajectories of Brain Abnormalities in Early Schizophrenia

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Editorial on the Research Topic

Trajectories of Brain Abnormalities in Early Schizophrenia

Several brain abnormalities in schizophrenia have been demonstrated by a large number of structural and functional neuroimaging studies. The nature and meaning of such abnormalities, their time of occurrence, whether they are static or progressive as well as the role of potential confounders of brain changes have been investigated by several studies over the last 40 years. The findings of these investigations support the notion that some structural and functional brain anomalies predate the onset of schizophrenia and are detectable to a larger extent in first-episode patients (FEP). Despite the large amount of literature on brain changes in the early stages of schizophrenia, the findings to date do not allow definite conclusions to be drawn about the pathophysiological trajectory of schizophrenia and to resolve the dispute between the so-called "neurodevelopmental" and "neurodegenerative" hypotheses of brain abnormalities of the disorder. The papers included in this Research Topic on "*Trajectories of Brain Abnormalities in Early Schizophrenia*" provide some new insights to address the question of which or how many trajectories of brain changes can be detected in the early phases of the disorder and to which extent they are related to the multidimensional outcome of the disorder.

Here we present a brief overview of the contents and highlights of the present Research Topic. A number of original papers investigated clinical and biological predictors of outcome in first-episode schizophrenia (FES). Takahashi et al. analyzed longitudinal gray matter changes in the insular cortex of FES patients during a 3 years Magnetic Resonance Imagine (MRI) follow-up evidencing dynamic volumetric changes at different time points over the early course of illness. Kim et al. investigated throughout diffusion tensor imaging (DTI) the association between white matter integrity and Theory of Mind (ToM) impairment in first-episode patients compared to healthy controls. The study findings suggested a possible neural basis for ToM deficits in schizophrenia. Moreover, In their contribution, González-Vivas et al. analyzed longitudinal changes in brain fMRI BOLD over a 2 years follow-up in first-episode patients and healthy controls. Interestingly, the study also took into account the potential moderating role of antipsychotic medication on brain functional measurements. Cheng et al. investigated the clinical predictors of persistent remission (PR) within the 1st year of antipsychotic treatment in a large sample of first-episode patients ($n = 301$). Among several psychopathological and neurocognitive variables considered, the results of the study showed that the severity of negative symptoms at baseline was the best predictor of PR within 1 year of antipsychotic treatment.

Two original studies in this issue investigated structural and functional brain parameters in patients at clinically (CHR) or genetically (GHR) high risk for psychosis. Takayanagi et al. performed a cross-sectional structural MRI study of the planum temporale (PT) comparing 73

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individuals with an at-risk mental state (ARMS) and 74 healthy controls using labeled cortical distance mapping. The study did not show significant between groups differences of PT measures, suggesting that structural changes associated with schizophrenia may occur just before or during the onset of the disorder. Collin et al. examined the default mode network (DMN) in children at familial high risk (FHR) for psychosis compared to healthy children. The study evidenced an hyperactivity of posterior DMN in pre-adolescent FHR children as compared to healthy controls. As suggested by the authors, this finding may posit DMN-related disturbances as a developmental brain abnormality associated with familial risk factors that predates psychosis.

Two electrophysiological studies in early schizophrenia also contributed to this special issue. Mackintosh et al. investigated the effect of antipsychotic medication on EEG parameters in FEP patients. The results demonstrated significant differences of EEG resting-state microstates between medicated and non-medicated FEP patients. Mazer et al. studied auditory event-related potentials (ERP) in a cross-sectional controlled study. In particular, the paper examined the modulation and habituation of ERPs early components N1 and P2 in 26 FES patients and 27 healthy participants. The study findings evidenced anomalies of sensory gating processes yet in the course of early schizophrenia.

Finally, some qualitative and quantitative reviews completed the present Research Topic, with an useful update on biological research in early schizophrenia. In their contribution, Kraguljac and Lathi critically considered a number of key scientific questions both methodologically and clinically relevant in the context of neuroimaging studies to understand the pathophysiology of schizophrenia. Yang et al. performed a selective review of 36 structural and functional longitudinal MRI studies in FES patients before and after antipsychotic treatment. Kose et al. conducted a qualitative review of the evidence regarding the potential role of peripheral inflammatory markers as predictors of treatment response in schizophrenia and the association between peripheral inflammatory markers with neuroimaging data. Merritt et al. reported a qualitative review to determine longitudinal structural MRI findings in GHR and CHR individuals for psychosis. Lastly, Hinney et al. investigated, through a meta-analytical approach, whether hippocampal volume may serve as a biomarker for psychosis. This quantitative review included those studies that compared hippocampal volume changes over time in patients at risk for psychosis who developed illness as compared to patients who do not have such a transition.

In conclusion, the present collection of research papers offers a multidisciplinary perspective of the topic of trajectories of brain abnormalities in early schizophrenia, which may help to understand the pathophysiology of the disorders and contributes to the discussion on the etiopathogenetic hypotheses of the disorder. The main implications provided from the studies collected in the topic can be summarized as follows: (1) there is evidence of dynamic structural and functional brain changes at different time points in the early course of schizophrenia; (2) brain changes in early schizophrenia involves both gray and white matter structures; (3) structural and functional brain anomalies are detectable even before the overt clinical onset of the disease as demonstrated by longitudinal studies in patients clinically or genetically at risk for schizophrenia; (4) antipsychotic medication represents a major confounder of brain changes over time in schizophrenia. This evidence once again questions the clinicians about the risk/benefit balance of antipsychotic treatment also in the early course of the disease.

With all these clinical and research implications in mind, we wish that the present Research Topic may receive interest and activate debate among the readers and contributors and solicit new ideas for original research and further hypotheses on this fascinating field of psychiatric research. The future directions of neuroimaging research in schizophrenia indicate the need to set new methodological standards both for developing truly innovative hypothesis-driven neuroimaging research and for reliably interpreting structural and functional multimodal imaging databases with the aim to overcome the current limits and to reach the target of diagnostic and prognostic biomarkers at the individual subject level. Otherwise, the scientific community will have to deal with redundant or weak findings with the potential risk of dissipating even well-grounded notions about the pathophysiology of schizophrenia deriving from almost 50 years of neuroimaging research.

AUTHOR CONTRIBUTIONS

AV and LDP wrote the paper. SB revised and completed the Editorial. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Which Subgroup of First-Episode Schizophrenia Patients Can Remit During the First Year of Antipsychotic Treatment?

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Objective: To investigate the persistent remission rate (PRR) and its predictors within the first year of antipsychotic treatment in first-episode schizophrenia (FES) patients.

Methods: In a sample of 301 FES patients who remained in antipsychotic treatment for 1 year, we assessed symptoms with the Positive and Negative Syndrome Scale (PANSS), cognition in six domains and functioning with the Personal and Social Performance Scale (PSP).

Results: In total, 75.4% (227/301) of FES patients remaining in antipsychotic treatment reached persistent remission (PR) in one year. The PSP score was higher in remitters than non-remitters at the endpoint of the 1-year follow-up ($P < 0.0001$). The PANSS negative score—but not the PANSS total score, positive score or general psychopathological score; PSP score; or cognitive performance at baseline—was negatively associated with PR. Lower scores for "abstract thinking" and "stereotyped thinking" were independent predictors of PR.

Conclusions: In FES, nearly 3/4 patients could achieve PR with 1 year of antipsychotic treatment, and having fewer negative symptoms, especially thinking and volition symptoms, can predict PR.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier NCT01057849.

Keywords: first-episode, schizophrenia, antipsychotic, remission, negative symptom

INTRODUCTION

The prognosis of schizophrenia is considered much worse than that of other psychoses (1). Patients with a first episode of schizophrenia tend to respond better to antipsychotics than chronic patients (2). Various guidelines suggest that first-episode schizophrenia (FES) patients should remain on antipsychotics for at least 1 year for maintenance treatment (3). However, only some FES patients

achieve remission in one year of antipsychotic treatment, with remission being the basic aim of such treatment and the basis for an ideal outcome.

It has been reported that the remission rate in FES patients is between 17.0 and 78.0% (4), and this wide range is partly due to the diverse criteria for remission. Remission defined only based upon symptom severity is not stable; approximately 70% of symptom remitters in FES experience symptom exacerbation within 1 year (5). In 2005, Andreasen et al. (with the Remission in Schizophrenia Working Group, RSWG) proposed criteria for persistent remission (PR) in schizophrenia: when eight items on the Positive and Negative Symptoms Scale (PANSS) received a score of less than four points (which was considered to indicate symptomatic remission) for more than 6 months. These criteria were considered to provide researchers and clinicians with a robust, well-defined outcome goal for the long-term treatment of schizophrenia and to facilitate comparison between different studies (6). Jager et al. revealed that the consistency between the criteria by the RSWG (including both symptom severity and minimum time threshold) and other criteria employed previously was between 52.6 and 80.0% (7).

Most studies reporting the persistent remission rate (PRR) of FES patients throughout 1 year of antipsychotic treatment were randomized controlled trials (RCTs) (8, 9). However, due to the strictness of the study design, patients in RCTs are assigned a certain antipsychotic and are excluded from the analysis if they switch to another antipsychotic. Approximately one-third of FES patients require a change in medication within their first year of treatment (10). Thus, the remission rate reported in traditional RCTs may reflect remission from one specific antipsychotic rather than a real-world picture of PRR throughout the 1-year antipsychotic treatment.

Most non-RCT longitudinal studies reported remission rates with criteria other than the criteria by the RSWG (11–15). Lally et al. conducted a meta-analysis of first-episode psychosis (FEP) studies that included longitudinal studies and excluded RCTs (16). According to the results, the symptomatic remission rate in FES reached 56.0%, as judged by diverse criteria and based on a wide follow-up duration ranging from 1 to 17 years. Only two of the included studies reported a PRR based on the criteria by the RSWG. One was conducted in Indonesia and followed 59 FES patients for 17 years. It was reported that 23.7% of the patients achieved both symptom and functional remission, and the remitters ceased antipsychotic use beginning in the 11th year (17). The other study was from Hong Kong and reported a PRR of 59.6% within 1 year in a sample of 104 FES spectrum disorder patients; however, medication information was not reported.

Thus, the PRR of FES during 1 year of antipsychotic treatment remains unclear. We aimed to examine the PRR and its predictors during 1 year of antipsychotic treatment for FES. We hypothesized that 1) more than half of the FES patients could remit during the 1-year antipsychotic treatment and 2) baseline sociodemographic, clinical and cognitive characteristics would predict PR.

METHODS

Participants and Setting

The data came from a 1-year randomized, open-label clinical trial conducted in 6 major psychiatric hospitals in China from 2008 to 2010 (18). The trial was approved by the ethics committees of the participating centers. Written informed consent was obtained after the participants received a complete description of the study.

FES patients with the following characteristics were recruited: illness duration of fewer than 3 years (the onset was determined in the SCID-I/P according to when the first symptom appeared), continuous antipsychotic treatment for fewer than 4 weeks and a cumulative period of intermittent antipsychotic treatment of fewer than 12 weeks. A 3-phase design was employed to mimic the reality of clinical practice (18). Phase I was a randomization phase (comparison of the three antipsychotics (risperidone, olanzapine and aripiprazole) has been published) (19). Patients who showed little or no benefit from the Phase 1 treatment were allowed to enter Phase 2, in which patients underwent a medication switch to one of the other two antipsychotics. Patients who did not respond to the second antipsychotic were allowed to enter Phase 3, which allowed the research psychiatrists to introduce other antipsychotics such as clozapine and augmentation or antipsychotic polypharmacy. Concomitant treatments such as antidepressants or mood stabilizers were permitted if necessary. The design aimed to keep the patients on antipsychotic treatment for as long as possible. The primary outcome in the original RCT was the baseline-to-endpoint change in the PANSS total score (19). This study was a secondary analysis of an RCT database and based on data of subjects who completed the 1-year follow-up. In total, 569 patients were recruited, and 301 subjects completed the 1-year follow-up (20). Data from the 301 patients were included in the analysis. There were no differences in the demographic, psychopathological and functional data between those who completed the 1-year follow-up and those who did not ($P > 0.05$).

Assessment and Evaluation

Basic demographic data were collected with a standard data collection form designed especially for this study. Clinical characteristics, including illness duration, acute onset (less than 3 months from symptom onset to full disease manifestation), and early onset (onset before 18 years) was drawn from the SCID-I/P. Psychopathology was measured with the PANSS (21). Function was evaluated with the Personal and Social Performance Scale (PSP) (22). Recruited patients were evaluated by a trained psychiatrist in each hospital at baseline and at week 4, 8, 12, 26, 39 and 52. Six cognitive domains (verbal learning and memory with the Hopkins Verbal Learning Test-Revised [HVLT-R]; visual learning and memory with the Brief Visuospatial Memory Test-Revised [BVMT-R]; speed of processing with the Trail Making Test Part A, Color Trails Test, category fluency test, Stroop Color Test and Wechsler Adult Intelligence Scale digit symbol-coding subtest; working

memory and attention with the Wechsler Memory Scale-spatial span subtest and paced auditory serial addition task; executive function with the Stroop Color-Word Test and Color Trails Test; and motor skills with the Grooved Pegboard Test) were measured at baseline (23, 24).

There were two to three psychiatrists responsible for the clinical assessments at each site. All interviewers attended a 1-week training workshop on the use of the rating instruments (the PANSS, PSP and cognitive tests) prior to the study and reached a high level of consistency (intraclass correlation coefficients or kappa values >0.75).

Primary Outcome

The primary outcome was PRR within 52 weeks, which was calculated as the number of patients who achieved PR within 52 weeks divided by the number of patients who completed the 52-week follow-up. PR was defined with the PANSS as a score on items P1, P2, P3, N1, N4, N6, G5, and G9 ≤3 for at least 6 consecutive months (6). The secondary outcomes were predictors of PR within 52 weeks.

Statistical Methods

Independent T-tests or nonparametric tests were used to compare the demographic, psychopathological and functional data between remitters and non-remitters. A chi-square test was used to compare categorical data, including gender and originally assigned antipsychotic.

Any variable that was significant in the univariate analysis was confirmed in the multivariate logistic regression analysis with the scores of the six cognitive domains (reported as diathesis factors in schizophrenia).

A final multivariate logistic analysis was conducted on the variables that were confirmed to be significant in the multivariate logistic analysis mentioned above to explore potential interactions.

RESULTS

Rate of Remission Within 1 Year of Antipsychotic Treatment

At the endpoint of the 1-year follow-up, 75.4% (227/301) of patients had achieved PR. In total, with the early discontinuers included in denominator, 39.9% (227/569) of patients achieved PR. At the endpoint, the PSP score was higher in remitters than non-remitters (P < 0.0001) (**Table 1**).

Demographic and Clinical Characteristics of the Sample

In the 301 patients who completed the first year of antipsychotic treatment, there was no difference between remitters and non-remitters in terms of baseline demographic and clinical characteristics, namely, psychiatric family history, illness duration, acute onset (less than 3 months from symptom onset to full disease manifestation), early onset (onset before 18 years) and concomitant antidepressants or mood stabilizers. Totally, 27 subjects accepted antidepressants, with fluoxetine equivalent dose (25.7 ± 8.9)mg (25, 26). Non-remitters were associated with more medication switch and higher daily antipsychotic dosage (in olanzapine equivalent) (27) during 1-year treatment, which indicated more treatment effort (**Table 2**).

Comparison Between Remitters and Non-Remitters

Univariate Analysis of the Baseline Characteristics

At baseline, the PANSS negative score was lower in remitters than in non-remitters; however, there were no differences in the PANSS total, positive and general psychopathological scores; PSP score; and cognitive performance (all P > 0.05) (**Table 3**). Of the seven items on the PANSS negative scale, the N2 "emotional withdrawal", N4 "passive/apathetic", N5 "abstract thinking" and N7 "stereotyped thinking" scores were lower in remitters (P < 0.01, P < 0.05, P < 0.01 and P < 0.05, respectively) than in non-remitters, but there were no differences in the N1 "blunted affect", N3 "poor rapport" and N6 "lack of spontaneity" scores.

Multivariate Analysis of the Baseline Characteristics

In the multivariate analysis including the PANSS negative scale score (P <0.05, OR = 0.947[0.906, 0.990]), N2 "emotional withdrawal" (P <0.05, OR = 0.789[0.626, 0.995]), N4 (P <0.05, OR = 0.799[0.646, 0.990]), N5 (P <0.05, OR = 0.761[0.602, 0.961]), and N7 "stereotyped thinking" (P <0.05, OR = 0.745 [0.588, 0.943]) scores, respectively with the 6 cognitive scores, their significance persisted.

In logistic regression analysis including N2 "emotional withdrawal", N4 "passive/apathetic", N5 "abstract thinking" and N7 "stereotyped thinking" as independent variables, N5 "abstract thinking" and N7 "stereotyped thinking" remained

TABLE 1 | Comparison of endpoint clinical characteristics between remitters and non-remitters.

	Remitters (N = 227)	Non-remitters (N = 74)	Remitters and non-remitters (N = 301)	P
Endpoint characteristics				
PANSS-total score	35.9(5.8)	48.2(13.1)	38.9(9.8)	0.000
PANSS-positive score	7.4(1.1)	10.0(4.8)	8.0(2.8)	0.000
PANSS-negative score	9.5(3.0)	15.3(5.8)	10.9(4.6)	0.000
PANSS-general psychopathological score	19.0(3.0)	23.0(6.0)	20.0(4.3)	0.000
PSP	80.0(9.3)	68.3(12.4)	77.2(11.3)	0.000

PANSS, positive and negative syndrome scale. Theoretical scores range from 30 to 210 (total score), from 7 to 49 (positive scale), from 7 to 49 (negative scale), and from 16 to 112 (general psychopathology scale). Higher scores indicate more severe psychopathology. PSP, personal and social performance scale. Higher scores indicate better function.

TABLE 2 | Baseline demographic characteristics and clinical characteristics of the population.

	Remitters N = 227	Non-remitters N = 74	Remitters and Non-remitters N = 301	p
Age (years)	24.8 (7.0)	24.9 (7.9)	24.8 (7.2)	0.527
Gender (Male)	126 (56.3%)	45 (60.8%)	171 (57.4%)	0.492
Marital status (Single)	184 (82.1%)	61 (82.4%)	245 (82.2%)	0.955
Education (years)	12.8 (2.8)	12.5 (2.8)	12.8 (2.8)	0.431
Positive psychiatric family history	17 (7.8)	10 (14.3)	27 (9.4)	0.105
Age of onset	24.2 (7.0)	24.4 (8.0)	24.2 (7.3)	0.638
Illness duration (months)	10.1 (10.3)	12.2 (11.2)	10.6 (10.6)	0.157
Acute onset	55 (29.6%)	15 (24.6%)	70 (28.3%)	0.454
Early onset	21 (22.6%)	12 (33.3%)	33 (25.6%)	0.209
Primary medication				0.556
Risperidone	86 (78.9%)	23 (21.1%)	109 (36.2%)	
Olanzapine	61 (72.6%)	23 (27.4%)	84 (27.9%)	
Aripiprazole	80 (74.1%)	28 (25.9%)	108 (35.9%)	
Daily dose (in olanzapine equivalent)	14.0 (4.2)	16.2 (3.5)	14.5 (4.1)	0.000
Medication switch	63 (27.8%)	32 (43.2%)	95 (31.6%)	0.013
Concomitant treatments				
Mood stabilizers	0	0	0	N/A
Antidepressants	19 (8.4%)	8 (10.8%)	27 (9.0%)	0.523

significant but N2"emotional withdrawal" and N4 "passive/apathetic" did not. Considering the potential overlap of N2 "emotional withdrawal" and N4 "passive/apathetic", we conducted two additional logistic regression analyses including N2 "emotional withdrawal", N5 "abstract thinking" and N7 "stereotyped thinking" and N4 "passive/apathetic", N5 "abstract thinking" and N7 "stereotyped thinking" respectively, and the significance of N5 "abstract thinking" and N7 "stereotyped thinking" persisted.

DISCUSSION

Nearly 3/4 FES patients, who completed the 1-year routine antipsychotic treatment, achieved relatively stable clinical recovery and functional recovery. Patients with fewer negative symptoms had a better chance of PR. One higher score on item N2 "emotional withdrawal", N4 "passive/apathetic", N5 "abstract thinking" or N7 "stereotyped thinking" could reduce the possibility of PR by nearly 1/5 to 1/4.

FES PRR Within 1 Year of Treatment

Gabeal et al. obtained an average PRR of 42.3% (2–3 years after the acute phase) based on the results from more than 10 FES studies conducted from 2006 to 2011 (5). A recent meta-analysis showed an FES symptomatic remission rate as high as 56.0% (16). All the studies mentioned above included the dropouts in the denominators when calculating the PRR. The PRR in this study was 39.9% (227/569) if the dropouts were included in the analysis, which is consistent with previous studies. This result suggests that more than 1/3 of FES patients achieved PR within the 1-year follow-up. However, including the dropouts in the denominator when calculating the PRR might lead to confusion. On the one hand, the dropouts may achieve PR after dropping out of the study, which might lead to underestimation of the rate. On the other hand, the rate could be greatly influenced by the

TABLE 3 | Comparison of baseline characteristics between remitters and non-remitters.

	Remitters (N = 227)	Non-remitters (N = 74)	Remitters and non-remitters (N = 301)	P
Baseline characteristics				
PANSS-total score	85.7 (13.7)	88.3 (15.4)	86.3 (14.2)	0.161
PANSS-positive score	23.4 (5.2)	23.4 (5.3)	23.4 (5.2)	0.880
PANSS-negative score	20.3 (7.2)	22.9 (5.3)	23.4 (5.2)	0.007
PANSS-general psychopathological score	42.0 (7.6)	42.0 (7.6)	42.0 (7.6)	0.741
PSP	42.2 (12.3)	41.5 (17.0)	42.0 (13.6)	0.252
Verbal learning	36.9 (11.7)	39.0 (10.8)	37.4 (11.5)	0.233
Visual learning	38.1 (11.9)	37.3 (10.1)	37.9 (11.5)	0.657
Working memory and attention	36.6 (9.9)	35.4 (10.2)	36.3 (9.9)	0.418
Information processing speed	36.3 (8.3)	34.6 (9.4)	35.9 (8.6)	0.179
Executive function	33.1 (10.7)	32.2 (9.6)	32.9 (10.4)	0.573
Fine motor	27.2 (10.6)	26.3 (10.9)	27.0 (10.7)	0.577

All the abbreviations are explained in the first footnote to ***Table 1****.*

dropout rate; thus, the PRR with the dropouts included might reflect a social or behavioral dimension rather than the outcome of antipsychotic treatment, although Lally et al. reported that remission in FEP was not associated with dropout rates (16).

When only patients who completed the 1-year follow-up were included in the denominators in RCTs, Boter et al. reported a PRR of 68.7% in the EUFEST study, and Crespo-Facorro et al. reported a PRR of 35.2% (9). Another RCT of 111 patients in Germany showed that the PRR was 58.6% (65/111); however, some patients also received psychological education or CBT for 8 weeks (5). The PRR in our study was much higher, which suggested that a relatively flexible regimen was needed to maximize the possibility of PR in FES.

One naturalistic follow-up study of 104 FEP patients in Hong Kong showed that the PRR was 59.6% (28), but this study did not define the antipsychotic treatment patients had received prior to recruitment. Our study recruited only FES patients with no or minimal antipsychotic exposure. Being previously untreated was a predictor of remission in general schizophrenia (11). The difference in the PRR between our study and the study by Chang et al. suggested that being previously untreated might also be a predictor of PRR in the FES population. Thus, most FES patients, who completed the 1-year antipsychotic treatment, achieved relatively stable symptomatic and functional outcomes.

Predictors of PR in FES

This study indicates that PR in FES patients who completed the 1-year antipsychotic treatment was not associated with gender, age, onset age (5, 8, 16), medication (9), or education level (14), which was consistent with previous studies.

Cognitive Impairment and PR

Cognitive impairment is considered a diathesis factor in schizophrenia. However, Boter et al. failed to demonstrate that cognitive impairment predicted PR in the EUFEST study (8). Ventura et al. also showed that cognitive impairment, including in vocabulary, comprehension and visual information processing speed, was not associated with the PRR in the FEP population (29). Although Simonsen et al. suggested that baseline information processing speed—but not verbal memory, verbal fluency, working memory and interference control—was better in remitters than in non-remitters, the significance disappeared in a multivariate analysis (14). This study confirmed that cognitive impairment was not associated with PR within the first year of antipsychotic treatment.

Baseline Symptoms and PR

Notably, negative symptoms were the only independent predictor of PR within the first year of antipsychotic treatment, consistent with several previous studies (28). Baseline symptoms (especially negative symptoms) predicted remission in FES patients in a systemic review (4), although Ceskova et al. followed 93 male FES patients for 1 year and found no difference in the baseline PANSS total score or subscale scores between remitters and non-remitters (30). A more recent meta-analysis of FEP suggested that baseline psychotic symptoms were not associated with remission; however, it did not explore the potential effects of subgroup symptoms (16).

We found that negative symptoms rather than overall symptoms might predict PR and further revealed that "emotional withdrawal", "passive/apathetic", "abstractive thinking" and "stereotyped thinking" but not "blunted affect", "poor rapport" and "lack of spontaneity and flow of conversation" predicted PR. This result suggested that only some negative symptoms are associated with PR.

"Emotional withdrawal" and "passive/apathetic" both refer to others' observations and are used to assess volition impairment in patients with schizophrenia. There is abundant evidence demonstrating daily activity reduction in schizophrenia; however, the potential predictive power of these symptoms had not been explored previously.

It is interesting that the two items ("abstractive thinking" and "stereotyped thinking") describing thinking impairment and not the items describing volition impairment were shown to independently predict PR. In other words, volition symptoms were mediated by thinking symptoms in their prediction of PR. P5 "abstractive thinking" refers to the ability to comprehend and abstract. N7 "stereotyped thinking" refers to the flexibility of thinking, that is, the ability to shift between two perspectives (or two beliefs about the world) according to the demands of the social situation. The Word Fluency Test in the cognitive assessment battery was used to assess the richness of thinking; however, performance on this test did not differ between remitters and non-remitters in a *post hoc* analysis. Thus, impairment in the ability to comprehend and abstract and in thinking flexibility rather than other thinking impairments (e.g., richness) might predict a lower likelihood of PR. Abstract thinking impairment is an established deficit in schizophrenia (31), and impairment in cognitive flexibility has been found in FES patients (32). This subgroup of negative symptoms has a high degree of overlap with cognitive symptoms. In fact, abstract thinking and stereotyped thinking are items of the cognitive rather than the negative component of the PANSS (33). It has been demonstrated that disorganization (with difficulty in abstract thinking as one of the three items) played a key (direct and indirect) role in real-life functioning in patients with schizophrenia (34). Comparelli et al., further demonstrated that difficulty in abstract thinking was correlated with social cognition and did not differ between early schizophrenia and late schizophrenia (35). However, there has been little research exploring the significance of these impairments in the prognosis of schizophrenia, though there has been some research exploring the underlying neural basis (32, 36). Our findings call for further studies with stricter designs to examine the predictive power of negative symptoms for PR, especially thinking symptoms and volition impairment rather than affective symptoms. Additionally, FES patients usually display mild or no negative symptoms, unlike chronic patients; indeed, in this study, the symptom severity as measured by the items on the negative subscale was generally "very mild" or "mild". This might also explain why there was no difference in the perseveration error in the Wisconsin Card Sorting Test

(WCST) or the completion time in the Color Trail II test between remitters and non-remitters in the *post hoc* analysis. However, these two variables reflect thinking flexibility in a rather limited and inflexible way, while the PANSS item N7 "stereotyped thinking" assesses comprehensive judgment of general information and thus better reflects mild impairment. Therefore, we speculate that even mild negative thinking or volition symptoms at baseline might predict a lower likelihood of PR in FES. More studies are needed to confirm this hypothesis.

Clinically, our findings suggested that FES patients with even mild difficulty in understanding others' words or shifting their perspectives according to the social situation or who exhibit a mild reduction in daily activities might be less likely to remit during the first year of antipsychotic treatment, despite the severity of their other symptoms, including positive symptoms and negative affective symptoms.

The study had several limitations. First, the follow-up period was 1 year, so the results cannot be generalized to a longer period. However, Ceskova et al. found that in male patients with FES, the remission rates after 1, 4 and 7 years of treatment were comparable, and patients who did not remit within the first year of treatment did not remit after 4 or 7 years of treatment either (37). It is possible that remission within a 1-year treatment period could be used to predict subsequent remission. Second, we focused on patients who completed the whole year of antipsychotic treatment; thus, we failed to provide information about remission in FES patients who discontinued their antipsychotic treatment, that is nearly half of the whole group. Kurihara et al. (17), who followed schizophrenia patients for 17 years, revealed that all remitters had ceased taking antipsychotics, which suggested that patients who discontinued their antipsychotics could also remit. The remission rate and its predictors in these patients need to be explored *via* studies with special designs and large samples. Third, patients who did not continue the follow-up may have received treatment from other psychiatric hospitals, the remission rate and its predictors in this group of patients were beyond the study. Fourth, we did not employ the MATRICS Consensus Cognitive Battery (MCCB) in cognitive assessment which is the most widely used and standardized neuropsychological test battery for assessing cognition in schizophrenia worldwide and was in the process of development when this trial was conducted. Social cognition included in the MCCB was not assessed in this study. Fifth, this study included FES patients with an illness duration not exceeding three years; thus, whether patients with an illness duration longer than 3 years are less likely to remit could not be determined by this study.

CONCLUSION

The present study showed that over 3/4 FES patients achieved PR within 1 year of antipsychotic treatment. Patients with no impairment in their comprehension ability, thinking flexibility and daily activities were more likely to achieve PR, indicating that thinking and volition negative symptoms define the subset of FES patients who are less likely to achieve ideal symptom outcomes in 1 year of antipsychotic treatment. Thus, assessing these symptoms in detail is necessary in clinical practice. Optimization of the current pharmacological and non-pharmacological strategies for treating this group of patients is warranted.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Peking University Sixth Hospital Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XY, YY, FY, ZL, CW, HD, and JZ designed the study. XY obtained funding and supervised the study. XZ and ZC analyzed the data. XY, ZC, and XZ interpreted the data and drafted the report. ZC, XH, LY, FY, ZL, CW, HD, JZ, and YY participated in the collection of data. All authors contributed to the article and approved the submitted version.

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Gray Matter Changes in the Insular Cortex During the Course of the Schizophrenia Spectrum

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Progressive gray matter reductions in the insular cortex have been reported in the early phases of schizophrenia (Sz); however, the trajectory of these reductions during the course of the illness currently remains unclear. Furthermore, it has not yet been established whether patients with schizotypal (SzTypal) features exhibit progressive changes in the insular cortex. This follow-up magnetic resonance imaging study examined volume changes in the short and long insular cortices (mean inter-scan interval = 2.6 years) of 23 first-episode (FE) and 17 chronic patients with Sz, 14 with SzTypal disorder, and 21 healthy controls. Baseline comparisons revealed smaller insular cortex volumes bilaterally in Sz patients (particularly in the chronic group) than in SzTypal patients and healthy controls. FESz patients showed significantly larger gray matter reductions in the insular cortex over time (left: –3.4%/year; right: –2.9%/year) than those in healthy controls (–0.1%/year for both hemispheres) without the effect of subregion or antipsychotic medication, whereas chronic Sz (left: –1.5%/year; right: –1.6%/year) and SzTypal (left: 0.5%/year; right: –0.6%/year) patients did not. Active atrophy of the right insular cortex during FE correlated with fewer improvements in positive symptoms in the Sz groups, while mild atrophy of the left insular cortex during the chronic phase was associated with the severity of negative symptoms in the follow-up period. The present results support dynamic volumetric changes in the insular cortex being specific to overt Sz among the spectrum disorders examined and their degree and role in symptomatology appear to differ across the illness stages.

Keywords: insular cortex, magnetic resonance imaging, schizophrenia, schizotypal disorder, progressive changes

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INTRODUCTION

Gray matter reductions in the insular cortex, particularly in the anterior portion (i.e., the short insula), which has emotional and language-related functions (1, 2), are one of the most definitive findings in schizophrenia (Sz) (3, 4). Further, previous functional neuroimaging evidences have suggested that abnormal activation and/or connectivity in the brain regions associated with the salience network, including the insular cortex, are involved in the production and persistence of auditory hallucinations

(5–7). Morphological changes of the insular cortex may exist in the first episode (FE) or even prior to illness onset (3, 8, 9), supporting its early neurodevelopmental pathology. However, longitudinal magnetic resonance imaging (MRI) studies demonstrated progressive gray matter loss during the course of Sz, which appears to be non-linear and most prominent in the early illness stages (10, 11). Although dynamic brain alterations in peri-Sylvian regions (such as the superior temporal gyrus and insula) around the onset of Sz have been suggested to contribute to positive psychotic symptoms (12), it currently remains unclear whether mild atrophy at the later illness stage is still involved in clinical manifestations. Due to the lack of detailed medication data in these previous studies (10, 11), it also has not yet been established whether antipsychotic medication significantly influences insular gray matter changes during the course of the illness. Furthermore, limited information is currently available on whether the putative pathophysiological trajectory of the insular cortex is specific to overt Sz or commonly exists within spectrum disorders.

Patients with schizotypal (SzTypal) disorder (13) or SzTypal personality disorder (14), a prototypical Sz spectrum condition, have biological and phenomenological commonalities with more severely ill patients with Sz (15). They may exhibit similar gray matter reductions in the temporal regions with overt Sz, which may represent a common susceptibility to Sz, but show less prominent changes in the fronto-limbic regions (16–18). Although only a few longitudinal MRI studies have been conducted on SzTypal patients, they are also characterized by the absence of the progressive gray matter reductions observed in the temporal regions of Sz (19, 20), which supports the notion that the active brain pathological process underlying the emergence of overt psychosis does not occur in SzTypal patients (15). On the other hand, although our previous cross-sectional study found no gray matter reductions in the anterior or posterior somatosensory (i.e., long insula) portions (1, 2) of the insular cortex in SzTypal patients (21), it is unknown whether they exhibit insular gray matter changes over time.

This longitudinal MRI study was conducted to investigate the trajectory of gray matter changes in insular subregions in the Sz spectrum (i.e., Sz and SzTypal disorder patients). Volume changes in the short and long insular cortices were compared between patients with FESz, chronic Sz, SzTypal, and healthy controls. Due to the different phenomenology between Sz and SzTypal patients in addition to the potential role of a dynamic pathological brain process in the development of psychosis (18), we predicted progressive insular atrophy in Sz (particularly the FE group), but not in SzTypal patients, which may be associated with symptomatology. We also examined the influence of antipsychotic medication on longitudinal insular changes.

MATERIALS AND METHODS

Participants

Study participants included 40 patients with Sz (23 FE and 17 chronic cases), 14 with SzTypal disorder, and 21 healthy controls (**Table 1**) who were scanned twice with an inter-scan interval of approximately 2 to 3 years using the same scanner/parameters; they were all right-handed and healthy physically without any previous history of serious medical diseases (including neurological illnesses and head trauma) or substance abuse disorder. The insular cortex volumes of 14/23 FESz, 4/17 chronic Sz, 12/14 SzTypal, and 14/21 healthy controls in this cohort were reported in our previous cross-sectional study (21); however, this was the first longitudinal study on the insular cortex using our data.

As described elsewhere (19, 22), Sz and SzTypal patients fulfilling the research criteria for ICD-10 (13) were recruited from the in- and outpatient clinics of the Department of Neuropsychiatry, Toyama University Hospital. Diagnoses were confirmed in a structured clinical interview [i.e., the Comprehensive Assessment of Symptoms and History (23)], supplemented by a detailed review of medical charts and clinical symptoms, which were rated at the time of scanning using the Scale for the Assessment of Negative/Positive Symptoms [SANS/SAPS (24)]. FESz patients were defined by an illness duration ≤ 1 year (N = 19) or under first psychiatric hospitalization (N = 4) at baseline (25, 26), while chronic Sz patients were defined as those with an illness duration > 3 years at baseline. The sample characteristics and recruitment strategy of our clinic-based SzTypal cohort were previously described in detail (19, 22, 27, 28); participants also met the DSM Axis II diagnosis of SzTypal personality disorder (14) and none developed overt psychosis during the follow-up period (mean = 2.9 years, SD = 0.8). They visited our hospital because of the distress or associated problems (e.g., irritability, anxiety and depressive symptoms, and suicidal ideation) stemming from their SzTypal features, which required clinical care including antipsychotic medications. Thus, our SzTypal cohort was considered to be more severely ill than SzTypal individuals among the general population. **Table 1** shows a summary of the medication status of participants as well as other clinical data.

Healthy controls, who were screened for a personal or family history of neuropsychiatric disorders among first-degree relatives (29), were recruited from the community, university students, and hospital staff. The Committee on the Medical Ethics of Toyama University approved the study protocol. All study participants provided written informed consent in accordance with the Declaration of Helsinki. When participants were under the age of 20 years, written consent was also obtained from the parent or guardian.

MRI Scanning

Participants were scanned twice at Toyama University Hospital by a 1.5T Magnetom Vision (Siemens Medical System, Inc., Erlangen, Germany) with identical protocols; T1-weighted 1.0-mm continuous sagittal images were obtained using three-dimensional gradient-echo sequence FLASH (time to echo = 5 ms, time repetition = 24 ms, flip angle = 40°, matrix size = 256 × 256, and voxel dimensions = 1 × 1 × 1 mm). As described previously (30), intracranial volume (ICV) was measured on reformatted 5-mm sagittal slices using the anatomical landmarks described by Eritaia et al. (31).

TABLE 1 | Demographic/clinical characteristics of study participants.

	C	SzTypal	FESz	Chronic Sz	Group comparisons
	(12M, 9F)	(10M, 4F)	(15M, 8F)	(7M, 10F)	
Age (years) [range]	24.1 ± 5.6 [18.0 to 38.0]	23.0 ± 4.9 [16.3 to 34.4]	23.5 ± 4.8 [17.9 to 32.7]	31.2 ± 7.1 [19.4 to 45.3]	F (3, 71) = 8.14, P < 0.001; C, SzTypal, FESz < Chronic Sz
Height (cm)	165.0 ± 7.3	166.6 ± 9.2	165.0 ± 7.9	163.2 ± 9.2	F (3, 71) = 0.54, P = 0.660
Education (years)	15.1 ± 2.3	12.5 ± 2.4	13.1 ± 1.6	14.2 ± 2.5	F (3, 71) = 5.23, P = 0.003; SzTypal, FESz < C
Parental education (years)	12.8 ± 2.8	12.1 ± 1.6	12.7 ± 2.1	11.8 ± 1.5	F (3, 71) = 0.92, P = 0.438
Inter-scan interval (years) [range]	2.6 ± 0.4 [2.0 to 3.2]	2.9 ± 0.8 [1.8 to 4.4]	2.6 ± 0.8 [1.0 to 4.5]	2.2 ± 0.8 [1.2 to 4.0]	F (3, 71) = 2.60, P = 0.059
Onset age (years)	–	–	22.4 ± 4.8	22.7 ± 5.8	F (1, 38) = 0.03, P = 0.865
Illness duration at baseline (months) [range]	–	–	9.5 ± 9.1 [1.2 to 40.8]	96.2 ± 37.7 [43.2 to 168.0]	F (1, 38) = 114.59, P < 0.001; FESz < Chronic Sz
Duration of medication at baseline (months) [range]	–	42.2 ± 60.2 [1.2 to 204.0]	7.8 ± 9.7 [0 to 37.2]	75.9 ± 60.8 [1.2 to 196.8]	F (2, 51) = 10.56, P < 0.001; FESz < Chronic Sz
Medication type during follow-up (typical/atypical/mixed)	–	5/8/1	3/16/4	5/9/3	Fisher's exact test, P = 0.49
Medication dose (HPD equivalent)					
Baseline (mg/day) [range]	–	6.4 ± 7.6 [1.2 to 29.5]	13.5 ± 11.4 [2.3 to 41.1]	10.9 ± 7.9 [2.7 to 33.1]	F (2, 51) = 2.48, P = 0.094
Cumulative dose during follow-up (mg) [range]	–	7030.7 ± 7243.2 [758.2 to 24303.0]	9526.4 ± 8609.2 [1333.0 to 37436.0]	11763.9 ± 11054.2 [849.1 to 43265.6]	F (2, 51) = 1.03, P = 0.365
Mean dose during follow-up (mg/day) [range]	–	6.2 ± 5.1 [0.9 to 17.1]	9.5 ± 7.2 [2.5 to 27.0]	15.1 ± 10.0 3.9 to 35.9]	F (2, 51) = 5.30, P = 0.008; SzTypal < Chronic Sz
SAPS total					
Baseline	–	17.6 ± 9.6 (N= 13)	29.0 ± 24.3 (N= 20)	31.9 ± 27.3 (N= 16)	F (2, 46) = 1.59, P = 0.216
Follow-up	–	13.6 ± 11.3 (N= 14)	17.0 ± 17.1 (N= 22)	33.7 ± 29.4 (N= 17)	F (2, 50) = 4.46, P = 0.016; SzTypal < Chronic Sz
SANS total					
Baseline	–	54.8 ± 22.1 (N= 13)	52.1 ± 25.5 (N = 20)	50.8 ± 16.4 (N= 16)	F (2, 46) = 1.21, P = 0.886
Follow-up	–	42.3 ± 16.6 (N= 14)	38.0 ± 22.5 (N= 22)	55.8 ± 19.1 (N= 17)	F (2, 50) = 3.96, P = 0.025; FESz < Chronic Sz

Values represent means ± SD unless otherwise stated. Groups were matched for gender (Chi-squared = 3.51, P = 0.319).
C, controls; F, female; FE, First-episode; HPD, haloperidol; M, male; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms. Sz, schizophrenia; SzTypal, schizotypal disorder.

Insular Cortex Measurements

The insular cortex was manually measured on reconstructed 1-mm continuous coronal slices of the gray matter component, which was automatically segmented by the signal intensity histogram distribution of the whole cerebrum, using Dr. View software (Infocom, Tokyo, Japan) (32). As fully described previously (21, 33), the short (anterior) and long (posterior) insular cortices were manually delineated by one rater (TT) blinded to the identity of participants and the time at which scanning was performed (baseline or follow-up). Specific anatomical landmarks for measurements (i.e., the orbito- and central insular sulci, superior and inferior circular insular sulci,

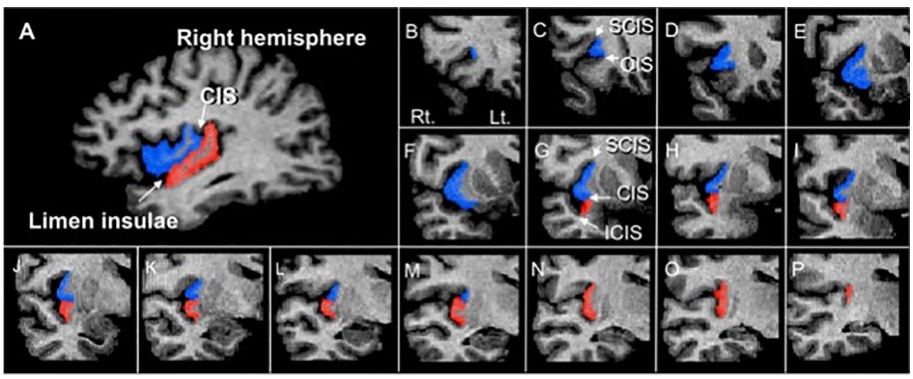

FIGURE 1 | A sagittal slice **(A)** and sample coronal slices **(B–P)** of short (blue) and long (red) insular cortices manually traced in this study. CIS, central insular sulcus; ICIS, inferior circular insular sulcus; OIS, orbitoinsular sulcus; SCIS, superior circular insular sulcus.

and limen insulae) were easily identified using sagittal and coronal views (**Figure 1**). The inter- (TT and MK) and intra-rater intraclass correlation coefficients (ICC) of the measurements in 10 randomly selected brains were all > 0.87.

Statistical Analysis

A one-way analysis of variance (ANOVA), the chi-squared test, and Fisher's exact test were performed to assess group differences in demographic and clinical data.

In cross-sectional comparisons of insular cortex volumes, absolute volume was analyzed using an analysis of covariance (ANCOVA) with the between-subject factor of diagnosis, within-subject variables of hemisphere and subregion (short, long), and covariates of age, ICV, and medication dose. Regarding longitudinal volume changes in the insular cortices, the dependent variable % volume change [100 × (absolute volume at the follow-up - absolute volume at the baseline)/ absolute volume at the baseline] was used; ANCOVA was performed using the between-subject factor of diagnosis, within-subject variables of hemisphere and subregion, and covariates of age at baseline, ICV, inter-scan interval, and cumulative dose of antipsychotics during scans. Post-hoc Spjotvoll & Stoline tests were used to follow up significant effects yielded in ANCOVA. The insular volumes used in these ANCOVAs (i.e., absolute volume and % volume change) were normally distributed (tested by the Shapiro-Wilk test). The statistical conclusions reported here did not change even when absolute volume changes in the insular cortex over time were assessed by ANCOVA with time (baseline, follow-up) as the within-subject variable, when gender was added as a covariate, when the covariates without significant group differences were excluded, or when only 19 patients with Sz with illness duration ≤ 1 year were included in the FESz group.

Relationships between % volume changes in the insular cortex and clinical variables [total SANS/SAPS scores (score changes between scans and scores at second scan) and cumulative medication doses during the follow-up] were investigated by Pearson's partial correlation coefficients controlled for the inter-scan interval and ICV. SAPS scores and medication doses, which did not have a normal distribution (tested by the Shapiro-Wilk test), were log-transformed. The insular volume was not subdivided into the short and long cortices because of the lack of prominent subregional effects for its longitudinal changes. To reduce the Type I error rate, relationships were tested based on previous hypotheses. Since dynamic brain changes around the onset of Sz may be associated with the development and treatment responses of positive and negative symptoms (11, 12), we examined the relationship between % volume changes in the insular cortex and SANS/SAPS score changes in the FESz group. Due to the lack of active symptom changes in the chronic stage (**Table 1**) as well as the notion that prolonged brain changes may lead to poor functional outcomes and severely negative symptoms (12, 34), the potential relationship between % volume changes in the insular cortex and total SANS scores in the follow-up was examined in chronic Sz patients. SzTypal patients were excluded from correlational analyses because of the lack of longitudinal insular changes. The results of these correlational analyses remained essentially the same even when we used no controlling factors (i.e., inter-scan interval and ICV).

A P-value of < 0.05 was considered to be significant. A Bonferroni correction was employed for correlation analyses.

RESULTS

Sample Characteristics

Groups in the present study were matched for gender, height, parental education, and the inter-scan interval, while the education level was lower in the FESz and SzTypal groups than in the control group. As expected, the chronic Sz group was characterized by an older age than all other groups, a longer illness/medication duration than the FESz group, and more severe symptoms than the other clinical groups (**Table 1**).

Cross-Sectional Comparisons of the Insular Cortex

Table 2 shows baseline comparisons, which revealed a smaller insular cortex in the FE and chronic Sz groups than in the SzTypal (post-hoc tests, *vs.* FESz and chronic Sz: $P < 0.001$) and control (post-hoc tests, *vs.* FESz: $P = 0.035$; *vs.* chronic Sz: $P < 0.001$) groups. The insular cortex was also significantly smaller in the chronic Sz group than in the FESz group (post-hoc test, $P = 0.004$). No significant group-by-subregion (**Table 2**) and group-by-hemisphere [F (3, 71) = 2.69, $p = 0.053$] interactions were observed.

Similar results were obtained in group comparisons in follow-ups, with a smaller insular volume being observed in the FE and chronic Sz groups than in the SzTypal and control groups (post-hoc tests, all $P < 0.001$) and no prominent subregional effect (**Table 2**). However, no significant differences were observed in the insular cortex volume between the FE and chronic Sz groups in follow-ups (post-hoc test, $P = 0.278$).

Longitudinal Comparison of the Insular Cortex

Volume reductions over time were significantly larger in the FESz group than in all other groups (post-hoc tests, *vs.* chronic Sz: $P = 0.009$; *vs.* SzTypal and controls: $P < 0.001$) (**Figure 2**), with no significant group-by-subregion (**Table 2**) and group-by-hemisphere [F (3, 71) = 1.99, $p = 0.123$] interactions.

We also tested the potential effect of the medication type during follow-ups [atypical ($N = 16$) vs. typical or mixed ($N = 7$)] on progressive insular atrophy in the FESz group, but did not find any effect.

Correlational Analyses

Greater volume reductions in the left ($r = 0.532$, $P = 0.028$) and right ($r = 0.596$, $P = 0.012$) insular cortices over time in the FESz group correlated with fewer improvements (or the deterioration) in positive symptoms rated by total SAPS scores, which survived the Bonferroni correction for multiple comparisons for the right hemisphere (**Figure 3**). This correlation was not found for

TABLE 2 | Brain measurements of study participants.

	C	SzTypal	FESz	Chronic Sz	Effect of diagnosis	Diagnosis × subregion
Intracranial volume (cm^3)	1495 ± 138	1611 ± 119	1476 ± 140	1527 ± 194	F (3, 70) = 2.84, P = 0.044[a]	–
Whole gray matter (cm^3)						
Baseline	698 ± 68	750 ± 73	685 ± 78	653 ± 69	F (3, 68) = 1.69, P = 0.177	–
Follow-up	694 ± 76	733 ± 59	661 ± 65	639 ± 71	F (3, 68) = 1.49, P = 0.225	–
% change/year	-0.3 ± 1.2	-0.8 ± 2.0	-1.2 ± 2.0	-1.2 ± 2.4	F (3, 67) = 0.88, P = 0.459	–
Whole insular cortex						
Baseline (mm^3)					F (3, 68) = 8.53, P < 0.001; Chronic Sz < FESz <C, SzTypal	F (3, 71) = 1.50, P = 0.223
L	8317 ± 784	8536 ± 970	7668 ± 1113	6723 ± 1003		
R	7859 ± 735	8566 ± 1015	7380 ± 896	6723 ± 906		
Follow-up (mm^3)					F (3, 68) = 9.26, P < 0.001; Chronic Sz, FESz < C, SzTypal	F (3, 71) = 2.49, P = 0.067
L	8324 ± 911	8643 ± 991	6999 ± 1116	6508 ± 1005		
R	7834 ± 768	8409 ± 850	6835 ± 913	6537 ± 936		
% change/year[b]					F (3, 67) = 7.55, P < 0.001; FESz < Chronic Sz, C, SzTypal	F (3, 71) = 0.89, P = 0.453
L	-0.1 ± 1.3	0.5 ± 1.4	-3.4 ± 3.7	-1.5 ± 2.2		
R	-0.1 ± 1.4	-0.6 ± 1.4	-2.9 ± 2.7	-1.6 ± 2.5		
Short insular cortex						
Baseline (mm^3)					–	–
L	5478 ± 690	5424 ± 661	5051 ± 688	4365 ± 771		
R	5025 ± 612	5505 ± 642	4777 ± 713	4342 ± 763		
Follow-up (mm^3)					–	–
L	5502 ± 790	5437 ± 648	4633 ± 674	4214 ± 700		
R	5017 ± 696	5434 ± 602	4444 ± 667	4196 ± 799		
% change/year[b]					–	–
L	0.0 ± 1.9	0.2 ± 1.8	-3.3 ± 3.3	-1.5 ± 2.2		
R	-0.1 ± 1.9	-0.4 ± 1.2	-2.8 ± 2.6	-1.9 ± 2.6		
Long insular cortex						
Baseline (mm^3)					–	–
L	2839 ± 532	3112 ± 627	2617 ± 650	2357 ± 593		
R	2834 ± 516	3061 ± 666	2603 ± 496	2381 ± 445		
Follow-up (mm^3)					–	–
L	2822 ± 526	3206 ± 641	2366 ± 645	2294 ± 614		
R	2817 ± 460	2975 ± 593	2391 ± 468	2342 ± 430		
% change/year[b]					–	–
L	-0.2 ± 2.6	1.1 ± 1.6	-3.7 ± 5.0	-1.3 ± 2.2		
R	-0.1 ± 2.1	-0.8 ± 2.6	-3.2 ± 3.3	-1.1 ± 2.7		

Values represent means ± SD.

C, controls; FE, First-episode; L, left; R, right; Sz, schizophrenia; SzTypal, schizotypal disorder.

[a]*Age was used as a covariate. Post-hoc tests showed no significant group differences.*

[b]*A negative value indicates a decrease in volume. Statistical analyses were based on % changes controlling for inter-scan intervals (see text).*

changes in total SANS scores (left, r = 0.204, P = 0.432; right, r = 0.097, P = 0.712).

In follow-ups on chronic Sz, volume reductions over time in the insular cortex correlated with higher total SANS scores on the left (r = 0.602, P = 0.018), but not right (r = 0.373, P = 0.171), hemisphere.

In the FE and chronic Sz groups, insular cortex volume changes did not correlate with cumulative medication doses between scans.

We also investigated whether a relationship exists between % gray matter reductions in the insular cortex and superior temporal gyrus (19) in FESz (N = 18), but found no correlation (left, r = −0.245, P = 0.360; right, r = 0.215, P = 0.424).

DISCUSSION

As far as we know, this is the first follow-up MRI study that investigated progressive gray matter changes in insular subregions at different stages of Sz (i.e., the FE and chronic phases) as well as in SzTypal disorder. The results obtained revealed significant longitudinal insular atrophy over time in the FESz group without prominent subregional or medication effects, which was associated with treatment responses to positive psychotic symptoms. We also detected mild (non-significant) insular atrophy in chronic Sz that might contribute to the severity of negative symptoms. In contrast, no insular volume changes were observed in SzTypal patients or the healthy controls during the follow-up period. These results support the dynamic pathophysiological trajectory of the insular cortex being specific to overt Sz among the spectrum disorders examined and also suggest that its degree and role in symptomatology may differ across the illness stages.

The present results obtained on dynamic gray matter atrophy during the course of Sz are consistent with the findings of a longitudinal MRI investigation on an independent cohort at various stages of psychosis, in which patients with psychotic

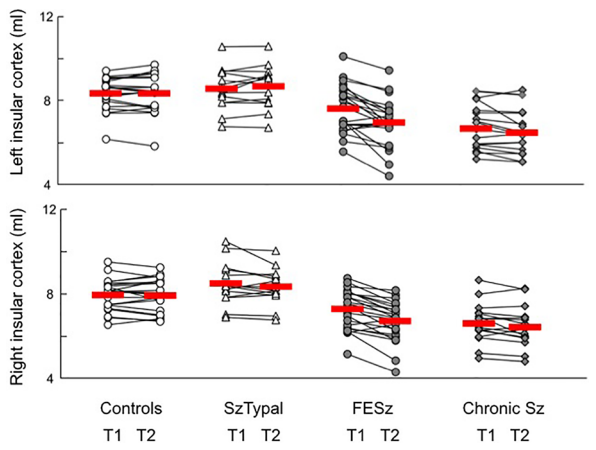

FIGURE 2 | Absolute volume of the insular cortex in participants. Due to the absence of the significant effect of subregion (i.e., short and long insular cortices), we showed the volumes of the whole insular cortex. The values of baseline (T1) and follow-up (T2) scans in each participant are connected with a straight line. Horizontal bars indicate the means of each group.

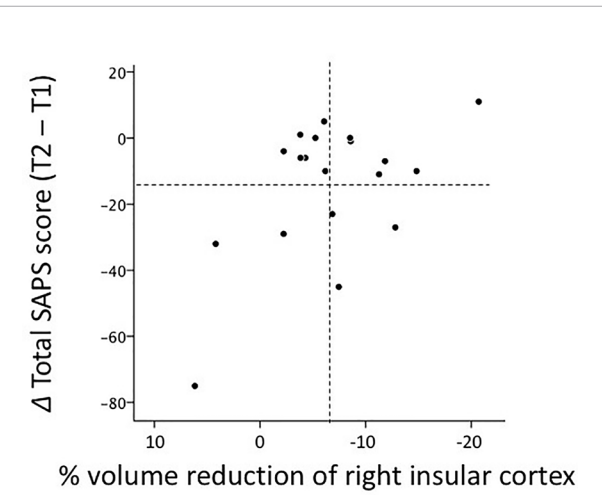

FIGURE 3 | Relationship between gray matter reductions in the right insular cortex over time and score changes in Scale for the Assessment of Positive Symptoms (SAPS) between baseline (T1) and follow-up (T2) scans (i.e., absolute total score at T2 - absolute total score at T1) in 19 patients with first-episode schizophrenia. Regarding % volume reductions, negative values indicate volume decreases. Dotted lines indicate the mean values (all values in the figure are within three standard deviations of the mean).

disorders (predominantly Sz) had a smaller insular volume even before illness onset, but exhibited further active gray matter reductions during the transition period (−5.0%/year) and thereafter (−2.2%/year), followed by mild atrophy over time in the chronic stages (−0.7%/year) (10, 11). Consistent with previous findings, we found that patients with greater insular gray matter loss during FE showed fewer improvements in or the deterioration of clinical symptoms (10, 11, 35), particularly positive psychotic symptoms, and also demonstrated that mild but prolonged atrophy at the later illness stages may still contribute to negative symptomatology. These results support the notion that "late neurodevelopmental" pathologies around illness onset may underlie the development of psychosis (36, 37) and that progressive brain changes, which may differ between the clinical subtypes (38), may persist even at the later illness stages at least in specific subgroups of Sz and cause continued clinical deterioration (12, 34). Furthermore, while the trajectory of insular changes and its relationship with psychotic symptoms in the early stages are consistent with previous findings obtained on the superior temporal gyrus (19, 39, 40), the lack of a direct relationship between longitudinal changes in these peri-Sylvian structures suggests regional specificity in dynamic brain changes of Sz.

In spite of the results obtained in this structural MRI study, the mechanisms underlying insular gray matter changes in Sz remain unclear. However, a reduced insular volume before or at the onset of psychosis (3, 8, 9), particularly for the short insula (4, 10), may be partly explained by a post-mortem histological finding suggestive of neuronal migratory disturbances during early neurodevelopment in this region (41). On the other hand, potential mechanisms for the ongoing insular atrophy observed may include the excessive elimination of synapses, anomalies in synaptic plasticity, and neurotoxic effects caused by a glutamatergic excess due to *N*-methyl-*D*-aspartate receptor hypofunction (36, 42). The dynamic brain pathology in Sz may (19, 43) or may not (44, 45) be ameliorated by antipsychotic medication; however, the present results showed that medication did not significantly affect insular gray matter changes. The findings of a previous cross-sectional MRI study on medication-naïve FESz also supported age-related insular atrophy being independent of antipsychotic medication (42). Nevertheless, further longitudinal studies ideally using multimodal techniques are needed to obtain a more detailed understanding of the longitudinal pathologies of Sz as well as the factors influencing these processes.

An important result of the present study was the absence of progressive gray matter changes in the insular cortex of SzTypal patients. In combination with previous cross-sectional findings showing that SzTypal patients are characterized by normal or even larger fronto-limbic structures (including the insular cortex) compared to healthy controls (18, 21, 22), the present results on SzTypal represent a potential protective factor against the overt psychosis and severe cognitive/social deficits associated with Sz (15). While the cross-sectional findings of common gray matter reductions in temporal regions (e.g., superior temporal gyrus) may underlie biological and phenomenological commonalities within the Sz spectrum (16–18), SzTypal patients do not appear to exhibit dynamic brain changes even in these temporal regions (19, 20). A recent follow-up MRI study showing the absence of progressive gray matter changes in the insular cortex in FE affective psychosis (35) also supports active pathological processes in the insular cortex being specific to overt Sz.

While this structural MRI study cannot directly address functional role of the insular abnormalities in the

pathophysiology of Sz, previous functional neuroimaging studies have suggested that the insular cortex (especially its anterior portion) is involved in the generation of inner speech as a part of the salience network and is aberrantly active during the auditory hallucinations in Sz (5, 46). Interestingly, alterations of activation and functional connectivity in salience networks likely exist at earliest stages of Sz (47, 48) and are associated with treatment response (6), with the progression during early illness stages (47). Although the trajectory of salience network deficits at later illness stages and their contribution to negative symptomatology remain unclear, our longitudinal findings of the insular volume in SzTypal patients, who are generally spared from overt psychosis such as hallucinations (15), and different stages of Sz may partly support the concept of salience network dysfunction in Sz (5).

Several potential confounding factors need to be considered. First, the present preliminary study was clearly limited by the small sample size examined. Despite the potential role of the subregional specificity of insular abnormalities (i.e., anterior cognitive/affective *vs.* posterior somatosensory portions) in the pathophysiology of Sz (4, 49) as well as detailed manual delineation that could reflect inter-individual morphological variations of the insular subregions (1, 2), we failed to identify a subregional effect in cross-sectional and longitudinal insular findings. Furthermore, although typical and atypical antipsychotics may exert different effects on brain morphology in the early stages of Sz (50), we did not observe any effects of the antipsychotic types on insular volume changes over time. These somewhat unexpected results may be partly explained by the limited statistical power caused by the small sample size. It should be also noted that potential contribution of prolonged brain changes to clinical deterioration needs to be tested in future using larger cohorts of chronic Sz. Another limitation of sampling is that we could not exclude the possibility of some sampling biases. Indeed, at follow-up, FESz patients exhibited lower SAPS scores than those of chronic patients (**Table 1**), raising the possibility that only the patients with good treatment response have been successfully followed up and participated in this longitudinal study. Second, we did not systematically assess cognitive or social functioning in the patient groups. Based on the role of the insular cortex in social/emotional processing and various cognitive functions as a component of the "limbic integration cortex" (1, 2), the potential contributions of dynamic insular changes on socio-cognitive measures in Sz warrant further study. Finally, although we found no relationship between progressive changes in the insular cortex and another peri-Sylvian structure [i.e., superior temporal gyrus (19)] in the FESz group, other key brain regions [e.g., prefrontal cortex (51)] need to be investigated in future studies in order to clarify the regional specificity of the present results. Especially, future whole brain automated assessment would complement our hypothesis-driven region-of-interest findings.

In summary, the results of this follow-up MRI study revealed non-linear gray matter reductions in the insular cortex during the course of Sz that were more prominent during the early phases, but persisted even at the chronic stage and were not affected by antipsychotic medication. These progressive brain changes at various illness stages differently contributed to symptom formation in Sz, but were not observed in SzTypal patients, who were spared from developing overt psychosis. These results may reflect a pathophysiological trajectory that is specific to overt Sz among the spectrum disorders tested.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because we do not have permission to share the data. Requests to access the datasets should be directed to TT, tsutomu@med.u-toyama.ac.jp.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Committee on the Medical Ethics of Toyama University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TT and MS conceived the concept and methods for the present study. TT performed statistical analyses and wrote the manuscript. DS, MN, and AF recruited participants and conducted clinical and diagnostic assessments. TT and MK analyzed MRI data. KN provided technical support for MRI scanning and data processing. AF, DS, and MN managed MRI and clinical data. YT and MS contributed to the writing and editing of the manuscript. All authors contributed to the article and approved the submitted version.

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EEG Microstate Differences in Medicated vs. Medication-Naïve First-Episode Psychosis Patients

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There has been considerable interest in the role of synchronous brain activity abnormalities in the pathophysiology of psychotic disorders and their relevance for treatment; one index of such activity are EEG resting-state microstates. These reflect electric field configurations of the brain that persist over 60–120 ms time periods. A set of quasi-stable microstates classes A, B, C, and D have been repeatedly identified across healthy participants. Changes in microstate parameters coverage, duration and occurrence have been found in medication-naïve as well as medicated patients with psychotic disorders compared to healthy controls. However, to date, only two studies have directly compared antipsychotic medication effects on EEG microstates either pre- vs. post-treatment or between medicated and unmedicated chronic schizophrenia patients. The aim of this study was therefore to directly compare EEG resting-state microstates between medicated and medication-naïve (untreated) first-episode (FEP) psychosis patients (mFEP vs. uFEP). We used 19-channel clinical EEG recordings to compare temporal parameters of four prototypical microstate classes (A–D) within an overall sample of 47 patients (mFEP $n = 17$; uFEP $n = 30$). The results demonstrated significant decreases of microstate class A and significant increases of microstate class B in mFEP compared to uFEP. No significant differences between groups were found for microstate classes C and D. Further studies are needed to replicate these results in longitudinal designs that assess antipsychotic medication effects on neural networks at the onset of the disorder and over time during illness progression. As treatment response and compliance in FEP patients are relatively low, such studies could contribute to better understand treatment outcomes and ultimately improve treatment strategies.

Keywords: electroencephalography, resting-state, schizophrenia, antipsychotic, neuroleptic, untreated, unmedicated, pathophysiology

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INTRODUCTION

Delusions, hallucinations, disorganized speech, catatonic behavior, and negative symptoms form the core of psychotic disorders [DSM-5®, (1)]. The lifetime prevalence of psychotic disorders is estimated at 0.75% (2). Compared to the general population, patients' life expectancy is estimated to be shortened by 15–20 years due to increased physical morbidity (3). Patients' everyday functioning

such as independent living, productive activity, and social functioning is often impaired, leading to high costs beyond their medical treatment (4). Good functional outcomes were found to be related to shorter duration of untreated psychosis (5) which calls for timely and effective treatment at an early illness stage. However, discontinuation rates within 18 months of antipsychotic treatment due to inefficiency or intolerable side effects were observed to be relatively high (64–82%) in psychotic disorders (6) with a recovery rate estimated at only 13.5% (7). This clearly calls for more research on antipsychotic medication and how EEG markers and neural networks differentiate between medicated and unmedicated patients with psychotic disorders.

Electroencephalography (EEG) is one method in neuroscience research that offers several advantages. Apart from being inexpensive, non-invasive, and easy to implement, EEG can capture the fast-changing dynamics of neuronal networks with high temporal resolution in frequency bands ranging from 1 Hz to up to 200 Hz (8, 9). This allows EEG to depict coupling patterns of neural activity that might not be captured by functional Magnetic Resonance Imaging (10). There is a large body of research that has studied neuronal network disruptions in psychotic disorders using EEG methods and extensive reviews exist on the topic (11–14).

The term "resting-state" refers to intrinsic patterns of the awake state in which participants are not performing an explicit mental or physical task (15) and are postulated to show the underlying intrinsic mechanisms of the brain which influence stimulus processing as well as behavioral phenomena (16). An accumulation of evidence has shown that EEG resting-state microstates are a suitable tool to study the temporal dynamics of resting-state brain networks: EEG microstates are spatial configurations of scalp global field power that remain stable for a short period of time (60–120 ms) and occur several times per second (17, 18). These short-lasting, non-overlapping configurations of brain electric states have been divided into four prototypical microstate classes A, B, C, and D that each have a different orientation of the scalp-electric field (19): Microstate A has a left occipital to right frontal orientation, microstate B a right occipital and left frontal, microstate C a symmetric occipital to prefrontal and microstate D a symmetric frontocentral to occipital orientation (17). These four classes explain 65–84% of EEG data variance (20) and were shown to have high test-retest reliability and cross-method consistency (21). The microstate classes are described by three statistical parameters; the duration of each class in milliseconds, mean number of occurrence per second and percentage of time covered by each class (17).

Microstates were hypothesized to be the fundamental building blocks of human information processing and were found to differ across sex groups (22), over the course of development (17, 22) and between different brain states such as sleep and wakefulness (23, 24). Studies using simultaneous EEG-fMRI methods have correlated microstate classes to different resting-state networks (25, 26). Furthermore, abnormal patterns have been described in various mental conditions (27–30), most notably in psychotic disorders: Microstate differences across all classes were found for medicated (31–35), as well as medication-naïve patients with psychotic disorders (30, 36–38) compared to healthy controls, as well as patients in the high-risk state of psychosis (31, 36, 39). Two recent meta-analyses found increased occurrence of microstate C and decreased duration of microstate D to be consistently reported across studies in medicated as well as medication-naïve patients with psychotic disorders (40, 41).

So far, it is not clear whether and how antipsychotic medication treatment plays a role in EEG resting-state microstate abnormalities in patients with psychotic disorders. Antipsychotics have been shown to modulate neural networks in fMRI studies (42, 43) and to have effects on microstate parameters by increasing the mean duration of all microstate classes in healthy individuals (44). However, so far only two studies investigated the effects of antipsychotic treatment on EEG microstates in patients with psychotic disorders. A cross-sectional study from more than two decades ago with chronic schizophrenia patients reported antipsychotic treatment to be negatively correlated with microstate duration in a dose-dependent way and average microstate duration was longer in unmedicated than medicated patients (45). Moreover, increased duration of microstate classes A and D, and decreased occurrence of microstate class C was reported in responders vs. non-responder schizophrenia patients following 2–8 week treatment with antipsychotics in a longitudinal design (37). However, the latter findings were based on a small sample size ($n = 14$) and have not yet been replicated.

The present study therefore aimed to investigate the effects of antipsychotic treatment on EEG resting-state microstate parameters by comparing medicated first-episode psychosis patients (mFEP) to a control group of patients who were medication-naïve (untreated first-episode psychosis; uFEP). Our comparisons were set out to investigate differences in parameters of microstate classes A-D that might be attributed to the medication status of the two patient groups beyond the effect of the disorder. As the results of previous studies have been inconsistent so far, we based our study hypotheses on a recent study by our group (36) in which we suggested that microstate A and B may be state markers for psychotic disorders. We therefore hypothesized antipsychotics to associate with microstate A and B and these microstates to differentiate the two patient groups.

METHODS

The data used in this paper was collected in the FePsy project (***Früherkennung von Psychosen***; Early Detection of Psychoses) of the University of Basel Psychiatric Clinics (UPK) during the time period from 2000–2013. The aim of the FePsy project was to improve early detection and intervention of psychosis. The study was approved by the local ethics committee and in accordance with the Declaration of Helsinki. Riecher-Rössler et al. (46, 47) provide a comprehensive overview of the FePsy study design.

Participants

All first-episode psychosis (FEP) patients included in the present paper were help-seeking consecutive referrals to the FePsy clinic at the psychiatric outpatient department of the University of Basel Psychiatric Clinics (UPK). Upon inclusion in the FePsy study, written informed consent was given by all participating

TABLE 1 | Sample demographics.

	mFEP	uFEP			
	***n* = 17**	***n* = 30**	**t/χ2**	***p***	***d***
Sex (M:F)	13:4	19:11	0.862	0.353	–
Age at diagnosis (years) (mean [SD])	27.68 (5.1)	28.63 (7.5)	−0.517*	0.608	0.148
BPRS (mean [SD])	47.66 (7.15)	53.68 (10.84)	−1.70	0.10	0.66
Total score					
Depression/anxiety	9.45 (3.24)	11.70 (4.39)	−1.54	0.13	0.58
Psychosis/thought disturbance	10.64 (2.46)	12.13 (3.37)	−1.33	0.19	0.50
Negative symptoms	5.41 (2.20)	5.72 (2.76)	−0.34	0.74	0.12
Activation	6.73 (3.16)	7.28 (3.50)	−0.45	0.65	0.16
Duration of illness (months) (mean [SD])	24.83 (22.61)	23.77 (35.36)	0.11	0.91	0.04
Comorbidities (ICD-10)			–	0.81**	–
F10-F19[1]	0	1			
F30-F39[1]	5	7			
F40-F49[1]	1	0			
F60-F69[1]	0	1			
CPZ equivalent dose (mean [SD])	210.29 (262.71)	n/a	–	–	–
Further medication			–	1**	–
Antidepressants	2	4			
Anxiolytics	4	7			
Mood stabilizers	0	0			
Other	1	2			
Current drug use			–	0.44**	–
Yes	11	20			
No	5	4			
Current alcohol use			–	1**	–
Yes	8	12			
No	8	12			
Cannabis use			–	0.52**	–
1)Earlier					
Yes	9	18			
No	7	5			
2)Currently					
Yes	6	9			
No	11	18			
Verbal IQ* (mean [SD])	103 (16.04)	107.28 (14.34)	−0.84	0.41	0.28
School education (years) (mean [SD])	10.71 (3.25)	11.20 (3.22)	−0.50	0.62	0.15
Education level			–	0.84**	–
Education ongoing	2	1			
Primary school	1	1			
Secondary school	9	11			
Upper/specialized secondary school	1	2			
High school without completion	0	2			
High school	3	6			
Current employment			–	0.71**	–
Yes	3	6			
No	13	17			
EEG total analysis time (seconds) (mean [SD])	300.30 (74.83)	299.20 (44.72)	0.055	0.957	0.018
EEG explained variance (%) (mean [SD])	77.43 (3.36)	77.36 (3.61)	0.073	0.942	0.020

*mFEP, medicated first-episode psychosis patients; uFEP, untreated, medication-naïve first-episode psychosis patients; BPRS, Brief Psychiatric Rating Scale; CPZ, Chlorpromazine; SD, standard deviation; d, Cohen's d effect size; *assessed with the German version of the multiple choice vocabulary test [Mehrfach-Wortschatz-Test; (52)]; **Fischer's exact test applied. [1]F10-F19, Mental and behavioral disorders due to psychoactive substance use; F30-F39, Mood [affective] disorders; F40-F49, Neurotic, stress-related and somatoform disorders; F60-F69, Disorders of adult personality and behavior. Significance level is 0.05.*

patients. The Basel Screening Instrument for Psychosis [BSIP; Riecher-Rössler et al. (47, 48)] was used to determine the FEP status, diagnostics were made according to ICD-10 (49), the Brief Psychiatric Rating Scale [BPRS; (50, 51)] was applied to assess patients' symptom severity, and the German version of the multiple choice vocabulary test [Mehrfach-Wortschatz-Test; (52)] was used to assess verbal IQ. The status of medication-naïve was defined by the absence of any lifetime antipsychotic treatment and illness duration for both groups was calculated based on the patient's reports in hindsight of the very first occurrence of psychotic symptoms with sufficient severity. As **Table 1** displays, intake of other medication did however occur in the uFEP group.

Exclusion criteria were applied as follows; (1) age < 18 years; (2) insufficient knowledge of German; (3) IQ < 70; (4) serious medical or surgical illness; (5) previous episode of psychosis due to substance abuse, and (6) psychotic symptomatology within a clearly diagnosed affective or borderline personality disorder.

EEG Recording and Pre-processing

A standard clinical EEG protocol of 20 min (incl. resting-state, eyes opening, photostimulation, and hyperventilation) was recorded by a trained lab assistant using 19 gold cup electrodes (Nicolet Biomedical, Inc.) of the International 10–20 system and referenced to linked ears. Participants were comfortably seated in a quiet room. The first 8 min of the entire clinical EEG recording corresponded to a resting-state eyes-closed recording which was used for the present analysis. During this, participants were asked to open their eyes for 6 s every 3 min to avoid drowsiness. When behavioral or EEG signs of drowsiness (e.g., slow rolling eye movements, alpha drop-out, increased beta, or theta activity) occurred, participants were asked to open their eyes. The sampling rate was 256 Hz and electrode impedances were always kept below 5 kΩ.

Brain Vision Analyzer (Version 2.0, Brain Products GmbH, Munich, Germany) was used for offline pre-processing. After bandpass (IIR; 0.5–70 Hz) and notch (50 Hz) filters were

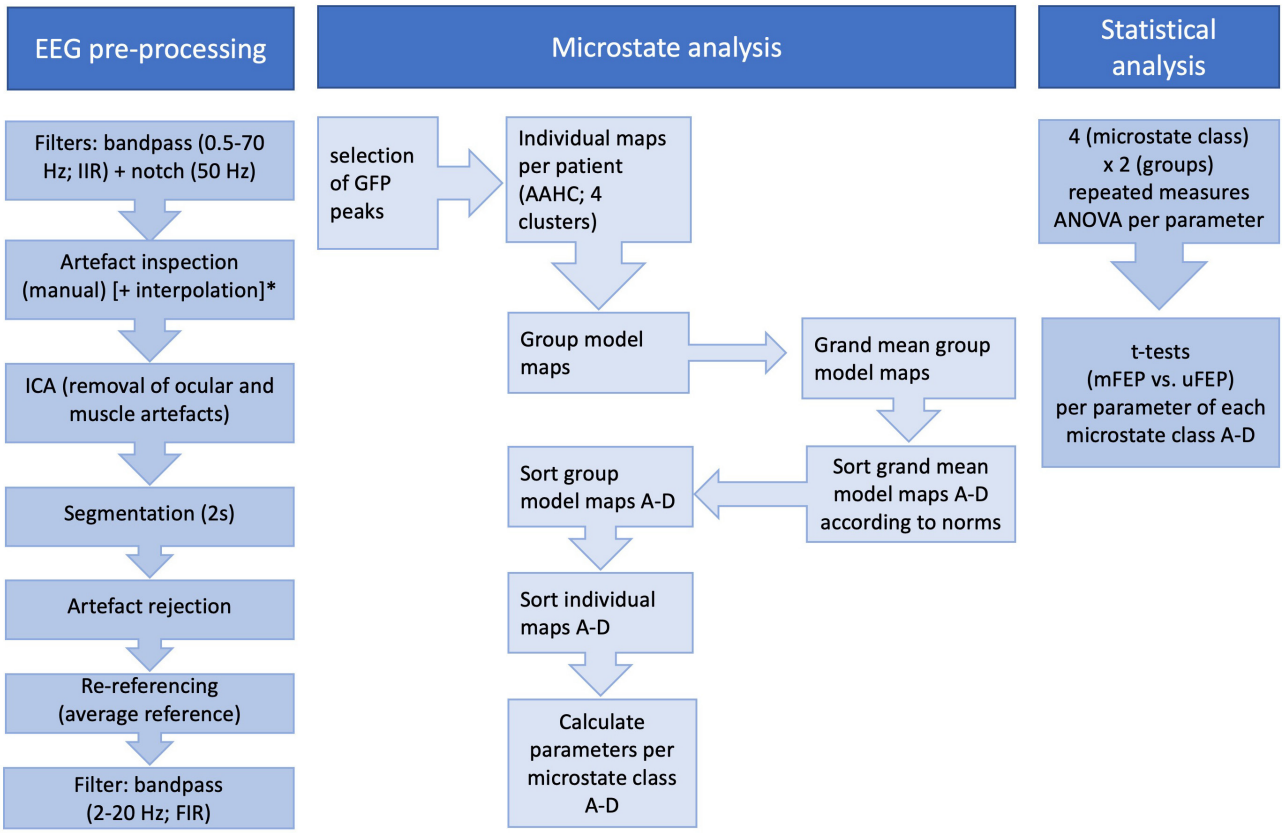

FIGURE 1 | All performed steps of EEG pre-processing, microstate analysis, and statistical analysis. ICA, Independent Component Analysis; GFP, Global Field Power; AAHC, Atomize-Agglomerate Hierarchical Clustering; *Interpolation was only performed for channels with severe artifacts across the whole recording.

applied, eyes-open epochs and epochs with prominent muscle artifacts or bad EEG signals were removed manually upon visual inspection by trained staff. After that, interpolation was applied for channels with severe artifacts across the whole recording and Extended Infomax ICA was used to remove ocular muscle artifacts. The continuous EEG recording was then divided into 2s segments and segments with residual artifacts were removed semi-automatically and by means of visual inspection based on consensus between at least two independent reviewers. Re-referencing was applied with a common average reference and the data was finally bandpass filtered (FIR; 2–20 Hz).

Microstate Analysis

The Microstate Analysis plug-in (Version 0.3; downloaded from http://www.thomaskoenig.ch/Download/EEGLAB_Microstates/) for EEGLAB (53) version 13.6.5b in Matlab (54) was used for the microstate analysis. First, the Global Field Power (GFP) was calculated for each time point of the recording. Since the signal-to-noise ratio is the highest for GFP peaks, microstate configurations remain stable around these peaks (17). Using Atomize-Agglomerate Hierarchical Clustering (AAHC), individual microstate maps for GFP peaks only were calculated for each participant based on the original momentary maps (55). Four microstate classes have been described to explain 65–84% (20) of the EEG variances. Based on this and for comparability with previous studies on psychotic disorders, the number of microstate clusters for the present study was also pre-set to four.

Group model maps were calculated separately for both patient groups using a permutation algorithm that minimized common variance across subjects (19). Based on these group models, a "grand-mean" model was calculated. The grand-mean model was then class-labeled into microstates A–D by using minimal Global Map Dissimilarity and model map norms from Koenig et al. (17). Next, the class-labeled "grand-mean" model maps were used as a template to assign the group model maps to the four class-labeled grand-mean maps. As a final step, the individual microstate maps were sorted according to the class-labeled group model maps. Three parameters were then extracted per microstate class: coverage (percentage of analysis time covered by each microstate class), duration (the average duration of a microstate class in milliseconds), and occurrence per second (total number of each microstate class per second). As the microstate toolbox ignores the first and last segment of the EEG data, only non-truncated microstate parameters are calculated. In addition, microstate transition probabilities (observed minus expected) were calculated. **Figure 1** depicts all analysis steps.

Statistical Analysis

A 4 (microstate class) × 2 (group) repeated measures ANOVA was applied to assess the interactional effect for each microstate parameter. Independent *t*-tests between the two groups (mFEP vs. uFEP) were conducted in order to determine group differences per parameter for each microstate class and demographic variables.

All analyses were carried out using SPSS 25 and R (56). Statistical tests in the present study are two-sided tests and the statistical level was set at $\alpha = 0.05$. When equal variances could not be assumed, the Greenhouse-Geisser correction for ANOVAs and the Welch-Satterthwaite method for the *t*-tests was applied. Microstate results were corrected for multiple comparisons within each parameter (57).

RESULTS

Group Characteristics

From a total of 59 FEP patients with available EEG data, 12 patients were excluded ex post facto due to unclear medication status. Thus, a total of 47 participants were included in the present analysis, consisting of 30 untreated, medication-naïve patients with first-episode psychosis (uFEP) and 17 medicated patients with first-episode psychosis (mFEP). There were no statistically significant differences between the two groups in age at diagnosis, sex distribution, illness duration (months), and symptom severity score as assessed with the Brief Psychiatric Rating Scale (51). **Table 1** displays the demographics of the two study groups and **Table 2** gives an overview of the ICD-10 diagnosis types per group which did not significantly differ between the two groups either. Approximately, a mean of 5 min resting-state recording per subject were used for further analysis (mFEP mean 300.3 s, and uFEP mean 299.2 s, respectively) which equals ∼150 epochs of 2 s length per subject of each patient group. If channels were interpolated, these did not exceed a maximum of 4 channels per participant (mean 0.61, SD 1.00; range 1–4 channels).

TABLE 2 | Overview of diagnosis types per group.

Type of psychotic disorder	ICD-10 Code	mFEP	uFEP	*p*
		n = 17	*n* = 30	0.154
Paranoid schizophrenia	F20.0	10 (58%)	14 (47%)	
Hebephrenic schizophrenia	F20.1	0	2 (7%)	
Undifferentiated schizophrenia	F20.3	1 (6%)	0	
Other schizophrenia	F20.8	1 (6%)	0	
Schizophrenia unspecified	F20.9	1 (6%)	4 (13%)	
Persistent delusional disorders	F22.0	2 (12%)	1 (3%)	
Acute and transient psychotic disorders	F23.x	1 (6%)	7 (23%)	
Schizoaffective disorder, depressive type	F25.1	0	2 (7%)	
Unspecified non-organic psychosis	F29	1 (6%)	0	

mFEP, medicated first-episode psychosis patients; uFEP, untreated, medication-naïve first-episode psychosis patients. Significance level is 0.05.

Microstate Parameters: Overall Results

Class-labeled group model maps were calculated separately for each participant group and are shown in **Figure 2**. The average global explained variance across both groups was 77.4% and the EEG total analysis time (seconds) did not significantly differ between groups (see **Table 1**).

Microstate Parameters: Between-Group Differences

The microstate class x group interactions were significant for all microstate parameters: coverage [$F_{(3,135)} = 11.603$, $p < 0.001$, $\eta_p^2 = 0.205$]; duration [$F_{(2.414,108.616)} = 7.698$, $p < 0.001$, $\eta_p^2 = 0.146$]; and occurrence [$F_{(3,135)} = 14.417$, $p < 0.001$, $\eta_p^2 = 0.243$]. Follow-up *t*-tests indicated significant decreases of mFEP compared to uFEP for microstate A coverage [$t_{(39.8)} = -3.87$, $p = 0.001$, $d = -1.14$], and occurrence [$t_{(44.5)} = -3.51$, $p = 0.003$, $d = -1.00$]. No significant group differences were found for microstate A duration [$t_{(34.3)} = -2.24$, $p = 0.094$, $d = -0.68$]. Significant increases in the mFEP compared to uFEP group were found for microstate B coverage [$t_{(44.5)} = 7.58$, $p < 0.001$, $d = -2.16$], duration [$t_{(25.5)} = 2.78$, $p = 0.040$, $d = 0.88$], and occurrence [$t_{(35.6)} = 7.39$, $p < 0.001$, $d = 2.22$]. No significant results were found for microstate C coverage [$t_{(38.1)} = -1.69$, $p = 0.198$, $d = -0.50$], duration [$t_{(45.0)} = -1.83$, $p = 0.146$, $d = -0.52$], and occurrence [$t_{(27.5)} = -0.79$, $p = 0.876$, $d = -0.25$], as well as microstate D coverage [$t_{(35.8)} = 0.22$, $p = 0.827$, $d = 0.07$], duration [$t_{(35.4)} = -0.23$ $p = 0.817$, $d = -0.07$], and occurrence [$t_{(31.5)} = 0.63$, $p = 0.876$, $d = 0.19$]. **Figure 3** and **Supplementary Table 1** display means for all microstate parameters. The transition probabilities from class A to B [$t_{(32.0)} = 3.97$, $p = 0.004$, $d = 1.21$] and class C to B [$t_{(44.9)} = 5.97$, $p < 0.001$, $d = 1.68$] were increased in mFEP compared to uFEP. The transition probabilities from class A to C [$t_{(34.2)} = -3.40$, $p = 0.016$, $d = -1.03$] and class C to A [$t_{(43.7)} = -4.69$, $p < 0.001$, $d = -1.35$] were decreased in mFEP compared to uFEP. Detailed results are displayed in **Supplementary Table 2**.

DISCUSSION

We compared EEG microstate dynamics in medicated and medication-naïve first-episode psychosis patients (mFEP and uFEP, respectively). The microstate parameters coverage (%), duration (ms) and occurrence/s of four microstate classes (A–D) were compared between the two patient groups. We were able to confirm the hypothesis of an association between antipsychotics and microstate classes A and B.

We observed decreased microstate A coverage, and occurrence in mFEP compared to uFEP. This finding is underlined by a decrease of transitions from microstate C to A in mFEP compared to uFEP. Previous studies in unmedicated patients have reported an increase in microstate A compared to healthy controls (19, 30, 36, 38). Here, we show a decrease in this class in medicated patients, suggesting a beneficial association of antipsychotics with microstate A. Converging with our results, a decrease of microstate A was observed in medicated first-episode

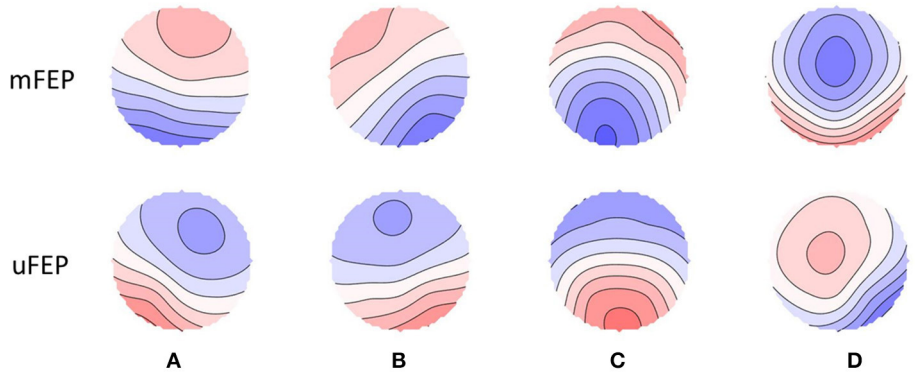

FIGURE 2 | Spatial configuration of the four microstate classes. Each row displays the four microstate classes **(A–D)** for both groups. Polarity is ignored. mFEP, medicated first-episode psychosis patients; uFEP, untreated, medication-naïve first-episode psychosis patients.

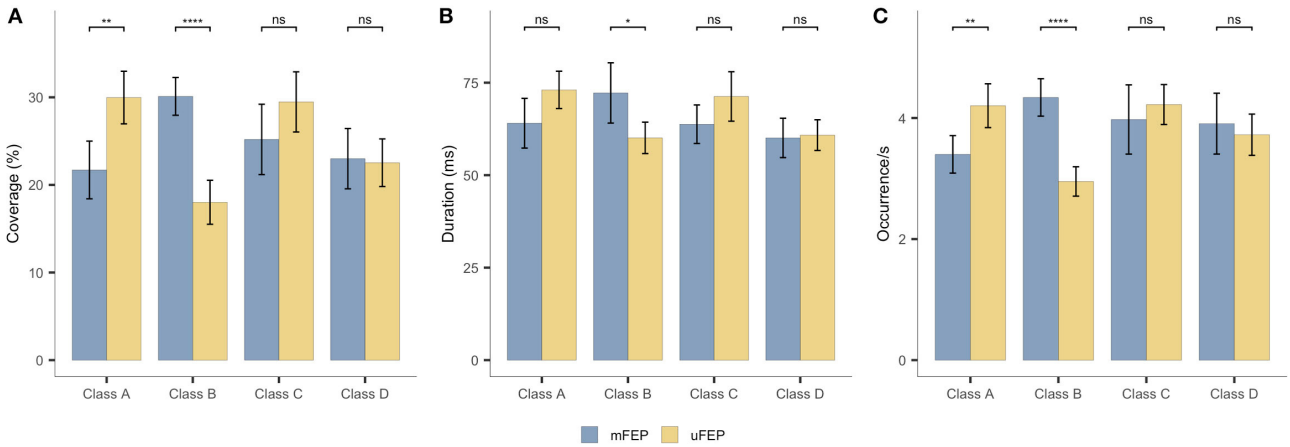

FIGURE 3 | Microstates statistics. Group averages of the temporal parameters: **(A)** coverage, **(B)** duration and **(C)** occurrence. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{****}p < 0.0001$.

patients compared to healthy controls (34) and microstate A was positively correlated with psychopathological symptoms such as depression (28) and negative symptoms of the avolition-apathy domain (33) in patients with psychotic disorders.

Interestingly, another study observed an increase in the same microstate class in more chronic medicated patients with schizophrenia spectrum disorder with up to 10.5 years of illness duration (SD 8.7) (32). Thus, illness progression (first-episode vs. more chronic) may be an important factor to consider in future studies of medication effects. Another modulatory aspect of microstate A was demonstrated by Kikuchi et al. (37): Although there was no pre- vs. post-effect after 2–8 weeks of antipsychotic treatment—possibly due to the small sample size of $n = 14$ and relatively short follow-up intervals—they observed increased microstate A in responders vs. non-responders.

Further between-group differences were observed for microstate B in which coverage, duration, and occurrence were increased in mFEP compared to uFEP. In addition, we observed more transitions from microstates A and C to microstate B in mFEP compared to uFEP. Compared to healthy controls, previous studies in unmedicated patients showed a decrease in microstate B (30, 38, 58). Again, the present study shows an opposite effect in medicated patients which could be an indication of a positive treatment effect for this class. This is further underlined by Andreou et al. (31) in which medicated first-episode patients also showed an increase in coverage of microstate B. On the other hand, Baradits et al. (32) found a decrease in all parameters of microstate B. However, inclusion of medicated schizophrenia patients with an average illness duration of 10.5 years in the latter study could again explain the difference in findings. This is in line with the recent suggestion that microstate B might be a specific state biomarker for psychotic illness progression (36).

Despite the fact that several studies found changes in microstate C between unmedicated (30, 37, 38) and medicated patients with psychotic disorders (33, 34, 37, 59) compared to healthy controls, we did not observe any significant differences between mFEP and uFEP in the present study. The absence of a difference might be explained by the fact that previous studies have reported the same finding, i.e., increase in microstate C compared to healthy controls, regardless of whether they assessed medicated or medication-naïve patient samples. Therefore,

it is conceivable that microstate C changes in patients are independent of medication status; however, larger studies are warranted to confirm our negative finding.

No significant differences in microstate D were observed between the two groups either. This is somewhat surprising, given that changes in microstate D are a central finding of studies comparing (both medicated and unmedicated) patients with psychotic disorders to healthy controls (19, 30, 32, 37, 38, 40, 59). Microstate D has further been associated with (positive) psychotic symptoms: a decrease was observed during periods of auditory hallucinations (60) and an increase in patients who responded well to antipsychotic medication (37). However, a study by Andreou et al. (31) comparing patients with FEP to a high-risk group with a similar symptom profile observed no differences in microstate D. The symptom severity scores of the patients in the present study did not significantly differ, with both groups being within the "markedly ill" range (61). This could explain why no differences in microstate D were observed. However, there is also an alternative explanation: We previously suggested that microstate D serves as a trait marker for psychotic disorders (36) in which case no effects of medication would be expected. Furthermore, a study by da Cruz et al. (40) suggested microstate D as endophenotype for psychosis in non-affected siblings of schizophrenia patients. To this end, studies with larger sample sizes are needed to further investigate medication effects on microstate D in patients with psychotic disorders.

Response status is an important issue to be considered in future studies investigating antipsychotic medication effects since it differs between individual patients (62, 63). As already mentioned, Kikuchi et al. (37) reported differences between patients that were classified as responders vs. non-responders to antipsychotic medication. However, their finding warrants replication, given that it was based on a small sample size ($n = 7$ per group). Unfortunately, it was not possible to trace response history for patients included in the present study; further studies should therefore investigate this issue. In addition, studies with longitudinal within-subject designs should explore the effects of antipsychotic medication treatment on EEG resting-state microstates, their association with individual response trajectories, as well as the role of patient baseline characteristics on medication effects. Ultimately, such studies could set the first steps into personalized medicine. This approach has been suggested for major depressive disorders and attention deficit disorders [for a review see Olbrich et al. (64)]. EEG resting-state microstates are particularly suited for this purpose, given that they have been suggested to be promising candidate biomarkers in psychotic disorders (32, 36, 40).

Further limitations of the present study have to be considered as well. Although the changes observed in medicated patients are in the expected direction, i.e., in the opposite direction of changes reported in previous studies comparing unmedicated patients to healthy controls, the inclusion of a matched healthy control sample would have been advantageous in completing the picture. Besides a healthy control group, a longitudinal design would have enabled us to confirm that the observed effects in medicated patients indeed correspond to a "normalization" of microstate parameters. A larger sample size than the one used here would have further increased statistical power of the results. Studies with high power are more likely to find true effects, e.g., correlation coefficients are estimated with a higher precision when sample sizes are increased (65). Moreover, it is due to the small sample size that we could not explore correlations between the four factors of the BPRS (with which the patients' symptom severities were measured) and the three parameters coverage, duration and occurrence of each microstate class A, B, C, and D. This could therefore be considered as a further limitation of this study.

In addition, cautiousness is warranted in the interpretation of our results, as a decrease or increase of a given parameter does not necessarily correspond to a "good" or "bad" outcome. Previous studies comparing first-episode patients (FEP), ultra-high-risk for psychosis patients and/or unaffected siblings of patients, and healthy controls have demonstrated that microstate changes do not always follow a linear pattern across different stages of psychotic disorders (31, 36, 40). Moreover, it has been suggested that some of the observed changes may reflect compensatory mechanisms rather than a deficit (31, 40). A further limitation of our study regards information which was not known for our sample and could have acted as confounding factor. This includes potentially different effects of individual antipsychotics (i.e., first vs. second generation antipsychotics) on EEG, medication duration, antipsychotic side effects, medication compliance, markers of socio-economic functioning, nicotine use, as well as the time of day of the EEG recording. Further confounding factors could have been age and sex distributions, as well as illness duration, drug consumption or other medication. However, all these variables did not significantly differ between groups.

Furthermore, two methodological points should be considered as well. First, based on previously established norms by Koenig et al. (17) the present study assessed four microstate classes. However, as suggested by Custo et al. (26) an increased number of microstates with a 7-map model might improve the explained global variance (20). Nevertheless, using four microstate classes has the important advantage of allowing direct comparisons of our results with previous studies in patients with psychotic disorders and high psychosis risk. Together with our relatively high global explained variance of 77%, we therefore deem our current method appropriate. As a second methodological limitation, it should be kept in mind that different pre-processing strategies, data selection methods and smoothing parameters (20) as well as differences in microstate analysis steps [e.g., the template used for microstate class assignment (21)] may influence microstate temporal parameters. In our study, we chose pre-processing and analysis parameters such as to ensure maximum comparability with a previous study by our group (36) but there may be differences compared to other studies. For future research in the field of EEG microstates, it would be very useful to harmonize methods in order to promote comparability.

CONCLUSION

Our findings suggest an association of antipsychotic medication with microstates A and B in first-episode psychosis patients. Further studies with large sample sizes and longitudinal designs are needed that directly compare medicated and medication-naïve patients as well as healthy controls, in order to

investigate antipsychotic medication effects on neural networks over time and throughout illness progression.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This study involving human participants was reviewed and approved by EKNZ Basel. The patients provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AR-R was responsible for the conception and design of the FePsy study. CA and SB contributed to the acquisition of data. CA, RB, and AM were responsible for the conception and design of the current microstate analysis whilst. AM, RB, and ES performed the statistical analysis. AM and RB wrote the first draft of the manuscript. All authors contributed to critical revision for important intellectual content and final approval of the submitted manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.600606/full#supplementary-material

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Structural MRI Study of the Planum Temporale in Individuals With an At-Risk Mental State Using Labeled Cortical Distance Mapping

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Background: Recent studies have demonstrated brain structural changes that predate or accompany the onset of frank psychosis, such as schizophrenia, among individuals with an at-risk mental state (ARMS). The planum temporale (PT) is a brain region involved in language processing. In schizophrenia patients, gray matter volume reduction and lack of normal asymmetry (left > right) of PT have repeatedly been reported. Some studies showed progressive gray matter reduction of PT in first-episode schizophrenia patients, and in ARMS subjects during their development of psychosis.

Methods: MRI scans (1.5 T field strength) were obtained from 73 ARMS subjects and 74 gender- and age-matched healthy controls at three sites (University of Toyama, Toho University and Tohoku University). Participants with ARMS were clinically monitored for at least 2 years to confirm whether they subsequently developed frank psychosis. Cortical thickness, gray matter volume, and surface area of PT were estimated using FreeSurfer-initiated labeled cortical distance mapping (FSLCDM). PT measures were compared among healthy controls, ARMS subjects who later developed overt psychosis (ARMS-P), and those who did not (ARMS-NP). In each statistical model, age, sex, intracranial volume, and scanning sites were treated as nuisance covariates.

Results: Of 73 ARMS subjects, 18 developed overt psychosis (12 schizophrenia and 6 other psychoses) within the follow-up period. There were no significant group differences of PT measures. In addition, significant asymmetries of PT volume and surface area (left > right) were found in all diagnostic groups. PT measures did not correlate with the neurocognitive performance of ARMS subjects.

Discussion: Our results suggest that the previously-reported gray matter reduction and lack of normal anatomical asymmetry of PT in schizophrenia patients may not emerge during the prodromal stage of psychosis; taken together with previous longitudinal findings, such PT structural changes may occur just before or during the onset of psychosis.

Keywords: psychosis, planum temporale (PT), clinical high risk (CHR) for psychosis, labeled cortical distance mapping, schizophrenia

INTRODUCTION

Structural anomaly of the superior temporal gyrus (STG) in individuals with schizophrenia has been shown in many studies (1). The planum temporale (PT), a multisensory region located on the posterior surface of STG, is involved in auditory speech processing and language comprehension (2). A recent meta-analysis revealed a robust bilateral volume reduction of PT (left: Cohen's $d = -0.775$; right: Cohen's $d = -0.349$) in schizophrenia patients compared with healthy controls (HC) (3). Although PT is thought to be an asymmetric (left > right) structure in healthy subjects (4), the leftward laterality is reduced or reversed in schizophrenia (5, 6). The reduction of leftward asymmetry of PT volume was also reported in first-degree relatives of schizophrenia (7). Some studies also demonstrated progressive gray matter reduction of PT in first-episode schizophrenia patients (8, 9) (the mean intervals between scans were 1.5 and 2.7 years, respectively).

Psychotic disorders, such as schizophrenia, are characterized by disabling features including low functional outcomes (10), prominent physical health problems (11) and premature mortality (12). Substantial attempts have therefore been made to predict, delay, or even prevent overt psychosis in individuals with an at-risk mental state (ARMS) for psychotic disorders (13, 14). We previously reported the progressive gray matter reduction of PT during the transition to psychosis in ARMS subjects (15). However, the precise chronology of PT structural changes remains unclear, i.e., whether it begins before or after the onset of psychosis.

Labeled cortical distance mapping (LCDM) is a novel image analyzing tool that computes the distances between labeled gray matter voxels and the gray/white matter cortical surface. LCDM can reliably characterize the morphometry of the laminar cortical mantle of cortical structures, such as cortical thickness and gray matter volume (16). Since this method is applied to a specific region of interest (ROI), it offers better tissue segmentation and is thus less susceptible to signal intensity inhomogeneity than whole-brain analyses. Using LCDM, we previously reported reduced thickness and less asymmetry in the volume of PT among schizophrenia patients compared with controls (17).

In the present study, we analyzed the PT morphology in ARMS subjects and HC using LCDM. We then examined whether PT structural changes had predated the future onset of frank psychosis in individuals with ARMS. In addition, we tested the associations between neurocognitive performance and PT measures among a sub-sample ($n = 36$) of ARMS subjects.

METHODS

Participants

We recruited 73 ARMS subjects and 74 HCs at three sites (Toho University Hospital, Tohoku University Hospital and Toyama University Hospital) having specialized clinical services for ARMS (18). The ARMS phase is defined by having either attenuated psychotic symptoms, brief limited intermittent psychotic symptoms or genetic risk and deterioration in functioning (19). We used the Comprehensive Assessment of At-Risk Mental State (CAARMS) (20) (University of Toyama and Tohoku University) or the Structured Interview for Prodromal Syndrome/Scale of Prodromal Symptoms (SIPS/SOPS) (21) (Toho University) for the diagnosis of ARMS. ARMS subjects were clinically followed for at least 2 years after MRI scanning to confirm whether they developed full-blown psychosis (ARMS-P) or not (ARMS-NP). The mean follow-up period for the ARMS-NP subjects was 6.5 ± 1.7 years (ranged 2.5–10 years). Development of psychosis was determined by the CAARMS or the SIPS criteria, as described in our previous study (22). We recruited sex- and age-matched HCs from the community, hospital staff, and students at each site.

All subjects were physically healthy at the time of MRI scanning. Exclusion criteria were detailed in our previous study (22). All subjects provided written informed consent. If the participants were minors, written informed consent was provided by their parents. This study was approved by the Committee on Medical Ethics at each site.

MRI Data Acquisition

The MRI scanners and data acquisition parameters used at each site were detailed in the **Supplemental Material**. All three sites used scanners with 1.5-tesla field strength.

FreeSurfer-Initialized Labeled Cortical Distance Mapping (FSLCDM)

Images were initially preprocessed with FreeSurfer (version 5.3) (23). Each preprocessed image was carefully inspected, and any errors were manually corrected. FreeSurfer extracts the surfaces of gray and white matter, and automatically segments 68 cortical regions of interest (ROIs) using the Desikan–Killiany Atlas (24), including the STG.

Extraction of PT

The PT was extracted from the Desikan–Killiany-defined STG following an established protocol (25). Boundaries of the PT were determined using a curvature-based surface tracking algorithm as follows: the boundary is defined by a path following the sulcus posterior to Heschl's gyrus from the medial to lateral extent, continues along a gyrus to the posterior ramus, and finally connects back to the starting point near the retro-insular (medial) end of Heschl's gyrus following a geodesic path. In cases with multiple Heschl's gyri or gyri that bifurcate at the lateral end, the more anterior gyrus is chosen as the PT boundary. **Figure 1** shows an example of an extracted PT on the left hemisphere.

LCDM

The cropped MRI was segmented into white matter (WM), gray matter (GM), and cerebrospinal fluid (CSF) using a mixture model averaging method (26, 27). The previously-developed method for generating LCDMs (28–30) was applied. To generate a distance map for the GM, the distance between each GM voxel and the closest GM/WM surface vertex was calculated at a $1 \times 1 \times 1$ mm resolution. GM voxels associated with a vertex in the PT surface were labeled as PT. Voxels in the range of -2 to 8 mm were used for the analysis. The result of LCDM is a probability distribution function of the GM distance from the PT GM/WM surface. Three PT measures, i.e., cortical thickness, GM volume and surface area, were estimated in this way. Cortical thickness was determined using the distance at the 95th percentile of the distance distribution. Due to outlier voxels at distances >6 mm, the volume of voxels with distance less than or equal to the 95th percentile was taken as the volume of the PT. The area of the gray/white matter boundary surface was calculated from the triangulated surface.

Neurocognitive Assessment

In 36 ARMS subjects, neurocognitive performance was evaluated using the Japanese version of the brief assessment of cognition in schizophrenia (BACS-J) (31) by trained psychiatrists or psychologists at baseline. The BACS-J includes brief assessments of verbal memory (list learning), working memory (digit sequencing task), motor function (token motor task), verbal fluency (category/letter fluency), attention and processing speed (symbol coding), and executive function (the Tower of London test).

Statistical Analysis

One-way analysis of variance (ANOVA), independent two-sample *t*-tests, or a chi-squared test were used to compare clinical measures across the diagnostic groups. PT measures (i.e., cortical thickness, volume, and surface area) were compared among the controls, ARMS-NP and ARMS-P groups using repeated measures analysis of covariance (ANCOVA), with diagnosis as the between-subject factor, hemisphere as the within-subject factor, and age, sex, intracranial volume (ICV), daily antipsychotic dosage, and scanning site as nuisance covariates. Repeated measures were applied to evaluate laterality (i.e., left vs. right). For the *post-hoc* pairwise comparison, we used Bonferroni's correction. The associations between PT measures and neurocognitive functions (i.e., BACS scores) in ARMS subjects were evaluated by calculating partial correlation coefficients adjusted for age, sex, ICV, antipsychotic use, and scanning site. Bonferroni's correction was again adopted for

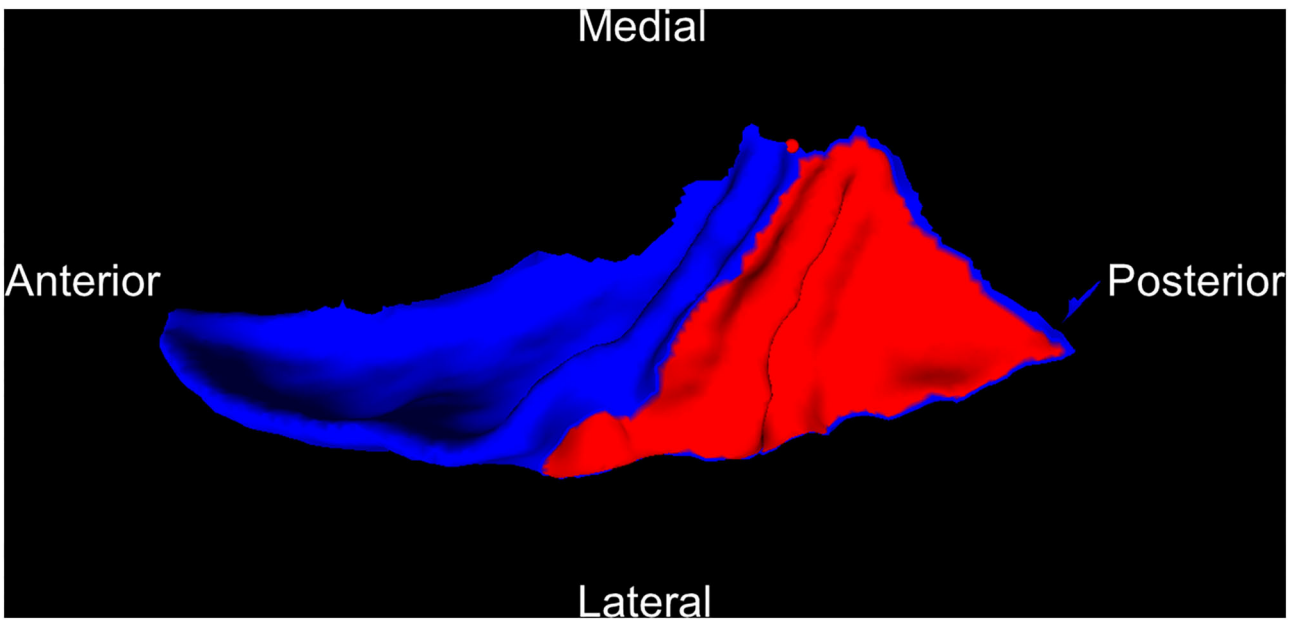

FIGURE 1 | An example of PT (red) cut from the superior temporal gyrus (blue) on the left hemisphere. PT, planum temporale.

these correlational analyses. The significance level was set at $p < 0.05$ (two-tailed).

RESULTS

Clinical Characteristics

Table 1 summarizes the clinical characteristics of the diagnostic groups. Eighteen of the 73 ARMS subjects developed frank psychosis (i.e., ARMS-P subjects) after MRI scanning. Based on the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) (20) criteria, the diagnoses of ARMS-P subjects comprised twelve schizophrenia cases, one delusional disorder case, one schizophreniform disorder case, and four cases with psychotic disorder NOS. Thirty of the 73 ARMS subjects (41%) were taking antipsychotics at baseline. Self-reported educational attainment was significantly higher in HC than in the ARMS-NP ($p < 0.001$) and ARMS-P ($p < 0.001$) groups. The BACS subscores did not differ between ARMS-NP and ARMS-P groups.

PT Measures

Repeated measures ANCOVA adjusted for age, sex, ICV, daily antipsychotic dosage and scanning site demonstrated significant main effects of side for volume ($F_{(2,144)} = 25.46$, $p < 0.001$) and surface area ($F_{(2,144)} = 26.47$, $p < 0.001$) of PT. *Post-hoc* testing showed that volume and surface area were larger on the left side ($p < 0.001$) than on the right in all diagnostic groups. Although there was a significant main effect of diagnosis for surface area ($F_{(2,138)} = 4.48$, $p = 0.013$), *post-hoc* test did not reach a statistically significant level. No other significant diagnostic effects were found. There were no significant side × diagnosis interactions (**Table 2**). There were no significant correlations between BACS subscores and PT measures in these 36 ARMS subjects.

DISCUSSION

We demonstrated significant leftward asymmetries of PT volume and surface area in both ARMS-P and ARMS-NP subjects. In addition, we did not find PT structural changes predating the onset of psychosis in the ARMS-P group. These results were consistent with previous studies (15, 32) in which PT structural changes in ARMS-P subjects compared to ARMS-NP or healthy subjects were not found at baseline. The mean duration between MRI scanning and the onset of psychosis was 40 weeks, which was comparable to those of the same previous studies (33 and 28 weeks) (15, 32). Taken together, PT structural changes may occur at a closer time point (i.e., >30–40

TABLE 1 | Demographic and clinical characteristics.

Variables	Group				
	HC	ARMS-NP	ARMS-P	Statistics	*p*
Total number of subjects	74	55	18		
Site					
Toyama	52	11	5		
Toho	5	19	4		
Tohoku	17	25	9		
Age (mean ± SD)	22.6 ± 4.3	22.3 ± 6.5	20.1 ± 4.3	$F = 1.7$	0.19
Sex (male/female)	37/37	21/34	5/13	$X^2 = 3.7$	0.16
Handedness* (right/both/left)	58/0/0	34/8/2	10/2/2		
Education years** (mean ± SD)	14.8 ±1.9	12.2 ± 2.6	12.3 ± 2.3	$F = 23.8$	<0.001
Parental education years*** (mean ± SD)	12.9 ± 2.2	13.5 ± 2.0	13.4 ± 1.6	$F = 0.86$	0.43
Weeks between scanning and onset of psychosis (mean ± SD)			40.1 ± 32.6		
Antipsychotics dose (mean mg ± SD, chlorpromazine equivalent)		145 ± 102	196 ± 130	$t = 1.1$	0.26
BACS-J subscores****					
Verbal memory (mean ± SD)		46.4 ± 10.1	50.7 ± 12.6	$t = 1.0$	0.32
Digit sequencing task (mean ± SD)		18.3 ± 5.0	21.0 ± 5.4	$t = 1.4$	0.18
Token motor task (mean ± SD)		70.9 ± 14.1	70.0 ± 8.1	$t = 0.18$	0.86
Category/letter fluency (mean ± SD)		40.2 ± 12.8	44.3 ± 10.2	$t = 0.87$	0.39
Symbol coding (mean ± SD)		63.3 ± 12.9	64.9 ± 19.2	$t = 0.28$	0.78
Tower of London (mean ± SD)		17.8 ± 2.5	18.1 ± 2.4	$t = 0.28$	0.73

**Data missing for 30 subjects.*
***Data missing for 7 subjects.*
****Data missing for 38 subjects.*
*****36 ARMS subjects (27 ARMS-NP and 9 ARMS-P subjects) underwent BACS-J.*
ARMS, at risk mental state; BACS-J, brief assessment of cognition in schizophrenia Japanese version; HC, healthy controls; NP, did not develop psychosis; P, developed psychosis; SD, standard deviation.

TABLE 2 | Comparisons of PT measures among healthy controls, non-converters, and converters.

	HC ($n = 74$)		ARMS-NP ($n = 55$)		ARMS-P ($n = 18$)		ANCOVA[a] Diagnosis		Side		Side × Diagnosis		*Post hoc*
Measures	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	***F***	***P***	***F***	***p***	***F***	***p***	
Left PT thickness (mm)	3.10	0.79	3.01	0.77	3.09	0.76	0.164	0.849	0.364	0.547	0.064	0.938	
Right PT thickness (mm)	3.08	0.84	2.89	0.89	3.03	0.78							
Left PT volume (mm^3)	2529	1025	2437	864	2520	936	0.851	0.429	**25.462**	**<0.001**	0.120	0.887	Left > Right
Right PT volume (mm^3)	1859	770	1741	882	2009	913							
Left PT area (mm^2)	850	236	880	212	939	316	4.48	0.013*	**26.469**	**<0.001**	0.184	0.832	Left > Right
Right PT area (mm^2)	658	223	703	336	755	277							*NS

[a]*Age, sex, intracranial volume, daily antipsychotic dosage and scanning site were entered as covariates.*

*ARMS, at risk mental state; HC, healthy controls; NP, did not develop psychosis; P, developed psychosis; PT, planum temporale; SD, standard deviation. The Bold values indicate significant main effects. *Did not reach a statistically significant level.*

weeks) before the onset of frank psychosis, or simultaneously with or immediately after the initial appearance of psychotic symptoms.

Other studies have demonstrated brain structure changes preceding the onset of psychosis, such as volume reduction or cortical thinning of the anterior cingulate cortex (22, 33, 34) and parahippocampal gyrus (35). These changes may reflect pre-existing vulnerability to psychosis, and may be useful as prognostic markers. In contrast, previous (15, 32) and current findings suggest that progressive PT structural changes, which have been reported in first-episode schizophrenia (8, 9), are closely associated with the first manifestation of psychotic symptoms (i.e., onset-related).

Although PT is normally an asymmetric (left > right) structure (4), this laterality is reportedly moderated, extinguished, or even reversed in patients with schizophrenia (6). Previous longitudinal studies suggest that the magnitude of progressive gray matter loss of PT is more prominent on the left side among first-episode psychosis and ARMS-P subjects (8, 9, 15). For instance, among ARMS-P subjects, an annual gray matter reduction of −5.2% on the left- and −3.9% on the right-side PT was reported (15). Therefore, the absence or reversal of leftward asymmetry of PT in established schizophrenia patients may have formed in the early stage of their psychosis.

Oertel et al. (7) demonstrated an intermediate reduction of the leftward asymmetry of the PT volume in first-degree relatives of schizophrenia patients (i.e., healthy subjects > relatives > probands) (7), while our data and previous studies (15, 32) did not detect such reduced laterality of PT measures in clinical high risk subjects. The mechanism of the emergence of reduced leftward asymmetry of PT structure might be different between clinical and genetical high risk individuals.

When conducting a study using ARMS patients, it can be challenging to obtain sufficient statistical power at a single site. We enrolled participants at three sites, and were able to obtain relatively a large sample size. Thus, the multi-site design is a strength of the present study, in addition to the employment of the novel LCDM imaging method.

Although previous studies demonstrated cognitive deficits in some domains (e.g., attention and working memory) in ARMS-P groups prior to the onset of psychosis (36, 37), we failed to replicate these results. A recent study by Jung et al. (38) found a positive correlation between verbal intelligence and PT volume in first-episode schizophrenia spectrum psychosis patients. We did not observe associations between PT measures and verbal performance in the ARMS group. The small number ($n = 36$) of ARMS subjects who underwent BACS and the difference in phase of psychosis may have influenced these inconsistent results. Because antipsychotics can affect both brain morphology (39) and cognitive function (40), it is also possible that the higher rate of antipsychotic use in our ARMS cohort biased the findings.

Our previous studies (15, 32) employed subjects recruited at the University of Melbourne, therefore the subjects of our previous and current studies do not overlap. Although current and previous studies are similar with regard to the subjects' age distribution, ARMS subjects in previous studies (15, 32) were antipsychotic-naïve at baseline while some of ARMS subjects in current study were taking antipsychotics. Nonetheless, the results of PT measures at baseline were similar among current and previous studies.

We should note some limitations. First, the MRI scanners, acquisition parameters, and the proportion of controls to ARMS subjects differed among the sites, and these differences may have confounded the results, although we treated site as a nuisance covariate in each statistical model and there were no diagnosis × site or hemisphere × diagnosis × site interactions. Second, the combined use of two criteria for ARMS (i.e., SIPS/SOPS or CAARMS) may have affected the results, although these two measures largely overlapped. Finally, the effects of antipsychotic medications on brain morphology could not be fully excluded (39), although we considered usage of antipsychotics in the statistical models.

In conclusion, our results did not support morphological changes of PT predating the onset of psychosis. Due to the cross-sectional design of this study, we were unable to examine whether PT measures change in accordance with the manifestation of psychotic symptoms. Longitudinal analyses with repeated scans are warranted in future studies.

DATA AVAILABILITY STATEMENT

The datasets generated during the current study will not be available for public use, since we do not have permission to share the data. Requests to access the datasets should be directed to the corresponding author, Yoichiro Takayanagi, takayanagi-matsu@umin.net.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of the Toho University School of Medicine, Ethics Committee, University of Toyama, the Ethics Committee of Tohoku University Graduate School of Medicine. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

MS and YT designed the study and wrote the protocol. TT, NK, AS, NO, MKa, SN, KM, and MM recruited subjects and were involved in clinical and diagnostic assessments. AF, MKi, and MN managed the MRI and clinical data. YT, SK, DS, and JR did the imaging processing. KN provided technical support for MRI scanning and data processing. YT performed statistical analyses and wrote the first draft of the manuscript. SK, TT, JR, and MS contributed to editing the manuscript. All authors have approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.593952/full#supplementary-material

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First-Episode Psychotic Patients Showed Longitudinal Brain Changes Using fMRI With an Emotional Auditory Paradigm

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Most previous longitudinal studies of functional magnetic resonance imaging (fMRI) in first-episode psychosis (FEP) using cognitive paradigm task found an increased activation after antipsychotic medications. We designed an emotional auditory paradigm to explore brain activation during emotional and nonemotional word processing. This study aimed to analyze if longitudinal changes in brain fMRI BOLD activation is present in patients vs. healthy controls. A group of FEP patients ($n = 34$) received clinical assessment and had a fMRI scan at baseline and follow-up (average, 25-month interval). During the fMRI scan, both emotional and nonemotional words were presented as a block design. Results were compared with a pair of healthy control group ($n = 13$). Patients showed a decreased activation at follow-up fMRI in amygdala ($F = 4.69$; $p = 0.04$) and hippocampus ($F = 5.03$; $p = 0.03$) compared with controls. Middle frontal gyrus was the only area that showed a substantial increased activation in patients ($F = 4.53$; $p = 0.04$). A great heterogeneity in individual activation patterns was also found. These results support the relevance of the type of paradigm in neuroimaging for psychosis. This is, as far as we know, the first longitudinal study with an emotional auditory paradigm in FEP. Our results suggested that the amygdala and hippocampus play a key role in psychotic disease. More studies are needed to understand the heterogeneity of response at individual level.

Keywords: first episode psychosis (FEP), fMRI—functional magnetic resonance imaging, longitudinal, emotional design model, paradigm, follow up

INTRODUCTION

Psychosis is a group of heterogeneous mental disorders characterized by important life disturbances, cognitive impairment, interpersonal problems, and, finally, high economic costs for health systems, including indirect costs such as unemployment and social support, and direct costs from hospitalizations during crises (1). First-episode psychosis (FEP) is defined as the first manifestation of a psychotic disorder meeting appropriate diagnostic symptom and time criteria (2), occurring in more than 3% of people at some point in life (3).

FEP has received a lot of interest from the scientific community in recent years, to increase recovery rates and prevent deterioration due to the emerging importance of an adequate and rapid response in the early stages of the disease (4–8). Prodromal factors have been investigated, conforming the clinical high-risk state for psychosis (CHR-P) knowledge based on two decades (9), seeking to clarify the most important risk factors that can predict the emerging of first symptom and answer why most high-risk individuals will never develop symptoms while being exposed to these risk factors, although meta-analyses report around 30% of high-risk individuals developing symptoms (1). In that sense, genetic and environmental interaction should also be considered, as they seem to work synergistically (6). In this sense, a great heterogeneity has been described within the CHR-P population, finding different subgroups prior to the emerging of FEP (10).

Despite this research effort, there are key remaining questions regarding FEP, the factors that explain the enormous clinical heterogeneity, the different course trajectories, and high relapse risks after improving pharmacological treatments and early interventions (6).

One main attempt to evaluate FEP is by using neuroimaging techniques. Most publications use MRI imaging measurements (11), ventricular dilation, and gray matter lost in chronic samples (12, 13), with similar results found in FEP patients (14). Treatment of naïve patients have shown gray matter deficits, mainly in the fronto-temporal, thalamo-cortical, and subcortical-limbic circuits (15, 16). There have been several attempts to link these structural findings with the outcomes and longitudinal trajectories of the disease, but clinical and methodological heterogeneity limits the conclusions (17).

Conversely, little is known about longitudinal changes in FEP during functional magnetic resonance imaging (fMRI) (18). One review, interested in the effects of medication on chronic patients, concluded that pharmacological antipsychotic treatments induce functional brain alterations in the frontal regions (19), but this conclusion has been reached by including different studies with an enormous methodological variance.

There are some problems with performing longitudinal fMRI studies: the cost of these techniques translates into low sample sizes across most studies (18, 19); the experimental dropouts in a difficult population to be recruited and evaluated; and the methodological heterogeneity during scans, which involves many different paradigms, usually visual or cognitive tasks (18). The type of task is a key issue in neuroimaging, since different areas of brain activation are shown as distinct task designs (such as emotional, cognitive, motor, attentional, verbal) and different sensory modalities (such as visual, auditory, resting state) are carried out. The distinctions between the strength of the MR scans are also noticeable, ranging from earlier studies with 1.5 T to later 7 T high field scanners, though their results are often intermixed.

Our group developed an emotional auditory paradigm based on some of the most common symptoms reported by FEP patients (20, 21). Some interesting results have been found using this method in chronic samples (22), but the issue of longitudinal activation changes in FEP remains unclear.

There are relatively few publications studying longitudinal activation changes in FEP cohorts. We recently conducted what seems to be the only systematic review about this question and gathered the results of 13 selected studies (18). First of all, there was a great methodological heterogeneity across the included studies, involving different scan powers, different intervals between scans, different regions of interest, and different tasks and modalities. Taken together the activation and connectivity studies, two main comparisons were carried out. First, the patient's group was compared with the healthy control's group in basal assessment, finding multiple studies with hypoactivation in several brain areas in the patients' group. The most frequently hypoactivated area was the prefrontal cortex, followed by limbic structures, occipital cortex, basal ganglia, thalamus, hippocampus, temporal cortex, and parietal cortex. The number of studies reporting hyperactivation in patients vs. controls was marginal. This was in contrast to the results of a previous selective review that concluded a hippocampal and subcortical hyperactivation pattern in naive patients (15).

Secondly, we compared the results of the second MR scans within the patient's group with respect to the basal assessment, with a general increased activation (which we called "normalization") in the vast majority of included studies, especially in prefrontal cortex, basal ganglia, parietal cortex, and occipital cortex. These results were explained in the reference studies as treatment effects (18).

Under our emotional auditory paradigm, an important role of amygdala in emotional processing in chronic patients with hallucinations can be observed (20). We hypothesize that evaluating a FEP with our emotional paradigm in fMRI will probably show different activation patterns, especially in amygdala, between patient and healthy control groups. We also expect that the activation will decrease in those regions after treatment. The purpose of this study is to compare the longitudinal activation results evaluated with an emotional auditory paradigm during fMRI scans in a FEP patient with a heathy control group. The potential of this method as a biomarker for FEP will be discussed.

MATERIALS AND METHODS

Participants

Patients were recruited from the outpatient psychiatry clinics. People from area 5 of Valencia, who experienced psychotic symptoms for the first time in life were submitted to the Valencia Clinic Hospital First-Episode Unit for evaluation and treatment. Control subjects were paired by age and educational level. All subjects, patients and controls, were older than 18 years old and provided written informed consent according to the Local Ethical Committee.

There were 35 adult patients with a first F20–F29 diagnosis. Diagnoses were based on the Structured Clinical Interview for DSM-IV Axis I Disorders. Two weeks after their diagnosis, all the patients underwent a semistructured interview including sociological information and clinical scales. After the clinical evaluation, they were proposed to be scanned with two fMRI scans, with a minimum interval of 6 months between them.

TABLE 1 | Sociodemographical characteristics of subjects.

	FEP patients group ($n = 35$)	Healthy controls group ($n = 13$)
Age (years at first scan)	29.92 ± 8.90	35.70 ± 10.74
Gender (male/female)	28/6	8/5
Education level	Illiteracy = 1	Illiteracy = 0
	Primary = 9	Primary = 1
	Secondary = 6	Secondary = 2
	High school = 9	High school = 4
	University = 10	University = 6
Work status	Active = 5	Active = 9
	Unemployed = 18	Unemployed = 2
	Disabled = 1	Disabled = 0
	Student = 11	Student = 2
Coexistence	Alone = 1	Alone = 4
	Origin family = 28	Origin family = 3
	Own family = 2	Own family = 4
	Other = 4	Other = 2
Interval (months between scans)	25.60 ± 19.50	19.68 ± 13.03

TABLE 2 | Clinical characteristics of subjects.

	Basal ($n = 35$)	Follow-up ($n = 35$)	*p*-values
CGI	4.23 ± 0.770	3.49 ± 1.040	0.002
GAF	62.20 ± 11.045	67.71 ± 15.007	0.040
PANSS: T	59.69 ± 13.809	47.17 ± 16.224	0.000
PANSS: P	15.06 ± 5.525	11.17 ± 4.914	0.002
PANSS: N	13.71 ± 4.430	11.34 ± 3.925	0.003
PANSS: PG	30.06 ± 6.708	24.17 ± 8.607	0.002
Medication	1st G APS = 35 (paliperidone = 12, olanzapine = 11, aripiprazole = 5, risperidone = 3, amisulpride = 2, quetiapine = 2)		
	APS combination = 9		
	Anticholinergics = 2		
	Benzodiazepines = 26		
	Antidepressants = 4		
	Mood stabilizers = 3		
	Mean CPZ equivalent dose: 266 mg. SD = 1.82		

Healthy controls were volunteers without financial remuneration recruited from the Valencia Clinic Hospital and Valencia University staff. They were selected after a mini personal interview to exclude people with the following: (a) personal or family clinical records of psychiatric illness; (b) people who suffered from a medical illness that potentially affected cerebral function; and (c) people who met present or past criteria for psychoactive drug abuse or dependence (except for tobacco). Sociodemographic data is gathered in **Table 1**.

Clinical Measurements

Patients were assessed by a personnel trained in FEP evaluation (JS). Interviews were conducted during the first episode and a few days after the start of treatment. All patients were assessed at least twice, coinciding with the time difference between scans. Pharmacological options were registered, even if depot administration was implemented, and others are combinations with non-antipsychotic medications.

The Clinical Global Impressions scale (CGI) and the Global Assessment of Functioning scale (GAF) were taken into account and complemented by the Positive and Negative Syndrome scale (PANSS). The results of clinical measurements in baseline and follow-up are summarized in **Table 2**.

fMRI Emotional Paradigm

An emotional auditory fMRI stimulation paradigm, designed by our group (20, 21), was employed in this study, consisting of 13 emotional Spanish words taking into account their frequency of presentation in the patient's hallucinations, and 13 neutral words with a similar number of syllables from a database (23). A set of earphones, connected by a pair of air tubes to an external audio player, was used. Two different fMRI acquisitions, neutral and emotional, were conducted for each subject. The neutral words were presented first. The paradigm used a block design approach to present the words. Four blocks of rest and four blocks of stimulation were interleaved and presented to each participant. Each block lasted 20 s. Subjects were informed before the MR acquisition about the experiment and were asked to focus their attention to the words.

MR Scanning Protocol

fMRI scans were obtained at baseline and follow-up with a 3-T magnet (Achieva, Philips Medical Systems, Best, The Netherlands) and a multitransmit parallel transmission technology. Brain fMRI images were obtained using a 32-channel head coil and a dynamic echo planar imaging (EPI) $T2^*$-weighted sequence (repetition time = 2,000 ms; echo time = 30 ms; flip angle 90; slice thickness = 3.50 mm with no interslice gap; acquisition matrix = 128 × 128; voxel size = 1.80 × 1.80 × 3.50 mm), covering the whole brain with 40 contiguous slices. The total fMRI acquisition duration was 160 s.

After acquisition, images were qualitatively reviewed by a radiologist and a computer engineer, to ensure data quality. Data was then anonymized and transferred to a workstation for postprocessing analysis.

Analyses

Statistical Parametric Mapping version 12 software (SPM, The Wellcome Center for Human Neuroimaging, London, UK) and MATLAB R2015a (The MathWorks, Natick, MA, USA) were used to process the fMRI series. First, images were spatially realigned to minimize potential movements during the MR acquisition. Motion maps were generated for each fMRI series and analyzed to discard those subjects with translation

movements (x, y, z) >1.80 mm (voxel size). No subjects were discarded after this step. Secondly, a slice timing correction was used to adjust for temporal delays between the first and the last slices in each fMRI dynamic. Then, a spatial normalization algorithm was applied to normalize data with respect to a standard template (MNI350, Montreal Neurological Institute). Finally, the normalized images were smoothed by a 6-mm FWHM Gaussian smoothing kernel.

A first-level analysis was conducted for each individual subject. In order to increase specificity, fMRI response was measured during emotional words in all subjects in areas previously reported as significant with the emotional paradigm, including amygdala, hippocampus, cingulated gyrus, insula, frontal, and temporal regions (21, 22, 24, 25). In these areas, a relative measurement of functional activation [percent signal change (PSC)] was calculated as the proportional signal difference between the signal averaged in the rest blocks and the signal averaged in the stimulation period was measured. To minimize the potential effect of spurious values, a robust strategy was used to obtain the mean and median values for each region of interest (ROI), discarding those values with two time differences, above or below the standard deviation of the PSC in each area. For each ROI and case, the PSC was computed voxel by voxel. To minimize the bias associated to multiple statistical comparisons and to control the expected number of false positives, a Bonferroni correction was applied at voxel level through a family-wise error (FWE) rate correction.

A full-factorial ANOVA model was constructed and evaluated to assess for changes in fMRI activation between subjects by accounting for two main factors: clinical group (patients vs. controls) and longitudinal acquisition (basal—MRI1 and follow-up—MRI2).

RESULTS

fMRI Response to Emotional Stimulation

Compared with the control subjects, FEP patients showed hyperactivated areas when the emotional stimulation was

TABLE 3 | Areas of hyperactivation in FEP patients vs. controls when emotional stimulation was applied.

MRI1 (basal)				MRI2 (follow-up)			
***T* Student**	**Coordinates**	**Label**	**Brodmann**	***T* Student**	**Coordinates**	**Label**	**Brodmann**
9.22	[−28, 16, 58]	Frontal_Mid_L	08	7.30	[−38, 40, 34]	Frontal_Mid_L	46
9.02	[−12, 46, 44]	Frontal_Sup_Medial_L	09				
8.92	[−46, 8, 34]	Frontal_Inf_Oper_L	48				
8.84	[−32, 16, 34]	Frontal_Inf_Oper_L	44				
8.72	[−38, 16, −24]	Temporal_Pole_Sup_L	38				
8.49	[48, 34, −16]	Frontal_Inf_Orb_R	47				

Left MRI1 (basal) and right MRI2 (follow-up) ($p < 0.05$ FWE-corrected).

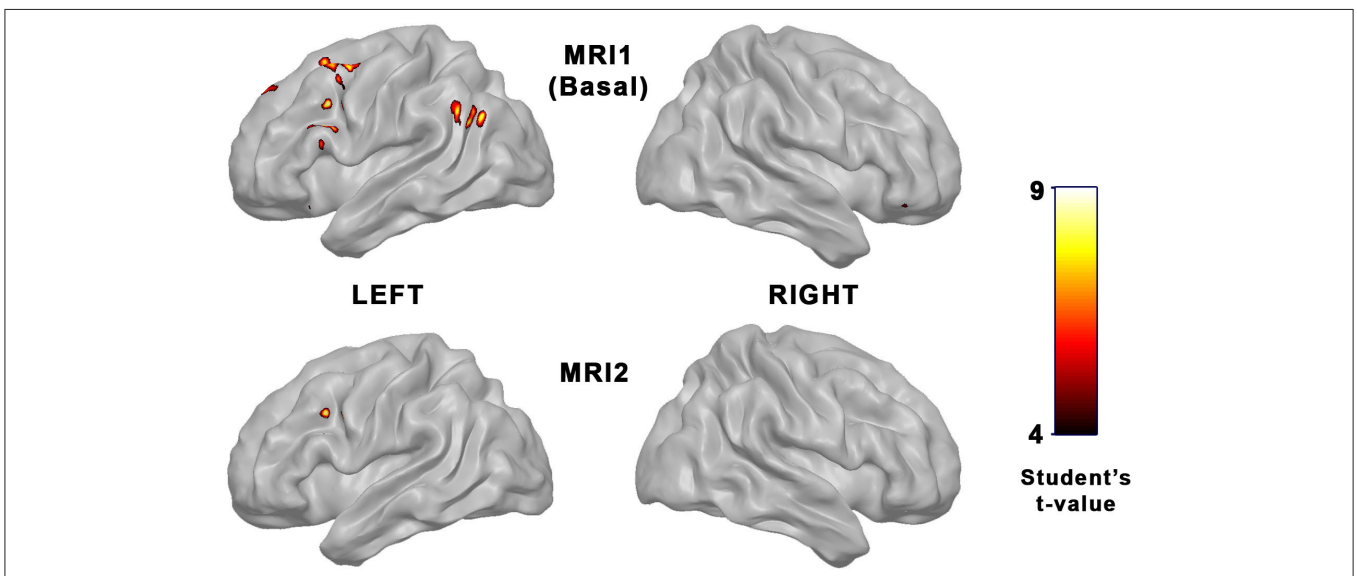

FIGURE 1 | Parametric maps showing areas of hyperactivation in FEP patients vs. controls when emotional stimulation was applied. **Top row:** Differences in basal fMRI evaluation. **Bottom row:** Differences in follow-up fMRI evaluation ($p < 0.05$ FWE-corrected).

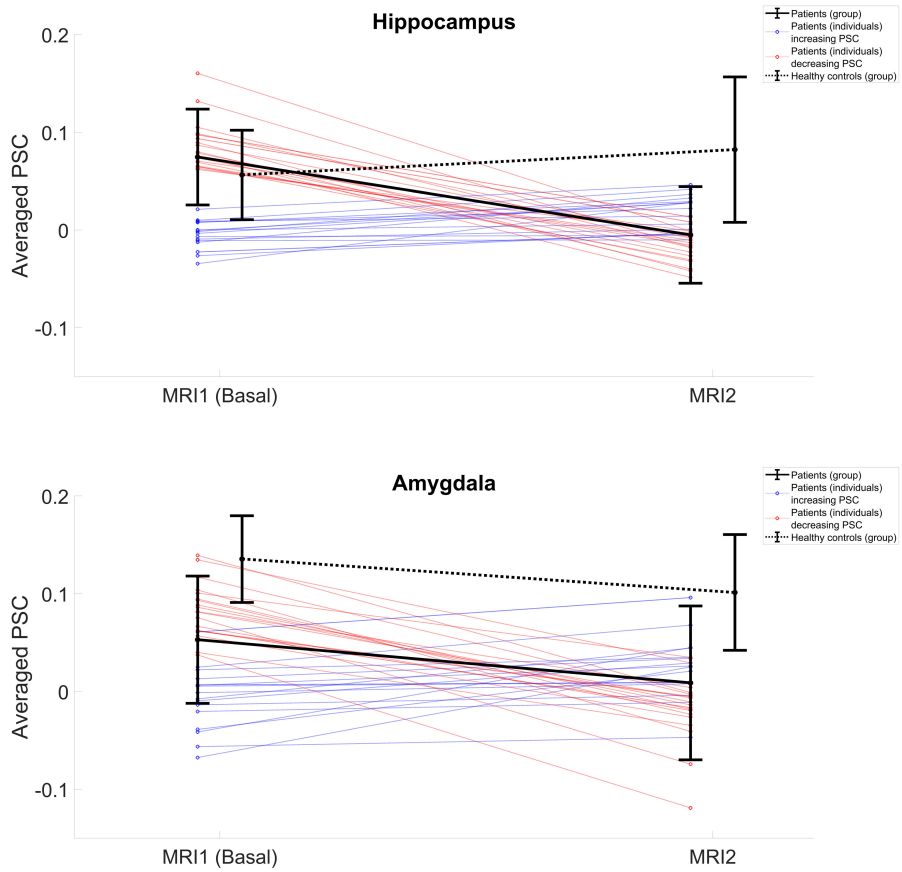

FIGURE 2 | PSC changes over time, from basal to follow-up fMRI examination. **Top row:** PSC in hippocampus. **Bottom row:** Values in amygdala. Black lines represent the averaged group values for FEP patients (continuous line) and healthy controls (dotted line). Colored lines represent the individual curves for patients who increment PSC over time (blue) and those who showed a longitudinal PSC decrement (red).

applied. In the first basal fMRI acquisition, the hyperactivated areas were located mainly at frontal and temporal regions. The follow-up fMRI examination showed lesser differences between FEP and healthy controls, with only a small portion of the middle frontal lobe being hyperactivated (see **Table 3** and **Figure 1**). A complete list of areas, figures, and tables showing the whole-brain full-activation maps for each group is available as **Tables S1**, **S2** and **Figures S1**, **S2**.

Effect Over Time

FEP patients showed a significant reduction in fMRI activation in the follow-up MRI examination of the hippocampus ($F = 4.81$; $p = 0.03$). Other areas including amygdala, cingulated gyrus, insula, frontal, and temporal regions did not show functional changes over time. Likewise, no significant differences were found in healthy control subjects in these areas between both fMRI examinations (see **Figure 2** and **Table 4**).

Although averaged-group values in the hippocampus showed statistically significant changes over time, a marked heterogeneity in the behavior of the curves was detected when observing particular subjects. While some patients showed a clear increase of PSC activation during follow-up fMRI evaluations, others exhibited a marked reduction over time (**Figure 2**).

Effect Over Clinical Groups

At baseline fMRI, FEP patients showed a significant reduction of activation compared with controls in the amygdala ($F = 4.67$; $p = 0.04$). By contrast temporal ($F = 3.96$; $p = 0.04$) and frontal ($F = 4.23$; $p = 0.04$) regions were hyperactivated in FEP patients. Other areas including the hippocampus, cingulated gyrus, and insula did not show significant differences between groups.

In the follow-up study, both amygdala ($F = 4.69$; $p = 0.04$) and hippocampus ($F = 5.03$; $p = 0.03$) showed a significant fMRI reduction in patients vs. controls while the middle frontal gyrus ($F = 4.53$; $p = 0.04$) showed a hyperactivation in patients (see **Figure 2** and **Table 5**).

An analysis of a possible interaction between clinical symptoms and longitudinal changes in fMRI was made through PANSS result data: general PANSS score, positive subscale, negative subscale, and general psychopathology subscale. No significant correlation between these scores and longitudinal fMRI changes were found (**Table 6**).

TABLE 4 | ANOVA showing functional PSC values of FEP patients (left) and healthy controls (right) for both, basal and follow-up fMRI evaluations.

	FEP patients				Healthy controls			
	PSC		*F*	*P*-value	PSC		*F*	*p*-value
	Basal (MRI1)	Follow-up (MRI2)			Basal (MRI1)	Follow-up (MRI2)		
Amygdala	7.82 (11.34)	2.70 (13.90)	1.58	0.21	12.09 (8.80)	11.75 (11.36)	0.33	0.57
Hippocampus	8.64 (8.30)	−1.01 (8.79)	4.81	0.03*	6.65 (9.57)	9.83 (13.67)	0.86	0.36
Cingulated Gyrus	5.15 (19.64)	0.15 (30.15)	0.69	0.41	−0.65 (17.82)	3.28 (20.69)	0.27	0.61
Frontal	2.06 (9.48)	3.51 (10.53)	0.06	0.80	−2.40 (9.47)	0.65 (10.41)	0.28	0.60
Temporal	7.89 (7.60)	4.66 (20.79)	0.01	0.93	5.05 (7.11)	14.23 (15.56)	0.95	0.34
Insula	−1.30 (19.85)	0.69 (24.85)	0.14	0.71	3.12 (12.03)	3.14 (16.84)	0.00	1.00

*$p < 0.05$.

TABLE 5 | ANOVA showing functional PSC values at basal (left) and follow-up (right) evaluation for FEP patients and healthy control subjects.

	Basal (MRI1)				Follow-up (MRI2)			
	PSC		*F*	*p*-value	PSC		*F*	*p*-value
	FEP patients	Healthy controls			FEP patients	Healthy controls		
Amygdala	7.82 (11.34)	12.09 (8.80)	4.67	0.04*	2.70 (13.90)	11.75 (11.36)	4.69	0.04*
Hippocampus	8.64 (8.30)	6.65 (9.57)	0.22	0.65	−1.01 (8.79)	9.83 (13.67)	5.03	0.03*
Cingulated gyrus	5.15 (19.64)	−0.65 (17.82)	0.87	0.36	0.15 (30.15)	3.28 (20.69)	0.12	0.73
Frontal	2.06 (9.48)	−2.40 (9.47)	4.23	0.04*	3.51 (10.53)	0.65 (10.41)	4.53	0.04*
Temporal	7.89 (7.60)	5.05 (7.11)	3.96	0.04*	4.66 (20.79)	14.23 (15.56)	2.27	0.14
Insula	−1.30 (19.85)	3.12 (12.03)	0.57	0.46	0.69 (24.85)	3.14 (16.84)	0.11	0.74

*$p < 0.05$.

In order to look at the possible antipsychotic effect on fMRI, chlorpromazine-equivalent doses were calculated and registered (**Table 2**). The relationship between longitudinal activation change and clinical variables has been calculated, showing that there is no correlation between longitudinal fMRI changes and antipsychotic dose (**Table 6**).

DISCUSSION

This first longitudinal study investigating fMRI changes in FEP using an emotional auditory paradigm reveals an increased activation at baseline that is reduced in follow-up. Interestingly, in our previous systematic review of fMRI longitudinal studies in FEP, the most common finding was just the opposite. Patients with FEP showed at baseline a hypoactivation mainly in PFC, basal ganglia, limbic system, hippocampus, and the ACC, which was increased ("normalized") after antipsychotic treatment during follow-up (18).

The most likely explanation for understanding the differences between our results and previous studies is the fMRI paradigm. Most previous fMRI longitudinal studies in FEP used resting states or different paradigms that included cognitive tasks. The main problem of using any kind of cognitive task in psychotic patients is the attentional bias as attentional deficits are one of the most common findings in FEP patients (26). In fMRI studies, these deficits correlate with general hypoactivation mainly in the PFC (27). Moreover, hypoactivation in the PFC has been mentioned classically as one of the most consistent findings in chronic schizophrenia (28). However, the type of paradigm we used in this study does not require a focus of attention or cognitive performance but rather reflects the brain's response to direct emotional stimulation. In support of this, a hyperactivation of the amygdala at baseline that decreased after treatment with cognitive therapy was observed in schizophrenia patients with persistent hallucinations (22).

The fact that amygdala and hippocampus showed the most significant changes deserves an explanation. First, both areas were the most clearly affected in our previous studies using the same paradigm in chronic patients (29). Secondly, these areas are implicated in the emotional response and memory, fitting with the Kapur's model in which the core of psychosis could be an abnormal "salience" to external stimuli (30) or, as more recently suggested, an abnormal connectivity between perceptual, emotional, and memory brain areas (31).

Quite relevant is the fact that everything mentioned so far relates with mean group variations in brain activation. It is important to consider the great individual heterogeneity in the results. This heterogeneity is not only in the baseline but also in the path of brain activation changes. Some patients show a decrease in brain activation during follow-up, while another group presents just the opposite (**Figure 2**). There are several possible explanations for these results. The

TABLE 6 | Correlations between differences in activation in amygdala and hippocampus and clinical variables (PANSS subscales measurements and pharmacological treatment in chlorpromazine equivalent doses) measured as longitudinal percentage change.

	DIFAMIG	DIFHIPOC	PC_P	PC_N	PC_G
DIFAMIG					
Pearson correlation	1	0.717**	−0.044	0.000	0.092
Sig. (2-tailed)		0.000	0.800	0.998	0.598
N	35	35	35	35	35
DIFHIPOC					
Pearson correlation	0.717**	1	−0.132	−0.041	0.117
Sig. (2-tailed)	0.000		0.451	0.813	0.503
N	35	35	35	35	35
PANSS_P					
Pearson correlation	−0.044	−0.132	1	0.959**	0.223
Sig. (2-tailed)	0.800	0.451		0.000	0.197
N	35	35	35	35	35
PANSS_N					
Pearson correlation	0.000	−0.041	0.959**	1	0.372*
Sig. (2-tailed)	0.998	0.813	0.000		0.028
N	35	35	35	35	35
PANSS_G					
Pearson correlation	0.092	0.117	0.223	0.372*	1
Sig. (2-tailed)	0.598	0.503	0.197	0.028	
N	35	35	35	35	35
CPZ_EQ					
Pearson correlation	−0.082	−0.041	−0.067	−0.131	−0.045
Sig. (2-tailed)	0.638	0.815	0.704	0.453	0.799
N	35	35	35	35	35

*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

simplest one is that the heterogeneity in brain activation is due to the clinical heterogeneity of the population. Our study sample was based on patients with first episodes of psychosis. The first psychotic episodes can evolve very favorably (brief reactive psychosis) or tend toward chronicity either in a continuous deterioration or in an episodic way (32). However, we did not find a clinical difference at baseline with regard to the pattern of longitudinal activation changes (see **Figures S1**, **S2** and **Tables S1**, **S2**). That said, it is possible to speculate that differences in brain activation are directly related with the clinical state at the moment of fMRI. So, the same patient could have a different degree of activation, depending on the moment of fMRI acquisition. Moreover, it is important to consider medication and psychosocial interventions as important confounding variables, and it is worth mentioning that patients were treated under naturalistic conditions with individualized therapeutic approaches. The results of this study showed the relevance of making an analysis at an individual base instead of just comparing the mean group.

This study has some limitations. Although most of the fMRI studies involve <30 patients, it remains limiting for the field, and this study must be interpreted wisely due to the relatively small sample size recruited. Differences between sample sizes in the HC and FEP groups and gender distribution should also be taken into account. The second limitation is about the different intervals between scans, particularly in the case of the FEP group. As we are comparing brain function after symptom's onset, the natural effects of neurodevelopment should be controlled by adjusting the time between scans. Thirdly, although we did not find a significant correlation between clinical symptoms and brain activation (**Table 6**) in our sample, like all FEP samples, there is a great clinical heterogeneity that it cannot be ignored. Different types of psychosis are included, which probably involve different disease phenotypes and, as we have shown in this paper, different pathways in brain function. Finally, according to this clinical heterogeneity, a wide range of pharmacological treatments appear in our sample. Although we did not find a significant relationship of the antipsychotic equivalent dose and fMRI activation, it cannot be ruled out that different combinations of medications in longitudinal studies may introduce changes in natural brain function. More analyses are needed, studying individual cases and possible patient subgroups [including genetic data (33)] to improve our knowledge of brain function and the course of psychosis.

Conversely, this study has some strengths that should be listed. The main strength is that this is the first longitudinal study investigating longitudinal fMRI changes in FEP samples with an emotional auditory paradigm. Paradigm election is a key question in neuroimaging, and there is a lack of longitudinal studies using noncognitive task during scans. Another positive point of this study is to incorporate clinical assessments in addition to neuroimage acquisition data. Neuroimaging and clinical data may be gathered to study disease course variables in subsequent analyses.

In conclusion, we have shown that brain activation under an emotional auditory paradigm during fMRI scans change longitudinally in FEP patients. A significant decrease in activation in the amygdala and hippocampus is observed in patients compared with healthy subjects. Still, we have also found a great clinical and activation heterogeneity, which may reflect different pathways of the disease.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of ethical restrictions. Reasonable requests to access the datasets should be directed to Julio Sanjuan, julio.sanjuan@uv.es.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by INCLIVA Ethical Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JS, CG-V, GG-M, LM-B, and EA designed the study. JS obtained the funding and supervised the study. GG-M made the postprocessing of fMRI data. PS-M made the clinical evaluation. RS-R made the imaging acquisition. MC-B contributed to the data analysis. CG-V wrote the first draft of the article. JS, CG-V, and GG-M wrote the final version. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.593042/full#supplementary-material

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SYSTEMATIC REVIEW
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Does Hippocampal Volume Predict Transition to Psychosis in a High-Risk Group? A Meta-Analysis

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Schizophrenia has a prodromal phase of several years in most patients, making it possible to identify patients at clinical high risk (CHR) for developing the disorder. So far, these individuals are identified based on clinical criteria alone, and there is no reliable biomarker for predicting the transition to psychosis. It is well-established that reductions in brain volume, especially in the hippocampus, are associated with schizophrenia. Therefore, hippocampal volume may serve as a biomarker for psychosis. Several studies have already investigated hippocampal volume in CHR groups. Based on these studies, the present meta-analysis compares the baseline left and right hippocampal volume of CHR patients who developed a psychosis with that of CHR patients without such a transition. Our results show no statistically significant effect of the hippocampal volume on the transition risk for psychosis.

Keywords: schizophrenia, psychosis, hippocampus, neuroimaging, high risk, at-risk mental state

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INTRODUCTION

Schizophrenia is a psychiatric illness that is typically preceded by a long prodromal phase (1). The disease has a significant impact on patients' quality-adjusted life years and an often unsatisfactory response to treatment (2). One of the main goals of psychiatric public health government programs is to establish criteria for early detection of schizophrenia. Such criteria could make it possible to implement various forms of secondary prevention to avoid or delay the onset of schizophrenia (3). A large number of studies have accordingly followed-up clinical high-risk (CHR) groups in order to investigate the factors associated with later development of a psychotic disorder (among them the NAPLS- and the PRONIA-project) (4–8). CHR-status is identified according to specific clinical criteria; the most widely established criteria define high-risk based on either (9–12).

a) "attenuated psychotic symptoms" (ASP) or "brief limited intermittent psychotic symptoms" (BLIPS) (these symptoms are manifestations which are typical for psychotic disorders, but which are either not sufficiently severe or too short to warrant the diagnosis itself)
b) genetic vulnerability for psychotic disorders accompanied by a notable downward shift in an individual's social functioning (measured, for example, by difficulties at work or by the inability to live autonomously).

In practice, criterion b is of little relevance in the actual setup of a concrete CHR-group (13). Thus, the dominance of clinical features further highlights the status of the CHR-group as a representation of the prodromal phase.

When CHR patients develop a psychotic disorder, this is called a "transition." The probability of transition was initially estimated to be between 35 and 40% in typical CHR-groups (14), but in recent studies, it was lower (15). This could be because of specific protective effects that arise from a diagnosis of CHR: for example, increased risk-awareness of the included person and support from family members, school officials, or other professionals (16).

The low transition rates in CHR-groups mean that it is not feasible to undertake a prophylactic treatment in all CHR patients, especially if such a treatment encompasses the use of antipsychotic medication with the accompanying side-effects.

To enhance the predictive value of CHR-criteria, it has been hypothesized that the inclusion of neuro-imaging data should be helpful (3, 17–19). Schizophrenia is known to be accompanied by volume enlargements in the ventricular regions (especially in the later stages of the disease) (20) and volume reductions in several brain areas, among them the frontal cortex, the amygdala, the parahippocampal gyrus and the hippocampus (21–37). It has also been suggested that these changes are progressive during the course of the illness (38). Especially hippocampal volume reductions might not only be a result of the disease, but instead have been suggested to be one of its causative factors (39–42). Such causative relationships might be explained by the immense role of the hippocampus in memory formation (43, 44). Hippocampal volume reductions and ensuing memory deficits could lead to false hypothesis-testing in CHR-individuals (caused for example by a functional shift from pattern separation to pattern completion) and this might make the individual more prone to psychosis (45). Should such neuroanatomical processes occur, lower hippocampal volumes (compared to healthy controls) should be observable before the actual onset of schizophrenia, which means during the prodromal phase. Such volumetric changes could be a useful biomarker and supplement the predictive value of risk-assessments based on the clinical criteria mentioned above, thus increasing the specificity of the CHR concept (46).

Several studies have carried out MRI-measurements of the hippocampus on members of CHR-groups, and have then compared the results to a parallel arm of healthy controls (47–57). The goal of these studies was to assess whether CHR patients have smaller hippocampal volumes compared to healthy controls *at baseline* (i.e., at the time of diagnosis of the CHR status) compared to healthy individuals. A selection of those studies has been pooled in a meta-analysis by Walter et al., which did not find any significant differences between CHR patients and controls (58). Following up on this finding, the aim of the present meta-analysis is to compare CHR-patients who made the transition to psychosis during the follow-up interval ("converters") with CHR-patients who did not ("non-converters"). This concept has first been employed in a study by Pantelis et al. (59). In the context of our meta-analysis, this procedure implies ignoring the control group of the investigated studies and retrospectively splitting up the case group (CHR patients) into two groups, defined by their transition status. Cases and controls are thus generated from the same cohort, e.g., the CHR-population. Methodologically, this has the significant benefit of reducing heterogeneity between the groups, which is a frequent challenge in case-control studies. Also, from a clinical viewpoint, it is a meaningful approach to remove a potential "dilution" effect that may have occurred in previous studies when combining converters and non-converters in one group.

MATERIALS AND METHODS

Eligibility Criteria

We included studies in our meta-analysis if they investigated individuals that met CHR-criteria. Studies had to assess CHR-status according to established criteria and the minimum follow-up period was to be 12 months, as adequate transition rates can be expected after this time (14). Another important factor for eligibility was the presence of the hippocampal volume as an absolute value and not in relation to other parts of the brain [as in voxel-based measurements (VBM)] because the latter values are not ideal for direct statistical comparison and may be compromised through position changes during image registration (19, 60).

We assembled eligibility criteria according to the PRISMA-P guidelines. The following paragraph summarizes the inclusion and exclusion criteria that we applied:

Inclusion criteria:

1. Risk status established according to international research diagnostic criteria for high clinical risk for psychosis (CAARMS, BSIP, PACE, SIPS/SOPS) or primary symptoms (SPIA)
2. Hippocampal volume obtained through the region of interest (ROI) analysis (manually tracing or automated segmentation) reported separately for members of the transition-group and the non-transition group
3. Availability of mean values (±SD) of left and right hippocampal volume
4. Publication in a peer-reviewed journal
5. Follow-up interval of at least 12 months.

Exclusion criteria:

1. A sample size of <10 participants
2. Comorbidity with medical or neurological illnesses in patients
3. Any post-mortem assessments
4. Studies on the chromosome 22q11.2 deletion syndrome.

We registered the study with PROSPERO in February 2019, and our study project was approved in April 2019.

Search Strategy and Selection Process

We conducted a systematic literature search in the public databases Medline and EMBASE on April 28, 2019. We repeated the search on May 28, 2019. We used the following search terms: "(MRI OR magnetic resonance imaging OR neuroimaging) AND (psychos* OR schizophrenia* AND high-risk OR at-risk mental state OR prodrom*) AND hippocamp*".

We removed duplicates using EndNote and two authors (BH and AW) screened the references based on the titles and abstracts. All potentially relevant references were read in

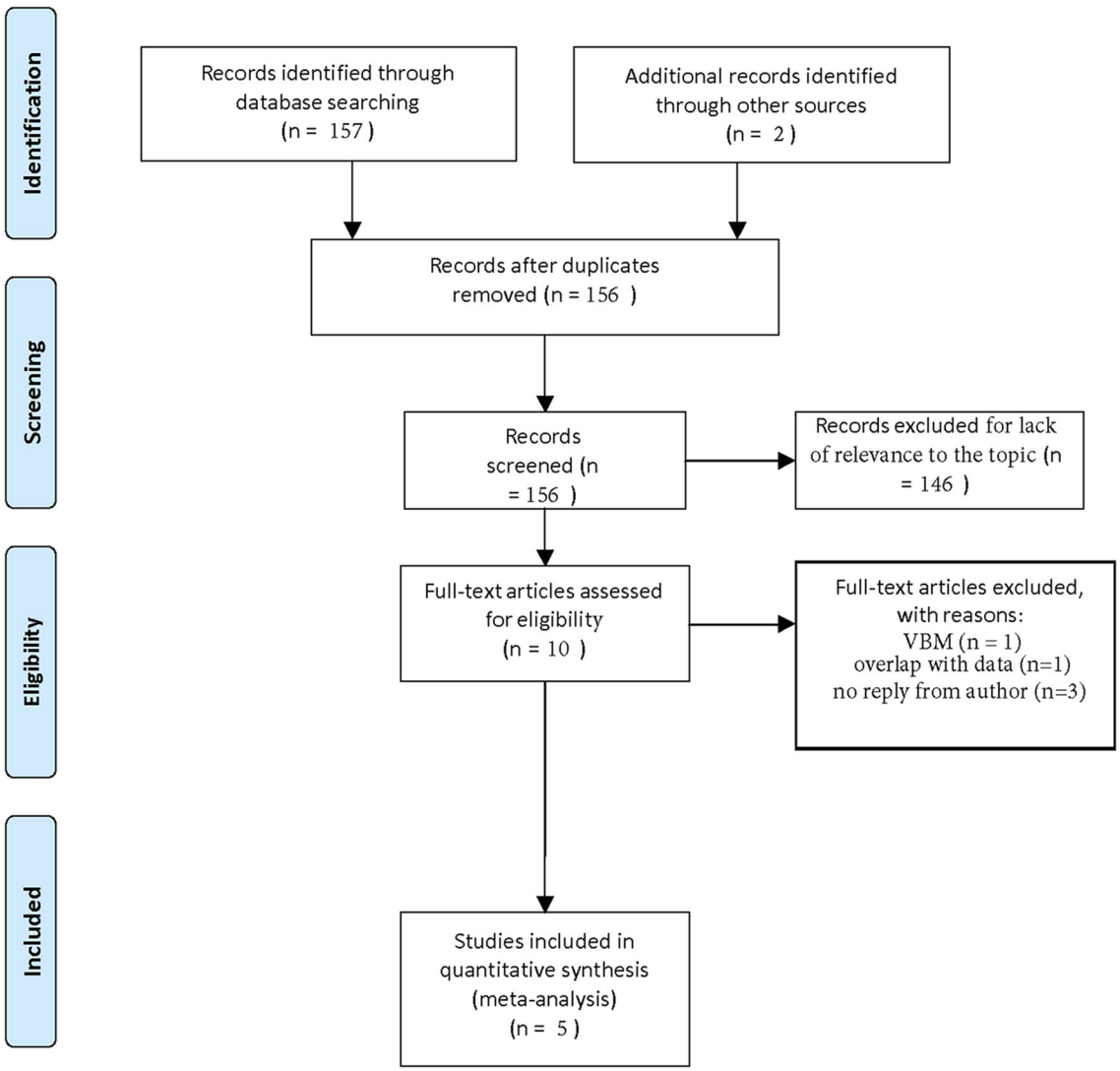

FIGURE 1 | Flow chart of selection process.

full-text and independently assessed by two authors (BH and AW). We resolved any disagreements by consensus. To identify potential additional studies that were not included in electronic databases, we screened the bibliographic references of all included articles.

In this fashion, we recovered 157 papers. Two additional articles were found by screening the references. One hundred and fifty six papers remained after removing duplicates. One hundred and forty six papers could be removed because they were not relevant to our topic or included reprints. Of the 10 remaining articles, we excluded one because it recorded hippocampal volume as a VBM-measurement (61) and we excluded one other study because its sample overlapped with a newer study that better fitted our inclusion criteria (57). In three additional cases, authors did not reply to our request for complete data extraction (47, 54, 56).

In this process, we could filter out five studies that could be included in our meta-analysis (48, 50, 52, 53, 55). The selection process is visualized in a flow-chart (see **Figure 1**).

Data Extraction

Necessary information was extracted by one reviewer (BH) and independently checked by a second reviewer (AW) and entered into a Numbers database. We identified and resolved discrepancies through discussion. Data items to be extracted were: first author name, the cohort, publication date, MRI resolution, hippocampal volume right/left (with standard deviation), number of men/women and mean age of participants (with standard deviation). In some cases, we contacted the authors of the original study in order to provide for the missing variables.

Hippocampal volume can be presented in two formats: as a "raw," uncorrected number or corrected for the intracranial volume (ICV). There is no consensus in the scientific community which format is more adequate. Hippocampal volume correlates with ICV, but this correlation is not proportional (62). Our goal was to carry out the statistical analysis with both the corrected and the uncorrected values; however, in two cases we could only retrieve the uncorrected values from the authors. All hippocampal volumes stated in this paper are thus the raw volumes in mm^3. They represent the mean values of the individual hippocampal measurements in each group (transition/non-transition-group).

Data Synthesis

We carried out a meta-analysis to assess the differences in the sizes of the left and right hippocampus in a CHR-group for psychosis. Using the data extracted from each paper (see section above), we built an evidence table to investigate possible between-study heterogeneity.

We then used the random-effects model to account for potential statistical heterogeneity, reporting the standardized mean difference and the respective 95% confidence interval (CI). We used standardized mean differences (SMD) due to the diversity of MRI-devices used (e.g., different resolutions) and applied the Hedges' g method (63). For calculating the pooled SMD using a random-effect model, we used the Dersimonian-Laird estimator for estimating the between-study variance (τ^2) (64). Forest plots were generated to show the individual and pooled effect measure, 95% confidence intervals (CI), the author's name, and study weights for the studies.

We assessed heterogeneity between the results of the studies by using the Cochran's Q test and quantified heterogeneity with the I-squared statistic. Heterogeneity based on the I-square is considered low, moderate, or high when the values are below 25%, between 25 and 75%, or above 75%, respectively.

We investigated sources of inter-study heterogeneity with the univariable random-effects meta-regression analysis that is based on the following primary study characteristics: year of publication, sample size, gender ratio, and MRI resolution. We weighted meta-regression analyses to account for both within-study variances of treatment effects and the residual inter-study heterogeneity.

We performed all analyses using the *metacont* function of the *meta* package in R 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) (65).

RESULTS

Systematic Review

All five studies that we could include in our meta-analysis were designed as case-control studies in which a healthy control group was compared to a CHR-group for psychosis in terms of baseline volumetric MRI-measurements. After baseline, the CHR-group was clinically followed up to determine transition status. As described above, we ignored the control-group in our analyses and only focused on the CHR-group.

In the following systematic review, we summarize and analyze the five studies regarding the way they established data for CHR-groups and regarding further study characteristics. We do not report special inclusion or exclusion criteria that are already understood due to the requirements we set for our meta-analysis (see section "Materials and Methods").

Dean et al. established CHR-status in an US-American sample using the "Structured Interview for Prodromal Syndromes" (SIPS) (48). Patients who had received antipsychotic medication before the interview were excluded, as were those with a lifelong drug dependence. Two members of the CHR-group who received antipsychotic medication between inclusion and follow-up (12 months later) were also excluded. This is noteworthy, as this may have underweighted the transition group. Reported drop-out rates in the CHR-group were low, with 16.7%. The study

TABLE 2A | Summary of group-diffferences between transition-group and non-transition group for each study (right hippocampus).

Author	Standardized mean difference	95% confidence interval	Weight (%)
Dean	0.7885	[−0.4054; 1.9823]	4.5
Pruessner	−0.0062	[−1.0716; 1.0592]	5.7
Buehlmann	0.0761	[−0.5746; 0.7268]	14.4
Cannon	−0.0189	[−0.3027; 0.2648]	55.6
Harrisberger	−0.475	[−1.0193; 0.0693]	19.8

"Weight" refers to the statistical weight within the random effects model.

TABLE 1 | Evidence table.

			Transition group				Non-transition group			
Author	**Year**	**Cohort**	***N* men**	***N* women**	**Mean age**	**SD age**	***N* men**	***N* women**	**Mean age**	**SD age**
Dean	2016	Boulder	2	1	19.33	2.08	20	15	18.89	1.39
Pruessner	2017	Montreal	2	2	21.14	5.1	11	11	19.97	3.15
Buehlmann	2010	Basel	11	5	26.4	6.5	11	10	23.4	6
Cannon	2015	NAPLS	36	19	19.18	3.77	213	147	19.78	4.23
Harrisberger	2016	Basel and Zurich	9	7	25.56	7.31	50	25	23.22	4.35

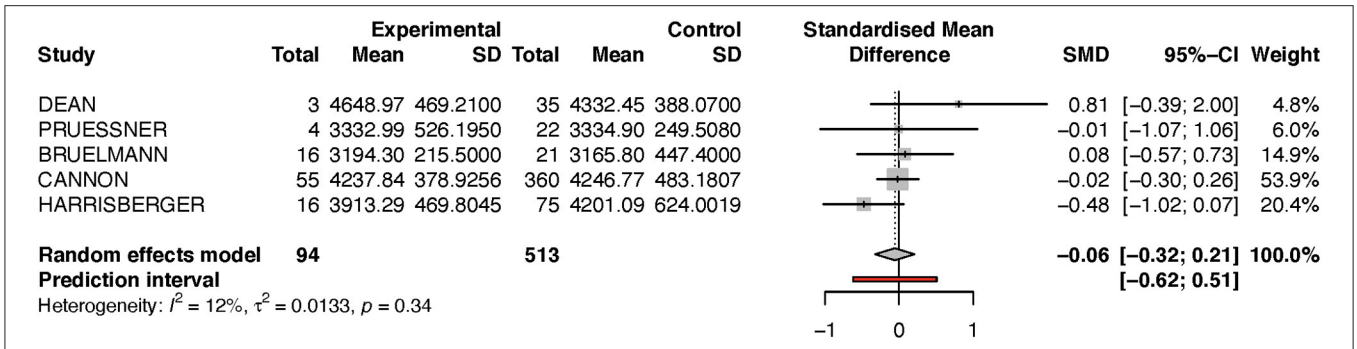

FIGURE 2 | Forest plot for Right hippocampus (full analysis).

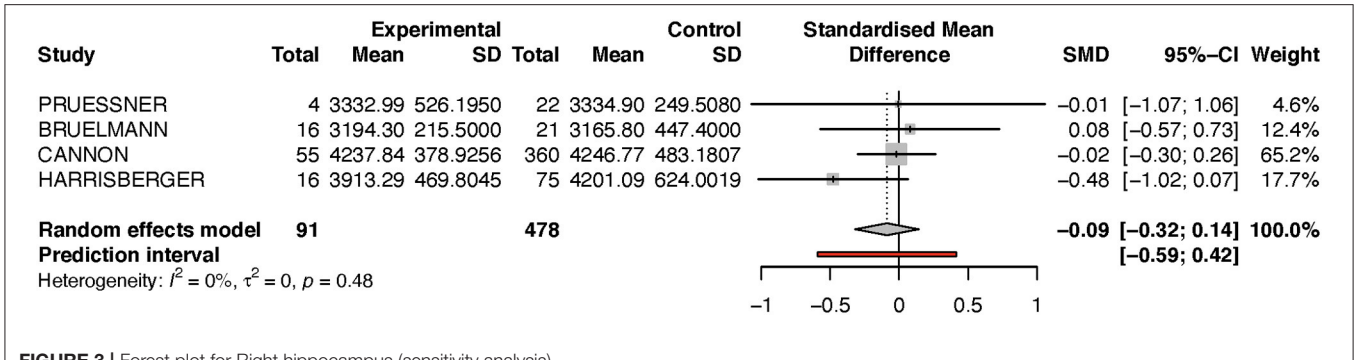

FIGURE 3 | Forest plot for Right hippocampus (sensitivity analysis).

had a rather short follow-up period of 12 months, which can be assumed to have only captured a part of the actual scope of transition. Scanning was done on a 3-Tesla device and automated segmentation with FreeSurfer (version 5.3.0) was used for image processing.

Cannon et al. also used the SIPS for CHR-inclusion in a US-American sample. There were no special exclusion criteria for the use of antipsychotic medication or drug abuse, as the study was done in a naturalistic setting. Drop-out rates were not reported, and the follow-up periods were short with 12 months (52). Scanning was performed on a 3-Tesla device and automated segmentation with FreeSurfer (version 5.2.0) was used for image processing.

Pruessner et al. used the "Comprehensive Assessment of At Risk Mental States" (CAARMS)-interview to establish CHR-status in a Canadian sample. Anyone with a history of substance use disorder or mental illness was excluded. Drop-out rates were not reported, and the regular follow-up interval was 2 years (55). Scanning was performed on a 1,5-Tesla device and automated segmentation with a self-designed tool (66) was used for image processing.

Harrisberger et al. used the "Basel Screening Instrument for Psychoses" (BSIP) in a Swiss sample to establish CHR status (53). Only antipsychotic-naive individuals were included in the CHR group. Drop-out was not reported, and the follow-up interval was 3 years. Scanning was performed on a 3-Tesla device and automated segmentation with the software FSL-FIRST (67) was used for image processing.

TABLE 2B | Summary of group-diffferences between transition-group and non-transition group for each study (left hippocampus).

Author	Standardized mean difference	95% confidence interval	Weight (%)
Dean	1.2041	[−0.0092; 2.4174]	9.5
Pruessner	−0.4011	[−1.4730; 0.6708]	11.4
Buehlmann	0.2221	[−0.4305; 0.8747]	20.7
Cannon	0.0975	[−0.1863; 0.3814]	34.1
Harrisberger	−0.5401	[−1.0858; 0.0056]	24.3

"Weight" refers to the statistical weight within the random effects model.

Buehlmann et al. used the "Personal Assessment and Crisis Evaluation" (PACE)-criteria for CHR-status in a Swiss sample (50) (there was no overlap with the study by Harrisberger et al.). The study was naturalistic and did not require any specific inclusion or exclusion criteria beyond those generally required for inclusion in our meta-analysis. Drop-out rates were not reported, and the follow-up interval was 3 years. Scanning was performed on a 1,5-Tesla device and manual tracing combined with AMIRA was used for image processing.

Participant Characteristics

The transition group (case group) consisted of 94 members (60 men, 34 women). The mean age was 21.57. The standard

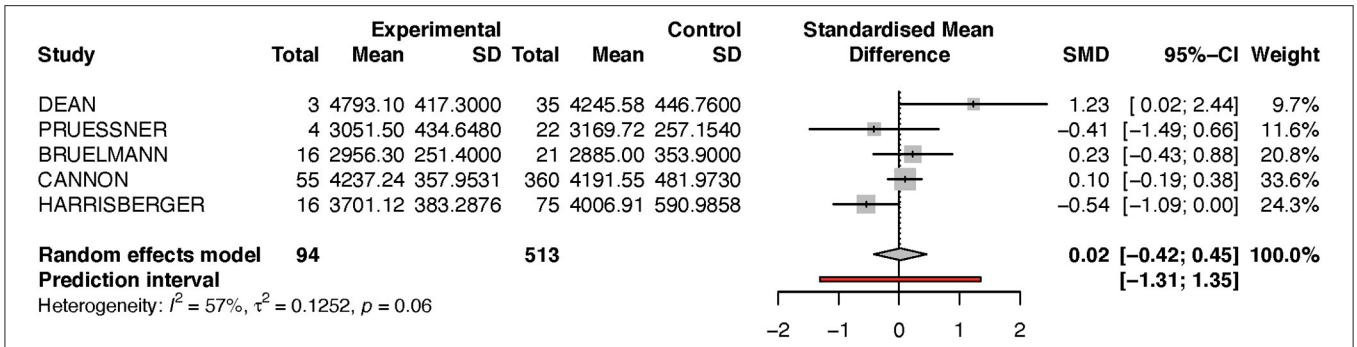

FIGURE 4 | Forest plot for Left hippocampus (full analysis).

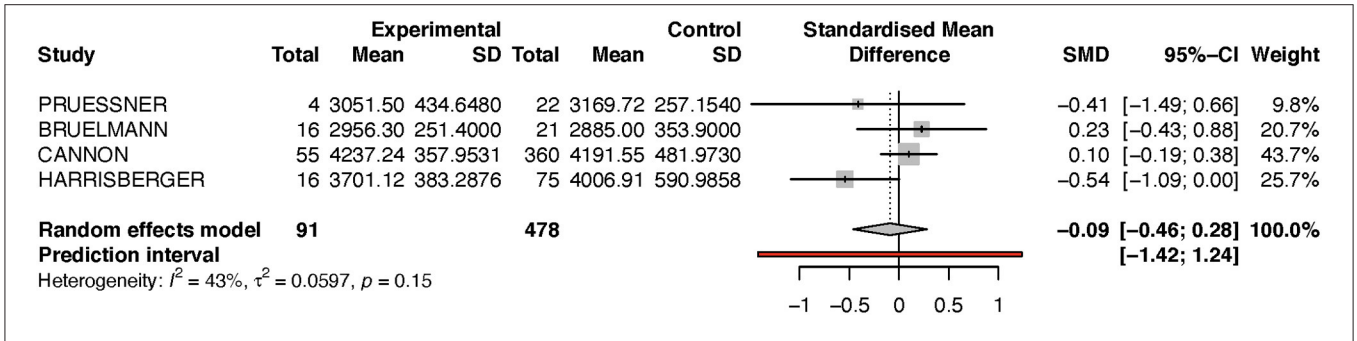

FIGURE 5 | Forest plot for Left hippocampus (sensitivity analysis).

TABLE 3 | Univariable meta-regression including all studies.

	Right hippocampus			Left hippocampus		
	Estimate	**95% CI**	***p*-value**	**Estimate**	**95% CI**	***p*-value**
Publication year (change per year)	−0.036	(−0.245, 0.174)	0.625	−0.065	(−0.382, 0.253)	0.562
Sample size (change per N)	−0.0001	(−0.004, 0.003)	0.943	−0.00001	(−0.006, 0.006)	0.982
Gender ration	0.138	(−1.620, 1.896)	0.818	0.194	(−2.613, 3.001)	0.84
MRI resolution	0.228	(−0.421, 0.878)	0.345	0.315	(−0.835, 1.464)	0.448

deviation of age (transition group) in the individual studies ranged from 2 to 7 years (see **Table 1** for details).

The non-transition group (control group) consisted of 513 members (305 men, 208 women). The mean age was 20.38. The standard deviation of age in the individual studies ranged from 1 to 4 years (see **Table 1** for details).

Results of Meta-Analysis

Due to the observed heterogeneity between the studies, we only report the results for the random-effects meta-analysis.

Looking at the right hippocampus, the standard mean difference shows that the volume of the right hippocampus is 6% less in the transition group than in the non-transition group (see **Table 2A** and **Figure 2**). The heterogeneity (I^2) between the studies is 12%, which indicates low heterogeneity.

Because the study of Dean et al. had a very small sample size, and because its results diverged from that of the other studies, we performed a sensitivity analysis by excluding this one study (see **Figure 3**). Performing this analysis reduced heterogeneity to zero, and moved the *p*-value closer to the direction of rejection of the null-hypothesis. Nevertheless, in both analyses, the results were not statistically significant and indicate at most a numerical trend.

For the left hippocampus, the heterogeneity (I^2) was much larger, with 57% (see **Table 2B** and **Figure 4**). The results have thus to be interpreted with caution, as is also indicated by the wide predictive interval. Initial analysis showed the left hippocampal volume to be 2% larger in the transition group. This is in contradiction to our hypothesis that the transition group has a smaller left hippocampus at baseline. However, when the sensitivity analysis was performed (again excluding the Dean et al. study, see **Figure 5**), this result was reversed, and the transition group's hippocampal volume was 9% smaller compared to the non-transition group. The results of both analyses for the left hippocampus are not statistically significant.

Results of Meta-Regression

We performed a meta-regression for the following variables: year of publication, sample size, gender ratio and resolution of MRI-device (see **Table 3**). None of the assessed variables in the meta-regression significantly contributed to the between-study heterogeneity.

DISCUSSION

Our meta-analysis investigated whether hippocampal volume at baseline predicts the transition to psychosis in a CHR-group. Our study did not find a statistically significant relationship between these parameters. However, we did find a trend that points into such a direction when looking at the right hippocampus. This trend was further confirmed after performing a sensitivity analysis. The investigated studies showed much more heterogeneous results for the left hippocampus. Interestingly, a study by Seidman investigating the parahippocampal gyrus as a vulnerability factor for schizophrenia also found more pronounced effects for the right side of the brain (37).

It remains to be seen if future studies can corroborate this trend. If so, it will be interesting to see whether such a result is bilateral or whether the unilateral quality (e.g., the prominence of changes in the right hippocampus) still holds true.

Looking at the results of the systematic review, the most rigorous study-protocol was provided by two studies that excluded a history of mental illness and of drug abuse. Thus, the most important potential confounders regarding hippocampal volume were removed. Two other studies excluded either one or the other of those preconditions. Very few studies reported drop-out rates in the CHR-group, and follow-up intervals varied considerably. Transition rates are generally assumed to be 18% after a follow-up of 6 months, 22% after 1 year, 29% after 2 years, and 36% after 3 years (14). Thus, only two of the five studies we analyzed employed the upper limit regarding follow-up.

Possible Clinical Implications

There is an ongoing debate about the concrete implications of risk predictions for members of CHR-groups. For a summary of the most important points in question, see Andreou and Borgwardt (19). For hippocampal volume to be of clinical use, a good cut-off margin between likely converters and non-converters will be required. This could provide clinicians with a biomarker that can be used to differentiate the CHR-group into an "extreme" risk group and a "reduced" risk group. Prophylactic treatment efforts could then be focused on those individuals who will most likely benefit from them.

Limitations and Future Directions

Certain limitations of our meta-analysis need to be discussed. First of all, the overall number of studies was rather small. Second, looking only at the hippocampal areas may underestimate the complexity of the neuronal network that underlies the development of paranoid schizophrenia, and in addition McHugo recently noted that it may not be the whole hippocampus that changes in volume before and during psychosis, but rather specific subfields (especially the anterior hippocampus) (68). More precisely, it might be necessary to not only test left-right-asymmetry between global hippocampus volume (as was done in our study), but also to conduct a differential regional analysis (e.g., anterior or posterior region of the hippocampus) or a subfield analysis (e.g., subiculum, cornu ammonis, dentate gyrus).

Thirdly, follow-up periods varied between the studies, and short follow-up times may have led to some false-negatives within the non-transition-group. This would reduce the likelihood of discovering any significant relationship between (premorbid) hippocampal brain volume and the likelihood of developing psychosis. All of these factors could modify a relevant relationship between hippocampal volume and transition risk.

Methodologically, two of our studies scanned the brains of study participants on a 1.5 Tesla device while the other three used 3 Tesla devices. It is possible that the resulting differences in resolution affected the accuracy of the measurement of the hippocampus, although there generally seems to be a high correlation between 1.5 and 3 Tesla measurements of hippocampal volume (69, 70). Similarly, while four out of the five studies used differing versions of automated segmentation with FreeSurfer or other Software for the measurements of the hippocampal volume, the paper by Buehlmann et al. used manual segmentation. Regarding the image processing, the MRI-sequences used (T1 or T2) might also have an impact on the volumetric measurements, but this was a data point that was not available to us. It must also be noted that correction of raw hippocampal volume for ICV might have had a significant effect on the outcome.

Finally, none of the papers we analyzed explicitly mentioned the diagnostic instruments used to establish transition. While it can be assumed that transition to psychosis was usually confirmed by applying the ICD-10 and/or DSM-IV criteria for schizophrenia through an experienced clinician, it should be noted that ICD-10 and DMS-IV criteria for schizophrenia do differ slightly and that "transition to psychosis" is not in every case equivalent with the development of schizophrenia. Velakoulis et al. have noted that hippocampal volume loss may be much less pronounced in diagnoses of the schizophreniform spectrum than in schizophrenia itself (56). The diagnostic instruments used to establish CHR-status (CAARMS, BSIP, PACE, SIPS) also varied. Taken together, there are a number of potential sources of heterogeneity that should be considered when conducting further studies on the topic.

On a more general level, the concept of a macroscopically visible biomarker (e.g., shrinkages of the hippocampus in volumetric MRI-measurements) may not capture the reality of the prodromal phase. It is quite possible that during the prodromal phase, it is not the volume of a whole-brain structure that changes, but rather the way neuronal populations communicate with each other. Other techniques would have to be adopted to capture such changes, for example, MRT-assessments of functional connectivity as done by Blessing et al. (71). Also, volumetric assessments can be enhanced by measurements of cortical thickness, surface area, and gyrification to capture a wider range of potential changes in brains of individuals who go on to develop a psychosis (19). It is also possible to determine

hippocampal volume at different time points (as was done by Cannon et al.) to determine a rate of change during the prodromal phase.

Implications for Members of CHR-Groups Who Are Non-converters

An important question is whether CHR-members in the non-transition group can be regarded as healthy individuals or whether they constitute a subclinical set of the psychotic spectrum. While some of those individuals will eventually make the transition to psychosis (albeit after the follow-up interval), there will be a significant proportion of non-converters. For this group of individuals, essentially two etiological scenarios are possible:

a) non-converters carry the same risk for development of a psychosis as the members of the transition-group, but due to favorable circumstances (for example a very healthy life-style) psychosis does not manifest. This would be in accordance with the diathesis-stress-model of schizophrenia (72).

b) non-converters do not carry a relevantly heightened risk for the development of a psychosis. They are thus "wrongfully" included in the CHR-set due to the intentionally low specificity-levels of criteria used in the establishment of risk-groups.

Our study cannot answer the question which of these scenarios is most likely. It would be beneficial to include the subgroup mentioned in a long-term follow-up to gain more statistical information on their outcome and CHR-members should also be evaluated according to the healthiness of the lifestyle they adopt.

Summary

In line with previous research, our meta-analysis indicates that there occur hippocampal volume changes in members of an ultra-high-risk-group before the transition to psychosis, but results did not reach significance thresholds. Larger samples are needed for future research in this area, and studies should not only look in more detail at the macroscopic level, but also assess the changes that occur on a functional level.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

SB and AW conceived the concept of the paper. BH and AW carried out the analysis of relevant literature. BH wrote the introduction, the results and the discussion section. BH and SA carried out the statistical analysis. SA wrote the Material and Methods section. CA revised the final manuscript. All authors contributed to the article and approved the submitted version.

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SYSTEMATIC REVIEW
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Longitudinal Structural MRI Findings in Individuals at Genetic and Clinical High Risk for Psychosis: A Systematic Review

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Background: Several cross-sectional studies report brain structure differences between healthy volunteers and subjects at genetic or clinical high risk of developing schizophrenia. However, longitudinal studies are important to determine whether altered trajectories of brain development precede psychosis onset.

Methods: We conducted a systematic review to determine if brain trajectories differ between (i) those with psychotic experiences (PE), genetic (GHR) or clinical high risk (CHR), compared to healthy volunteers, and (ii) those who transition to psychosis compared to those who do not.

Results: Thirty-eight studies measured gray matter and 18 studies measured white matter in 2,473 high risk subjects and 990 healthy volunteers. GHR, CHR, and PE subjects show an accelerated decline in gray matter primarily in temporal, and also frontal, cingulate and parietal cortex. In those who remain symptomatic or transition to psychosis, gray matter loss is more pronounced in these brain regions. White matter volume and fractional anisotropy, which typically increase until early adulthood, did not change or reduced in high risk subjects in the cingulum, thalamic radiation, cerebellum, retrolenticular part of internal capsule, and hippocampal–thalamic tracts. In those who transitioned, white matter volume and fractional anisotropy reduced over time in the inferior and superior fronto-occipital fasciculus, corpus callosum, anterior limb of the internal capsule, superior corona radiate, and calcarine cortex.

Conclusion: High risk subjects show deficits in white matter maturation and an accelerated decline in gray matter. Gray matter loss is more pronounced in those who transition to psychosis, but may normalize by early adulthood in remitters.

Keywords: high risk psychosis, MRI, DTI, neuroimaging, clinical high risk (CHR), ultra high risk (UHR), psychotic like experiences, genetic high risk for psychosis

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INTRODUCTION

Schizophrenia is posited to be a neurodevelopmental disorder, in which genetic and environmental factors interplay (1). A better understanding of the neurobiological changes that occur prior to the onset of disorder could identify new treatment targets to prevent transition to schizophrenia. With this aim, numerous studies have reported cross-sectional differences in brain structure

between subjects at high risk of developing schizophrenia and healthy volunteers. Such studies typically involve young persons ranging from adolescence to early adulthood, at a time of dynamic brain maturation. In order to fully recognize how brain development is altered in the run up to schizophrenia, it is key to conduct longitudinal studies in the prodrome. Therefore, we aimed to summarize longitudinal studies that track neuroimaging measures over time in individuals at genetic or clinical high risk of developing schizophrenia, and those in the general population who experience psychotic symptoms.

In general, neuroimaging studies examine three types of high risk cohorts; (i) help-seeking individuals who exhibit a reduction in functioning as well as attenuated psychotic symptoms or genetic risk for schizophrenia (clinical high risk; CHR, also known as an ultra-high risk of developing psychosis; UHR, or at-risk mental state; ARMS), (ii) individuals who exhibit attenuated psychotic symptoms and are not help seeking (psychotic experiences group; PE), and (iii) those with at least one relative diagnosed with schizophrenia (genetic high risk group; GHR) (2). The highest rate of transition is seen in the CHR group (36% after 3 years) (3), whereas transition rates are lower in the GHR (10–15%) (4) and PE groups (10%) (5). A meta-analysis of 14 cross-sectional voxel-based morphometry studies reported reduced gray matter in the anterior cingulate, middle frontal and temporal cortex in UHR subjects compared to healthy volunteers, and gray matter reductions were [more pronounced in schizophrenia] (6). A recent meta-analysis also reported decreased gray matter in frontal brain regions but increased gray matter volume in cingulate, right thalamus, left superior temporal gyrus and right fusiform gyrus (7), and it has been proposed that consequent volume reductions may occur with psychosis onset (8). In normal development, gray matter volume falls relative to total brain volume during adolescence and plateaus in the twenties (9). It is unclear from cross-sectional studies whether high risk subjects have a stable trait of lower gray matter, whether these differences emerge during brain maturation, or emerge following the onset of psychosis.

White matter development is more extended over the lifespan relative to gray matter. White matter volume increases over childhood and adolescence to reach peak levels in mid-adulthood, which coincides with the average age of schizophrenia onset. During this time the connectome is strengthened by increasing axonal diameter and myelination of white matter tracts (10). Fractional anisotropy (FA) values from diffusion tensor imaging (DTI) are sensitive to these changes in white matter microstructure. Cross-sectional studies report reduced FA in subjects at genetic and clinical high risk compared to healthy volunteers (11). As FA typically increases until mid-adulthood, it is not clear whether high risk groups have altered white matter trajectories or a stable deficit over time, or whether they recover from this deficit.

Longitudinal studies can also determine whether brain trajectories differ in high risk subjects who go on to transition to schizophrenia, compared to those who do not. A number of clinical services are now specialized to identify CHR individuals, however two-thirds of CHR individuals do not go on to develop psychosis, and it is not currently possible to predict who will transition (3). A meta-analysis of 25 cross-sectional studies found decreased prefrontal, cingulate, insular and cerebellar gray matter volume in subjects who went on to transition to psychosis compared to those who did not (12). Moreover, a large multisite study found less parahippocampal gray matter volume in those who later developed psychosis (13). Machine learning of brain structure measures alone seem to be insufficient for individual outcome prediction, although the addition of clinical measures increases prediction accuracy (14). Longitudinal measures may offer more sensitivity to detect differences between transition groups, partly by taking into account individual differences but also by revealing trajectories which may aid better prediction models.

In this systematic review, we included longitudinal structural and diffusion weighted Magnetic Resonance Imaging (MRI) studies examining participants at an enhanced risk of developing schizophrenia. We aimed to examine whether neurodevelopmental trajectories differ between (i) those with either psychotic experiences (PE), genetic (GHR) or clinical high risk (CHR, also known as UHR), compared to healthy volunteers, and (ii) those who transition compared to those who do not transition to psychosis. We hypothesized, first, that altered neurodevelopmental trajectories would be present in high risk populations (PE, GHR, and CHR) in comparison to healthy volunteers. Secondly, we predicted that these patterns of altered brain development would be more pronounced in subjects who remain symptomatic or transition to psychosis, compared to those who remit or do not transition.

METHODS

The systematic review was pre-registered on PROSPERO (CRD42020199065), and adhered to PRISMA guidelines. PubMed (including MEDLINE) and PsychInfo databases were searched to identify journal articles published from inception until 6 June 2020, to search titles and abstracts using the following search terms: (mri OR fmri OR dti OR brain OR "grey matter" OR "gray matter" OR "white matter" OR neuroimaging OR fa OR "fractional anisotropy" OR myelin OR magnetic resonance imaging OR diffusion tensor imaging OR "resting state" OR structural OR connectivity OR "diffusion weighted" OR "DW MRI" OR "Brain development") AND ("Psychosis risk" OR UHR OR CHR OR "clinical High Risk" OR "at risk mental state" or GHR or "psychotic experience" or "psychosis spectrum" or "clinical risk" OR ["genetic risk" and (psychosis or schizophrenia)] OR ["ultra high risk" and (psychosis or schizophrenia)] OR ["ultra-high risk" and (psychosis or schizophrenia)] OR ["high risk" and (psychosis or schizophrenia)] OR "risk" and (psychosis or schizophrenia) OR (emerging and psychosis) OR (psychopathology and youth) OR (prodromal and psychosis) OR (subthreshold and psychosis)) AND (follow* OR longitudinal* OR prospective OR "birth cohort" or development or trajectory OR progressive). References of previous reviews were also searched. All longitudinal studies reporting structural MRI measures in

a high risk group with a comparison group (either healthy volunteers, or comparisons between transition and non-transition high risk groups), or exploring an association with psychotic symptom scores or polygenic risk score for schizophrenia were included in the systematic review. Studies using overlapping samples were included, providing different MRI analyses had been applied. Study quality was assessed by the following criteria: (i) blinded groups at the analysis stage, (ii) participant drop out reported, and (iii) correction for multiple comparisons.

Clinical high risk subjects, also defined as ultra high risk or individuals meeting an at risk mental state, are referred to as "CHR" in this review. CHR, GHR, and PE subjects are referred to collectively as high risk subjects (HR).

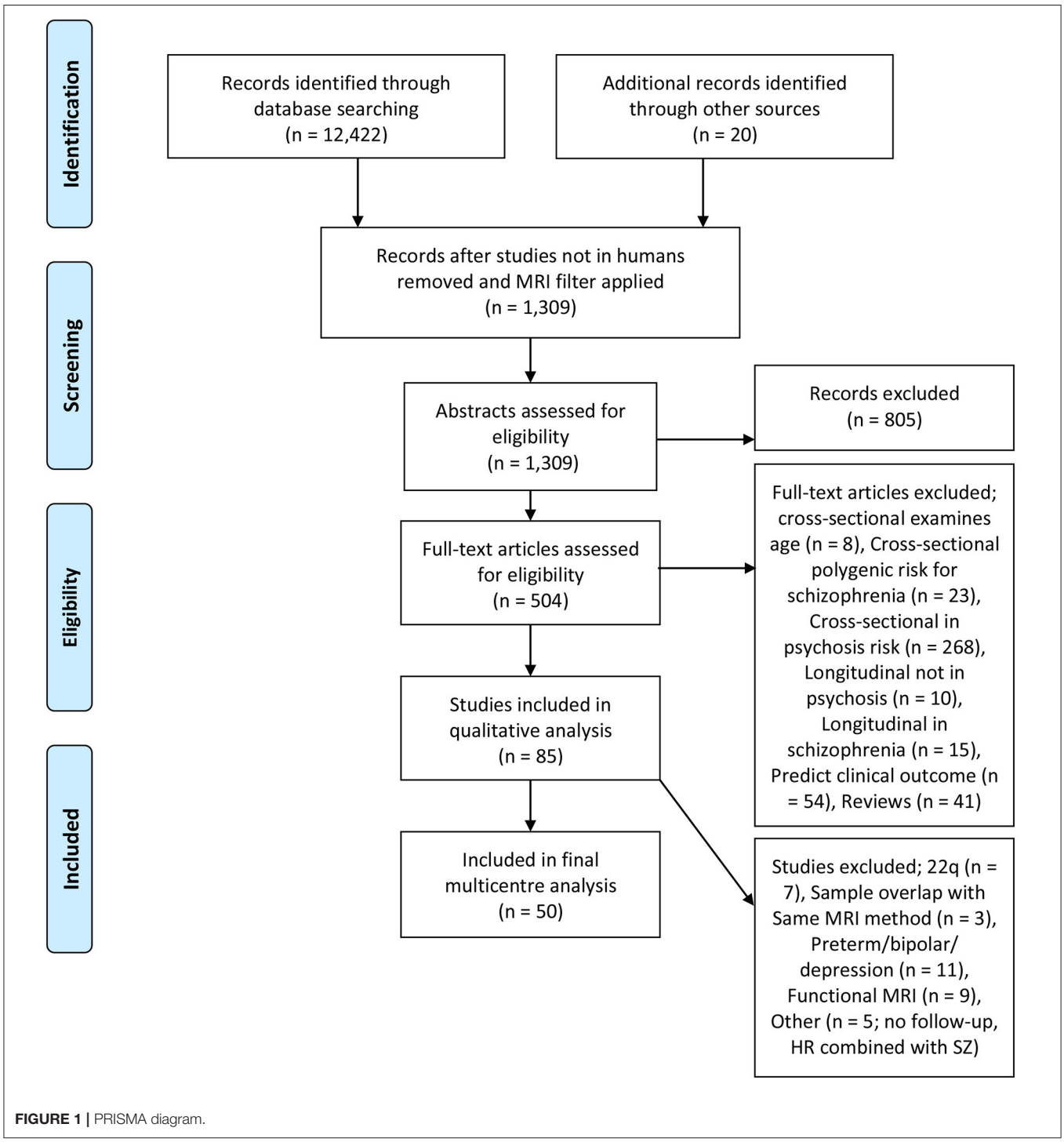

FIGURE 1 | PRISMA diagram.

TABLE 1 | Studies of gray matter indices included in the systematic review, with summary statistics on the final row.

Cohort	References	CHR = 1, GHR = 2, PE = 3	HV (*n*)	HR (*n*)	HR-T (*n*)	HR-NT (*n*)	HR-S (*n*)	HR-NS (*n*)	Age of HR (yrs)	Follow up (yrs)	AP naive	Cortical thick-ness	Volume	Surface area	Quality: B/DO/CMC
Toho University	Katagiri et al. (15)	1	16	42	5	37			22.3	1	✗		✓		✗✗✗
ADAPT	Damme et al. (16)	1	38	81					19	1	✗			✓	✗✗✓
NAPLS	Cannon et al. (17)	1	135	274	35	239			19.3	1	✗	✓			✗✓✓
	Chung et al. (18)	1	135	274	35	239			19.3	1	✗	✓			✗✗✓
	Chung et al. (19)	1	132	267	37	230			19.3	2	✗	✓			✗✗✓
Singapore	Ho et al. (20)	1	54	93			41	52	21.4	2	✓		✓		✗✗✓
NIMH COS Study	Gogtay et al. (21)	2	52	52					16.2	10	✓	✓			✗✓✓
	Mattai et al. (22)	2	86	43					13.4	6	✓	✓			✗✓✓
	Zalesky et al. (23)	2	102	86					18	10	✓	✓			✗✗✓
	Greenstein et al. (24)	2	110	80					14.9	10	✓		✓		✓✗✗
	Mattai et al. (25)	2	79	78					14.9	10	✓		✓		✗✗✗
Sibling pair, Utrecht	Brans et al. (26)	2	33	11					41.2	5	✓		✓		✗✗✗
Twin pair, Utrecht	Hedman et al. (27)	2	54	19					38.7	5	✓	✓		✓	✗✓✓
Dutch Prediction of Psychosis	Ziermans et al. (28)	1	30	43	8	35			16.1	2	✗	✓	✓		✓✓✓
	de Wit et al. (29)	1	24	35			18	17	15.4	6	✗	✓	✓	✓	✓✓✗
Edinburgh High Risk Study	Lawrie et al. (30)	2	20	66			19	47	23.1	2	✓		✓		✗✗✗
	Job et al. (31)	2	19	65			18	47	21.4	2	✓		✓		✗✓✓
	Mcintosh et al. (32)	2	36	146	17	72	57		21.2	10	✓		✓		✓✓✗
	Bois et al. (33)	2	36	142	17	68	57		21	2	✓	✓		✓	✓✗✓
	Bois et al. (34)	2	36	142	17	68	57		21	2	✓		✓		✗✓-
Edinburgh Study of Comorbidity	Moorhead et al. (35)	3	45	53					15.9	1.5	✓		✓		✗✓✓
	McKechanie et al. (36)	3	NA	43					16.2	6	✗		✓		✗✓✓
FEPSY project	Walter et al. (37)	1	NA	23	10	13			24.2	5	✗		✓		✓✗-
	Walter et al. (38)	1	NA	18	8	10			25.7	5	✗		✓		✓✗-
	Borgwardt et al. (39)	1	NA	20	10	10			24.7	4	✗		✓		✗✗✓
OASIS	Fusar-Poli et al. (40)	1	14	22	5	17			24.5	2	✗		✓		✗✓✓
PACE	Pantelis et al. (41)	1	NA	21	10	11			19.7	3	✗		✓		✗✓✗
	Sun et al. (42)	1	NA	35	12	23			19.9	4	✗			✓	✓✗✓
	Takahashi et al. (43)	1	22	35	12	23			19.9	4	✗		✓		✓✗✗
	Takahashi et al. (44)	1	20	31	11	20			19.9	4	✗		✓		✓✓-
Ludwig Maximilians	Koutsouleris et al. (45)	1	28	25	12	13			23.2	4	✗		✓		✗✓✓
Western Psychiatric Institute and Clinic	Bhojraj et al. (46)	2	36	56					15.4	1	✓	✓		✓	✓✗-
	Bhojraj et al. (47)	2	27	23					15.4	1	✓		✓		✓✗✗
	Prasad et al. (48)	2	33	31					16.3	1	✓	✓	✓	✓	✗✓✗

(Continued)

TABLE 1 | Continued

Cohort	References	CHR = 1, GHR = 2, PE = 3	HV (*n*)	HR (*n*)	HR-T (*n*)	HR-NT (*n*)	HR-S (*n*)	HR-NS (*n*)	Age of HR (yrs)	Follow up (yrs)	AP naive	Cortical thick-ness	Volume	Surface area	Quality: B/DO/CMC
IMAGEN	Yu et al. (49)	3	NA	706					14.4	4	✓		✓		X✓✓
Dublin & Kildare	Calvo et al. (50)	3	25	25					13.5	2	✓		✓		XX-
Barcelona	Sugranyes et al. (51)	2	34	58					11.3	2.3	✗	✓		✓	✓✓✓
	Sugranyes et al. (52)	2	49	79			20	59	12.1	4	✗	✓	✓	✓	✓✓✓
Totals:		17 GHR, 17 CHR, 4 PE	1560	3343	261	1128	287	222	Mean 19.7	Mean 3.9	19	14	26	9	Mean 1.4/3

GHR, Genetic high risk; CHR, Clinical high risk; T, transition; NT, no transition; S, symptomatic; NS, no symptoms; HR, high risk; HV, Healthy Volunteers; PE, psychotic experiences; AP, antipsychotic medication; NA, Not Applicable; Quality, Blind/Drop-Out Reported/Correct for Multiple Comparisons.

RESULTS

The literature search identified 50 studies from 22 high risk (HR) cohorts, including 2,473 HR subjects and 990 healthy volunteers (HV) (**Figure 1**, PRISMA diagram). Twenty-six studies examined CHR subjects (also defined as ultra high risk or individuals meeting an at risk mental state), 19 studies examined GHR subjects, and 5 studies examined individuals with PE. Thirty-eight studies examined gray matter (**Table 1**) and 18 examined white matter (**Table 2**). The average age of the HR group was 21.4 years (SD 9.7) at baseline, with the follow-up scan occurring on average 3.4 years later (SD 2.7). CHR groups were assessed by the Comprehensive Assessment of At Risk Mental State, the Structured Interview for Prodromal Syndromes, the Basel Screening Instrument for Psychosis, and the Bonn Scale for the Assessment of Basic Symptoms. Four cohorts assess PE; (1) The Edinburgh Study of Comorbidity examines adolescents with cognitive impairment and schizotypal features which have been classified as PE in this review, assessed via the Structured Interview for Schizotypy, (2) The IMAGEN study used the Community Assessment of Psychic Experiences (CAPE) which takes into account frequency and distress of symptoms, (3) Calvo et al., used the SOCRATES template, which documents the presence of perceptual abnormalities and unusual thought content with no frequency or duration criteria, (4) The PNC cohort used the Scale of Prodromal Symptoms, and individuals were required to possess significant sub-threshold symptoms that persisted for at least two clinical assessments (on average 20 months apart). Detailed summaries of each study can be found in the **Supplementary Tables 1, 2**.

Longitudinal Brain Trajectories in High Risk Subjects Compared to Healthy Volunteers

For studies of gray matter comparing HR groups to healthy volunteers (HV), 20 out of 24 studies measuring brain volume, cortical thickness, or surface morphology, reported altered gray matter trajectories in HR (**Table 3**). Altered gray matter development is seen regardless of the type of HR group examined; a significant change over time compared to HV was reported in 13 out of 16 studies of GHR, 4 out of 5 studies in CHR, and 3 out of 3 studies of PE. Significant results were primarily in the temporal (16 studies), frontal (9 studies), parietal lobe (6 studies), cingulate cortex (6 studies), and whole brain (6 studies).

In the temporal cortex, the majority of studies (13 studies) found a reduction in cortical thickness or volume over time in HR subjects, whereas 2 studies reported no change over time in HR, but a decrease (48) or an increase in HV (34). One study did not detect changes over time but instead found lower hippocampal volume at both timepoints in HR (50). In the frontal cortex and cingulate, gray matter volume, cortical thickness and surface morphology reduced over time in HR in the majority of studies, with the exception of two studies. One study found increased gray matter in the right inferior frontal gyrus and anterior cingulate, but reduced in bilateral superior frontal gyrus, although an interaction between group and time was not assessed (40). One study found less steep decreases in surface area over time in CHR in frontal and parietal areas (29). In the parietal

TABLE 2 | Studies of white matter indices included in the systematic review, with summary statistics on the bottom row.

Cohort	References	CHR = 1, GHR = 2, PE = 3	HV (*n*)	HR (*n*)	HR-T (*n*)	HR-NT (*n*)	Age of HR (yrs)	Follow up (yrs)	AP naive	MRI analysis	Quality: blind/drop-out/correct for multiple comparisons
Sibling pair cohort	Brans et al. (26)	2	33	11			41.2	5	✓	Struct: Volume	✗✓✗
Dutch Prediction of Psychosis	Ziermans et al. (28)	1	30	43	8	35	16.1	2	✗	Struct: Semiautomated volume + VBM	✓✓✓
	de Wit et al. (29)	1	24	35	18	17	15.4	6	✗	Struct: Volume	✓✓✗
Edinburgh Study of Comorbidity	Moorhead et al. (35)	3	45	53			15.9	1.5	✓	Struct: TBM	✓✓✗
Ludwig-Maximilians	Koutsouleris et al. (45)	1	28	25	12	13	23.2	4	✗	Struct: VBM Multivariate	✗✓✓
PACE	Walterfang et al. (53)	1	NA	21	10	11	20.5	1.3	✗	Struct: VBM	✗✓✓
NIMH COS study	Gogtay et al. (54)	2	57	49			16.1	5	✓	Struct: TBM	✗✗✓
LBC1936 birth cohort	Alloza et al. (55)	NA	NA	488			76.4	3	✓	DTI: Tractometry and connectomic	✗✓✓
Toho University	Katagiri et al. (56)	1	16	42	5	37	22.3	1	✗	Struct: ROI volume (Corpus Callosum)	✗✗✗
	Saito et al. (57)	1	16	46	7	39	22.9	1	✗	DTI: Tractometry (Corpus Callosum)	✗✓✗
	Katagiri et al. (58)	1	16	41	7	34	22.8	1	✗	DTI: cross-sectional whole-brain TBSS followed by longitudinal ROI analysis	✗✓✓
Copenhagen	Krakauer et al. (59)	1	23	30			24.1	1	✗	DTI: Whole-brain TBSS	✗✓✓
ADAPT	Bernard et al. (60)	1	21	26			18.7	1	✗	DTI: Tractometry (hippocampal–thalamic)	✗✗-
	Mittal et al. (61)	1	15	15			18.5	1	✗	DTI: Atlas-based TBSS ROI analysis (Superior Cerebella Peduncles)	✓✓-
	Bernard et al. (62)	1	24	26			18.7	1	✗	DTI: Tractometry (Cerebello-thalamo-cortical)	✗✓✓
Genetic Risk and Outcome of Psychosis	Domen et al. (63)	2	49	55			30.9	3	✓	DTI: Atlas-based TBSS ROI analysis (2x19 regions)	✗✓✓
OASIS	Carletti et al. (64)	1	32	22	5	17	23.4	2	✗	DTI: Cluster-level suprathreshold voxel analysis	✗✓✓
PNC	Roalf et al. (65)	3	89	38			15.5	2	✗	DTI: Whole-brain TBSS followed by Atlas-based ROI analysis	✗✓✓
Totals:		3 GHR, 12 CHR, 2 PE, 1 Older adults	518	1,066	72	203	Mean 24.6	Mean 2.3	5	8 Structural, 3 Tractometry, 1 Connectomic, 2 Whole-brain-TBSS, 3 ROI-TBSS, 1 Cluster-level DTI	Mean 1.7/3

GHR, Genetic high risk; CHR, Clinical high risk; T, transition; NT, no transition; S, symptomatic; NS, no symptoms; HR, high risk; HV, Healthy Volunteers; PE, psychotic experiences; AP, antipsychotic medication; NA, Not Applicable.

TABLE 3 | List of studies examining gray matter indices, indicating significant differences between groups either at baseline (BL) or a significant group x time interaction.

Dataset	References	BL: HR vs. HV	Time: HR vs. HV	Time: CHR-T vs. CHR-NT	BL: Predict Transition	Significant brain regions for HR vs. HV over time										Significant brain regions for CHR-T vs. CHR-NT over time									
						Whole brain	Frontal	ACC	Temporal	Parietal	Occipital	Thalamus	Amygdala	Basal Ganglia	Cerebellum	Ventricle	Whole brain	Frontal	Insula	ACC	Temporal	Parietal	Occipital	Nucleus Accumbens	Cerebellum	Ventricle
Toho University	Katagiri et al. (15)	NA	NA	NA	✗																				
ADAPT	Damme et al. (16)	✓	✗	NA	NA																				
NAPLS	Cannon et al. (17)	NA	NA	✓	✗													↓ CT							↑ Vol
	Chung et al. (18)	NA	NA	NA	NA																				
	Chung et al. (19)	NA	NA	NA	NA																				
Singapore	Ho et al. (20)	NA	NA	✓	✗																↓ Vol				
NIMH COS Study	Gogtay et al. (21)	✗	✓	NA	NA		↓ CT		↓ CT	↓ CT															
	Mattai et al. (22)	✗	✓	NA	NA		↓ CT		↓ CT	↓ CT															
	Zalesky et al. (23)	NA	✓	NA	NA				↓ Con		↓ Con														
	Greenstein et al. (24)	✓	✓	NA	NA										↓ Vol										
	Mattai (25)	✗	✗	NA	NA																				
Sibling pair, Utrecht	Brans et al. (26)	NA	✗	NA	NA																				
Twin pair, Utrecht	Hedman et al. (27)	NA	✓	NA	NA	↓ CT			↓ CT																
Dutch Prediction Psychosis	Ziermans et al. (28)	✗	✓	✓	✗				↓ CT								↓ Vol			↓ CT	↓ CT	↓ CT	↓ CT			
	de Wit et al. (29)	NA	✓	✓	NA	↔ SA	↔ SA ↑ Vol	↓ SA	↓ Vol ↓ CT	↔ SA ↓ GI	↓ SA ↓ GI ↓ Vol	↓ Vol				↑ Vol	↓ CT* SA*	↓ Vol* ↓ CT* ↓ SA		↓ Vol ↑ GI	↓ Vol* ↓ CT* ↔ CT	↓ Vol* ↓ CT*		↓ Vol*		↑ Vol
Edinburgh High Risk Study	Lawrie et al. (30)	✓	✗	✓	NA																↓ Vol				
	Job et al. (31)	NA	Effect of time	Effect of time	NA			↓ Vol	↓ Vol	↓ Vol					↓ Vol										

(Continued)

TABLE 3 | Continued

Dataset	References	BL: HR vs. HV	Time: HR vs. HV	Time: CHR-T vs. CHR-NT	BL: Predict Transition	Significant brain regions for HR vs. HV over time										Significant brain regions for CHR-T vs. CHR-NT over time									
						Whole brain	Frontal	ACC	Temporal	Parietal	Occipital	Thalamus	Amygdala	Basal Ganglia	Cerebellum	Ventricle	Whole brain	Frontal	Insula	ACC	Temporal	Parietal	Occipital	Nucleus Accumbens	Cerebellum	Ventricle
	Mcintosh et al. (32)	✓	✓	✓	✗	↓ Vol	↓ Vol		↓ Vol									↓ Vol								
	Bois et al. (33)	✗	✓	✗	✓	↓ CT, ↔ SA	↓ CT	↓ CT			↔ CT															
	Bois et al. (34)	NA	✓	✗	NA				↔ Vol																	
Edinburgh Study of Comorbidity	Moorhead et al. (35)	NA	✓	NA	NA				↓ Vol				↓ Vol													
	McKechanie et al. (36)	NA	NA	NA	NA																					
FEPSY project	Walter et al. (37)	NA	NA	✗	✓																					
	Walter et al. (38)	NA	NA	✗	NA																					
	Borgwardt et al. (39)	NA	NA	✓	✓													↓ Vol			↓ Vol	↓ Vol			↓ Vol	
OASIS	Fusar-Poli et al. (40)	✓	Effect of time	Effect of time	✓		↑↓ Vol	↑ Vol						↓ Vol	↑ Vol						↓ Vol					
PACE	Pantelis et al. (41)	NA	NA	Effect of time	✓													↓ Vol		↓ Vol	↓ Vol		↑ Vol		↓ Vol	
	Sun et al. (42)	NA	NA	✓	NA													↓ SA								
	Takahashi et al. (43)	NA	NA	✓	✗																↓ Vol					
	Takahashi et al. (44)	NA	NA	✓	✓														↓ Vol							
Ludwig Maximilians	Koutsouleris et al. (45)	NA	✓	✓	✓		↓ Vol	↓ Vol	↓ Vol	↓ Vol	↓ Vol			↓ Vol	↓ Vol	↑ Vol				↓ Vol		↓ Vol				↑ Vol
Western Psychiatric Institute and Clinic	Bhojraj et al. (46)	NA	✓	NA	NA				↓ SA																	
	Bhojraj et al. (47)	✓	✓	NA	✓		↓ Vol	↓ Vol	↓ Vol																	
	Prasad et al. (48)	✓	✓	NA	NA	↓ SA	↓ SA, ↓ Vol, ↑ CT		↓ Vol, ↑ CT	↓ Vol, ↑ CT	↓ SA, ↓ Vol															
IMAGEN	Yu et al. (49)	NA	✓	NA	NA				↔ Vol																	

(Continued)

TABLE 3 | Continued

Dataset	References	BL: HR vs. HV	Time: HR vs. HV	Time: CHR-T vs. CHR-NT	BL: Predict Transition	Significant brain regions for HR vs. HV over time											Significant brain regions for CHR-T vs. CHR-NT over time									
						Whole brain	Frontal	ACC	Temporal	Parietal	Occipital	Thalamus	Amygdala	Basal Ganglia	Cerebellum	Ventricle	Whole brain	Frontal	Insula	ACC	Temporal	Parietal	Occipital	Nucleus Accumbens	Cerebellum	Ventricle
Dublin & Kildare	Calvo et al. (50)	✓	Effect of group	NA	NA				↓ Vol*																	
Barcelona	Sugranyes et al. (51)	✓	✓	NA	NA	↔ SA																				
	Sugranyes et al. (52)	NA	NA	✓	✓												↓ CT ↓ SA* NT vs. HV: ↔ SA+Vol						↓ CT			
TOTAL:		9/14	20/24	15/19	9/15	6	9	6	16	6	4	1	1	2	4	2	3	6	1	4	9	4	3	1	3	3

Whole brain, Frontal, ACC, Temporal, Parietal, Occipital, Thalamus, Amygdala, Basal Ganglia, Cerebellum, Ventricle, Whole brain, Frontal, Insula, ACC, Temporal, Parietal, Occipital, Nucleus Accumbens, Cerebellum, Ventricle
BL: HR vs. HV
Time: HR vs. HV
Time: CHR-T vs. CHR-NT
BL: Predict Transition

*Arrows indicate altered trajectories between groups in specified brain region, ↓ indicate a decrease in the HR or CHR-T group compared to HV or CHR-NT respectively, ↑ indicate an increase and ↔ indicate no change over time in HR whereas an increase/decrease is seen in HV. HR, high risk; HV, healthy volunteer; CHR-T, clinical high risk transition; CHR-NT, no transition; ACC, Anterior cingulate cortex; NA, Not Applicable (for example studies examine other contrasts such as medicated vs. unmedicated); CT, cortical thickness; Vol, gray matter volume; Conn, structural connectivity; SA, surface area; GI, gyrification. *volume was lower in HR vs. HV at both timepoints but there was no group × time interaction.*

lobe, the majority of studies reported reduced gray matter volume and cortical thickness over time in HR, bar the aforementioned study (29) and another study which found increased cortical thickness but reduced volume over time (48). For whole brain, differences were found in cortical surface area and gray matter. A number of studies found smaller longitudinal decreases in global surface area in HR compared to healthy volunteers (29, 33, 51), although one study found a reduction in GHR (48). For whole brain gray matter, greater reductions over time in GHR compared to HV were reported (32), and more pronounced global cortical thinning in discordant twin pairs compared with healthy control twin pairs, although no difference in surface area was observed in this study (27).

For studies of white matter comparing HR groups to HV, 9 out of 13 studies reported altered trajectories in HR groups (5/7 studies in CHR, 2/3 studies in GHR, 1/2 in PE, 1 in subjects with polygenic risk scores for schizophrenia). Altered trajectories were reported principally in whole brain, in the cingulum and in the thalamic radiation (3 studies) amongst other regions (**Table 4**). Studies measuring white matter volume found reduced volume over time or showed smaller increases compared to HV, in the whole brain, parietal lobes and in the corpus callosum of HR subjects (3 out of 5 volume studies). Slower white matter growth in the parietal lobe normalized by age 14 in GHR subjects (54).

Most tract-based spatial statistics (TBSS) and tractography studies focused their analysis on regions of interest (ROI) rather than on the whole brain, finding a reduction or no change in FA in HR groups, whereas FA increased over time in HV; 2 studies examined the cerebellar tracts (61, 62), and 1 study measured tracts connecting the thalamus and hippocampus (60). For whole brain TBSS analyses, mean FA values reduced over time in GHR but increased for HV in the whole brain, the right cingulum, and the left posterior thalamic radiation, with a smaller increase in the right retrolenticular part of the internal capsule (63). Two whole brain TBSS studies did not find altered neurodevelopmental trajectories in HR, but instead found lower FA at baseline (59) or through both timepoints (65). Of these, Krakauer et al. (59) reported reduced FA in the right anterior thalamic radiation (ATR), left corticospinal tract (CST) and left superior longitudinal fasciculus (SLF), and Roalf et al. (65) reported lower FA in the CST and in the cingulum bundle of the hippocampus (CGH). Lower FA at baseline in the SLF may normalize over time, as another TBSS study found that FA in this tract increased over the course of 1 year in UHR subjects (59). A study in an older age cohort (mean age 76 years) found that polygenic risk score for schizophrenia correlated with increased mean diffusivity over time in the splenium, arcuate, ATR and cingulum, which may reflect reduced neuropil or increases in cerebrospinal fluid (55).

Longitudinal Brain Trajectories in Subjects That Transition to Psychosis

For studies of gray matter comparing HR groups based on transition status (pre vs. post), 15 out of 19 studies report altered gray matter trajectories in those whose symptoms persist or transition to psychosis compared to those whose symptoms remit or those who do not transition to psychosis. Significant findings centered on the temporal (9 studies) and frontal cortex (6 studies), with fewer findings in the parietal lobe and anterior cingulate cortex (4 studies) (**Table 3**). Studies consistently reported greater reductions in gray matter volume, cortical thickness and surface area over time in those who remained symptomatic or transitioned to psychosis, with the exception of one study (29). In this study both resilient and non-resilient CHR individuals showed decreased cortical thickness over time in the superior temporal cortex and posterior cingulate gyrus, which started out lower in non-resilient subjects, however, the non-resilient group showed a slower rate of change than the resilient group. Furthermore, in the anterior cingulate cortex the study reported greater volume reductions over time in the non-resilient CHR group but an increase in gyrification over time. In general, studies comparing transition and non-transition groups alongside HV found greater cortical thinning in frontal and temporal lobes, as well as the caudate and insula, which were not apparent in the non-transition group when compared to HV (17, 20, 28, 32, 43, 44, 52).

For studies in CHR (rather than GHR), 11 out of 13 studies report altered trajectories in subjects who were most unwell. No studies in subjects with PE examined transitioned patients, although one study subtyped PE subjects based on negative symptom severity, finding widespread gray matter loss in those with more severe negative symptoms (36). In GHR 4 out of 6 studies found significant longitudinal changes based on clinical presentation (5 studies from the Edinburgh High-Risk cohort). Differing results in GHR subjects from the Edinburgh High-Risk cohort depend on the applied MRI analysis method. The most reliable results are described by Bois et al. (33), which was one of two studies in this cohort to apply correction for multiple comparisons. In this study, cortical thickness did not change over time according to clinical status, but differed in the whole GHR group compared to HV. As GHR subjects were split into three clinical groups; well, symptomatic and transitioned, this cohort may have been under-powered to detect differences between groups, and only a small proportion of participants transitioned in this cohort ($n = 8$).

For white matter, only 5 studies examined whether brain development differs in those who transition to psychosis and those who do not (**Table 4**), and all found greater reductions in white matter volume or FA in the former group, principally in the corpus callosum (3 studies) and in white matter regions near the superior fronto-occipital fasciculus (SFOF) (2 studies). One study used DTI methods and found reduced FA over time in transitioned subjects in a cluster of voxels in the anterior limb of the left internal capsule (left ALIC), the body of the corpus callosum (bCC), left superior corona radiata (SCR), and left SFOF (64), with an increase over time in non-transitioned subjects. Four studies measured white matter volume; 3 studies found reduced volume over time in the corpus callosum, left inferior frontal occipital fasciculus (IFOF), calcarine cortex, and whole brain of transitioned subjects (28, 45, 53). The other study of white matter found that corpus callosum volume reduced over time in all groups (healthy volunteers, resilient and non-resilient UHR) but that corpus callosum volume was highest in

TABLE 4 | List of studies examining white matter, ticks indicate significant differences between groups either at baseline (BL) or a significant group × time interaction.

Dataset	References	BL: HR vs. HV	Time: HR vs. HV	Time: CHR-T vs. CHR-NT	BL: Predict Transition	Significant brain regions for HR vs. HV over time															Significant brain regions for CHR-T vs. CHR-NT over time						
						Whole brain	Cingulum	Fronto-occipital fasciculus	Cerebellum	Cerebello-thalamo-cortical	Parietal	Splenium	Arcuate	Thalamic radiations	SLF	Inferior longitudinal fasciculus	Thalamic – hippocampal	Internal capsule	Forceps major	Corticospinal	Corpus collosum	Whole brain	Fronto-occipital fasciculus	Cerebellum	Calcarine cortex	Internal capsule	Corona radiata	Corpus collosum
Sibling pair cohort	Brans et al. (26)	NA	✗	NA	NA																							
Dutch Prediction Psychosis	Ziermans et al. (28)	✗	✓	✓	✗	↔ Vol															↓ Vol						
	De Wit et al. (29)	NA	✗	✓	NA																						↓ Vol*
Edinburgh Study Co-morbidity	Moorhead et al. (35)	NA	✗	NA	NA																						
Ludwig-Maximilians	Koutsouleris et al. (45)	NA	✓	✓	NA																↓ Vol						↓ Vol
PACE	Walterfang et al. (53)	NA	NA	✓	✓																	↓ Vol	↑ Vol	↓ Vol			
NIMH COS study	Gogtay et al. (54)	✗	✓	NA	NA						↔ Vol																
LBC1936 birth cohort	Alloza et al. (55)	✗	✓	NA	NA		↑ MD					↑ MD	↑ MD	↑ MD													
Toho University	Katagiri et al. (56)	NA	NA	NA	NA																						
	Saito et al. (57)	✓	NA	NA	✓																						
	Katagiri et al. (58)	✓	NA	NA	✗																						
Copenhagen	Krakauer et al. (59)	✓	Effect of time	NA	NA										↑ FA												
ADAPT	Bernard et al. (60)	NA	✓	NA	✓												↓ ↔ FA										
	Mittal et al. (61)	✗	✓	NA	NA				↓ FA																		

(Continued)

TABLE 4 | Continued

Dataset	References	BL: HR vs. HV	Time: HR vs. HV	Time: CHR-T vs. CHR-NT	BL: Predict Transition	Significant brain regions for HR vs. HV over time																Significant brain regions for CHR-T vs. CHR-NT over time						
						Whole brain	Cingulum	Fronto-occipital fasciculus	Cerebellum	Cerebello-thalamo-cortical	Parietal	Splenium	Arcuate	Thalamic radiations	SLF	Inferior longitudinal fasciculus	Thalamic – hippocampal	Internal capsule	Forceps major	Corticospinal	Corpus collosum	Whole brain	Fronto-occipital fasciculus	Cerebellum	Calcarine cortex	Internal capsule	Corona radiata	Corpus collosum
	Bernard et al. (62)	NA	✓	NA	NA					↓ FA																		
Genetic Risk and Outcome of Psychosis	Domen et al. (63)	✗	✓	NA	NA		↓ FA	↓ FA						↓ FA				↔ FA										
OASIS	Carletti et al. (64)	✗	NA	✓	✗																		↓ FA			↓ FA	↓ FA	↓ FA
PNC	Roalf et al. (65)	NA	Effect of group	NA	NA		↓ FA*	↓ FA*	↓ FA*					↓ FA*	↓ FA*	↓ FA*			↓ FA*	↓ FA*								
TOTAL:		3/9	9/13	5/5	3/6	3	3	1	1	1	1	1	1	3	2	1	1	1	1	1	1	1	2	1	1	1	1	3

Whole brain, Cingulum, Fronto-occipital fasciculus, Cerebellum, Cerebello-thalamo-cortical, Parietal, Splenium, Arcuate, Thalamic radiations, SLF, Inferior longitudinal fasciculus, Thalamic–ippocampal, Internal capsule, Forceps major, Corticospinal, Corpus collosum, Whole brain, Fronto-occipital fasciculus, Cerebellum, Calcarine cortex, Internal capsule, Corona radiata, Corpus collosum
BL: HR vs. HV, Time: HR vs. HV, Time: CHR-T vs. CHR-NT, BL: Predict Transition

Arrows indicate significant difference between groups over time in specified brain region, ↓ indicate a decrease in the HR or CHR-T group compared to HV or CHR-NT respectively, ↑ indicate an increase and ↔ indicate no change over time in HR whereas an increase is seen in HV. HR, high risk; HV, healthy volunteer; CHR-T, clinical high risk transition; CHR-NT, no transition; NA, Not Applicable; Vol, white matter volume; MD, mean diffusivity; FA, fractional anisotropy; SLF, superior longitudinal fasciculus; FA, lower in HR vs. HV at both timepoints but no group × time interaction.*

resilient UHR, intermediate in HV and lowest in non-resilient UHR (29). This contrasts with 2 studies reporting that the level of reduced white matter volume over time was intermediate in non-transitioned subjects between that seen in HV and transitioned subjects (28, 45), although no studies using DTI methods compared clinical subgroup trajectories to HV.

Cross-Sectional MRI Differences at Baseline

Since the majority of studies find that "brain development" differs in HR groups compared to HV, with the most pronounced changes seen in subjects that transition to psychosis, this leaves open the question of whether differences are present cross-sectionally at the baseline timepoint. At baseline, 9 out of 14 studies report lower gray matter volume, cortical thickness, and surface area in HR subjects compared to HV in the frontal (5 studies), temporal (4 studies) and parietal lobe (4 studies) (**Table 3**). As more studies report longitudinal differences (20 out of 24), this suggests that longitudinal studies may have greater sensitivity to detect differences in gray matter. For white matter, a similar trend is seen, with 3 out of 9 studies finding lower fractional anisotropy at baseline between HR and HV, in the corpus callosum, CST, SLF, and ATR (**Table 4**), whereas 9 out of 13 studies detected longitudinal differences.

It is of interest whether baseline structural measures can predict clinical outcome in HR, as this could guide clinical interventions. At baseline, 9 out of 15 studies found lower gray matter volumes in those who went on to transition compared to those who did not, in the frontal (5 studies), parietal (4 studies), insula, and temporal lobe (3 studies). This is lower than the proportion of studies that detected longitudinal differences between clinical subgroups (15 out of 19 studies). For baseline measures of white matter, 3 out of 6 studies found higher white matter volume or FA in those who went on to transition compared to those who did not, with higher volume in the SLF and SFOF (53) and higher FA in the corpus callosum (57). Also in CHR higher FA in hippocampal-thalamic tracts was associated with more severe positive symptoms 12 months later (60). Taken together with the longitudinal findings in the left SFOF of transitioned subjects, it appears that those with higher FA values and white matter volume at baseline show the largest reductions over time. The proportion of studies finding white matter differences at baseline is lower than the proportion of studies that detected longitudinal differences between transition and non-transition groups (5 out of 5 studies).

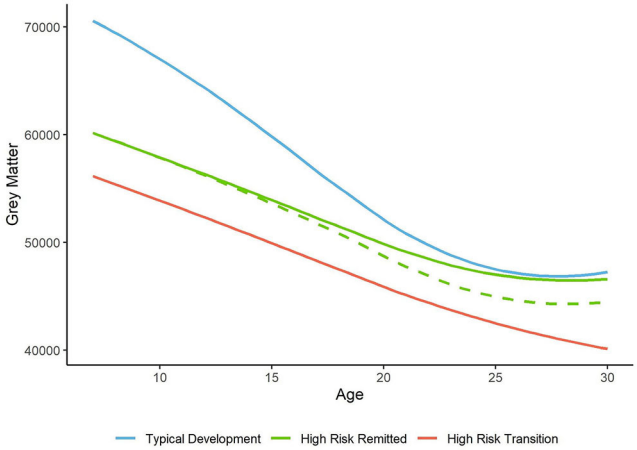

FIGURE 2 | Hypothetical trajectories of whole brain gray matter. In typical development, gray matter volume and thickness reduce in late childhood, and plateau in mid adulthood [blue line, based on (9)]. In high risk subjects, gray matter volume and thickness is lower than healthy volunteers. In those whose symptoms improve this deficit may persist (dashed green line) or recover (solid green line). In those who transition to psychosis, lower gray matter is found at baseline and longitudinally compared to non-transition subjects (red line).

DISCUSSION

The aim of this systematic review was to examine whether neurodevelopmental trajectories differ between (i) high risk subjects (HR) compared to healthy volunteers (HV), and (ii) those who transition to psychosis compared to those who do not. HR subjects, regardless of subtype (CHR, GHR, and PE), show an accelerated decline in gray matter primarily in the temporal cortex, and also the frontal, cingulate and parietal cortex. In those who remain symptomatic or transition to psychosis, there was a greater reduction in these same brain regions. Altered gray matter trajectories may normalize by early adulthood in HR cohorts whose sub-threshold symptoms resolve, whereas brain abnormalities progress in those whose symptoms do not remit. White matter volume and diffusion anisotropy, which usually increase until early adulthood, did not change or were reduced in HR subjects, principally in the cingulum and thalamic radiation amongst other regions including the cerebellum, retrolenticular part of internal capsule, and tracts connecting the hippocampus and thalamus. In subjects who transitioned to psychosis, there was reduced FA or volume principally in the superior and inferior fronto-occipital fasciculus and the corpus callosum, as well as the anterior limb of the left internal capsule, superior corona radiata and calcarine cortex.

In normal development, gray matter volume reduces from late childhood until the early twenties as a result of synaptic pruning and increased intra-cortical myelination (9, 66). Gray matter declines first in somatosensory areas, and last in higher-order association areas such as the dorsolateral prefrontal cortex, inferior parietal, and superior temporal gyrus (67, 68). This review suggests that latent vulnerability to schizophrenia is associated with premature gray matter loss in multiple higher-order brain regions. Diverging gray matter trajectories in the frontal and temporal cortex of HR populations are consistent with gray matter changes seen in schizophrenia (69, 70). In studies which include a patient group, reduced gray matter in HR appear to be intermediate between changes seen in schizophrenia and HV (23, 24), although one study reports a similar decline in cortical thickness in both patients and their healthy co-twins (27) and one study reports reduced hippocampal volume in schizophrenia patients but not GHR subjects (25).

Brain development differs in those who go on to transition from those who do not. Although greater reductions in temporal, frontal, cingulate, and parietal lobe gray matter are observed in HR subjects as a whole, more pronounced changes in these same regions are observed in those who transition to schizophrenia, particularly in the temporal cortex. A number of hypothetical neurodevelopmental models may explain the diverging gray matter trajectories in HR subjects depending on clinical outcome (**Figure 2**). For HR subjects that do not transition, gray matter volume may initially be lower than HV, but during adolescence non-transition subjects have a slower trajectory of typical gray matter loss, allowing typically developing subjects to "catch up" to the same level of gray matter volume, as shown in the NIMH cohort and the Barcelona cohort (21, 52). This infers premature gray matter loss in HR or a neurodevelopmental deficit in gray matter volume, which no longer differs from HV later on in development. Alternatively, remitted HR subjects may retain this deficit in gray matter volume, but to a lesser extent than that seen in subjects who transition to psychosis. The former is most likely, as studies generally do not find an intermediate level of gray matter loss in remitted subjects compared to HV and transitioned subjects (17, 20, 28, 43, 44, 52). Cognition may be affected in HR subjects whose brain trajectories later "normalize," as initial gray matter deficits alongside protracted loss are associated with poor intelligence (71), which is reported to be lower in GHR groups (72).

Gray and white matter differences between transition and non-transition subjects were more likely to be detected using longitudinal measures than baseline measures, and thus may offer predictive value to guide clinicians' care. Recent studies infer that cross-sectional brain structure measures offer additional predictive value to using clinical ratings alone (14, 73). Moreover, machine learning of "brain age," the deviation between chronological and neuroanatomical age, has successfully identified CHR subjects from HV (74), further supporting the presence of accelerated brain aging in these subjects. To date, these multivariate models have not included cross-sectional or longitudinal DTI measures or longitudinal measures of gray matter. This review indicates that longitudinal studies better capture subtle changes in brain maturation, and so these measures may offer a higher degree of prediction accuracy.

White matter volume and diffusion anisotropy (measured by FA) typically increase until early adulthood, however in HR these measures did not change, reduced over time or showed smaller increases compared to HV. ROI analyses in HR reported reduced FA over time in the cerebellum and tracts connecting the thalamus and hippocampus (60–62), whereas whole brain analyses most commonly found reduced FA in the thalamic radiation and cingulum in HR subjects compared to HV (55, 63, 65). Some studies did not find an interaction between group and time, and instead report lower FA at both timepoints in the SLF, ATR, corticospinal tracts, and the cingulum (59, 65). The absence of an interaction may occur when FA values stabilize in HV in mid-adulthood. Reduced FA is consistent with findings in schizophrenia, which are widespread throughout the brain, with the strongest effect in the anterior corona radiata and corpus callosum (75, 76). When psychotic disorder patients were examined alongside HR groups, baseline FA was lowest in patients, intermediate in CHR and highest in controls (64). Psychotic disorder patients had lower whole-brain mean FA at both timepoints, whereas FA reduced over time in GHR and slightly increased in HV (63). This suggests accelerated aging begins in prodromal individuals, which creates a later deficit when psychosis emerges. Depending on age, lower FA may represent delayed neurodevelopment (before mid-adulthood) or premature aging (after mid-adulthood) (**Figure 3**). Another possible interpretation would be an overdevelopment of secondary white matter pathways in HR, causing reduced FA in regions with increased crossing fibers.

It is unclear whether altered white matter development "recovers" in HR, as although one study found that slower white matter growth normalized by age 14 (54), the majority of studies detected reduced FA and volume after this age. Instead the level of white matter volume reduction may be intermediate in non-transitioned subjects between that of transitioned subjects and HV (28, 45), meaning that non-transitioned subjects show a neurodevelopmental deficit which may not recover. Alternatively, white matter volume or FA may increase in non-transitioned subjects as a compensatory process; one study found that FA increased over time in these subjects but reduced in those who transitioned (64), and one study reported that corpus callosum volume reduced over time in all groups, but was consistently larger in resilient UHR, intermediate in HV and lowest in non-resilient UHR groups (29). Therefore, further work is needed to establish whether low FA in HR represents a stable deficit, accelerated aging or a neurodevelopmental delay which recovers.

In those who transition, reduced volume or FA over time was principally reported in the IFOF, the SFOF and the corpus callosum, as well as the anterior limb of the internal capsule and superior corona radiata, which are white matter regions showing the strongest alterations in schizophrenia (76). Cross-sectional studies report higher white matter volume and FA at baseline in those who went on to transition compared to those who did not, in a number of brain regions (57, 60) including the SFOF (53). If white matter integrity then reduces over time, this could suggest premature development and aging of white matter in transitioned subjects. Although longitudinal studies assessed here generally found higher FA at baseline, this is in contrast with the wider cross-sectional literature (11). Further studies in those who go on to transition are needed to conclude whether FA is initially higher (premature development) or lower (neurodevelopmental deficit), which then progressively reduces beyond that seen in non-transition subjects (neurodegenerative) (**Figure 3**).

There are significantly fewer longitudinal studies investigating white matter compared to gray matter in HR, in particular those examining white matter in transition and non-transition subjects, which were limited to small sample sizes (ranging from $n = 5$ to $n = 18$). Eight studies measured white matter volume, which (a) has less anatomical specificity than tractography and (b) are inherently coarser measures than the microstructural metrics offered by DTI. Ten studies used

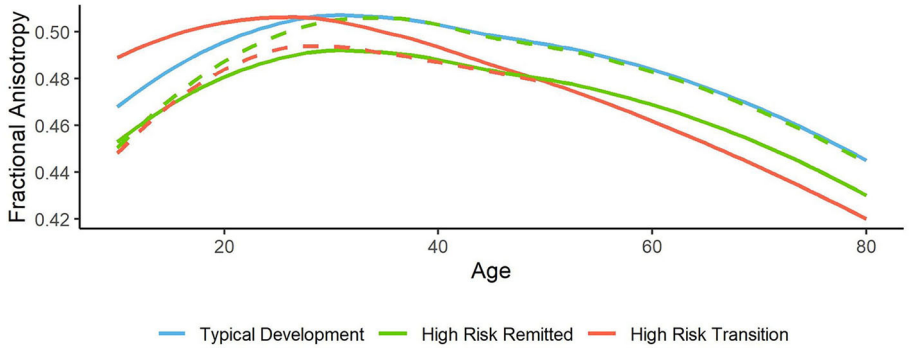

FIGURE 3 | Hypothetical trajectories of whole brain white matter. For typical white matter development, fractional anisotropy values peak in mid adulthood, and reduce around age 40, with a steep decline after age 60 [blue line, based on (77)]. Lower FA values are observed in high risk subjects; which may be stable over time (green line), or reflect a neurodevelopmental delay which recovers over time (dashed green line). In patients who transition, pre-mature development and aging may occur (red line), as some studies find higher FA levels in CHR-T subjects at baseline and a greater reduction over time. Alternatively those who go on to transition may possess initial deficits which later progress further than non-transition subjects (red dashed line).

DTI, half of which focused on ROI or specific tract analyses rather than whole-brain approaches, which may not provide a complete picture of white matter differences between groups. The specificity of the observed white-matter changes is limited, even with DTI, as they are often reported in regions of overlapping tracts and complex white matter microstructure. For example, the reported alterations in transitioned subjects point toward areas of crossing or overlapping fibers in the frontal lobe, which these studies have referred to as the SFOF. The existence of the SFOF in humans has been disputed (78–80), and the results from these studies may instead refer to corticostriatal and thalamic peduncle fibers interconnecting the cortex with the striatum and the thalamus. More advanced diffusion-weighted MRI techniques based on multi-shell MRI acquisition sequences can derive more detailed measures of the cellular environment, and will help to disentangle which specific tracts underlie the white matter changes (81).

The studies included in the systematic review have a number of limitations. Firstly, the majority of studies include participants who are taking antipsychotic medication. Treatment with antipsychotics is associated with reductions in global gray matter volume and enlarged lateral ventricles (82). This can bias results, particularly if the majority of the transition group are medicated whereas the non-transition group are not (41). However, in the largest study to date, reductions in cortical thickness in those who transitioned remained significant when analyses were restricted to unmedicated subjects (17), whilst another study found trend-level associations after excluding medicated subjects (52). Future studies could make use of sampling psychotic experiences in the general population, which were examined by 5 studies in this review. These samples are not help seeking, and thus rarely receive antipsychotic medication.

The majority of studies were of low to medium quality, and a third of studies examining gray matter did not correct for multiple comparisons. As changes in HR are more subtle than those seen in schizophrenia, it is recommended that future studies use a priori small volume correction (SVC) in regions of interest, such as the medial temporal lobe. For example, one study detected gray matter loss in those with psychotic experiences compared to those without, but only when SVC was applied in the temporal lobe (35). Brain differences in HR are not global, or localized to discrete regions, but instead appear to affect certain networks such as the fronto-parietal, and limbic-temporal networks. Although SVC will increase the power to detect subtle changes, these must be complemented with whole brain and network based approaches. Lastly, an important issue in the reporting of MRI studies is publication bias, which cannot be formally assessed by a systematic review. A number of studies examined brain changes over time in HR and HV groups separately, whereas future studies should report interaction analyses between group and time.

In conclusion, HR subjects show accelerated gray matter loss in the temporal, frontal, cingulate and parietal cortex. This is alongside reduced white matter volume and reduced FA over time in the thalamic radiation and cingulum, which may reflect a neurodevelopmental deficit in white matter maturation or premature aging. Over time gray matter trajectories may converge between HR and HV groups, but not in those who remain symptomatic or transition to disease. Transitioned subjects show progressive gray matter reductions in the temporal and frontal lobes, and reduced white matter in the SFOF, IFOF, corpus callosum, and corona radiata, on a continuum with that seen in schizophrenia. Longitudinal gray and white matter measures were more likely to detect differences between transition and non-transition subjects than baseline measures, and thus may offer predictive value to guide clinicians' care. The availability of advanced neuroimaging technologies will allow future studies to better track white matter changes in the prodrome, which may offer promising markers of clinical outcome.

DATA AVAILABILITY STATEMENT

The original contributions generated in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

KM, PL, and AI: extracted data. KM, PL, and AD: wrote the manuscript. All authors: contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.620401/full#supplementary-material

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Hyperactivation of Posterior Default Mode Network During Self-Referential Processing in Children at Familial High-Risk for Psychosis

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Patients with schizophrenia spectrum disorders show disturbances in self-referential processing and associated neural circuits including the default mode network (DMN). These disturbances may precede the onset of psychosis and may underlie early social and emotional problems. In this study, we examined self-referential processing in a group of children (7–12 years) at familial high risk (FHR) for psychosis ($N = 17$), compared to an age and sex-matched group of healthy control (HC) children ($N = 20$). The participants were presented with a list of adjectives and asked to indicate whether or not the adjectives described them (self-reference condition) and whether the adjectives described a good or bad trait (semantic condition). Three participants were excluded due to chance-level performance on the semantic task, leaving $N = 15$ FHR and $N = 19$ HC for final analysis. Functional MRI (fMRI) was used to measure brain activation during self-referential vs. semantic processing. Internalizing and externalizing problems were assessed with the Child Behavior Checklist (CBCL). Evaluating main effects of task (self > semantic) showed activation of medial prefrontal cortex in HC and precuneus/posterior cingulate cortex (PCC) in FHR. Group-comparison yielded significant results for the FHR > HC contrast, showing two clusters of hyperactivation in precuneus/ PCC ($p = 0.004$) and anterior cerebellum / temporo-occipital cortex ($p = 0.009$). Greater precuneus/PCC activation was found to correlate with greater CBCL internalizing ($r = 0.60$, $p = 0.032$) and total ($r = 0.69$, $p = 0.009$) problems. In all, this study shows hyperactivity of posterior DMN during self-referential processing in pre-adolescent FHR children. This

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finding posits DMN-related disturbances in self-processing as a developmental brain abnormality associated with familial risk factors that predates not just psychosis, but also the prodromal stage. Moreover, our results suggest that early disturbances in self-referential processing may be related to internalizing problems in at-risk children.

Keywords: schizophrenia, self-referential processing, default mode network, familial high-risk, psychosis

INTRODUCTION

Schizophrenia spectrum disorders are widely considered to be disorders of brain development, even though their most characteristics symptoms do not appear until the first manifestation of psychosis, typically in adolescence or early adulthood (1, 2). The neurodevelopmental model of schizophrenia accounts for observations that children who have an increased risk to develop psychosis show delays in neuromotor, language, and cognitive development and socio-emotional problems (3, 4). These findings suggest that psychosis may be the end result of abnormal neurodevelopmental processes that start years before illness onset (5).

There are various theories as to why psychotic symptoms take so long to manifest when the underlying etiology is likely neurodevelopmental in nature. On such theory is the "two-hit" hypothesis, which posits that early genetic and environmental risk factors may disrupt certain aspects of brain development, but only to the extent that they render an individual vulnerable to a "second hit." This second hit, such as exposure to trauma or substance abuse, would then be the catalyst for the actual manifestation of the illness (6). Another theory is that early, subtle, deficits in brain development may progress beyond a threshold critical for the expression of psychotic symptoms as a function of otherwise normal neuro-maturational events (7). For example, early dendritic spine deficits may be aggravated by (in itself normal) synaptic pruning in adolescence and only then become detrimental to brain and cognitive functioning.

To clarify the developmental trajectory leading up to the manifestation of psychosis, we need to understand the timing of brain and socio-cognitive abnormalities that have been observed in patients with established illness. One consistent finding in schizophrenia is that patients show disturbances in self-related processing, which have been attributed to abnormal processing of the default-mode network (DMN) and related structures (8–11). The DMN comprises medial prefrontal cortex (MPFC), precuneus/posterior cingulate cortex (PCC), and lateral parietal cortex and the cortical midline sections in particular—i.e., MFPC and precuneus/PCC—are thought to be involved in internally focused processes (12, 13). Disturbances in self-referential processing have been linked to delusions, hallucinations, poor insight, and social deficits (14) and have been hypothesized to "represent an early, premorbid (i.e., pre-prodromal) indicator of schizophrenia risk that results from abnormalities of the structure and function of the neural circuitry of self" (14). However, there are few neuroimaging studies in pre-adolescent FHR children, and none that have directly studied neuroimaging correlates of self-referential processing.

To address this knowledge gap, we investigated a group of children between 7 and 12 years of age who are at Familial High Risk (FHR) for psychosis because they have a parent or sibling affected by psychotic illness. A data-driven analysis of resting-state functional MRI (fMRI) in this sample revealed abnormal functional connectivity of posterior superior temporal gyrus with a set of language and DMN-associated brain regions (15). In the current study, we studied brain activation during self-referential processing using a commonly used fMRI self-reference paradigm that was adapted to meet the developmental level of children in this age range. Based on theoretical accounts of self-referential processing as a premorbid indicator of schizophrenia (referenced above) and previous findings of DMN abnormalities in unaffected relatives of patients with schizophrenia (16, 17), we hypothesized to find hyperactivity of DMN midline regions during self-referential processing in FHR children relative to HC. If the current study confirms this hypothesis, it would confer important new information about the timing of DMN changes in psychotic illness development.

Moreover, as FHR children show elevated levels of behavioral problems (18, 19), we set out to assess putative disturbances in self-related processing for associations with behavioral data. Childhood behavioral problems are generally classified into two broad categories: internalizing and externalizing problems (20). Disturbances in self-referential processing may relate specifically to internalizing problems. For example, excessive worrying or rumination has been related to negative self-referential processing and a heightened focus on negative emotional states, in association with activation of core DMN regions (21, 22). Moreover, specific behavioral problems, including withdrawn behavior and thought problems, have been associated with increased risk for developing psychosis (23, 24). This association may also be mediated by self-processing deficits, as difficulties in distinguishing self-relevant from self-irrelevant information may render the perception of neutral environmental stimuli as abnormally salient and thereby contribute to the development of psychosis (-like) symptoms (25). Therefore, we aimed to investigate how putative disturbances in self-related processing relate to childhood behavioral indicators of future psychopathology.

MATERIALS AND METHODS

Participants

A total of 37 children, ages 7–12 years, participated in this study. Our sample included 17 FHR children and 20 age/sex-matched healthy control (HC) children. Three children (two FHR, one

HC) showed chance-level performance on the behavioral task (see behavioral data analysis for details) and were therefore excluded from further analysis. The remaining 15 FHR had at least one first-degree relative affected by psychotic illness (see **Table 1** for details) and originated from a total of 10 families, including three sibling pairs and one set of three siblings. The remaining 19 HC originated from 16 families and included three sibling pairs. Exclusion criteria for HC included a family history of psychosis or bipolar disorder in first-degree relatives, personal lifetime history of a major mental disorder, and a lifetime history of antipsychotic treatment. Exclusion criteria for FHR participants included current or recent use (within the last 30 days) of anti-psychotic medication. Current or recent use (defined as within four half-lives of the concerned medication) of any other psychotropic medication was an exclusion criterion for all participants. Intellectual disability (i.e., IQ < 70) was also an exclusion criterion for both groups. Participants were recruited at the Department of Psychiatry of Beth Israel Deaconess Medical Center (BIDMC) in Boston. BIDMC's Institutional Review Board (IRB) approved the study. Parental consent to participate in the study was obtained for all participants, and the participants themselves provided assent.

TABLE 1 | Demographic and clinical information.

	FHR ($N = 15$)	HC ($N = 19$)	Statistics
Age in years, mean (sd) [range]	9.6 (2.0) [7.0 – 12.4]	9.3 (1.7) [7.2 – 12.2]	$F_{(1,33)} = 0.3$, $p = 0.572$
Sex, M/F	5 / 10	9 / 10	$\chi^2 = 0.7$, $p = 0.409$
WISC IQ, mean (sd) [range]	102.9 (15.0) [73 – 132]	111.5 (17.0) [81 – 153]	$F_{(1,33)} = 2.5$, $p = 0.126$
DSM-diagnosis			$\chi^2 = 9.4$, $p = 0.025$
ADHD	4	0	
ADHD/ODD	2	0	
No diagnosis	6	14	
Data missing	3	5	
CBCL scores			
Internalizing problems, mean (sd) [range][a,b]	6.9 (8.6) [0 – 33]	1.8 (2.5) [0 – 10]	$F_{(1,32)} = 6.0$, $p = 0.020$
Externalizing problems, mean (sd) [range][a,b]	8.1 (8.6) [0 – 34]	1.7 (4.1) [0 – 18]	$F_{(1,32)} = 6.9$, $p = 0.013$
Total problems, mean (sd) [range][a,b]	31.7 (29.4) [2 – 119]	8.8 (12.1) [0 – 54]	$F_{(1,32)} = 9.5$, $p = 0.004$
Affected relative, parent / sibling	10 / 5	N/A	
Diagnosis proband, SCZ / SA / other	8 / 5 / 2	N/A	
Motion, scrubbed volumes (%) across 2 runs, mean (sd) [range]	7.2 (3.6) [1.7 – 15.5]	7.1 (3.8) [1.1 – 17.1]	$F_{(1,33)} = 0.0$, $p = 0.993$

Statistical comparisons were performed using analysis of variance (ANOVA) for continuous and chi-squared tests for categorical variables.

[a] *Data missing for one participant.*

[b] *There was one major outlier in Childhood Behavior Checklist (CBCL) scores (i.e., all > 3 sd above the mean) (**Supplementary Figure 1**). Group-effects were highly similar if this participant was excluded (all $p \leq 0.02$).*

ADHD, attention deficit hyperactivity disorder; ODD, oppositional defiant disorder.

Clinical Evaluation

Clinical Assessment

All HC and FHR participants were assessed for current psychiatric disorders using the SCID for Childhood Diagnoses (Kid-SCID) (26). Clinical diagnoses of affected family members of FHR participants were confirmed using the Structured Clinical Interview for DSM-IV (SCID) (27), combined with an evaluation of their medical history and interviewing at least one informant, and determined in consensus during meetings attended by senior clinicians (LJS, MSK, RMG).

Cognitive Assessment

Overall IQ was estimated using subtests from all four domains of the Wechsler Intelligence Scale for Children-IV (WISC-IV) (28).

Behavioral Assessment

Behavioral problems were assessed using the Child Behavior Checklist (CBCL) (29). The CBCL includes eight subscales (anxious/depressed, withdrawn, somatic complaints, social problems, thought problems, attention problems, rule breaking, and aggressive behaviors) and two broadband domains: internalizing problems (consisting of withdrawn, somatic complaints, and anxious/depressed subscales) and externalizing problems (consisting of rule breaking and aggressive behavior scales).

Demographic, clinical, cognitive, and behavioral variables are summarized in **Table 1**.

fMRI Self-Reference Task

To assess self-referential processing, participants performed a self-reference task during fMRI, in which they were presented with two lists of 24 adjectives, describing positive (e.g., friendly, honest) and negative (e.g., boring, rude) traits. The lists were presented in six blocks of 4 words each, alternating between a semantic and a self-reference condition. The average number of letters and syllables per word was similar between valences and across the lists.

Semantic Condition

In the semantic condition, participants were asked to determine for each presented word, whether it described a good or bad trait, using a two-alternative forced-choice button press ("good" or "bad").

Self-Reference Condition

In the self-reference condition, participants were asked to determine for each presented word whether it described them or not, using a two-alternative forced-choice button press ("me" or "not me").

Behavioral Data Analysis

Semantic Condition

Semantic performance, measured as the percentage of correct responses during the semantic condition, was assessed for each participant to gauge task engagement and performance. Three participants (i.e., one HC and two FHR, mean age of 8.1 years) were found to perform around chance-level, responding correctly to an average (sd) [range] of 58.3% (4.2%) [54.2–62.5%] of semantic stimuli, and were excluded from further analysis.

Self-Reference Condition

For each participant, the percentage of semantically good and bad adjectives associated with "me" were computed as a measure of positive and negative self-appraisal, respectively.

Statistical Analysis

Semantic performance and positive and negative self-appraisal were compared between groups using Analysis of Variance (ANOVA) and assessed for correlations with clinical variables (i.e., CBCL scores and IQ) in each group separately.

Imaging

Image Acquisition

MRI scans were acquired on a Siemens Magnetom Trio 3T scanner, using a commercially available 32-channel radio frequency brain array coil (Siemens AG, Healthcare Sector, Erlangen, Germany). A single-shot gradient-echo sequence was used to collect task functional MRI (task-fMRI) data (88 functional volumes per run, TR = 2,000 ms, TE = 30 ms, 3 mm isotropic voxels, duration 2'56" per run). A 3-dimensional high-resolution T1-weighted structural scan was collected for anatomical localization (MPRAGE, TR = 2,530 ms, TE = 3.39 ms, inversion time = 1,100 ms, FA = 7°, voxel size 1.3 × 1 × 1.3 mm^3).

Image Preprocessing

Preprocessing of imaging data was performed with FSL Version 5.0.9 (FMRIB, Oxford, UK) (30) and included brain extraction using FSL's BET (Brain Extraction Tool) (31), normalization to MNI space, and motion correction using MCFLIRT (intra-modal motion correction tool) (32). The remaining fMRI signals were spatially blurred with a 5 mm full-width-at-half-maximum (FWHM) Gaussian kernel. A subject-dependent number of individual nuisance regressors for removing outlier time points were created with FSL's Motion Outliers tool, which uses the spatial root mean square of the data after temporal differencing (DVARS) to identify intensity outliers, using the standard boxplot outlier threshold set in FSL. The threshold for exclusion was set at >20% of scans identified as outliers; none of the participants exceeded this threshold.

fMRI Analysis and Experimental Design

Analysis of fMRI task-data was performed using FSL FEAT (FMRI Expert Analysis Tool) Version 6.00 (33). Brain activation for self-reference vs. semantic processing ("self-ref > semantic") was calculated separately for each run of each participant. To this end, first-level GLM analyses included two regressors modeling the self-reference and semantic condition per run. These regressors were modeled as a boxcar function with values one, respectively, convolved with a single gamma hemodynamic response function. The global mean time series of each preprocessed run, six motion parameters, and the motion outliers were added to the GLM as nuisance regressors. The resulting individual contrast images were entered into a second level fixed-effects analysis including both runs for each participant. In third-level analysis, mixed effects Analysis of Variance tests were conducted to assess main effects of task and group (FHR > HC and HC > FHR) were conducted. Significant effects were followed up with *post-hoc* testing. All analyses were performed on a whole-brain level. Results are reported with *Z*-statistic (Gaussianised T/F) images thresholded using clusters determined by $Z > 3$ and a (corrected) cluster significance threshold of $p = 0.01$ (34, 35) after correcting for age and sex.

Associations With Clinical Measures

Group-differences in brain activation during self-referential processing were assessed for correlations with clinical variables. To this end, signal intensity values from each participant's contrast parameter estimates for the significant clusters were extracted using Featquery (36) and assessed for correlations with CBCL scores and IQ. In addition, exploratory analyses were performed to assess correlations with CBCL subscale scores and associations with emotion regulation strategies measured with the Emotion Regulation Questionnaire (ERQ) (37, 38) were assessed in a *post-hoc* analysis.

RESULTS

Group Characteristics

Group-comparisons on demographic characteristics confirmed that the groups were well-matched for age and sex. Average IQ was almost nine points lower in FHR than HC, but this group-difference was not statistically significant ($p = 0.13$), possibly due to sample size. Approximately 40% of FHR had a DSM-diagnosis (mainly ADHD), while there were no DSM-diagnoses in the HC group ($\chi^2 = 10.2$, $p = 0.02$). FHR showed more internalizing, externalizing, and total problems on CBCL (all $p \leq 0.02$). See **Table 1** and **Supplementary Figure 1** for details.

Behavioral Results

There were no significant group-differences in semantic performance or positive and negative self-appraisal (**Table 2**). In FHR, semantic performance and negative self-appraisal were associated with IQ, such that higher IQ was associated with better semantic performance ($r = 0.63$, $p = 0.013$) and lower negative self-appraisal ($r = -0.59$, $p = 0.018$) (**Supplementary Figure 2**).

fMRI Results

Main Effect of Task per Group

Assessing main effects of task in each group revealed activation clusters in bilateral MPFC/ACC in HC and precuneus/PCC in FHR (**Figure 1A**, **Table 3**).

Group-Effects

The FHR > HC contrast yielded two clusters of hyperactivation in FHR. The largest cluster was localized in right precuneus/PCC. A second cluster was found in bilateral anterior cerebellum and inferior temporo-occipital cortex, including parahippocampal and lingual gyrus (**Figure 1B**, **Table 3**). No significant clusters were found for the HC > FHR contrast.

Validation Analyses

To ensure that effects were not driven by familial ties within subject groups, group-effects were reassessed in a subset including only unrelated individuals ($N = 26$, including 10 FHR and 16 HC), which confirmed increased activation in FHR vs. HC for both the precuneus/PCC ($p = 0.003$) and cerebellar ($p = 0.019$) cluster (see **Supplementary Materials** and **Supplementary Figure 3** for details). In addition, to ascertain that the current results were not driven by the preponderance of ADHD diagnoses in the FHR group, we compared cluster activation levels between FHR with and without an ADHD diagnosis, and between each of these groups and HC, which confirmed that the current results were not accounted for by psychiatric diagnosis (see **Supplementary Materials** including **Supplementary Figure 4**).

TABLE 2 | Behavioral results.

	FHR (*N* = 15)	HC (*N* = 19)	Statistics
Semantic condition			
Semantic performance (%)	89.1 (9.9) [66.7 – 100]	89.7 (7.8) [70.8 – 100]	$F_{(1,33)} = 0.0$, $p = 0.864$
Self-reference condition			
Positive self-appraisal (%)	87.6 (12.1) [66.7 – 100]	89.7 (9.8) [66.7 – 100]	$F_{(1,33)} = 0.3$, $p = 0.565$
Negative self-appraisal (%)	20.0 (15.5) [0 – 58.3]	18.7 (19.0) [0 – 66.7]	$F_{(1,33)} = 0.0$, $p = 0.829$

Semantic performance, measured as the percentage of correct responses during the semantic condition, and positive- and negative self-appraisal, measured as the percentage of semantically good and bad adjectives associated with "me," per subject group.

Characterization of Cerebellar Cluster

The cerebellar section of the second cluster was projected onto a cerebellar flat map (39) (**Figure 2A**) and compared to a functional atlas (**Figure 2B**), which showed that the cerebellar cluster spans areas related to left/right hand presses and active maintenance/verbal fluency.

Associations With Clinical Measures

Activation in the precuneus/PCC cluster was associated with CBCL internalizing and total problems in FHR, such that higher activation was associated with increased internalizing ($r = 0.60$, $p = 0.032$) and total ($r = 0.69$, $p = 0.009$) problems (**Figures 3A,B**). The cerebellar cluster did not show significant behavioral associations. IQ was not associated with activation in either cluster. Neither cluster showed an association with motion (both $p > 0.38$).

Exploratory Analysis

Given the association between precuneus/PCC activation and CBCL total problems, exploratory analyses were performed to assess correlations with CBCL subscale scores. These analyses showed associations with CBCL thought problems ($r = 0.91$, $p < 0.001$), social problems ($r = 0.70$, $p = 0.005$), and withdrawn ($r = 0.66$, $p = 0.011$) subscales (**Supplementary Materials**, **Supplementary Figure 5**).

Post-hoc Analysis

Following the observation that activation in the right precuneus/PCC cluster was associated with internalizing problems, a *post-hoc* analysis was performed to test for

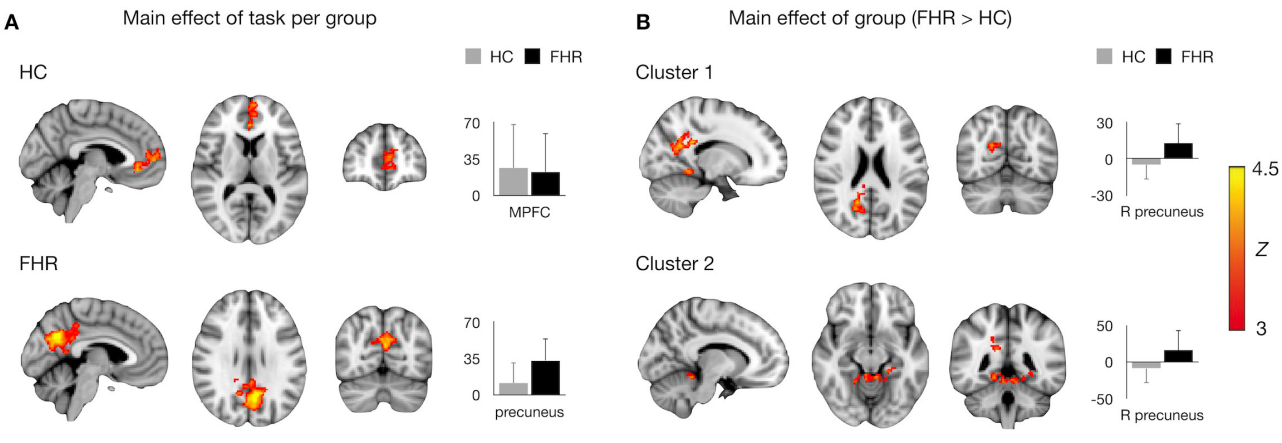

FIGURE 1 | Main effects of task and group on brain activation. **(A)** Mean activation during self-referential processing (self-reference > semantic) per group. MNI coordinates for HC: x = −4, y = −68, x = 28, consistent with MPFC/ACC; for FHR: x = −4, y = 48, z = 10, consistent with precuneus/PCC. **(B)** Significant clusters in the FHR > HC contrast. MNI coordinates for cluster 1: x = 16, y = −64, z = 22, consistent with right precuneus/PCC; cluster 2: x = −10, y = −44, z = 22, consistent with anterior cerebellum/parahippocampal gyrus/lingual gyrus. Significant clusters are overlaid on the MNI template brain. Bar charts depict mean (sd) activation per group.

TABLE 3 | Neural activation during self-referential processing.

Brain regions	Side	BA	MNI			Voxels (No.)	*Z*-max	*P*-value
			x	y	z			
HC								
MPFC / ACC	L/R	9, 10, 24, 32	−4	36	−8	691	4.18	<0.0001
FHR								
Precuneus / PCC	L/R	23, 29, 31	−6	−62	32	1,608	5.34	<0.0001
FHR > HC								
Precuneus / PCC	R	31	16	−40	26	378	4.37	0.004
Anterior cerebellum / Parahippocampal gyrus / Lingual gyrus	L/R	I-V[a] 27, 35 19	−20	−34	−8	319	4.06	0.009

Activation clusters for self-reference > semantic processing, showing main effect of task for HC and FHR groups, and for the FHR > HC group-contrast. No significant clusters were detected for the HC > FHR contrast.
MNI, Montreal Neurological Institute; BA, Brodmann area.
[a]*For cerebellar regions, we list lobules rather than BA area.*

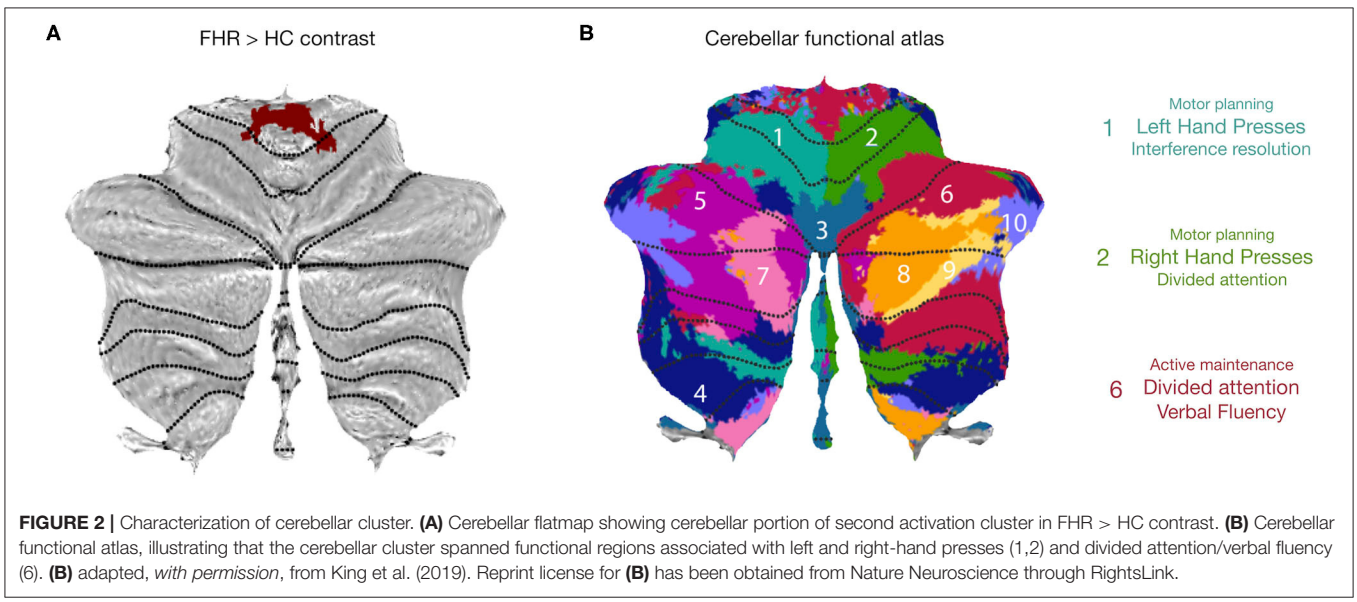

FIGURE 2 | Characterization of cerebellar cluster. **(A)** Cerebellar flatmap showing cerebellar portion of second activation cluster in FHR > HC contrast. **(B)** Cerebellar functional atlas, illustrating that the cerebellar cluster spanned functional regions associated with left and right-hand presses (1,2) and divided attention/verbal fluency (6). **(B)** adapted, *with permission*, from King et al. (2019). Reprint license for **(B)** has been obtained from Nature Neuroscience through RightsLink.

associations with emotion regulation strategies. A significant correlation was observed between precuneus/PCC activation and ERQ reappraisal in FHR, such that more frequent use of cognitive reappraisal as a strategy for emotion regulation was associated with less prominent hyperactivation of precuneus/PCC ($r = -0.66$, $p = 0.008$; **Figure 3C**).

DISCUSSION

In this study, we examined functional brain activation related to self-referential processing in children with a familial risk for psychosis. While making judgments on whether or not a list of adjectives described them, in contrast to making a semantic evaluation on whether the words described a good or bad trait, FHR children were found to show hyperactivation of posterior DMN regions including precuneus/PCC as compared to a group of age- and sex-matched HC children. This finding suggests that DMN hyperactivation, as has been observed in adult patients with schizophrenia, dates back at least to middle to late childhood, and thus predates the manifestation of the illness by many years.

The current results are highly consistent with previous literature showing a pattern of anterior DMN (MPFC) hypoactivation and posterior DMN (precuneus/PCC) hyperactivation during self-related processing in (adult) patients with schizophrenia (8–10, 16, 40, 41) and their unaffected relatives (16, 17). Replicating these findings in FHR children confirms and extends these earlier results by showing that DMN-related abnormalities are present in children with a familial risk for psychosis, years before the typical age of onset. Given the young age of our sample, our results indicate that DMN changes also predate adolescence and the maturational

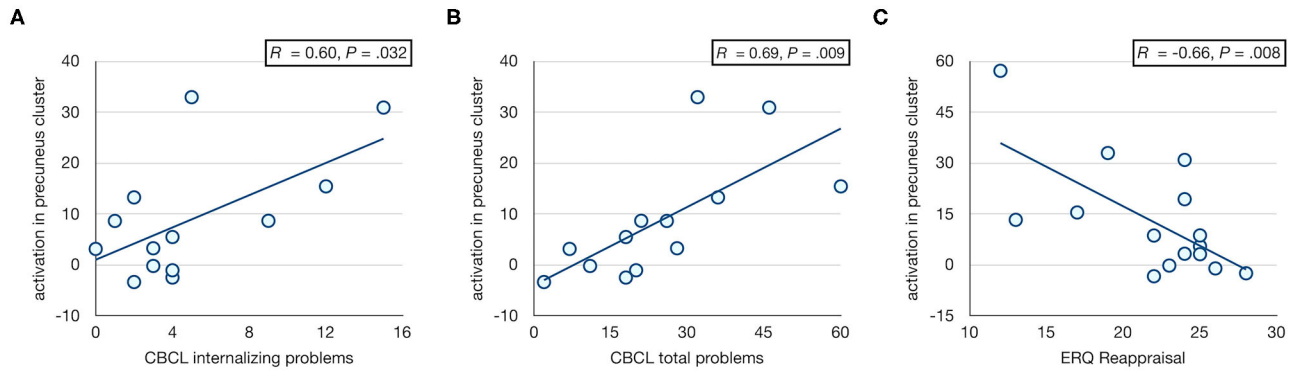

FIGURE 3 | Associations with CBCL scores. Scatter plots showing associations between activation in right precuneus/PCC cluster and CBCL internalizing **(A)** and total **(B)** problem scores, and ERQ cognitive reappraisal **(C)** in FHR. The major CBCL outlier (**Supplementary Figure 1**) was omitted from the correlation analysis with CBCL scores. Including this participant yielded similar but less significant correlations (i.e., $r = 0.50$, $p = 0.072$ and $r = 0.56$, $p = 0.039$ for internalizing and total problems, respectively).

brain changes that take place during this developmental epoch. Taken together, our findings thus support hypotheses that abnormal DMN-related self-referential processing is a developmental brain abnormality associated with familial risk for psychosis.

Dissimilar results have also been reported by studies investigating self-referential processing in psychotic illness. For example, van der Meer et al. reported precuneus/PCC *hypo*activation for a self-vs.-baseline contrast in schizophrenia patients (42) and Zhang et al. found similarly located hypoactivations in bipolar disorder patients, with schizophrenia patients showing an intermediate effect (43). Other regions, including the left inferior temporal gyrus, bilateral temporal poles (44), and left lateral frontal cortex (45) have also been implicated. These divergent results may relate to differences in experimental paradigms including baseline conditions (42). In particular, the studies referenced here used either non-valenced statements of general knowledge or a lexical control condition rather than positive vs. negative semantic evaluations as used in e.g., Holt et al. (9) and our current study.

Another important finding of the current study is that hyperactivation of precuneus/PCC in FHR was found to correlate with CBCL internalizing and total problems. This finding is of interest as internalizing problems—e.g., feeling anxious, sad, self-conscious, worrying about the future, and rumination—have been linked to maladaptive (excessive) self-focus and aberrant activity in self-referential brain circuits (46, 47). Clinical staging models of psychotic illness development emphasize that internalizing problems in childhood, followed by depressive symptoms in adolescence, may be the antecedents of later psychopathology ranging from major depression to bipolar disorder and schizophrenia (48, 49). Moreover, exploratory correlational analyses with CBCL subscale scores showed that precuneus/PCC hyperactivation may be associated with thought problems, social problems, and withdrawn behavior. The associations with the thought problems and withdrawn subscales specifically suggest that the observed hyperactivity in posterior DMN may be related to ruminative thinking or basic self-disturbances. In light of the aforementioned studies noting the clinical utility of CBCL thought problems and withdrawn subscales as an adjunctive risk screening measure to aid in early detection of at-risk youth (23, 24), these findings suggest that FHR children who are characterized by more severe internalizing and thought problems and more pronounced hyperactivity of posterior DMN may be at greater risk to develop an affective or non-affective psychotic disorder.

This finding is important as it offers opportunities for early intervention. Mindfulness meditation, for example, has been shown to reduce internalizing symptoms, presumably by promoting a shift from narrative self-focus to present-centered experiential awareness [for review, see (21)]. These changes have been linked to modulations of hyperactive self-referential brain systems (50–52). Consistent with the premise that clinical staging models may improve the logic and timing of interventions in psychiatry (53), using mindfulness-meditation or a similar intervention to address internalizing problems and self-related neural processing deficits in high-risk children may prevent or delay progression to later stages of disorder. Importantly, studies have shown that mindfulness training is both feasible in school-aged children and effective in modulating stress and associated neural systems (54). Moreover, emerging evidence suggests that mindfulness training augmented with real-time fMRI neurofeedback to modulate DMN activity may be effective in reducing symptoms in established psychotic illness (55).

To follow up on the observed association between precuneus/PCC activation and internalizing symptoms, we assessed potential correlations with emotion-regulation strategies. Two strategies that are measured with the ERQ were tested: expressive suppression and cognitive reappraisal. Expressive suppression is the process of inhibiting ongoing emotion-expressive behavior; e.g., holding back tears when feeling sad in public. In contrast, cognitive reappraisal is

construing a potentially emotion-eliciting situation in a way that changes its emotional impact. For example, viewing a job interview as an opportunity to find out how well a job would fit their person and vice versa, rather than as a test of one's worth. Out of the two, reappraisal has been found to have a more positive influence on affect, relationships, and well-being, and is viewed as the more adaptive emotion regulation strategy (37, 56). Interestingly, FHR children who endorsed using this strategy more habitually were found to show less precuneus/PCC hyperactivation, consistent with studies showing that overactive self-referential processing may impair top-down emotion regulation (21, 57). Furthermore, the association with cognitive reappraisal may be construed as further evidence that (cognitive) modulation of self-referential brain systems is both possible and potentially beneficial to at-risk individuals.

In addition to the precuneus/PCC cluster, FHR children also showed hyperactivation of a cluster encompassing anterior cerebellum and parahippocampal gyrus. High-risk studies have noted that hyperactivity (58, 59) and volume reductions (60–63) of the parahippocampal cortex predate the onset of psychosis and are most pronounced in at-risk youth who go on to develop full psychosis. Evidence on cerebellar abnormalities predating psychosis is scarce but includes evidence for volume reductions of the anterior cerebellum in high-risk youth (64). Moreover, data from patients with schizophrenia is consistent with hyperactivity and hyperconnectivity of the anterior cerebellum (65, 66). Our current finding of anterior cerebellum / parahippocampal hyperactivity in pre-adolescent FHR children suggests that similar changes observed in patients and high-risk youth predate not just psychosis but also the onset of prodromal symptoms.

This study has a number of limitations to consider when interpreting the current results. The first and main limitation is our sample size, which may have reduced our ability to detect more subtle group-differences. Recruiting children in this age range who have a parent or sibling with a psychotic disorder is difficult, as patients affected by psychosis are less likely to have children (67) and considering the destabilizing effects that psychosis can have on families, especially if it affects (one of) the parents. In addition, as psychotic disorders tend to manifest in late teens or early twenties, most people who are diagnosed with schizophrenia no longer have siblings in the 7–12 years range. As a result, recruiting such a young sample of children with a parent or sibling affected by psychosis is highly challenging and we believe that our data and findings are thus a valuable resource to advance our understanding of trajectories of brain abnormalities in early schizophrenia. Moreover, we note that despite our modest sample size, we found robust effects that survived conservative voxel- and cluster-level thresholds (35). Second, our subject groups were not matched on current DSM diagnosis as 40% of the FHR children had a diagnosis of ADHD with or without co-morbid ODD, while none of the HC children had a DSM-diagnosis. However, it is important to appreciate that childhood developmental disorders are common in FHR individuals and may be linked to (genetic) risk factors for schizophrenia (68). As such, including only FHR without any DSM-diagnoses is likely to produce an overly healthy subset of FHR that may exclude much of the important risk signal. Moreover, direct comparison of FHR with and without current DSM diagnoses did not show group-effects. Third, our processing involved spatial normalization to a standard adult template rather than an age-specific template. The use of age-appropriate templates for normalization is thought to be particularly important in children under 6 years of age (69), but has been shown to improve results in older children as well (70, 71). Important advantages of using age-appropriate templates include reduced individual variation and thus greater statistical power to detect group-differences (71). Although we do not assume that the impact of spatial normalization procedures would affect our groups differentially, we note that the lack of age-specific templates signifies a limitation to our study. Fourth, our results are inherently limited by known confounds of fMRI, including head motion and cardio-respiratory influences. We dealt with these issues to current standards and found no group-differences in motion parameters, but we cannot exclude the possibility that motion and physiological influences impacted our results. Finally, the inclusion of siblings in each subject group may have inflated group-effects. However, reassessing the main findings in a subset of only unrelated individuals confirmed our main results.

In summary, the results of this study in a unique sample of FHR children between 7 and 12 years of age suggest that hyperactivity of posterior DMN during self-referential processing develops many years before the typical manifestation of psychosis in association with familial (possibly reflecting genetic) risk factors. Moreover, our study links aberrant self-referential processing to increased levels of internalizing problems and less frequent use of cognitive reappraisal for emotion regulation. These findings have implications for our understanding of the developmental timeline of DMN abnormalities in schizophrenia spectrum disorders and may inform strategies for early intervention: aiming to reduce internalizing problems by modulating DMN-related self-referential processing in the early premorbid stage.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: the raw data from this study is not publicly available because participants did not agree for their data to be shared publicly. De-identified processed data that support the findings of this study are available from the corresponding author, upon reasonable request. Requests to access these datasets should be directed to gcollin@mit.edu.

ETHICS STATEMENT

This study involved human participants and was reviewed and approved by the Institutional Review Board (IRB) of Beth Israel Deaconess Medical Center (BIDMC), Boston, MA, USA. Written informed consent to participate in this study was provided by the participants' parents/legal guardians and participants provided assent to participate in the study.

AUTHOR CONTRIBUTIONS

LS, MK, JG, HT, and SW-G contributed to conception and design of the study, and the acquisition of funding. EM, RM-G, and HT contributed to data acquisition. LS, RM-G, and MK led clinical consensus meetings. GC and CB performed the statistical analysis. GC wrote the first draft of the manuscript. CB wrote sections of the manuscript. SA contributed to the cerebellar analyses. GC, CB, SA, MS, and SW-G contributed to data interpretation. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.613142/full#supplementary-material

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SYSTEMATIC REVIEW
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The Role of Peripheral Inflammation in Clinical Outcome and Brain Imaging Abnormalities in Psychosis: A Systematic Review

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Promising research investigating the association between inflammatory biomarkers and response to antipsychotic and/or adjunctive therapy, observed by improvement in psychiatric assessment, is emerging. Increased inflammation has been suggested to contribute to higher severity of symptoms/treatment resistance through the effects that this has on brain structure and function. The present systematic review aims to clarify the potential role of peripheral inflammatory markers as predictors of clinical outcomes and their association with neuroimaging markers in patients with psychosis. Systematic searches of the literature using the databases PsychInfo, OVID Medline, and Embase were conducted to collate studies investigating the association of inflammatory biomarkers with clinical outcome in patients with psychotic disorders and studies examining the relationships between inflammatory biomarkers and neuroimaging data. Seventeen studies on predictors of clinical outcome and 14 on associations between neuroimaging data and inflammatory biomarkers in psychosis were identified, and risk of bias was assessed using the Newcastle-Ottawa Scale (NOS). The main inflammatory markers associated with clinical outcome in psychosis were interleukin (IL)-6, IL-10, and C-reactive protein (CRP). High levels of CRP and IL-6 were associated with worse clinical outcome and deterioration of symptoms over time; in contrast, increased levels of IL-10 were associated with greater symptoms improvement. Smaller hippocampal volume and reduced cortical thickness were the main neuroimaging markers associated with increased peripheral inflammation. The heterogeneity across the studies (i.e., treatments strategies, duration) suggests that potential prediction power of inflammatory biomarkers could partially depend on the methodologies, supported by the overall NOS ratings of the studies. Future studies may need to consider whether a combination of these inflammatory and neuroimaging markers could further improve our ability of predicting clinical outcome in patients with psychosis.

Keywords: inflammation, neuroimaging, biomarker, psychosis, predictor, treatment response

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INTRODUCTION

Psychotic disorders are severe mental health disorders that cause abnormal thinking and perceptions. Although a good number of patients with psychotic disorders will achieve clinical remission after starting antipsychotic treatment, there remains a considerable number of patients who will continue to present persistent psychotic symptoms despite pharmacological treatment (1). Finding the best approach to predict clinical response to antipsychotic treatment is essential if we want to improve treatment strategies for patients currently not responding to antipsychotic treatment. Inflammatory biomarkers have been recently suggested to hold potential as predictors of clinical outcome in patients with psychotic disorders. At the same time, researchers call for an increasing need for combinations of different biomarkers to improve the predictive ability of biomarkers tested in isolation (2). In this context, a better understanding of the association between inflammatory markers and measures of brain structure and function could help us to identify the best neuroimaging markers that could be used in combination with inflammatory ones to improve the prediction of clinical outcome in patients with psychosis.

The presence of a relationship between increased peripheral inflammation and psychotic disorders is well-established in the literature (3–13). One recent review (8) investigated cytokine alterations in patients with schizophrenia and the association with severity of symptoms. The review concluded that these cytokine alterations are not only occurring more consistently in patients with schizophrenia compared with controls, but also suggests that sub-groups of patients such as drug-free patients, recent onset/first episode psychosis patients, or stable patients may have differing cytokine and inflammatory profiles. All the reviews and meta-analyses conducted so far have, however, not focused specifically on investigating the role of inflammatory markers in predicting clinical outcomes, in terms of response to treatment or prediction of changes in symptoms over time. A thorough review of the studies conducted on this topic so far is paramount to understand whether the use of inflammatory markers could be supported in future research and trials that want to target patients with worse clinical outcomes. In the long term, these could help patients bypass the delay in getting the treatment best tailored for them. The present paper builds on the previous reviewed evidence of increased levels inflammatory markers in psychosis and their association with severity of symptoms and focus on the aspect of prediction of clinical outcomes which has not been specifically reviewed in previous papers.

The main inflammatory markers studied in patients with psychotic disorder include C-reactive protein (CRP) and cytokines analyzed from blood samples. CRP is an acute phase protein synthetized by the liver in response to factors released by macrophages and adipocytes; it plays a role in innate immunity as an early defense system against infections and its levels increase following secretion of interleukin (IL)-6 by macrophages and T cells. Cytokines are small protein produced by a broad range of immune cells, including macrophages, lymphocytes and mast cells and represent important signaling molecules for the regulation of the immune response. Interleukin (IL)-6, IL-1β, tumor necrosis factor (TNF)-α are among the cytokines more frequently found to be elevated in patients with psychosis (7, 8) and are mostly viewed as pro-inflammatory cytokines. Other cytokines such as IL-10 have also been reported to be abnormally regulated in patients with psychosis (8); IL-10 is better known for its anti-inflammatory effect. Increased levels of inflammatory markers or an unbalance between pro- and anti-inflammatory cytokines can potentially affect brain structure and function as mainly shown in models of depression, by affecting neurogenesis, neuroplasticity and glutamate function (14).

Neural changes across various brain regions and structures have been suggested as one of the mechanisms through which elevated peripheral inflammation could contribute to development of psychosis and treatment resistance in patients with psychosis. Some studies have previously reported associations between increased peripheral inflammation and brain structure and function abnormalities in psychosis (15–17) as well as in healthy controls (18, 19) and patients with depression (20–25). The natural progression of this research is to investigate which neural changes are mostly associated with abnormalities in inflammatory response in patients with psychosis to facilitate our understanding of the possible neural pathways between increased inflammation and poor clinical outcome in psychosis.

This systematic review aimed to investigate (1) whether peripheral inflammatory biomarkers, such as CRP and cytokines, predict clinical outcome in patients with psychosis and (2) how neural changes detected by various neuroimaging techniques, such as magnetic resonance imaging (MRI), may be associated with these inflammatory markers.

METHODS

In the present review, two parallel systematic searches of the literature were conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

TABLE 1 | Summary of star allocation and final rating calculation in accordance with the Newcastle-Ottawa Quality Assessment Scale criteria used to assess the quality of each study.

Quality rating	Selection	Comparability	Exposure	Calculation method
Good	3 or 4 stars	1 or 2 stars	2 or 3 stars	Must meet ALL three conditions to gain rating
Fair	2 stars	1 or 2 stars	2 or 3 stars	Must meet ALL three conditions to gain rating
Poor	0 or 1 star	0 stars	0 or 1 stars	Can meet ANY of the three conditions to gain rating

(PRISMA) guidelines (**Appendix A** in **Supplementary Material**) (26). The search included studies published up to June 2020.

Inflammatory Markers and Clinical Outcome

To identify relevant studies investigating the efficacy of inflammatory biomarkers in predicting clinical outcome in psychosis, a systematic search across the databases PsychInfo, OVID Medline, and Embase was conducted. This search was performed by using three categories of keywords across the databases—"inflammatory markers," "psychosis," and "treatment response." The database search began with these categories; the keywords ["peripheral biomarker" OR "peripheral marker" OR "inflammation" OR "inflammatory*" OR "cytokine" OR "interleukin*" OR "IL-6" OR "IL-1" OR "CRP" OR "c reactive protein" OR TNF*" OR "tumo* necrosis factor"] AND ["psychosis" OR "psychotic disorder" OR "schizophrenia"] AND ["treatment*" OR "treatment response" OR "antipsychotic*"] were used. In addition to electronic searches, we manually searched relevant meta-analyses and reference lists of the retrieved articles for eligible studies that may have been missed.

Studies were included if they met the following inclusion criteria: (1) studies focusing on individuals with a diagnosis of psychotic disorder at the time of the assessment, (2)

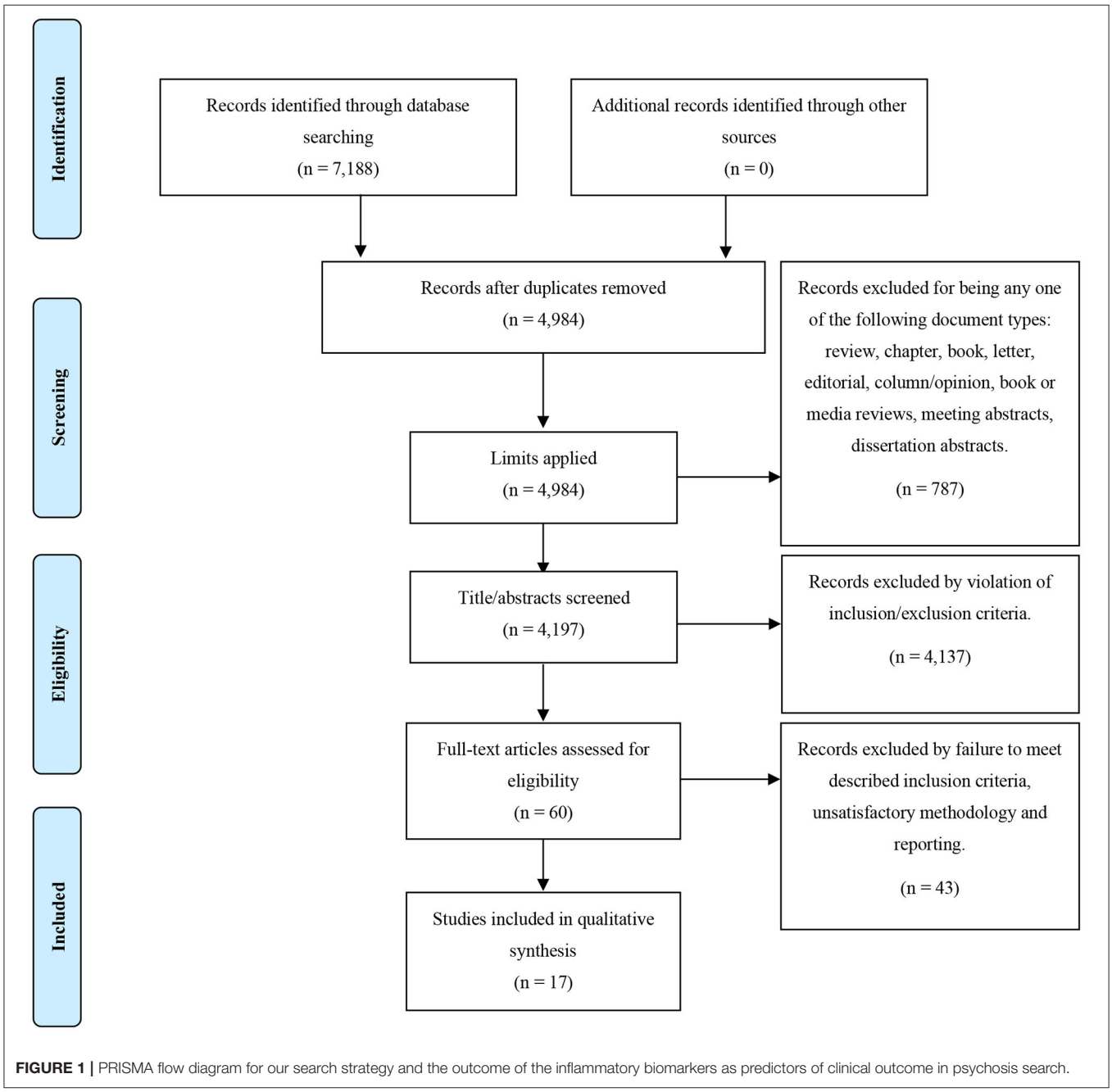

FIGURE 1 | PRISMA flow diagram for our search strategy and the outcome of the inflammatory biomarkers as predictors of clinical outcome in psychosis search.

at least one inflammatory biomarker measured at least at one time point, and (3) longitudinal design. Studies were excluded if they met one of the following criteria: (1) comorbidity of malignancy or chronic inflammatory disorder, (2) review articles, (3) meta-analysis, (4) conference abstracts (5) posters, (6) book/chapters, (7) case reports, (8) editorials, and (9) letter to the editor/non-research letter/discussion.

Inflammatory and Neuroimaging Markers

To identify papers which investigated neuroimaging findings in relation to inflammation in psychosis, a parallel systematic search was conducted. This similarly used three categories of search terms across the same databases—"inflammatory markers," "psychosis," and "neuroimaging"—and included the same keywords as before except replacing "treatment*" OR "treatment response" OR "antipsychotic*" with "neuroimage*" OR "brain scan" OR "magnetic resonance imaging" OR "MRI" OR "functional magnetic resonance imaging" "fMRI" OR "resting state" OR "connectivity" OR "neuroimage*" OR "positron emission tomography" OR "PET scan" OR "computer tomography" OR "CT scan" OR "single photon emission computer tomography" OR "SPECT" OR "diffusion weighted imaging" OR "diffusion tension imaging."

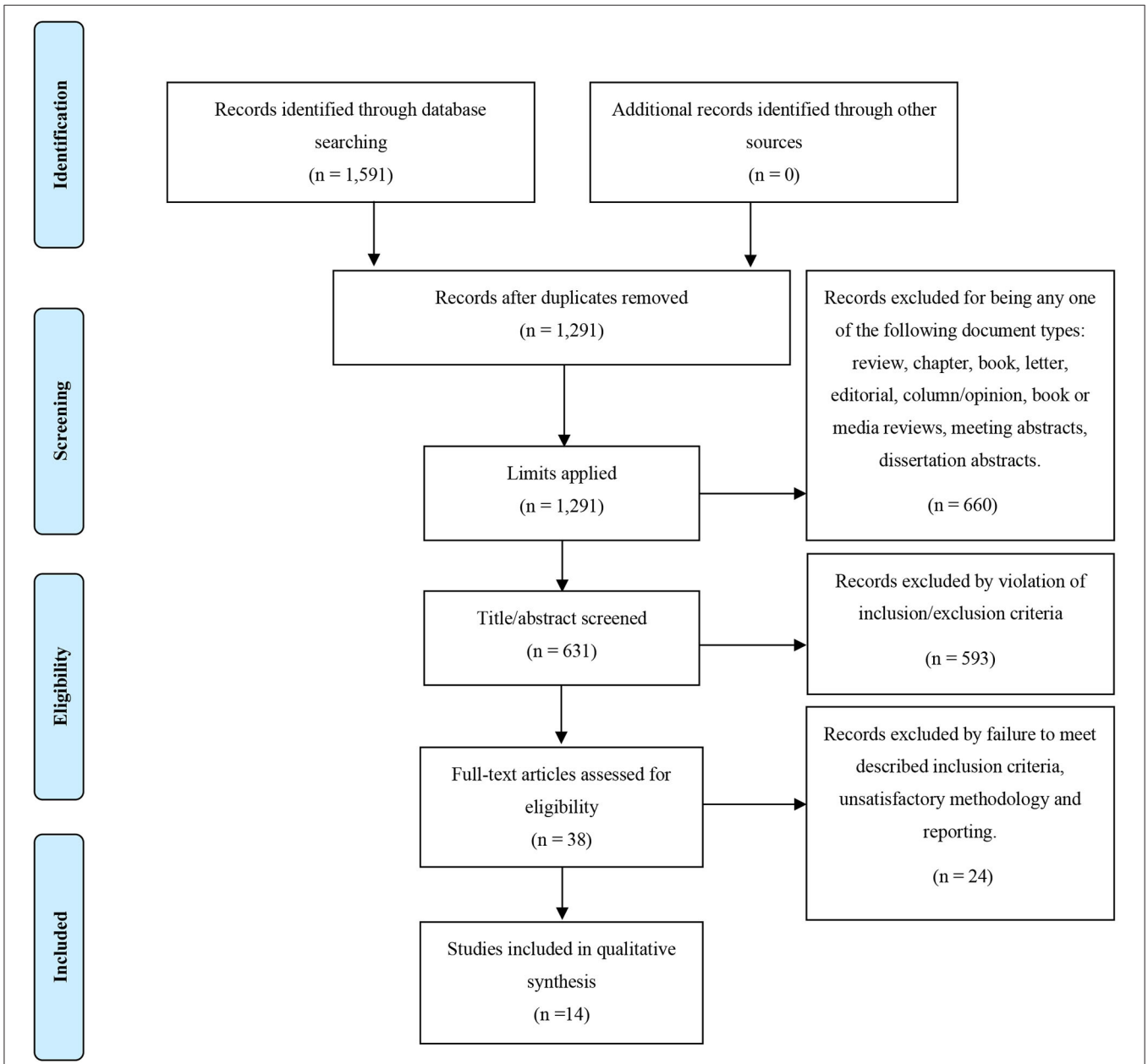

FIGURE 2 | PRISMA flow diagram for our search strategy and the outcome of the inflammatory biomarkers and neuroimaging in psychosis search.

TABLE 2 | Demographics of participants from the 17 studies investigating inflammatory biomarkers as predictors of clinical outcome in psychosis.

Study	Total sample	Cases (%women)	Controls (%women)	Mean age of cases (SD)	Mean age of controls (SD)	Country	Drug	Dose	Comorbidities	Covariate adjustments
Borovcanin et al. (28)	82*	47 (60%)	35 (0%)	35.84 (1.75)	35.46 (1.78)	Serbia	Various	Various	None	Age, sex
Chen et al. (29)	195	95 (40%)	100 (45%)	30.37 (0.87)	31.55 (0.66)	China	RISP + DXM [OR] RISP + Placebo	DXM 60 mg/day	Smoking	Age, sex
Crespo-Facorro et al. (30)	84	56 (35.7%)	28 (57.1%)	26.6 (6.6)	27.1 (3.7)	Spain	RISP, OLZ, HAL	RISP 3–6 mg/day; OLZ 5–20 mg/day; HAL 3–9 mg/day	Smoking	Age, sex
Ding et al. (31)	91	ES 28 (53.6%) Placebo 26 (46.2%)	29 (51.7%)	ES 42.4 (12.7) Placebo 49.7 (9.4)	41.8 (8.5)	China	Escitalopram, Placebo	5 mg/day for the first 3 days, 10 mg/day for day 4 to week 4, and 20 mg/day for weeks 5–8	None	None mentioned
Fathian et al. (5)	208	208 (32.2%)	–	33.5 (13.1)	–	Norway	Various	Various	None	Metabolic syndrome, smoking, being medication naïve, illicit drug use, and educational level
Gonzalez-Blanco et al. (32)	50	50 (38%)	–	30.8 (7.1)	–	Spain	Various	Various	None	Age, sex, smoking, BMI, duration of illness, antipsychotic doses
Hatziagelaki et al. (33)	14	14 (50%)	–	26.5 (6.02)	–	Greece	OLZ	15 mg ($n = 6$) or 20 mg ($n = 8$)	None	None mentioned
He et al. (34)	71	35 (43%)	36 (54%)	26.1 (9.7)	25.8 (5.1)	China	OLZ equivalents	8.19 mg/day (SD = 7.73)	None	Age, sex, BMI, dose
Luo et al. (35)	148	68 (57%)	80 (19%)	34.29 (11.17)	26.77 (5.37)	China	Various	Various	None	Age, sex, alcohol use, smoking
Mondelli et al. (36)	79	49 (32.7%)	30 (36.7%)	28.2 (0.9)	27 (0.8)	United Kingdom	Various	Various	None	Childhood trauma, number of recent stressors, perceived stress
Nettis et al. (37)	88	42 (40.5%)	46 (60.9%)	30.3 (9.8)	28.7 (9.2)	United Kingdom	Various	Various	None	Sociodemographics, BMI, triglycerides
Noto et al. (38)	53	31 (38.7%)	22 (40.9%)	25.8 (6.4)	25.0 (6.7)	Brazil	RISP	Various	None	Age, sex
Sobis et al. (39)	17	17 (41.2%)	–	51.1 (11.8)	–	Poland	ARI	Various	Type 2 diabetes, hypertension ($n = 1$); Arrhythmia ($n = 1$); Smoking ($n = 14$)	Age, BMI, duration of illness, weight, waist circumference

(Continued)

TABLE 2 | Continued

Study	Total sample	Cases (%women)	Controls (%women)	Mean age of cases (SD)	Mean age of controls (SD)	Country	Drug	Dose	Comorbidities	Covariate adjustments
Strzelecki et al. (40)	60	Sarcosine 30 (33.3%) Placebo 30 (50%)	–	Sarcosine 36.9 (11.4) Placebo 40.2 (10.1)	–	Poland	Various + sarcosine	Various	None	Age, sex, smoking, BMI and body fat
de Witte et al. (41)	530	180 (34.4%)	350 (41.1%)	30 (10)	32 (10)	Germany	Various	Various	None	Age, sex, smoking, BMI
Zhang et al. (42)	108	RISP 41 (26.8%) HAL 37 (18.9%)	30 (26.7%)	RISP 43.8 (6.4) HAL 43.7 (8.1)	40.4 (10.3)	China	RISP, HAL, Placebo	RISP 6 mg/day; HAL 20 mg/day	None	Age, sex, smoking, duration of illness
Zhang et al. (43)	75	MINO low dose 25 (48%) MINO high dose 25 (52%) Placebo (52%)	-	MINO low dose 33.04 (7.78) MINO high dose 33.24 (6.48) Placebo 33.68 (6.18)	–	China	RISP, MINO	MINO low = 100 mg/day; MINO high = 200 mg/day	None	Baseline PANSS scores

**This sum excludes the 78 first-episode psychosis patients included as a third; DXM, Dextromethorphan; RISP, Risperidone; OLZ, Olanzapine; HAL, Haloperidol; ES, Escitalopram; MINO, Minocycline; ARI, Aripiprazole.*

Studies were included if they met the following criteria: (1) studies investigating neuroimaging abnormalities in patients with a clinical diagnosis of psychosis at the time of assessment, (2) at least one inflammatory biomarker measured at least at one time point—for consistency between this search and the previous which looked at biomarkers and treatment outcome, and (3) use of at least one neuroimaging technique. Studies were excluded if they met the same exclusion criteria described in section Inflammatory Markers and Clinical Outcome, with the exception that both longitudinal and cross-sectional design studies were included. Positron Emission Tomography (PET) studies which reported results on translocator protein (TSPO) expression, but not TSPO associations with peripheral markers were excluded from the final selection. This process is outlined further with the PRISMA diagram in **Figure 2**.

Key information including sample demographics, study drugs, and covariate adjustments as well as major findings for each selected study were collated.

Quality Assessment and Risk of Bias

Full text screenings and quality assessments for each of the included papers were conducted by one researcher (MK); these were then verified by a second researcher (VM) and any uncertainties were discussed with the other authors until a decision on whether or not to include the paper in the review was reached.

To assess the quality of each study, we used the Newcastle-Ottawa Scale (NOS) (27) for assessing the quality of non-randomized cohort and case-control studies. The NOS is comprised of eight items covering three domains—selection (including representativeness and source of sample), comparability (including study design and considerations in analysis), and exposure (for cohort studies, the exposure domain is instead the "outcome" domain). Each paper can be assigned a score of 9 stars and was rated in accordance with the guidelines outlined in the **Table 1** legend as either "good," "fair" or "poor." The criteria used to assess the quality rating to each paper can be found in **Appendix B** (**Supplementary Material**).

RESULTS

Study Inclusion and Quality

The literature search of studies investigating inflammatory markers in relation to clinical outcome yielded 7,188 papers which then underwent deduplication. After duplicates were removed, 4,197 papers were identified; following screening of titles to exclude any studies irrelevant to the topic of inflammation in psychotic disorder, 60 papers underwent full-text screenings. Out of these 60, 17 papers met inclusion criteria and were included in the review. This process is demonstrated in full, with the PRISMA flow diagram, in **Figure 1**. Demographics of the participants from the 17 studies and information on covariates included in the studies' analyses are presented in **Table 2**.

The literature search of studies investigating inflammatory markers in relation to neuroimaging markers yielded a total of 1,591 papers. After applying our defined limits, 631 papers

were identified and screened by title and abstract to remove irrelevant papers; the remaining 38 studies underwent full-text screenings. Out of these 38, 14 papers met inclusion criteria and were included in the review. This process is demonstrated in full, with the PRISMA flow diagram, in **Figure 2**. Demographics of the participants from the 14 studies are presented in **Table 3**.

Regarding quality of papers, from the total of 31 studies from both literature searches, 17 were rated "good" (10 from the clinical outcome search and seven from the neuroimaging search), five were rated "fair" (all of which were from the clinical outcome search) and 9 were rated poor (six for the clinical outcome search and one from the neuroimaging search). Full results for the risk of bias quality assessment can be found in **Table 4** for case-control studies and **Table 5** for cohort studies.

The summarized findings are presented in **Table 6** (for the clinical outcome search) and **Table 7** (for the neuroimaging search). We will present below separately the results from the studies investigating the association between C-reactive protein and clinical outcome and the results from the studies investigating the association between cytokines and clinical outcome.

C-Reactive Protein and Clinical Outcome

Out of the 17 studies identified in the search on clinical outcome, five investigated levels of CRP with treatment outcome and changes in symptoms severity. Clinical outcome was defined by the symptom profile at follow-up or by changes in symptoms severity measured with the PANSS. Duration of follow-up ranged across the studies from 4 weeks (39) to 52 weeks (37). All five of the studies investigated patients on antipsychotic medication and 1 of these studies tested the effects of add-on antidepressant medication (4).

Three of the five studies (5, 32, 37) identified significant associations between baseline CRP levels and changes in symptoms severity and treatment outcome at follow-up. More specifically, González-Blanco et al. (32) found that baseline high levels of CRP (3–10 mg/L) were associated with deterioration in positive, negative, and general symptoms as measured by PANSS at 1-year follow-up ($p < 0.05$), while patients with lower levels of CRP (≤3 mg/L) showed improvements in psychotic symptoms across these same domains ($p < 0.05$). Furthermore, in conjunction with age, high levels of CRP predicted total and general symptoms whilst high level CRP in conjunction with Body Mass Index (BMI) and female sex predicted positive symptoms. Similarly, Fathian et al. (5) found that a reduction in CRP levels during the first month of treatment predicted greater cognitive improvement at 6-month follow-up, though they did not investigate correlations with severity of symptoms measured with PANSS. The third study used a different approach by combining baseline levels of CRP with BMI and triglycerides levels in one single immune-metabolic factor. The study showed that this combined metabolic factor predicted poor treatment response, defined as deterioration in overall psychotic symptoms over time, and worse scores of both negative and positive symptoms at 1-year follow-up (37).

Two of the studies examining CRP did not find significant correlations between baseline CRP and later symptoms severity or treatment outcome at follow-up. Both studies focused on a shorter follow-up period, compared with the three positive studies mentioned above. In particular, Ding et al. tested effects

TABLE 3 | Demographics of participants from the 14 studies investigating associations between inflammatory biomarkers and neuroimaging abnormalities in psychosis.

Study	Total sample	Cases (%women)	Controls (%women)	Mean age of cases (SD)	Mean age of controls (SD)	Country of participants
Bossù et al. (44)	100	71 (37%)	29 (31%)	41.8 (11.6)	41.9 (11.6)	Italy
Cannon et al. (45)	170	35 (29%)	135 (46%)	18.8 (3.8)	20.5 (4.6)	United States
De Picker et al. (46)	31	14 (0%)	17 (0%)	32.2 (8.3)	27.2 (5.5)	Belgium
Fillman et al. (47)	86	43 (41.9%)	43 (51.2%)	33.6 (range = 20–48)	32.5 (range = 22–48)	Australia
Hoseth et al. (48)	345	109 (45.9)	236 (55.9%)	30 (13)	35 (17)	Norway
Jacomb et al. (49)	156	85 (40%)	71 (52.1%)	35.8 (8.6)	32.2 (8.3)	Australia
(50)	506	250 (49.6%)	256 (49.2%)	42.5 (14)	41.8 (12.7)	Japan
Lesh et al. (51)	122	69 (12%)	53 (36%)	19.9 (3.5)	19.5 (3.3)	United States
Lizano et al. (52)	887	554 (51.8%)	333 (55.3%)	35.5 (12.5)	37.0 (12.4)	United States
Miller et al. (15)	97	31 (39%)	66 (39%)	34 (0.7) 43 (0.6)	34 (0.7) 43 (0.6)	Finland
Mondelli et al. (16)	79	49 (32.7%)	30 (36.7%)	28.2 (0.9)	27 (0.8)	United Kingdom
Prasad et al. (17)	68**	IL-6 33 (45.5%) CRP 37 (43.2%)	IL-6 23 (69.6%) CRP 27 (66.7%)	IL-6 26.39 (8.57) CRP 26.49 (8.21)	IL-6 25.44 (5.50) CRP 26.68 (6.41)	United States
Tsai et al. (53)	32	32 (71.8%)	–	58.8 (7.3)	–	Taiwan
Wu et al. (54)	88	44 (40.9%)	44 (54.5%)	31.25 (11.09)	34.32 (8.23)	China

***Not all recruited participants were included in the IL-6 or CRP analyses, hence the inconsistency between total, IL-6, and CRP sample sizes.*

TABLE 4 | Results of the systematic quality assessment in accordance to the Newcastle-Ottawa Scale for case-control studies.

Study ID	Selection					Comparability		Exposure				
	Case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	SCORE	Matched in design?	Score	Ascertainment of exposure	Same method for both?	Same Non-response rate?	Score	Adequacy
Studies investigating inflammatory biomarkers as predictors of treatment outcome in psychosis												
Borovcanin et al. (28)	Yes*	No	No	No	1	Yes**	2	Yes*	No	No	1	Poor
Chen et al. (29)	Yes*	Yes*	No	No	2	Yes**	2	Yes*	Yes*	No	2	Fair
Crespo-Facorro et al. (30)	Yes*	Yes*	Yes*	Yes*	4	Yes**	2	Yes*	Yes*	No	2	Good
Ding et al. (31)	Yes*	Yes*	No	Yes*	3	No	0	Yes*	Yes*	No	2	Poor
He et al. (34)	Yes*	Yes*	Yes*	Yes*	4	Yes**	2	Yes*	Yes*	Yes*	3	Good
Luo et al. (35)	Yes*	Yes*	Yes*	Yes *	4	No	0	Yes*	Yes*	No	2	Poor
Mondelli et al. (36)	Yes*	Yes*	Yes*	Yes*	4	No	0	Yes*	Yes*	No	2	Poor
Nettis et al. (37)	Yes*	Yes*	Yes*	Yes*	4	Yes*	1	Yes*	Yes*	No	2	Good
Noto et al. (38)	Yes*	Yes*	Yes*	Yes*	4	Yes**	2	Yes*	Yes*	No	2	Good
de Witte et al. (41)	Yes*	Yes*	Yes*	Yes*	4	Yes**	2	Yes*	Yes*	No	2	Good
Zhang et al. (42)	Yes*	Yes*	Yes*	Yes*	4	Yes**	2	Yes*	Yes*	No	2	Good
Studies investigating associations between inflammatory biomarkers and neuroimaging abnormalities in psychosis												
Bossù et al. (44)	Yes*	Yes*	Yes*	Yes*	4	Yes**	2	Yes*	No	N/A	1	Poor
Cannon et al. (45)	Yes*	Yes*	Yes*	Yes*	4	Yes*	1	Yes*	Yes*	No	2	Good
De Picker et al. (46)	Yes*	No	No	Yes*	2	Yes*	1	Yes*	Yes*	Yes*	3	Fair
Fillman et al. (47)	Yes*	Yes*	Yes*	No	3	Yes*	1	Yes*	No	N/A	1	Fair
Hoseth et al. (48)	Yes*	Yes*	Yes*	Yes*	4	Yes**	2	Yes*	Yes*	N/A	2	Good
Jacomb et al. (49)	Yes*	Yes*	Yes*	Yes*	4	Yes**	2	Yes*	Yes*	N/A	2	Good
Kudo et al. (50)	Yes*	Yes*	Yes*	Yes*	4	Yes**	2	Yes*	Yes*	N/A	2	Good
Lesh et al. (51)	Yes*	No	No	Yes*	2	Yes*	1	Yes*	Yes*	N/A	2	Fair
Lizano et al. (52)	Yes*	No	No	Yes*	2	Yes**	2	Yes*	Yes*	N/A	2	Fair
Miller et al. (15)	Yes*	Yes*	No	Yes*	3	Yes*	1	Yes*	Yes*	Yes*	3	Good
Mondelli et al. (16)	Yes*	Yes*	Yes*	Yes*	4	Yes*	1	Yes*	Yes*	N/A	2	Good
Prasad et al. (17)	Yes*	No	No	No	1	Yes**	2	Yes*	Yes*	N/A	2	Poor
Wu et al. (54)	Yes*	Yes*	Yes*	Yes*	4	Yes**	2	Yes*	Yes*	N/A	2	Good

Scoring criteria (i.e., what terms must be met to earn a star?) and adequacy (i.e., how many stars must be scored in each of the three domains to determine the studies quality?) can be found in ***Table 3*** *and* ***Appendix B*** *(****Supplementary Material****).*

TABLE 5 | Result of the systematic quality assessment in accordance to the Newcastle-Ottawa Scale for cohort studies.

Study	Selection					Comparability		Outcome				
	Representativeness of the cases	Selection of non-intervention cohort	Ascertainment of exposure	Outcome of interest was not present at start	SCORE	Matched in design?	SCORE	Assessment of outcome	Follow-up long enough for outcomes? (≥2 months)	Adequacy of follow-up cohorts	Score	Adequacy
Studies investigating inflammatory biomarkers as predictors of treatment outcome in psychosis												
Fathian et al. (5)	Yes*	N/A	Yes*	Yes*	3	Yes*	1	Yes*	Yes* - 6 months	No	2	Good
Gonzalez-Blanco et al. (32)	Yes*	N/A	Yes*	Yes*	3	Yes**	2	Yes*	Yes* - 1 year	Yes*	3	Good
Hatziagelaki et al. (33)	No	N/A	Yes*	Yes*	3	No	0	Yes*	Yes* - 2 months	Yes*	3	Poor
Sobis et al. (39)	No	N/A	Yes*	Yes*	2	Yes**	2	Yes*	No - 1 month	No	1	Poor
Strzelecki et al. (40)	Yes*	Yes*	Yes*	Yes*	4	Yes**	2	Yes*	Yes* - 6 months	Yes*	3	Good
Zhang et al. (43)	Yes*	Yes*	Yes*	Yes*	4	Yes*	1	Yes*	Yes* - 3 months	Yes*	3	Good
Studies investigating associations between inflammatory biomarkers and neuroimaging abnormalities in psychosis												
Tsai et al. (53)	Yes*	N/A	Yes*	Yes*	3	No	0	Yes*	N/A	N/A	1	Poor

Scoring criteria (i.e., what terms must be met to earn a star?) and adequacy (i.e., how many stars must be scored in each of the three domains to determine the studies quality?) can be found in ***Table 3*** *and* ***Appendix B*** *(****Supplementary Material****).*

TABLE 6 | Summary of findings for selected studies investigating inflammatory biomarkers and clinical outcomes.

Study	Treatment	Duration	Type	Biomarkers	Assessment	Major findings: correlations	Major findings: predictors
Borovcanin et al. (28)	Unspecified	30 days	AAP, TAP	IL-23	PANSS	IL-23: No significant correlation between changes and PANSS scores at baseline nor at 30-day follow-up.	/
Chen et al. (29)	[RISP + DXT] or [RISP + placebo]	11 weeks	AAP, ATVS	IL-1β, TNF-α	PANSS	IL-1β/TNF-α/BDNF ratio: No significant correlations between levels and PANSS scores at 11 weeks.	/
Crespo-Facorro, (30)	RISP, OLZ, HAL	6 weeks	AAP, TAP	IL-12	BPRS, SANS, SAPS	IL-12: No significant correlations between changes in IL-12 levels from baseline to 6-week follow-up and BPRS, SANS nor SAPS scores at 6 weeks.	/
Ding et al. (31)	[OLZ + RISP] or [RISP + ARI] or OLZ or RISP (WITH Escitalopram)	8 weeks	AAP, AD	IL-6 and CRP	PANSS	IL-6: Positive correlation between changes from baseline to 8-week follow-up and changes in PANSS-Negative, PANSS-Total, and PANSS-Cognitive scores. IL-6: Positive correlations between both baseline and 8-week follow-up levels with PANSS-Negative, PANSS-Total, and PANSS-Cognitive scores. CRP: No significant correlation with PANSS scores.	Baseline IL-6 predicted reduction in PANSS-Negative, PANSS-Total, and PANSS-Affective scores.
Fathian et al. (5)	RISP, OLZ, Quetiapine, or Ziprasidone	24 weeks	AAP	CRP	PANSS, CDSS, RBANS	/	Lower baseline CRP predicted cognitive improvement, as measured by the RBANS, following treatment.
Gonzalez-Blanco et al. (32)	Chlorpromazine	Follow-up study	TAP	CRP	PANSS	/	CRP 3–10 mg/L + age predicted both PANSS-Total and PANSS-General scores. CRP 3–10 mg/L + BMI + female sex predicted PANSS–Positive scores.
Hatziagelaki et al. (33)	OLZ	8 weeks	AAP	IL-2, IL-17F, IL-17A, IL-22, IL-1β, IL-21, IL-23, IL-27, IL-4, IL-6, IFN-γ, TNF-α, TGF-β1, TGF-β2, TGF-β3	PANSS	IL-6: Positive correlation between baseline levels and PANSS-Negative score at follow up. IL-6: Positive correlation between baseline levels and % change in PANSS-Negative score from baseline to follow-up. IL-27: Positive correlation between baseline levels and PANSS-Negative score at follow up. IL-27: Positive correlation between baseline levels and % change in PANSS-Negative score from baseline to follow-up.	Higher baseline IL-6 and also higher baseline IL-27 both predicted PANSS-Negative percentage change over time and greater improvement in PANSS-Negative score at 8-week follow-up.
He et al. (34)	Various including RISP, OLZ, HAL, ARI, clozapine, amisulpride	6 months	AAP	IL-1β, IL-4, IL-6, IL-8, IL-12, TNF-α, IFN-γ	PANSS, CGI	IL-6: Positive correlation between baseline levels and PANSS-Negative score.	Higher baseline IL-6 predicted greater improvement in PANSS-Negative score at follow-up. Lower baseline IL-8 predicted greater improvement in PANSS-Negative score at follow-up.

(Continued)

TABLE 6 | Continued

Study	Treatment	Duration	Type	Biomarkers	Assessment	Major findings: correlations	Major findings: predictors
Luo et al. (36)	RISP, ARI, Clozapine Quetiapine OLZ, Ziprasidone,	69 days (±45.66)	AAP	TNF-α, IL-18, IL-6	PANSS	IL-6: Positive correlation between baseline levels and PANSS-Negative scores IL-6: Positive correlations between follow-up levels and PANSS-Positive, PANSS-Negative, and PANSS-Total scores. IL-6: Positive correlations between changes in levels and follow-up PANSS-Positive, PANSS-Negative, and PANSS-Total scores. IL-18: No significant correlation with PANSS scores. TNF-α: No significant correlation with PANSS scores.	/
Mondelli et al. (36)	RISP, OLZ, ARI, Quetiapine	12 weeks	AAP	IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, TNF-α, IFN-γ	PANSS	IFN-γ: Positive correlation between baseline levels and PANSS-Negative score at follow-up.	Higher IL-6 at baseline predicted poorer clinical outcome at follow-up, as measured by PANSS-Total scores. Higher IFN-γ at baseline predicted poorer clinical outcome at follow-up (PANSS-Total)
Nettis et al. (37)	RISP, OLZ, ARI, HAL, Quetiapine, Zuclopenthixol	52 weeks	AAP, TAP	hsCRP; Factor 1: CRP, BMI, and Triglycerides (TG)	PANSS	Factor 1: Positive correlation with PANSS-Positive, PANSS-Negative, PANSS-Total, and PANSS-Global scores	Factor 1 (CRP, BMI and TG) at baseline predicted 1-year follow-up treatment response, shown by percentage improvement.
Noto et al. (38)	RISP	10 weeks	AAP	IL-1β, IL-10, IL-13, IL-6, IL-7, IL-15, IL-5, IL-12, IL-1RA, IL-2, IL-17, sIL-2R, IL-4, IL-8, IFN-γ, and TNF-α	PANSS	IL-6: Positive correlations between levels and PANSS-Negative, PANSS-Psychosis, PANSS-Affective, and PANSS-Excitation. IL-8: Positive correlations between levels and PANSS-Negative, PANSS-Psychosis, PANSS-Affective, and PANSS-Excitation.	Higher baseline levels of IL-10 and sTNF-R1 predicted greater improvement at 10-week follow-up, as measured by PANSS-Negative and PANSS-Positive scores.
Sobis et al. (39)	ARI	4 weeks	AAP	IL-6, TNF-α, IL-1β, IFN-γ, sTNF-R1, IL-12, IL-23, IL-1Ra, TGF-β1, IL-4, and IL-10 and CRP	PANSS	IL-10: Negative correlations between follow-up levels and follow-up PANSS-Positive, PANSS-Negative and PANSS-Total scores. IL-6/IL-10 ratio: Positive correlation between follow-up levels and follow-up PANSS-Positive, PANSS-Negative, PANSS-Total, and PANSS-Global scores.	/
Strzelecki et al. (40)	[Unspecified Antipsychotic + Sarcosine] or Placebo	6 months	AAP, TAP, GTI	TNF-α	PANSS, CDSS	TNF-α: Positive correlation between levels and CDSS score at baseline. No correlations between TNF-α and any PANSS scores.	Baseline TNF-α did not predict response to sarcosine, as measured by PANSS scores.

(Continued)

TABLE 6 | Continued

Study	Treatment	Duration	Type	Biomarkers	Assessment	Major findings: correlations	Major findings: predictors
de Witte et al. (41)	RISP, OLZ, Quetiapine	6 weeks	AAP	IFN-γ, IL-1α, IL-1RA, IL-5, IL-10, IL-12, IL-15, IL-18, TNF-α	PANSS	IL-10: Positive correlations between changes in levels from baseline to 6-week follow-up and PANSS-Negative, PANSS-Total, and PANSS-General scores. IL-1Ra: No correlations between changes in levels from baseline to 6-week follow-up and any PANSS scores.	/
Zhang et al. (42)	RISP, HAL	12 weeks	AAP, TAP	IL-2, IL-6	PANSS	IL-2: Positive correlation between reduction in levels and reduction in PANSS-Total scores IL-2: Negative correlation between baseline levels and reduction in PANSS-Positive scores.	Lower baseline IL-2 (with lower superoxide dismutase activity and female sex) was associated with greater clinical response, as measured by PANSS scores.
Zhang et al. (43)	RISP, MINO	12 weeks	AAP, TCAB	IL-1β, IL-6, TNF-α	PANSS, SANS	In high-dose minocycline group: IL-6: Positive correlation between reduction in levels and reduction in PANSS-Negative scores. IL-1β: Positive correlation between reduction in levels and reduction in PANSS-Negative scores. In low-dose minocycline group: IL-6: Positive correlation between reduction in levels and reduction in PANSS-Negative scores. IL-1β: Positive correlation between reduction in levels and reduction in SANS scores.	/

SCZ, schizophrenia; FEP, first episode psychosis; DXM, Dextromethorphan; RISP, Risperidone; OLZ, Olanzapine; HAL, Haloperidol; ES, Escitalopram; MINO, minocycline; ARI, Aripiprazole; AAT, atypical antipsychotic; TAP, typical antipsychotic; ATVS, Antitussives; GTI, glycine transport inhibitor; TCAB, tetracycline antibiotic; CRP, c-reactive protein; TNF-α, tumor necrosis factor-alpha; IL-#, interleukin-#; PANSS, Positive and Negative Syndrome Scale, CDSS, Calgary Depression Scale for Schizophrenia; BPRS, Brief Psychiatric Rating Scale; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

of adjunctive treatment with escitalopram over an 8-week period (31) and although they did not find any significant correlation between CRP and PANSS scores, they reported a reduction in CRP levels after 8-weeks of treatment. Sobiś et al. tested the effects of airpiprazole on inflammatory markers over a 4-week period and although they did not find any significant correlation between CRP and PANSS scores, they also identified reduction in CRP over the 4-week treatment (39).

Cytokines and Clinical Outcome

Out of the 17 studies identified in the search on clinical outcome, 14 investigated levels of cytokines with treatment outcome and changes in symptoms severity. Of note, four of these studies investigated the use of an adjunctive treatment to the prescribed antipsychotic medication; predictors amongst these studies would be predictors of response to add-on minocycline (43), escitalopram (31), sarcosine (40), or dextromethorphan (29) rather than to conventional antipsychotic. The main significant findings were found for the studies testing the effects of add-on minocycline (43) and add-on escitalopram (31) as reported more in detail below.

We found 9 studies investigating IL-6 levels in relation to either clinical outcome or changes in symptoms. Six studies highlight a significant positive correlation between either baseline IL-6 and follow-up PANSS scores or changes in IL-6 and changes in PANSS scores, particularly with PANSS negative symptoms, including the results from two studies with add-on treatment with minocycline or escitalopram (31, 33–35, 38, 43). Four of the 9 studies specifically investigated IL-6 as a predictor of treatment outcome and they all reported baseline IL-6 levels as a successful predictor of treatment response at follow-up (31, 33, 34, 36). Only two studies did not identify a specific correlation between baseline IL-6 levels and changes in symptom severity over 4-week and 12-week trials with aripiprazole or haloperidol/risperidone respectively (39, 42), although the aripiprazole trial reported a reduction in IL-6 levels over the 4-week treatment period (39). Reduction in IL-6 levels from baseline to follow-up were also found to be associated with improvement in cognitive performance and follow-up PANSS positive ($r = 0.260$, $p < 0.01$), negative ($r = 0.366$, $p < 0.01$), and total ($r = 326$, $p < 0.01$) symptoms (35). Similarly, a reduction in in IL-6 levels was associated with an improvement in negative symptoms in patients receiving add-on treatment with a high dose of minocycline (43).

We found seven studies investigating IL-1β levels in relation to either clinical outcome or changes in symptoms. Only one study reported a significant finding, showing correlation between a decrease in IL-1β levels and improvement in negative symptoms only in patients who received add-on minocycline treatment (43).

We found 4 studies investigating IL-2, IL-4, and/or IL-10 levels in relation to either clinical outcome or changes in symptoms. Zhang et al. (42) found that a decrease in IL-2 following antipsychotic treatment significantly correlated with reduction in positive ($r = 0.38, p < 0.01$) and total ($r = -0.36, p < 0.01$) PANSS sub-score domains. This study also confirmed that higher baseline levels of IL-2 in patients is predictive of poorer response to antipsychotic medication. The other three studies did not find any significant finding with IL-2. No significant finding was reported when looking at the association with IL-4 levels. With regards to IL-10, we found significant findings in three out of four studies. In particular, de Witte et al. showed that IL-10 reduction over time was significantly correlated with improvement in negative ($r = 0.41$, $p < 0.05$), general ($r = 0.37$, $p < 0.05$), and total PANSS scores ($r = 0.45$, $p < 0.05$) after 6-week treatment with antipsychotic (41).

Further, Noto et al. showed that higher baseline levels of IL-10 predicted greater improvement in negative and positive symptoms at 10-week follow-up (38). Finally, Sobiś et al. showed that elevated IL-10 levels were negatively correlated with PANSS-Negative ($p = 0.03$), -Positive ($p = 0.022$), and -Total ($p = 0.008$) sub-scores at 4-week follow-up (39).

We found 5 studies investigating IL-8 and 1 study investigating IL-27 levels in relation to either clinical outcome or changes in symptoms. Lower baseline IL-8 levels predicted greater reduction in PANSS-Negative scores, marking greater improvement in negative symptoms at 6-month follow-up (34). Higher levels of IL-27 at baseline was associated with greater improvement in negative symptoms at 8-week follow-up in a sample of first-episode psychosis patients (33). No other significant finding was reported for these two cytokines in the remaining studies.

Although levels of TNF-α were investigated in 9 studies, no significant association was found between this particular cytokine and clinical outcome or changes in symptoms.

Finally, although six studies investigated IFN-γ levels, only one reported association between this marker and treatment response at 12-week follow-up (36). Other cytokines were investigated in 2 or fewer studies and the results are reported in **Table 6**.

Association Between Inflammatory and Neuroimaging Markers

In the neuroimaging studies identified by our search, the most consistently used neuroimaging technique was MRI with 13 studies; one of these studies also included the use of PET imaging. Only one study used Diffusion Tensor Imaging (DTI) as neuroimaging technique. The results are summarized in **Table 7**.

The hippocampus was the region of interest most commonly studied in association with inflammatory markers ($N = 8$). Increased levels of IL-6 levels were associated with smaller total hippocampal volumes in two studies (15, 16). One study (48) found elevated levels of osteoprotegerin—a tumor necrosis factor receptor—associated with smaller total hippocampal volume, though no correlations with other cytokines, including TNF-α, nor IL-6, were found in the same study. Kudo et al. (50) observed negative association between sTNF-R2 and hippocampal volume while Tsai et al. (53) found sTNF-R1 was positively associated with right amygdala volume. Bossù et al. reported an association between lower levels of pro-inflammatory cytokine IL-18 and smaller hippocampal volumes (44). Fillman et al. reported an association between general elevated inflammation (measured by a specified range of cytokines) and deterioration of Broca's area

TABLE 7 | Summary of findings for selected studies investigating inflammatory and neuroimaging markers.

Study	NI	Observed region	Key biomarkers	Major findings
Bossù et al. (44)	MRI	Hippocampus	IL-18	Lower amounts of free IL-18 were related to smaller hippocampal volume measures in patients with SCZ.
Cannon et al. (45)	MRI	Prefrontal, superior temporal, and parahippocampal regions	TNF-α, IFN-γ, IL-2, IL-10, IL-1RA, CCL2	Rate of prefrontal cortical thinning from baseline to follow-up had significant negative association with higher levels of pro-inflammatory biomarkers – greater in converters (CHR to FEP)
De Picker et al. (46)	PET, MRI	Cerebellum, brainstem, cingulate cortex, thalamus, basal ganglia, amygdala, hippocampus	TSPO, IL-6, IL-8, TNFα, CRP, IL-1RA	Plasma CRP and quinolinic acid were independently associated with lower regional volume of distribution. No significant associations between any peripheral immune markers and TSPO uptake.
illman et al. (47)	MRI	Broca's, Wernicke's	IL-1β, IL-2, IL-6, IL-8 and IL-18	Higher cytokine levels associated with greater reduction in left pars opercularis (Broca's area) volume. IL-1β mRNA levels negatively correlated with left pars opercularis volume
Hoseth et al. (48)	MRI	Hippocampus	Plasma sTNF-R1, osteoprotegerin, IL1-Ra and IL-6	A trend ($p = 0.09$) toward a negative association (b = 0.10) between osteoprotegerin and the volume of the total hippocampal formation after controlling for age, sex, estimated intracranial volume and diagnosis. No significant correlations between any measured cytokines and hippocampal volumes.
Jacomb et al. (49)	MRI	Cortical thickness	CRP	Higher CRP levels were associated with lower cortical thickness. CRP significantly predicted cortical thickness in most regions (frontal pole, medial orbital frontal, lateral orbitofrontal, temporal pole, middle temporal, entorhinal, insula, and paracentral regions).
Kudo et al. (50)	MRI	Hippocampus	Plasma sTNFR2	Higher sTNFR2 levels significantly associated with smaller hippocampal volume in patients with schizophrenia
Lesh et al. (51)	MRI	Total GM and WM	IL-1β, IL-2, IL-4, IL-6, IL-10, IL-12p70, IFN-γ, and TNF-α	Higher IFN-γ levels negatively correlated with whole-brain GM volume. Trend toward a negative correlation between IFN-γ and left middle frontal gyrus thickness. No correlations of cytokines with cortical thickness were observed
Lizano et al. (52)	MRI	Choroid plexus	IL-1b, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-12p70, IFN- γ, TNF- α, CRP	Higher IL-6 levels associated with larger choroid plexus volume in probands.
Miller et al. (15)	MRI	Hippocampus	CRP, IL-6, IL-17, IL-1α, IL-1β, IL-4, IL-8, IP 10, and MCP1	Higher blood IL-6 levels were a predictor of smaller left and right hippocampal volumes, between ages 34 and 43 years. Significant association between IL-6 levels and hippocampal volumes.
Mondelli et al. (16)	MRI	Hippocampus	BDNF, IL-6, TNF-α	Increased IL-6 expression significantly predicted a smaller left hippocampal volume. IL-6 mRNA levels correlated with left hippocampal volume.
Prasad et al. (17)	DTI	WM and connectivity; Fractional anisotropy and radial diffusivity.	IL-6, CRP	IL-6 levels negatively correlated with fractional anisotropy and positively correlated with radial diffusivity—localized to the forceps major, the inferior longitudinal fasciculus and the inferior fronto-occipital fasciculus. CRP levels negatively correlated with fractional anisotropy within forceps major.
Tsai et al. (53)	MRI	Total GM and WM, hippocampus, amygdala, prefrontal, orbitofrontal, frontal lobe.	Plasma IL1-β, sIL-2R, sIL-6R, IL-1Ra, and sTNF-R1	Higher plasma sTNF-R1 levels significantly associated with lower volume in right amygdala. Higher plasma sIL-2R levels significantly associated with lower volume in the left anterior cingulum. Higher plasma IL-1Ra levels were associated with greater volume of right anterior cingulum

(Continued)

TABLE 7 | Continued

Study	NI	Observed region	Key biomarkers	Major findings
Wu et al. (54)	MRI	Cortical thickness, surface area, and cortical and subcortical GM volumes.	IFN-γ, IL-1β, IL-2, IL-6, IL-8, IL-10, and TGF-β	IL-6 levels significantly associated with the cortical thickness in the left pars opercularis, superior temporal gyrus, right middle temporal gyrus, and pars triangularis. IL-10 levels significantly associated with cortical thickness in right caudal anterior-cingulate cortex and GM volume in frontal gyrus and cingulate cortex. IL-6 levels significantly associated with GM volume in the right lingual gyrus IL-8 levels significantly associated with GM volume in the left medial orbital frontal cortex IL-10 levels significantly associated with GM volume in the left lateral and medial orbital frontal cortex, rostral middle frontal gyrus, right caudal middle frontal gyrus, superior frontal gyrus, isthmus-cingulate cortex, lingual gyrus, and precuneus cortex. None of these were associated with subcortical structures' GM volumes.

SCZ, schizophrenia; NI, neuroimaging technique; GM, gray matter; WM, white matter; FEP, first episode psychosis; CHR, clinical high risk; AAT, atypical antipsychotic; TAP, typical antipsychotic; TCAB, tetracycline antibiotic; CRP, c-reactive protein; TNF-α, tumor necrosis factor-alpha; IL-#, interleukin-#; PANSS, Positive and Negative Syndrome Scale, BLE, Brief Life Events questionnaire; PSS, Perceived Stress Scale; CECAQ, Childhood Experience of Care and Abuse Questionnaire; SIPS, Structured Interview for Prodromal Syndromes; SOPS, Scale of Prodromal Symptoms; SCID, Structured Clinical Interview for DSM-IV.

volume; further, IL-1β mRNA were negatively correlated with volume of this region (47).

Several studies also investigated associations between levels of inflammatory cytokines and cortical thickness. Jacomb et al. (49) reported significant negative association between CRP levels and cortical thickness, and CRP was a reliable predictor of cortical thickness in a wide range of brain regions. Similar findings were reported in a later study (54) in which increased levels of both IL-6 and IL-10 were shown as significantly associated with cortical thickness in a range of brain regions. In contrast, no such correlations were observed by Lesh et al. (51) between CRP, nor with any cytokines, and cortical thickness. Finally, in a study on clinical high risk for psychosis and first episode psychosis patients (45), higher levels of pro-inflammatory markers were negatively associated with rates of cortical thinning between baseline and 12-month follow-up.

We found only 1 DTI study which analyzed the association between peripheral inflammatory markers and brain connectivity, showing a negative correlation between IL-6 and CRP levels with fractional anisotropy within the forceps major (17).

IL-6 was the marker most frequently investigated in association with neuroimaging markers ($N = 9$, plus one study looking at sIL-6R); five of these found significant associations between levels of IL-6 and differences in brain structures, including the two studies finding association with hippocampal volume (15, 16), the study finding association with cortical thickness (54) and the study showing association with fractional anisotropy in the forceps major (17). The fifth study reporting significant association between neuroimaging markers and IL-6 found an association between elevated levels of IL-6 and larger choroid plexus volume (52). Further details of the studies and their findings can be found in **Table 7.**

DISCUSSION

To our knowledge, this is the first comprehensive systematic review of the literature investigating the potential role of inflammatory biomarkers as predictors of clinical outcome and their association with neuroimaging markers in patients with psychosis. The following key findings were identified: (1) IL-6, IL-10, and CRP were most consistently correlated with clinical outcome, either as predictors of treatment response or associated with changes in symptoms severity over time, and (2) increased inflammatory markers were mainly associated with smaller hippocampal volumes and reduced cortical thickness in patients with psychosis.

Rather limited research investigating the relationship between various inflammatory biomarkers and treatment efficacy has been conducted (5, 10–12, 55), and thus, the present systematic review highlighted key areas that future research in the field may investigate, including which biomarkers may be most useful to observe and which methodologies appear to work best.

CRP is well-established in the literature as an efficient biomarker of inflammatory state (5, 12, 31, 32). Three studies indicated that decreasing levels of CRP between baseline and follow-up were significantly correlated with improvements in symptom severity following treatment (5, 32, 37). These studies were also the same ones to highlight the predictive power of baseline CRP levels on treatment outcome at follow-up. Of note, these studies had significantly longer durations, with the shortest lasting 24 weeks between baseline and follow-up (5). In contrast, the two other CRP studies (31, 39) which did not show an association of CRP with clinical outcome had signicantly shorter time frames (8 weeks and 4 weeks respectively). This could potentiall suggest CRP as a better marker for long term follow-ups, while other inflammatory markers (such as IL-6) may better suited for shorter term follow-up (1–3 months). Furthermore,

of the two studies which did not yield significant correlation between CRP and symptoms severity, Ding et al. (31) investigated the use of adjunctive antidepressant escitalopram, so potentially suggesting that CRP levels are indicative for change in symptoms or prediction of clinical response to antipsychotic treatment only when used independently of any add-on medication.

When looking at the relationship between cytokines and clinical outcome, we found that higher IL-6 levels were associated with worse clinical outcome or deterioration in symptoms over time. Interestingly, one study testing the effect of add-on anti-inflammatory treatment with minocycline reported that the reduction in IL-6 levels induced by the minocycline treatment was associated with an improvement in negative symptoms (43), suggesting that IL-6 would be a potential marker not only to identify patients with worse clinical outcome but that it could also be used to stratify patients populations for add-on treatment with anti-inflammatory medications. IL-10 was the other cytokine which was mostly associated with clinical outcome. IL-10 is mainly viewed as an anti-inflammatory cytokine. Interestingly, three studies reported an association between high levels of IL-10 and greater symptoms improvement and less severe symptoms at follow-up (38, 39, 41), suggesting that an anti-inflammatory response as mediated by IL-10 pathway may contribute to a treatment-induced recovery in psychosis. Future studies would need to consider the possible balance between pro- and anti-inflammatory pathways (IL-6/IL-10 ratio) and how this could also contribute to clinical outcome.

The mechanisms through which peripheral inflammation could contribute to worse clinical outcome are still partly unclear. However, it has been suggested that peripheral inflammation could potentially lead to immune activation in the Central Nervous System (CNS) and affect neuroplasticity, neurogenesis and influence neurotransmitter signaling including the glutamate pathway (14). Only few studies have investigated levels of cytokines in cerebrospinal fluid showing increased levels of pro-inflammatory cytokines such as IL-6, IL-1β, and IL-8 in the CSF of patients with psychotic disorders (12); however, we could not identify any study on CSF cytokines which looked specifically at their association with clinical outcome in patients with psychosis. Other evidence supporting the presence of central inflammation in patients with psychosis derives mainly from post-mortem studies suggesting the presence of activated microglia, the main cells regulating immune response in the brain (9). Various pathways have been suggested in the peripheral immune-to-brain communication including increased permeability of the blood brain barrier, the lymphatic system, and infiltration of peripheral immune cells, such as macrophages, to the brain (56). Unfortunately, the investigation of neuroinflammation in humans *in vivo* is particularly challenging as we lack neuroimaging techniques and tools to be able to identify the low-grade inflammation that characterizes patients with psychosis. The last decades have seen an increase in PET studies using ligands binding the translocator protein (TSPO) as a potential tool to study microglia activation in patients with psychiatric disorders. However, recent studies cast doubt on the efficacy of TSPO ligands as markers of neuroinflammation in psychiatry (57).

In this context our systematic review on the association between peripheral inflammatory markers and neuroimaging findings in patients with psychosis could potentially open other avenues to identify central markers relevant to the peripheral immune-to-brain communication.

Most of the studies identified in this systematic review consistently demonstrate a significant association between increased peripheral inflammation and smaller hippocampal volume and reduced cortical thickness. The association between elevated levels of IL-6 and larger choroid plexus volume is also an interesting finding as the choroid plexus is a particular brain area where the blood brain barrier is usually less tight and could therefore represent one main structure involved in the communication between peripheral inflammation and the brain (52).

Quality Assessment and Risk of Bias

The NOS was used to assess the quality of the 31 papers included in the present systematic review (27, 58). In 26 of these studies, participant groups were matched by at least age and in 17 papers samples were matched by age and at least one other factor. The remaining five studies which did not have matched samples raises some concerns about the possibility of confounding variable, however, in 2 of these studies a range of factors such as age, sex, alcohol and smoking (35) and childhood trauma and perceived stress (36) were considered covariate adjustments in analysis. Amongst case-control studies ($N = 24$), studies performed better than anticipated with 13 studies achieving a NOS adequacy rating of "good" compared to 6 with a rating of "poor" and 5 "fair"; amongst cohort studies ($N = 7$), the split was far closer to even with 4 studies achieving a rating of "good" and 3 achieving "poor." With regards to the 3 domains, most studies performed well by reporting sampling methodologies sufficiently; for most, cases were validated by researchers and clinicians directly with the use of structured interviews and/or reference to medical records. The exposure domain was where many studies performed their worst; specifically, with regards to response-rates and attrition which many studies did not provide any information on. While over half of the papers ($N = 17$) did achieve a NOS rating of "good," 14 did not and as such the trustworthiness of observations and quality of papers should be scrutinized. However, it should be noted that a majority of the shortcomings in the selection and exposure (or outcome for the cohort studies) domains are as a result of a failure to sufficiently report information rather than deficiencies in methodology. For further details on performances across the three domains, see **Table 4** for case-control studies and **Table 5** for cohort studies.

Limitations

The heterogeneity in the methodologies and treatment approaches in the reviewed studies is a limit for the interpretation of findings; with the relatively small sample of papers included, this only further hinders our ability to draw decisive conclusions. However, this literature review aims to present the data as it currently stands comprehensively and concisely, so while this diversity should be highlighted, the consistencies between the studies such as observed inflammatory biomarkers, sample sizes

and demographics, and statistical analyses allow us to still draw valuable conclusions and suggestions for future studies and clinical trials. Another potential limitation is represented by the observational design of most studies that implies a reduced reliability to prove causal associations; experimental medicine studies in preclinical models using immune challenges may be better placed to understand causality.

CONCLUSION

The findings of this systematic review may be used as guidance for future research which aims to use the most promising inflammatory and neuroimaging markers when investigating prediction of clinical outcome in psychosis. The heterogeneity among the examined studies, in terms of analyzed biomarkers and implemented treatments strategies, indicates that the ability of these inflammatory biomarkers to predict clinical outcome are highly dependent on the combinations of treatments, markers and symptoms that are measured. Levels of IL-6, IL-10, and CRP appeared to be the most promising inflammatory biomarkers for prediction of clinical outcome in patients with psychosis, though further research is needed to establish their validation. Interestingly smaller hippocampal volume and reduced cortical thickness were consistently associated with levels of peripheral inflammation; future studies may need to consider whether a combination of these inflammatory and neuroimaging markers could further improve our ability of predicting clinical outcome in patients with psychosis.

AUTHOR CONTRIBUTIONS

MK was responsible for conducting the systematic searches, reviewing the studies for eligibility and drafted the first draft of the manuscript. VM conceived the study, oversaw the systematic searches and contributed to the drafting of the manuscript and to the intepretation of the results. CP and PD contributed intellectually to the interpretation of the results. All authors reviewed and contributed to the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.612471/full#supplementary-material

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White Matter Correlates of Theory of Mind in Patients With First-Episode Psychosis

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Deficits in theory of mind (ToM) are considered as a distinctive feature of schizophrenia. Functional magnetic resonance imaging (fMRI) studies have suggested that aberrant activity among the regions comprising the mentalizing network is related to observed ToM deficits. However, the white matter structures underlying the ToM functional network in schizophrenia remain unclear. To investigate the relationship between white matter integrity and ToM impairment, 35 patients with first-episode psychosis (FEP) and 29 matched healthy controls (HCs) underwent diffusion tensor imaging (DTI). Using tract-based spatial statistics (TBSS), fractional anisotropy (FA) values of the two regions of interest (ROI)–the cingulum and superior longitudinal fasciculus (SLF)–were acquired, and correlational analysis with ToM task scores was performed. Among the patients with FEP, ToM strange story scores were positively correlated with the FA values of the left cingulum and left SLF. There was no significant correlation between FA and ToM task scores in HCs. These results suggest that the left cingulum and SLF constitute a possible neural basis for ToM deficits in schizophrenia. Our study is the first to demonstrate the white matter connectivity underlying the mentalizing network, as well as its relation to ToM ability in patients with FEP.

Keywords: social cognition, theory of mind, schizophrenia, first episode psychosis, DTI, TBSS, white matter

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INTRODUCTION

Social cognition abnormalities are core features of schizophrenia (1, 2). Among many aspects of social cognition, deficits in theory of mind (ToM) are consistently reported in patients with schizophrenia across different stages of the disease (3–5). ToM is the mentalizing capacity to infer others' thoughts, intentions, beliefs, and emotions (6). Compared to its severity in other psychiatric disorders, ToM impairment is more severe in schizophrenia (7) and is strongly associated with psychopathology, neurocognitive function, and general functioning (1, 7–11). The impairment has trait-like characteristics that precede the onset of illness and persist across disease progression, even after remission (12–14). Moreover, ToM deficits have been reported as a possible predictor of illness onset among individuals with high-risk psychosis (15). Taken together, these observations suggest the significance of ToM in understanding the pathophysiology of schizophrenia.

Over the last few decades, the neural correlates of ToM have been largely investigated using the functional magnetic resonance (fMRI) approach (16, 17). According to studies in healthy subjects, the mentalizing network, including the medial pre-frontal cortex (mPFC), temporoparietal junction (TPJ), and precuneus/posterior cingulate cortex (PCC), is activated during the performance of various ToM tasks, regardless of task modality (2, 17–20). In schizophrenia, the aberrant activities of the mPFC, TPJ, and precuneus/PCC within the mentalizing network were related to ToM deficits (21–26).

To specify the direct structural connections among the abovementioned ToM regions, white matter studies are necessary. However, there are insufficient number of studies, despite the crucial roles of white matter structures in connecting distal cortical areas (17). Particularly in schizophrenia, only a few studies have attempted to investigate the relationship between white matter and social cognition, such as face perception (27), emotion attribution (28), empathy (29), and social relationships (30). Structural abnormalities that may cause disrupted neural activations and ToM impairment in schizophrenia have not yet been studied.

To explore the white matter neural correlates of ToM deficits in schizophrenia, the cingulum and superior longitudinal fasciculus (SLF) were selected as the white matter regions of interest (ROIs). According to the previous fMRI studies in schizophrenia and DTI literature from healthy individuals and those with other diseases, the two ROIs connect the crucial nodes of mentalizing network as the cingulum passes mPFC and precuneus/PCC and SLF passes through the PFC and TPJ (17, 31–33).

The aim of this study was to investigate the association between ToM deficits and the cingulum and the SLF. With respect to ToM performance, it was hypothesized that patients with FEP would have decreased ToM abilities compared to those of HCs. Additionally, considering previous findings, impaired ToM abilities in FEP patients were hypothesized to be related to the FA reduction in the cingulum and SLF.

METHODS

Participants

Thirty-five patients with FEP and 29 HCs participated in the study. Age, sex, and handedness were matched between the groups. All participants were part of a prospective cohort study recruited from the psychosis clinic at Seoul National University Hospital. Past and current psychotic symptoms of the patients were evaluated using the Positive and Negative Syndrome Scale (PANSS) (34), and a Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) was administered. Additionally, Global Assessment of Functioning (GAF) and Hamilton Depression Rating Scale (HAM-D) scores were collected. The inclusion criteria for FEP patients were being aged between 15 and 37 years old with a brief psychotic disorder, schizophreniform disorder, schizophrenia, or schizoaffective disorder. The duration of the illness of all FEP individuals was less than a year. Individuals were excluded from the HC group if they had a past or current SCID-I Non-patient Edition (SCID-NP) axis I diagnosis and any first- to third-degree biological relatives with a psychiatric disorder. The exclusion criteria for both groups were substance abuse, medical illness that could cause psychiatric symptoms, intellectual disability (intelligence quotient [IQ] <70), neurological disorders, or previous head injury. The study procedures were explained in detail to all participants, who then provided written informed consent. This study was approved by the Institutional Review Board of Seoul National University Hospital.

Behavioral Measures

ToM was assessed with the short form of two verbal ToM tasks: the false belief and strange story tasks (35–38). All tasks were translated into Korean by psychiatrists and clinical psychologists, taking cultural backgrounds into accounts (39). The false belief task consisted of first-order (35) and second-order (36) tasks. The first-order task was used to evaluate whether the subject recognized a character's false belief about reality. The second-order task questioned a character's understanding of the other character's mental state. Each task is comprised of a short vignette with a picture and two questions: one for the comprehension test and the other to assess the subjects' capacity to infer the character's thoughts (justification question). The maximum total score of the false belief task was 12 points.

The strange story task (38) consisted of eight vignettes, each accompanied by a picture and two questions: one for comprehension test and the other to measure subjects' cognitive capacity to infer the character's mental state and emotion in complex naturalistic situations. The task included two examples for each of the four types of stories: double bluff, white lie, persuasion, and misunderstanding. The maximum score of the story task was 26.

Image Acquisition and DTI Pre-processing

All participants underwent magnetic resonance imaging scanning on a 3T scanner (MAGNETOM Trio Tim Syngo MR B17, 12 channel head coil, Siemens, Erlangen, Germany) at Seoul National University Hospital. Diffusion tensor images were acquired via echo-planar imaging with the following parameters: TR 11400 ms, TE 88 ms, matrix 128 × 128, FOV 240 mm and a voxel size of 1.9 × 1.9 × 3.5. Diffusion-sensitizing gradient echo encoding was applied in 64 directions using a diffusion-weighting factor b of 1,000 s/mm^2. One volume was acquired with b factor of 0 s/mm^2 (without gradient).

The diffusion images were pre-processed via three steps with the FSL software package (version 5.0.10; https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). First, the eddy-current correction was applied to correct distortions and subject movements. Then, the skull was removed by the brain extraction tool (BET). After the BET process, raw brain images underwent visual inspection, and one healthy control was excluded because the dorsal surface of the brain was not covered in the MRI. As the final step, DTIFIT was applied to fit the diffusion tensor model, and individual FA values were obtained.

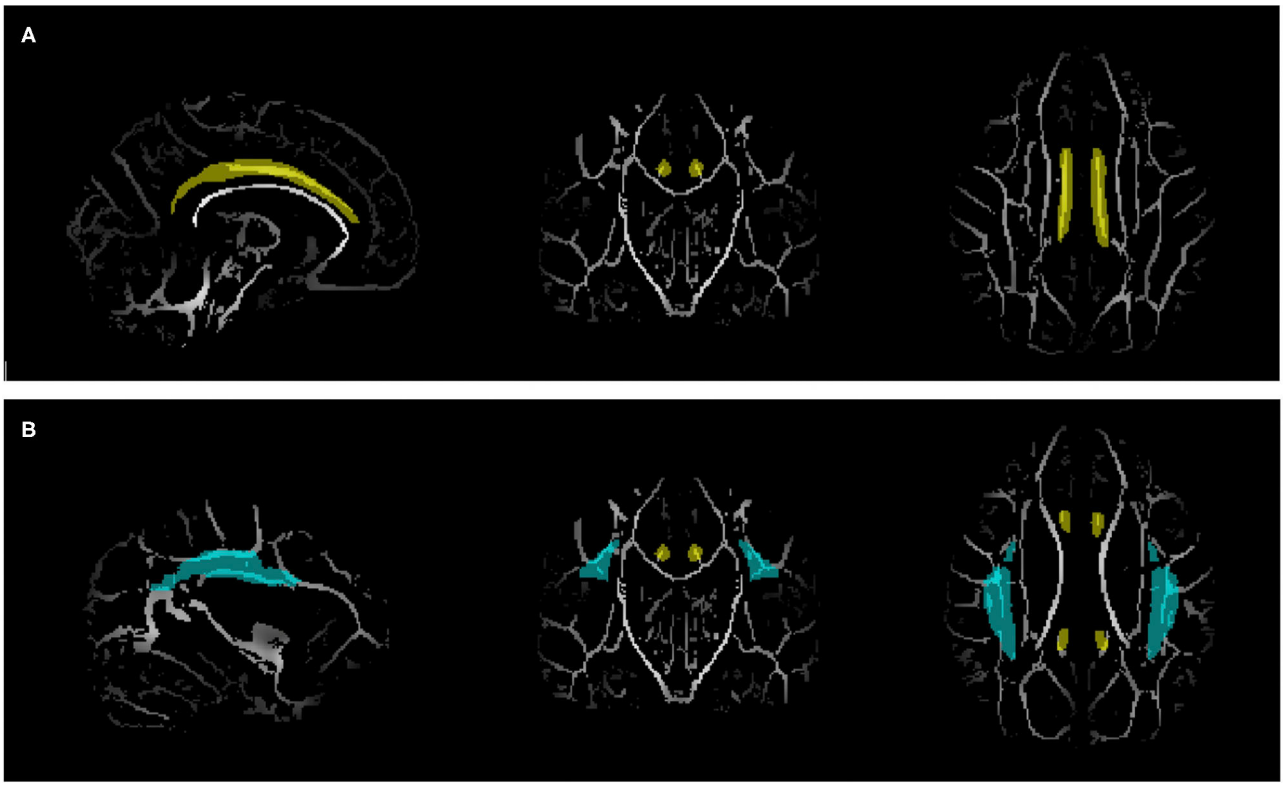

FIGURE 1 | Region of interest (ROI) masks obtained from Johns Hopkins University ICBM-DTI-81 white-matter labels atlas overlaid on the white matter skeleton. **(A)** Cingulum (Yellow). **(B)** Superior longitudinal fasciculus (blue).

Region of Interest

To test the structural connectivity among the mentalizing network, two white matter tracts were selected as the regions of interest (ROI). The tracts included the left and right cingulum, which pass through the PFC and precuneus, and the left and right SLF, which pass through the mPFC and TPJ. The ROI masks were obtained from Johns Hopkins University ICBM-DTI-81 white-matter labels atlas (40–42) (**Figure 1**).

DTI Processing

Voxel-wise statistical analysis was performed using tract-based spatial statistics (TBSS) in FSL (43, 44). First, a brain mask was generated as a pre-processing step. Then, all subjects' FA images were aligned into a 1 mm × 1 mm × 1 mm Montreal Neurological Institute (MNI) 152 space via FMRIB's Non-linear Image Registration Tool (FNIRT). The aligned images were all merged into a single 4D image file, and the mean FA image was created. A 4D image of the FA skeleton was generated from the mean FA with a threshold of 0.2.

Voxel-wise significant differences between the FEP and HC were investigated using the randomize tool in TBSS. Before processing, age, sex, and handedness were demeaned and fed into the design matrix and contrast file as covariates. The randomize was carried out with 5,000 permutations and threshold-free cluster enhancement (TFCE). The left and right cingulum and SLF masks were used as ROI masks. The threshold for significance was $p < 0.05$.

Statistical Analysis

The age, sex, and handedness of the final set of subjects were tested to determine whether the variables matched between the groups. The normality of the ToM task scores (e.g., false belief and strange story) was verified, and the scores were compared between the groups via the Mann-Whitney test.

To explore the correlation between ToM task results and the white matter integrity of ROIs, the individual mean FA of each ROI was acquired from 3D individual skeleton images. The individual images were obtained by splitting the 4D skeleton image, which was created from TBSS analysis. Correlation analyses were performed for each mean FA of the cingulum and SLF for both the left and right sides with the false belief and strange story. All statistical analyses were performed using SPSS, version 25 (IBM, Armonk, N.Y.).

RESULTS

Demographic Data

The demographic data of the subjects are presented in **Table 1**. There were no significant differences in the sex ratio, age, handedness, IQ, and education year between the FEP and HC groups.

TABLE 1 | Demographic and clinical characteristics of the subjects.

Variables	FEP patients	HCs	Statistics	
	($n = 35$)	($n = 28$)	χ^2, F or t	p
Age (years)	23.40 ± 5.76	21.68 ± 3.48	−0.612	0.543
Sex (male/female)	16/19	15/13	0.384	0.535
Handedness (right/left)†	30/5	26/2	0.804	0.370
IQ	98.11 ± 13.94	100.50 ± 10.63	0.748	0.458
Education (year)	13.26 ± 2.02	13.79 ± 1.89	−1.187	0.235
Parental SES score	2.71 ± 0.86	2.79 ± 0.63	4.28	0.233
PANSS total	68.54 ± 12.00			
PANSS positive	16.23 ± 4.61			
PANSS negative	17.63 ±4.64			
PANSS general	34.69 ± 6.80			
GAF	47.8 ± 11.31			
HAM-D	10.54 ± 4.83			
Olanzapine equivalent dose of antipsychotics (mg/day)	9.07 ± 8.54			

Data are given as the mean ± S.D.
† Classified using Annett Hand Preference Questionnaire.
FEP, first-episode psychosis; HC, healthy control; SES, socioeconomic status; PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning; HAM-D, Hamilton Depression Rating Scale.

TABLE 2 | Theory of mind task results.

Variables	FEP patients	HCs	Statistics	
	($n = 35$)	($n = 28$)	Z	p
False belief task	7.54 ± 2.24	9.68 ± 2.21	−3.506	0.000
Strange story task	20.06 ± 2.84	22.75 ± 1.65	−4.049	0.000

Data are given as the mean ± S.D.
FEP, first-episode psychosis; HC, healthy control.

Theory of Mind Task Scores

The Mann-Whitney test revealed significant group differences in the two ToM task scores (**Table 2**). FEP patients exhibited significantly worse performance than HCs in the false belief task ($z = -3.506$, $p < 0.001$) and strange story task ($z = -4.049$, $p < 0.001$). The ToM task results are presented in **Figure 2**.

TBSS Data and Correlations

TBSS analysis showed no significant voxel-wise difference in any of the ROI regions between FEP and HC groups. To explore the relationship between ToM and white matter integrity, correlational analyses were performed. The results, presented in **Figure 3**, showed a significant positive correlation between the FA value of the left cingulum and strange story task scores in FEP patients ($r = 0.35$, $p = 0.039$). Also, a significant positive correlation was observed between the FA value of the left SLF and the scores of the strange story task ($r = 0.374$, $p = 0.027$) in FEP patients. No correlation was found between the FA values and false belief scores in FEP patients. There was no significant correlation among the FA values and any ToM task in HCs.

DISCUSSION

The present study was designed to explore the structural basis of theory of mind (ToM) deficits in schizophrenia. To the best of our knowledge, this is the first attempt to demonstrate the relationship between white matter integrity and ToM in first-episode psychosis (FEP). The results of the false belief task and strange story task showed that the patients with FEP had impaired ToM abilities. The correlation analysis revealed positive associations between the integrity of left ROIs and ToM deficits in FEP patients. However, this correlation was not observed in the healthy controls (HCs). These findings underscore the crucial roles of the left cingulum and left SLF as the structural basis of impaired ToM abilities in FEP.

ToM Abilities in FEP

The ToM task results were consistent with previous studies that showed decreased ToM performance in FEP patients (5, 45, 46). In this study, two verbal ToM tasks–the false belief task and strange story task–were conducted. The false belief task is the most heavily researched ToM task and is used to assess participants' ability to understand others' mental states, such as thoughts and intentions. The strange story task, invented to measure higher-order ToM, is employed to evaluate the ability to infer not only the thoughts or intentions but also the emotions of others in complex naturalistic situations (38). In the false belief task, FEP patients scored significantly lower than healthy controls, suggesting that the patients have an impaired ability to recognize others' mental states. Similar to the false belief results, the strange story scores of FEP patients were also significantly lower than those of HCs, suggesting the difficulties patients have in inferring others' mental states and emotions in complex situations. These results are in line with previous findings showing ToM deficits as a distinctive feature of schizophrenia, which is found not only in chronic patients but also in the early course of the disease and even in remission (12, 14, 47). As previous meta-analysis studies have suggested, these ToM impairments may be related to the functional outcome of the patients and could be able to predict prognosis (1, 9, 11).

White Matter Integrity and ToM Abilities

The two ROIs–the cingulum and SLF–were selected based on the atlas-listed white matter tracts that are reported to connect the nodes of the mentalizing network; the mPFC, TPJ, and precuneus/PCC. Our results suggest that the integrity of these white matter ROIs are positively correlated with the strange story task performance in FEP. The correlations were maintained in significant level ($p < 0.05$) even after controlling age and olanzapine equivalent antipsychotic doses (**Supplementary Tables 3**, **5**). This finding is in line with recent DTI studies in healthy children and other patient groups reporting that ToM abilities were associated with the integrity of the cingulum and SLF (31–33, 48).

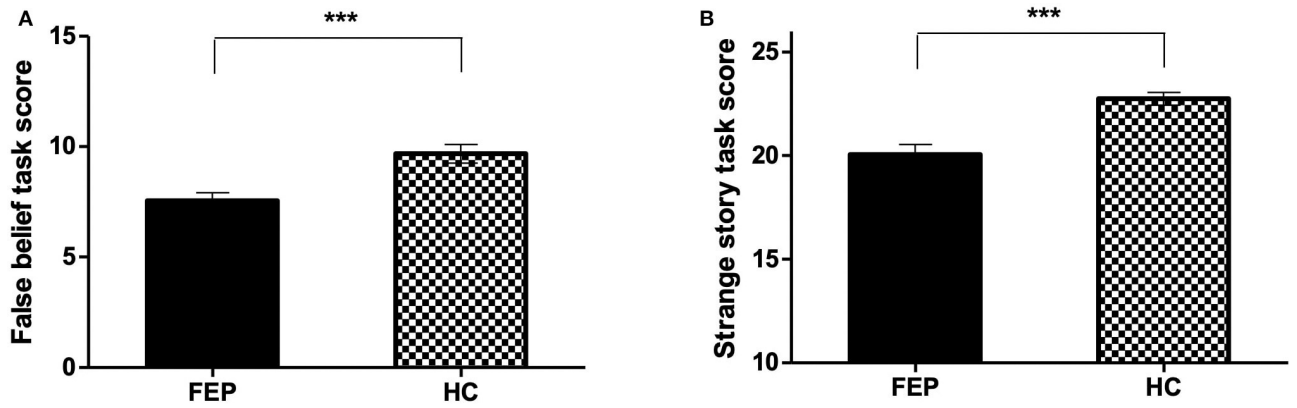

FIGURE 2 | Individual scores of theory of mind tasks (false belief task, strange task) tested using Mann-Whitney. **(A)** False belief scores of FEP patients and HCs ($Z = -3.506$, $p < 0.001$). **(B)** Strange story scores of FEP patients and HCs ($Z = -4.049$, $p < 0.001$). FE, first-episode psychosis; HC, healthy control. $^{***}P \leq 0.001$.

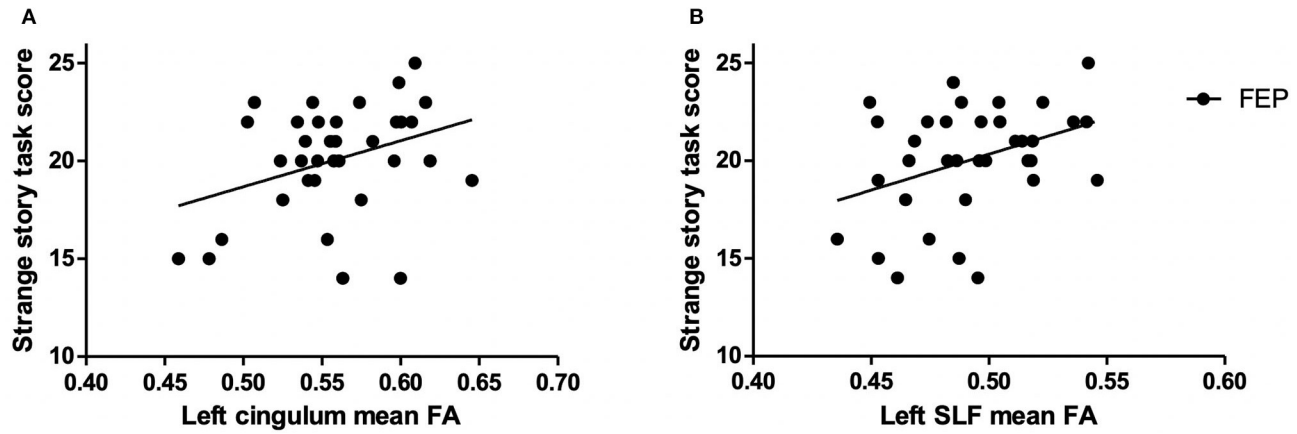

FIGURE 3 | Correlations between the mean fractional anisotropy (FA) values and the strange story task score in first-episode psychosis (FEP) patients. **(A)** The mean FA of the left cingulum and the strange story score ($r = 0.350$; $p = 0.039$). **(B)** The mean FA of the left superior longitudinal fasciculus (SLF) and the strange story score ($r = 0.374$; $p = 0.027$).

The cingulum is an association fiber tract that starts from the mPFC and passes through the PCC and precuneus. More precisely, a probabilistic tractography study has revealed that among the listed tracts in the atlas, the cingulum overlaps with 62.59% of the dorsomedial pre-frontal cortex (dmPFC)–PCC fibers and 92.01% of the ventromedial pre-frontal cortex (vmPFC)–PCC fibers (17). The cingulum is known to be involved in attention, memory, and emotional processing (49, 50) and has been postulated as a major white matter tract comprising the mentalizing network (31). In schizophrenia, decreased FA in the cingulum has been reported in both chronic and FEP patients (51–55) and has been linked to both positive and negative symptoms and decreased neurocognition (56, 57).

The SLF is a large association fiber bundle that connects the parietal, occipital and temporal lobes with the frontal cortex (58, 59). The SLF is a core structure involved in attention, memory, language, and emotions (60–63). According to a probabilistic tractography study, 45% of fibers between the dmPFC and TPJ overlap with the SLF (17). Similar to the cingulum, abnormalities in the SLF have been observed in schizophrenia (64–66) and in association with symptoms and neurocognition (67, 68). Along with our results, the abovementioned observations provide converging evidence that the cingulum and SLF are key structures underlying the symptoms and both social and non-social cognitions of schizophrenia.

In this study, only the strange story task scores that reflect higher order ToM were correlated with white matter integrity in FEP patients. According to previous research, complex and higher-order ToM continues to mature until adulthood (47, 69, 70). Several imaging studies have demonstrated neural activations and brain structures related to higher-order ToM change throughout adolescence (71–73). This evidence suggests that the correlation between strange story scores and white matter may reflect an abnormal developmental trajectory of higher-order ToM and related white matter structures in schizophrenia. These findings corroborate the

neurodevelopmental hypothesis of schizophrenia (74, 75) and could offer insight into the pathophysiology of the disease, especially focusing on the prodromal stage and early phase.

In contrast to the results of FEP patients, no correlation between the ToM task scores and WM integrities were found in HCs. There can be several reasons for this. First, the homogeneity of the HC group could have led to smaller intragroup variations of the task scores. It is known that age and education level are associated with theory of mind ability (76) but those factors were strictly controlled in this study. Second, it is possible that HCs are less dependent on the direct white matter pathways connecting the mentalizing network regions. Instead, they could use various direct and indirect structural connections among distal brain regions to subserve ToM ability since their neural structures are relatively intact compared to schizophrenia patients. Conversely, schizophrenia patients may utilize large white matter bundles such as cingulum and SLF for ToM process due to the extensive neural degeneration. To specify the association of white matter structures and ToM ability in healthy participants, further research is needed with other ToM task modalities, such as "reading the mind in the eyes" test and subjects with different conditions.

Another finding of the study is that only the left ROIs showed correlation with the ToM task scores in FEP patients. This result matches with the studies of children with traumatic brain injury and patients with surgical resection for diffuse low-grade glioma that reported associations between the left cingulum and ToM abilities (33, 77). These observations suggest that the key white matter structures underlying ToM deficits in FEP may be lateralized to the left hemisphere. However, several studies have indicated that the bilateral or right cingulum is related to ToM abilities (31, 78). Such inconsistency is also evident in findings related to the SLF (32, 48, 78–81).

Despite the inconsistent results, there are studies that have proposed the right SLF may play a crucial role in ToM abilities, while the left contributes mainly to language processing (78, 82). This argument is in contrast to our findings, which showed a relation between the left SLF and ToM ability in FEP patients. There are several possible explanations for this discrepancy. First, different subject groups may result in different outcomes. The "right social brain" argument was developed based on studies of healthy participants and brain damaged patients. However, multiple fMRI studies in schizophrenia and FEP patients have reported bilateral abnormalities in ToM networks (21, 83, 84). This observation suggests that the association between white matter and ToM in schizophrenia may be different than that in other groups.

In addition, the laterality difference between other subject groups and FEP patients may reflect Crows' lateralization hypotheses of schizophrenia (85). Numerous studies have indicated reduced or altered asymmetry in both brain functional connectivity and structures in schizophrenia patients (86, 87), and such alterations are also found in FEP patients (68, 85). These abnormalities in brain asymmetry and functional outcomes are related to developmental problems and the laterality changes in accordance with age (88). Therefore, factors such as the age of onset are closely related to abnormal brain asymmetry (89). Along with the variance in ToM task modalities and heterogeneity among FEP groups, altered or reduced brain asymmetry may have affected the results differently. Since this is the first attempt to investigate the specific white matter structure underlying ToM deficits in schizophrenia, future studies will be necessary to provide reliable evidence on the structural basis of ToM impairment.

Limitations

Several limitations must be taken into consideration when interpreting the present results. First, no significant differences in FA values between FEP patients and HCs were found in this study. Several DTI studies have reported that the arcuate fasciculus, SLF, and cingulum are intact in FEP patients (90–92), while others have reported white matter alterations in the SLF and cingulum (54, 65). Such inconsistencies may reflect the heterogeneity of the FEP subjects. Symptoms, medications, age of onset, treatment intervention, and other factors may affect white matter changes differently. Additionally, if abnormal structures in FEP patients were located in small sub regions within the cingulum or SLF, the ROI-based TBSS approach would not be able to detect these abnormalities. Since the cingulum and SLF are widely distributed fiber tracts connecting various distal brain regions, averaging the FA values across the whole ROI risks losing some valuable information. To address these issues and to define precise fiber tracts related to impaired ToM in FEP, a probabilistic tractography analysis while controlling the covariates would be necessary in future studies. Second, unlike previous studies the FEP patients in this study were on antipsychotics at the time of scanning and ToM measurements. Antipsychotics are known to be associated with structural alteration in brain (93). However, there was no correlation between olanzapine equivalent antipsychotic doses of the FEP patients and their FA values of white matter ROIs in this study (**Supplementary Table 2**). Also, the additional partial correlational analysis revealed that the positive correlations between higher order ToM and left cingulum and left SLF were maintained in significant level ($p < 0.05$) even after controlling the effect of antipsychotics. Although, given the previous studies that antipsychotics are associated with white matter alteration (94), it may be beneficial to investigate the relationship between white matter and ToM in drug-naïve FEP patients in future studies.

CONCLUSION

Our study was the first to demonstrate the association between FA values in two white matter tracts, the cingulum and the SLF, and ToM ability in FEP patients. This white matter study using DTI methods extends our insight into the neural basis of ToM and suggests that the left cingulum and SLF are vital structures underlying the impairment of ToM in schizophrenia.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Academic Affairs Institutional Review Board Seoul National University Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

NK: conceptualization, methodology, software, validation, formal analysis, investigation, data curation, writing–original draft, writing–review and editing, and visualization. TL: conceptualization, methodology, validation, writing–review and editing, and supervision. WH: conceptualization, methodology, and writing–review and editing. YK: software and writing–review and editing. SK: validation, investigation, and writing–review and editing. S-YM: investigation and writing–review and editing. SL: investigation and writing–review and editing. SO: investigation and writing–review and editing. JK: conceptualization, writing–review and editing, resources, supervision, project administration, and funding acquisition. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.617683/full#supplementary-material

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REVIEW
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Neuroimaging as a Window Into the Pathophysiological Mechanisms of Schizophrenia

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Schizophrenia is a complex neuropsychiatric disorder with a diverse clinical phenotype that has a substantial personal and public health burden. To advance the mechanistic understanding of the illness, neuroimaging can be utilized to capture different aspects of brain pathology *in vivo*, including brain structural integrity deficits, functional dysconnectivity, and altered neurotransmitter systems. In this review, we consider a number of key scientific questions relevant in the context of neuroimaging studies aimed at unraveling the pathophysiology of schizophrenia and take the opportunity to reflect on our progress toward advancing the mechanistic understanding of the illness. Our data is congruent with the idea that the brain is fundamentally affected in the illness, where widespread structural gray and white matter involvement, functionally abnormal cortical and subcortical information processing, and neurometabolic dysregulation are present in patients. Importantly, certain brain circuits appear preferentially affected and subtle abnormalities are already evident in first episode psychosis patients. We also demonstrated that brain circuitry alterations are clinically relevant by showing that these pathological signatures can be leveraged for predicting subsequent response to antipsychotic treatment. Interestingly, dopamine D2 receptor blockers alleviate neural abnormalities to some extent. Taken together, it is highly unlikely that the pathogenesis of schizophrenia is uniform, it is more plausible that there may be multiple different etiologies that converge to the behavioral phenotype of schizophrenia. Our data underscore that mechanistically oriented neuroimaging studies must take non-specific factors such as antipsychotic drug exposure or illness chronicity into consideration when interpreting disease signatures, as a clear characterization of primary pathophysiological processes is an imperative prerequisite for rational drug development and for alleviating disease burden in our patients.

Keywords: pharmacological challenge, treatment response, duration of untreated psychosis, functional MRI, magnetic resonance spectroscopy, diffusion weighted imaging, first episode psychosis, antipsychotic naïve

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INTRODUCTION

Schizophrenia is a complex neuropsychiatric disorder with a diverse clinical phenotype that manifests in variable levels of positive and negative symptoms and cognitive impairment. Even though the course of the illness can be variable, for many patients the disease is chronic and debilitating, resulting in a substantial personal and public health burden (1). Available pharmacological interventions can alleviate positive symptoms, but effective treatments across symptom dimensions are lacking and a cure remains elusive. This can in part be attributed to the gaps in the knowledge of the underlying brain pathology. To close these gaps, tremendous efforts geared toward elucidating key pathophysiological brain signatures and at advancing our mechanistic understanding of the illness are undertaken with the ultimate goal to lower disease burden and improve long-term outcomes for patients.

Neuroimaging offers versatility in terms of capturing different aspects of brain pathology *in vivo*, including brain structural integrity deficits, functional dysconnectivity, and altered neurotransmitter systems, positioning the field well to contribute to the discovery of clinically relevant biological processes in schizophrenia. The first mechanistic discovery studies utilizing neuroimaging date back to the 1970s and 80s, when ventricular enlargement was described as a potential diagnostic marker (2–4). Since these early studies, the field has grown exponentially; more than 16,000 neuroimaging manuscripts in schizophrenia spectrum disorder patients have been published (**Figure 1**). Even though major strides toward delineating relevant pathophysiological processes have been made, progress in the field has been impeded by a number of confounding factors that make interpretation of data difficult. This ultimately hampers the development of a comprehensive explanatory model capturing the complex underlying pathophysiology and integrating findings from diverse imaging modalities. Two principal confounding variables need to be considered when interpreting neuroimaging studies. These are antipsychotic medication exposure and illness chronicity, which impact virtually all imaging measures. This has resulted in a debate to what extent brain imaging alterations reported in schizophrenia studies reflect primary disease pathology (5). To make further progress, it is imperative to disentangle confounding effects from illness specific brain signatures. Investigating the impact of antipsychotic medications in longitudinal brain imaging studies and studying patients in the early illness stages who have had no prior antipsychotic medication exposure affords the opportunity to characterize antipsychotic drug action, mitigate confounds and gain a more in depth understanding of the nature of the illness.

Our group's work has been dedicated to contribute to the efforts in delineating the schizophrenia pathophysiology and in disentangling disease signatures from those of antipsychotic medications and disease chronicity. In the following paragraphs, we discuss a number of key scientific questions and take the opportunity to reflect on our progress toward advancing the mechanistic understanding of the illness.

KEY SCIENTIFIC QUESTIONS IN NEUROIMAGING RESEARCH IN SCHIZOPHRENIA

What Can We Learn From Longitudinal Neuroimaging Studies That Investigate Antipsychotic Drug Effects?

Antipsychotic medications are the cornerstone of treating patients with schizophrenia spectrum disorders. They principally act on the dopamine D2 receptors (6), but also modulate a number of other neurotransmitter systems (7, 8), affect receptor expression profiles, have downstream effects on protein synthesis (9), and impact brain plasticity (9). Given the complexity of antipsychotic drug action, it is plausible that molecular imaging geared at investigating the dopamine system and other imaging markers are impacted by these medications. Longitudinal brain imaging studies that contrast neural signatures in the same patients before and after they are treated can shed light on modulatory effects of antipsychotic medications on brain structure, function and neurochemistry [for reviews of the larger field, see (10–15)]. We have conducted several studies utilizing different imaging techniques to broadly characterize antipsychotic drug effects on neural signatures (**Table 1**).

Our structural imaging studies show mixed results in terms of antipsychotic medication effects. We observed antipsychotic medication related changes in cortical thickness (17), but not in white matter microstructural integrity or radial fiber trophy (a surrogate marker for white matter volume) (18, 19). The disparity in effects across tissue classes is perhaps not surprising, given the different anatomical, functional and neurochemical makeup of these tissues. For example, brain derived neurotrophic factor (BDNF) is a neurotrophin that regulates synaptic plasticity (37, 38) and spine density (39). The 66met allele has been associated with diminished activity-dependent BDNF secretion (40) and decreased cortical volumes (41) but not with white matter integrity in healthy subjects (42). BDNF also is found to be abnormally low in schizophrenia (43) and can be increased by second generation antipsychotics (44). It is therefore possible that antipsychotic medication related modulation of BDNF results in alleviation of dendritic deficits in the outer layers of the cortex (45), which would be reflected in an increase in cortical thickness, but not white matter integrity. Alternatively, it is possible that the acute gray matter tissue response can be captured at the time scale at which we investigated structural changes, but the duration is not sufficient to demonstrate subtle changes in white matter architecture and microstructure that may become more evident with longer duration of antipsychotic treatment.

Our longitudinal task based and resting state functional neuroimaging studies consistently show changes associated with antipsychotic drugs at different time scales, ranging from a single dose drug administration to several weeks of treatment. Our findings are in agreement with drug challenge studies in healthy subjects demonstrating that dopamine antagonism affects brain function (46) and animal studies showing that antipsychotics can be used to restore cortical synchronization and functional connectivity after disruption with hallucinogenic

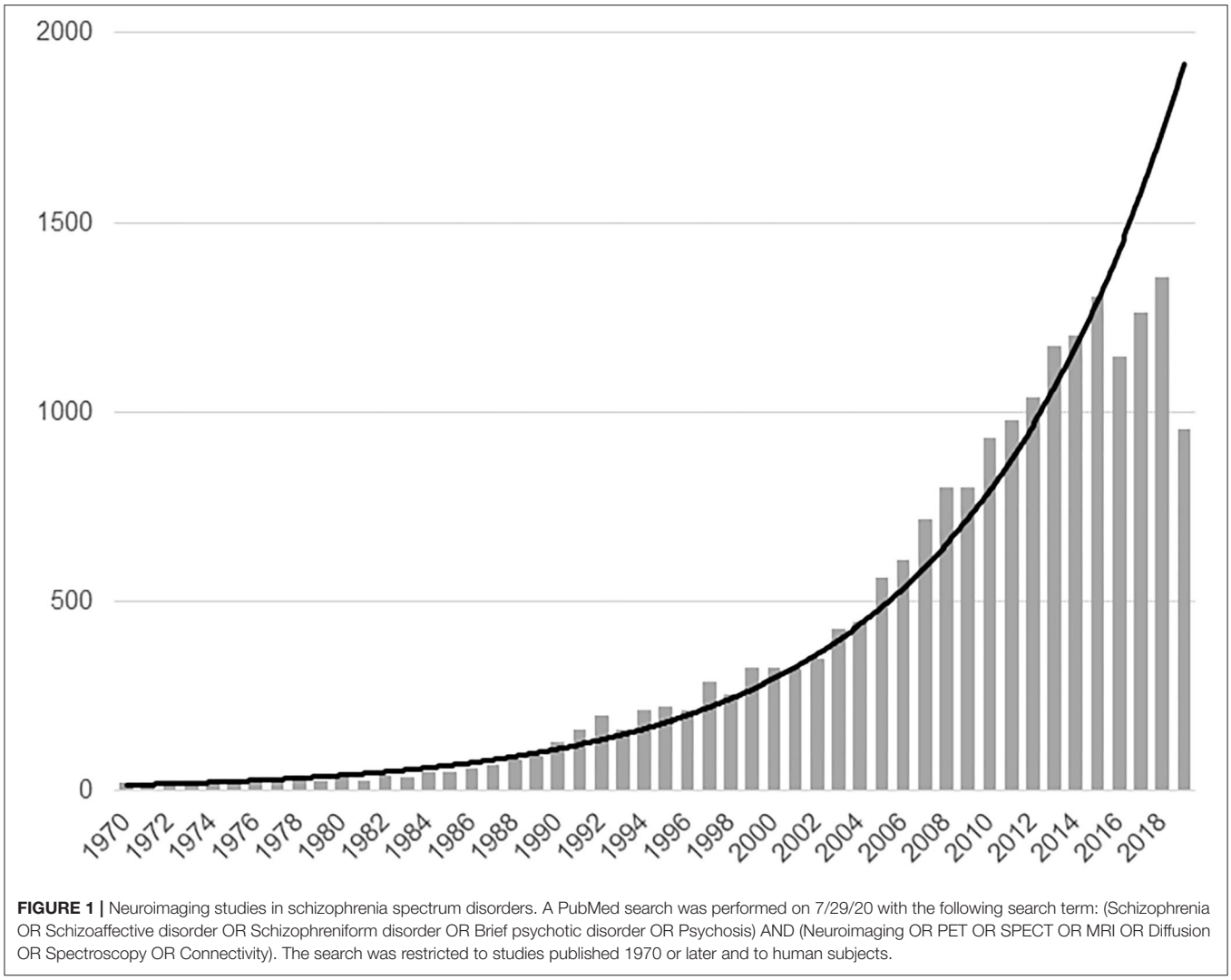

FIGURE 1 | Neuroimaging studies in schizophrenia spectrum disorders. A PubMed search was performed on 7/29/20 with the following search term: (Schizophrenia OR Schizoaffective disorder OR Schizophreniform disorder OR Brief psychotic disorder OR Psychosis) AND (Neuroimaging OR PET OR SPECT OR MRI OR Diffusion OR Spectroscopy OR Connectivity). The search was restricted to studies published 1970 or later and to human subjects.

agents (47, 48). When interpreting our functional data in context of differences between patients and healthy controls, we show that antipsychotic treatment appears to, at least partially, restore abnormal brain function to levels that are more similar to those of healthy controls. We also observed a recurring theme of brain regions that are functionally modulated by antipsychotic treatment. Relevant areas include the anterior cingulate cortex, medial prefrontal cortex, hippocampus, caudate and putamen. This suggests that cortico-striatal circuitry may be functionally remodeled by antipsychotic medications. Interestingly, anterior cingulate and medial frontal cortex function (35, 49–52) and cortico-striatal connectivity have also been identified as critical for antipsychotic drug action by other groups (53, 54). When examining brain function on a more global level, we found that antipsychotic medications affect brain network topology, i.e., global efficiency and clustering, but not dynamic connectivity states (26, 29), which is consistent with the idea that antipsychotic medications partially but not fully restore abnormal brain function.

In our magnetic resonance spectroscopy studies, we unexpectedly did not find changes with antipsychotic medications on glutamate levels. Several lines of evidence describe complex interactions between the dopamine and glutamate systems and identify glutamate receptor complexes as potentially important indirect targets for dopamine D2 receptor blockers (55–57), suggesting antipsychotic medications may affect glutamate levels. A number of prior studies report a decrease of glutamate in the temporal lobe (58), striatum, and the anterior cingulate cortex (59), though the group failed to replicate the latter in a subsequent report (60). It is possible that this discrepancy is due to differential effects of various antipsychotic medications on the glutamate system. Alternatively, risperidone may affect glutamate levels only in a subset of patients, or the shifts in glutamatergic neurotransmission may be too subtle to be captured with magnetic resonance spectroscopy, which measures tissue metabolites rather than compartment specific levels.

Our data also suggest that heterogeneity in the patient population may need to be taken into account when examining

TABLE 1 | Neuroimaging studies of antipsychotic drug effects from by the authors.

Authors	Year	n (HC/SZ)	Treatment duration	Imaging marker	Region of interest	Baseline group differences	Effects of antipsychotic treatment on imaging marker
Structural MRI							
Nelson et al. (16)	2018	23/37	6 weeks	Graph theory measures	Whole brain	HC< SZ in clustering, local efficiency and modularity	Baseline group differences in clustering, local efficiency, and modularity were no longer present after antipsychotic treatment
Nelson et al. (17)	2020	23/34	6 weeks	Cortical thickness, local gyrification index	Whole brain	HC> SZ in cortical thickness in the left brain hemisphere and global gyrification. HC> SZ in gyrification in the inferior frontal cortex, temporal cortex, insula, pre/postcentral gyri, temporoparietal junction, and supramarginal gyrus	Greater increase in cortical thickness after treatment was associated with a more favorable clinical response to treatment
Diffusion imaging							
Kraguljac et al. (18)	2019	42/42	6 weeks	Fractional anisotropy, mean diffusivity, radial diffusivity, radial fiber trophy	Whole brain	HC> SZ in fractional anisotropy in the medial temporal white matter, SZ> HC in mean diffusivity in the cingulum bundle	No change in microstructural diffusion indices or radial fiber trophy (surrogate marker of white matter volume)
Kraguljac et al. (19)	2019	42/42	6 weeks	Orientation dispersion index, extracellular free water	Whole brain	HC< SZ in orientation dispersion	No change in diffusion indices
Task fMRI							
Hutcheson et al. (20)	2015	20/21	1 week	BOLD response (episodic memory retrieval task), effective connectivity	11 regions of interest	HC< SZ in BOLD response in the middle cingulate gyrus during successful memory retrieval. HC> SZ in six effective connectivity paths, within frontal nodes, fronto-temporal projections and posterior to frontal projections. HC< SZ in four effective connectivity paths	Decrease in BOLD response in the middle frontal gyrus, postcentral gyrus, precuneus, superior parietal lobule, angular gyrus, and caudate. For effective connectivity, the number of edges increased after treatment. Five paths, within the frontal nodes, and frontal to posterior projections showed lesser connectivity after treatment, whereas 19 paths showed greater connectivity after treatment
Cadena et al. (21)	2018	20/22	6 weeks	BOLD response (Stroop task)	Whole brain	HC> SZ BOLD response in the ACC, caudate, putamen and midbrain	Increase in BOLD response in the ACC and caudate, decrease in BOLD response in the putamen, and midbrain
Cadena et al. (22)	2018	20/22	6 weeks	BOLD response (Stroop task)	Whole brain	HC> SZ BOLD response in the salience network and posterior default mode network	
Cadena et al. (23)	2019	20/22	6 weeks	Functional connectivity	Fronto-striatal network	HC< SZ in connectivity between the ACC, caudate and midbrain, HC> SZ between ACC and putamen	Decrease in connectivity between ACC, putamen, midbrain, and caudate
Gurler et al. (24)	2020	17/17	6 weeks	BOLD response (episodic memory encoding task)	Whole brain	HC> SZ in BOLD response in the right insula, hippocampus, inferior frontal and temporal cortex. SZ> HC in BOLD response in the PCC and precuneus	Increase in BOLD response in the hippocampus

(Continued)

TABLE 1 | Continued

Authors	Year	n (HC/SZ)	Treatment duration	Imaging marker	Region of interest	Baseline group differences	Effects of antipsychotic treatment on imaging marker
Resting state fMRI							
Hadley et al. (25)	2014	21/21	1 week	Seed based functional connectivity, fALFF	Ventral tegmental area/midbrain (connectivity), whole brain (fALFF)	HC> SZ VTA connectivity to the ACC, superior, middle and inferior frontal gyri, insula, precuneus, inferior parietal cortex, thalamus, hippocampus, caudate, putamen and cerebellum. HC> SZ in fALFF in the ACC, MPFC, precuneus, PCC. HC< SZ in fALFF in the cerebellum	Ventral tegmental area/midbrain connectivity to the thalamus increased after treatment. fALFF increased in the dorsolateral prefrontal cortex and fronto-insular regions after treatment
Hadley et al. (26)	2016	32/32	6 weeks	Graph theory measures	Whole brain	HC< SZ in global clustering. HC> SZ in global efficiency	Global clustering decreased in good but not poor treatment responders. Global efficiency decreased in good but not poor responders
Kraguljac et al. (27)	2016	34/34	6 weeks	Seed based functional connectivity	Anterior and posterior hippocampus	HC< SZ in left anterior hippocampus connectivity with areas of the default mode network. HC> SZ in right anterior hippocampus connectivity to the PCC, precuneus, calcarine sulcus. HC> SZ in right posterior hippocampus connectivity to the ACC, supplemental motor cortex, inferior parietal cortex, PCC and precuneus	After treatment, connectivity between the right posterior hippocampus, ACC, and caudate increased, right anterior and posterior hippocampus connectivity to the lingual gyrus increased. Right anterior hippocampus connectivity to the auditory cortex and caudate decreased. Left anterior and posterior hippocampus connectivity to the auditory cortex decreased
Kraguljac et al. (28)	2016	34/34	6 weeks	Seed based functional connectivity	DMN, ECN, SN and DAN	HC< SZ in the ECN, SN, and DAN	DAN connectivity decreased after treatment
Lottman et al. (29)	2017	35/34	1 week, 6 weeks	ICA based static and dynamic functional connectivity	whole brain	HC< SZ within network connectivity in the cognitive control network and mixed increase and decrease in between network connectivity for static connectivity. SZ> HC in subcortical and somato-motor network connectivity in some instances in the sparsely connected state in dynamic connectivity	No change in static or dynamic connectivity after 1 or 6 weeks of treatment, respectively
MRS							
Cadena et al. (22)	2018	20/22	6 weeks	Glx	ACC	HC> SZ in Glx	No change in neurometabolites
Kraguljac et al. (30)	2019	31/61	6 weeks	Glx, NAA, Cho	ACC, hippocampus	HC< SZ in hippocampus Glx	No change in neurometabolites
Birur et al. (31)	2020	22/29	6 weeks, 16 weeks	Glx, NAA, Cho, Cr	MPFC	No group differences	No change in neurometabolites
PET							
Lahti et al. (32)	2003	0/6	12+/10 weeks (HAL); 23±12 weeks (CLOZ)	rCBF	Whole brain	Not applicable	HAL and CLOZ increased rCBF in the ventral striatum and decreased rCBF in hippocampus and ventrolateral frontal cortex. The rCBF increase associated with HAL was greater than that with CLOZ in the dorsal and ventral striatum; the rCBF increase with CLOZ was greater than that with HAL in cortical regions, including the ACC and dorsolateral frontal cortex

(Continued)

TABLE 1 | Continued

Authors	Year	n (HC/SZ)	Treatment duration	Imaging marker	Region of interest	Baseline group differences	Effects of antipsychotic treatment on imaging marker
Lahti et al. (33)	2004	12/6	12+/10 weeks (HAL); 23 ± 12 weeks (CLOZ)	rCBF	ACC	HC< SZ in rCBF during sensory motor control task HC> SZ in rCBF during decision task. No group differences at rest	CLOZ, but not HAL, reversed the abnormal ACC rCBF pattern in unmedicated patients
Lahti et al. (34)	2005	0/12	single dose	rCBF	Whole brain	Not applicable	rCBF increased in the striatum, thalamus, and ACC but decreased in frontal, temporal, and cerebellum regions after single dose HAL. rCBF increased in the ventral striatum, ACC, and temporal cortex but decreased in the thalamus and lingual cortex after single dose olanzapine. Both drugs activated the caudate nucleus
Lahti et al. (35)	2009	0/29	1 week, 6 weeks	rCBF	Whole brain	Not applicable	After 6 weeks of treatment both HAL and olanzapine increased rCBF in the pre- and post-central cortex, ventral striatum, and caudate, and decreased rCBF in the anterior cingulate and medial frontal cortex
Bolding et al. (36)	2012	0/29	1 week, 6 weeks	rCBF, functional connectivity	Whole brain, ROI analysis	Not applicable	rCBF increased in the striatum and decreased in the MPFC after 1 week of treatment. rCBF increased in the thalamus and decreased in the putamen, hippocampus, and middle frontal cortex between week one and six of treatment. Functional connectivity between the middle frontal cortex and nucleus accumbens increased after 1 week of treatment, connectivity between the middle frontal cortex and hippocampus decreased after 6 weeks of treatment
Multimodal imaging							
Cadena et al. (22)	2018	20/22	6 weeks	ACC Glx, BOLD response (Stroop task)	Whole brain	Glx and BOLD response in the salience network and posterior default network correlated in HC but not SZ at baseline	After treatment, the relationship between Glx and BOLD response changed direction in both groups
Gurler et al. (24)	2020	17/17	6 weeks	hippocampus Glx, BOLD response (memory encoding task)	Whole brain	In SZ but not in HC, hippocampal Glx and BOLD response the posterior DMN correlated. The relationship between BOLD signal in the DMN and hippocampal Glx was significantly different between groups	After treatment, the correlation between Glx and BOLD response was not significant and was not significantly different from HC

ACC, anterior cingulate cortex; BOLD, Blood oxygen dependent level: Cho, choline; CLOZ, clozapine; Cr, Creatine; DAN, dorsal attention network; DMN, default mode network; ECN, executive control network; fALFF, fraction of the amplitude of low frequency fluctuations; Glx, glutamate+glutamine; HAL, haloperidone; HC, Healthy control; ICA, independent component analysis; MPFC, medial prefrontal cortex; NAA, N-acetyl-aspartate; PCC, posterior cingulate cortex; rCBF, regional cerebral blood flow; ROI, region of interest; SN, salience network; SZ, patients with schizophrenia.

antipsychotic medication related changes in neural signatures. We demonstrated in several studies that changes in brain structure and function following antipsychotic treatment may be more prominent in patients with a favorable clinical response, compared to those who show little improvement with medications (17, 26, 27). It is tempting to speculate that the variability in modulatory effects of antipsychotics is reflective of differences in brain pathology. It is possible that patients who respond favorably to medications do so because they still have actively destructive, yet reversible, neurobiological changes that can be ameliorated with antipsychotic treatment. In contrast, poor responders may be beyond the period of active deficit process formation in their brain and the pathological state becomes more permanent, rendering antipsychotic medications ineffective both on a clinical level and in reversing structural and functional brain injury. If that is the case, it should be possible to leverage neuroimaging data to aid in the prediction of response to antipsychotic treatment. Much of the work described here has been performed in patients who had prior antipsychotic medication exposure, and in mixed groups of antipsychotic medication-naïve patients previously medicated patients. Adequately powered longitudinal studies conducted in exclusively medication-naïve patients are direly needed to reduce the possible effects of illness chronicity and prior antipsychotic medication exposure on changes related to antipsychotic medication treatment.

Can Neuroimaging Data Aid in Predicting Subsequent Clinical Response to Antipsychotic Treatment?

The current strategy for management of psychosis spectrum disorders consists of sequential treatment with different antipsychotic medications based on trial and error. Unfortunately, it is not possible to predict how a patient will respond to treatment based on clinical assessments alone. To make progress in this context, we have conducted a number of studies geared toward characterizing neural signatures in unmedicated and antipsychotic medication-naïve patients that predict a subsequent favorable response to antipsychotic treatment (**Table 2**). Here, the ultimate goal is to realize the potential of neuroimaging in guiding treatment decisions based on the underlying brain pathology [for further review of the topic, see (63, 64)].

In structural imaging studies, we found that both gray and white matter integrity at baseline are predictive of subsequent response to antipsychotic treatment. Lower cortical thickness and greater basal ganglia volumes [basal ganglia volumes are increased in patients, possibly as a result of antipsychotic drug exposure (65)] are associated with better treatment response (17, 61). This suggests that greater baseline alterations in gray matter are indicative of a favorable clinical outcome. In contrast, greater alterations in whole brain fractional anisotropy, a non-specific marker of white matter integrity, and in whole brain orientation dispersion, a measure of fiber complexity, were associated with subsequent poor treatment response, suggesting that greater alterations in white matter are indicative of poor clinical outcomes (18, 19, 62).

Our functional neuroimaging studies, both positron emission tomography (PET) and functional MRI, found consistent associations between more intact brain function at baseline and a favorable subsequent response to antipsychotic medications. Here again we found a recurring theme of brain regions and networks that were relevant for clinical outcomes, specifically anterior cingulate cortex, hippocampus, thalamus, striatum and caudate, as well as the default mode network and dorsal attention network. Interestingly, we also found that the degree of normalization in brain function after 1 week of antipsychotic medication was predictive of clinical outcomes after 6 weeks of treatment (35, 36). Our data suggest that both baseline function and early functional changes may be important predictors of treatment response.

Our magnetic resonance spectroscopy studies investigated neurometabolite levels in the anterior cingulate cortex and the hippocampus (30). We found that N-acetyl-aspartate (NAA), a marker of neuronal health, in the anterior cingulate cortex and glutamate in the hippocampus at baseline were associated with response to risperidone after 6 weeks of treatment. At first glance, the association between low cortical NAA and good response to treatment appears counter-intuitive. It is striking, however, that greater alterations in both NAA and glutamate are linked to better treatment response. One could speculate that these features point toward an excitation/inhibition imbalance and a deprived neuronal state that is reversible by successful antipsychotic treatment.

Taken together, our studies suggest two groups of neuroimaging markers that are relevant for subsequent antipsychotic treatment response. The first is a set of markers for which greater abnormalities predict subsequent poor response to antipsychotic treatment. These markers are largely centered around the theme of brain connectivity, where greater abnormal functional connectivity and white matter integrity deficits are indicative of worse response to antipsychotic treatment. The second is a set of markers where greater abnormalities predict a favorable response to antipsychotic treatment. These markers include cortical thickness, subcortical brain volumes and neurometabolites levels. Abnormalities in these imaging features may signify a deprived neuronal state or a disequilibrium in the excitation/inhibition balance that may be reversible with successful antipsychotic treatment. Overall, our findings suggest that the brain is structurally and functionally "wired" in a way that does or does not favor response to antipsychotic medication treatment. However, based on these studies, it remains unclear if the neural signatures relevant for antipsychotic treatment response are also core features of the schizophrenia pathophysiology or not. To disentangle core illness features from confounds of antipsychotic medication exposure as well as illness chronicity, it is imperative to characterize neuroimaging signatures in antipsychotic medication-naïve first-episode psychosis patients.

TABLE 2 | Selected baseline neuroimaging markers that are relevant to the prediction of subsequent antipsychotic drug response.

Authors	Year	*n*	Illness stage	Duration of treatment	Imaging marker	Association between baseline imaging findings and subsequent antipsychotic treatment response
Structural MRI						
Hutcheson et al. (61)	2014	23	mixed	6 weeks	Regional subcortical brain volume	Higher volumes of the caudate, putamen, and pallidum predicts better antipsychotic treatment response.
Nelson et al. (17)	2020	34	Mixed	6 weeks	Cortical thickness, local gyrification index	Lower cortical thickness in the prefrontal cortex, pre- and post-central gyri, cingulate, and insula is associated with favorable subsequent response to treatment. Gyrification index is not predictive of treatment response.
Diffusion imaging						
Kraguljac et al. (62)	2020	66	First episode	16 weeks	Fractional anisotropy, mean diffusivity, radial diffusivity, axial diffusivity	Lower whole brain baseline fractional anisotropy predicts poorer antipsychotic treatment response.
Kraguljac et al. (19)	2019	42	Mixed	6 weeks	Orientation dispersion index, extracellular free water	Higher baseline whole brain orientation dispersion index predicts poorer antipsychotic treatment response.
Task fMRI						
Cadena et al. (22)	2018	22	Chronic	6 weeks	BOLD response (Stroop task)	Greater BOLD response in the striatum and midbrain predicts better antipsychotic treatment response.
Cadena et al. (23)	2019	22	Chronic	6 weeks	Functional connectivity	Greater connectivity between the ACC and putamen predicts better antipsychotic treatment response.
Resting state fMRI						
Hadley et al. (25)	2014	21	Mixed	1 week, 6 weeks	Seed based functional connectivity of the ventral tegmental area, whole brain fALFF	Baseline ventral tegmental area connectivity to the dorsal ACC and supplemental motor cortex was positively correlated with treatment response. Baseline connectivity between the ventral tegmental area and the DMN was negatively correlated with treatment response.
Kraguljac et al. (27)	2016	34	Mixed	6 weeks	Seed based functional connectivity of the hippocampus	Baseline connectivity between the hippocampus, ACC, caudate nucleus, auditory cortex, and calcarine sulcus predicts subsequent antipsychotic treatment response.
Kraguljac et al. (28)	2016	34	Mixed	6 weeks	Seed based functional connectivity of the DMN, ECN, SN, and DAN	Baseline connectivity of the DAN to the cuneus, precuneus, superior and inferior parietal lobes, lingual gyrus, middle occipital lobe, and calcarine sulcus is positively correlated with antipsychotic treatment response.
MRS						
Kraguljac et al. (30)	2019	61	Mixed	6 weeks	Glx, NAA, Cho	Lower NAA in the ACC and higher Glx in the hippocampus at baseline were associated with better response to treatment at trend level.
PET						
Lahti et al. (35)	2009	29	Chronic	1 week, 6 weeks	rCBF	Greater increase in rCBF in the ventral striatum and greater decrease in rCBF in the hippocampus after 1 week of treatment was associated with a good response to antipsychotic medication after 6 weeks of treatment.
Bolding et al. (36)	2012	29	Chronic	1 week, 6 weeks	Functional connectivity	Functional connectivity between the middle frontal cortex and left hippocampus after 1 week of treatment predicted response to antipsychotic treatment after 6 weeks.

ACC, anterior cingulate cortex; BOLD, blood oxygen dependent level; CEN, central executive network; Cho, Choline; DAN, dorsal attention network; DMN, default mode network; fALFF, fractional amplitude of low frequency fluctuations; Glx, glutamate+glutamine; NAA, N-acetyl-aspartate; Rcbf, regional cerebral blood flow; SN, salience network.

TABLE 3 | Neuroimaging studies of antipsychotic medication-naïve first episode psychosis patients from our group.

Authors	Year	*n* (HC/FEP)	Imaging marker	Region of Interest	Group differences
Structural MRI					
Maximo et al. (68)	2019	0/55	Gray matter volume, cortical thickness, cortical surface area	DMN, CEN, SN	Greater duration of untreated psychosis was associated with reduced surface area in the salience network and central executive network. Cortical thickness and duration of untreated psychosis were correlated in the SN and DMN.
Briend et al. (69)	2020	40/40	Gray matter volume	Hippocampus subfields	HC> FEP in whole hippocampus volume, as well as volume of the CA1, molecular layer, subiculum, presubiculum, and hippocampal tail.
Nelson et al. (17)	2020	23/22	Cortical thickness, gyrification index	Whole brain	HC> FEP in gyrification in the precentral and postcentral gyri, and at trend level in cortical thickness.
Diffusion imaging					
Kraguljac et al. (18)	2019	42/30	Fractional anisotropy, mean diffusivity, radial diffusivity	Whole brain	HC> FEP in fractional anisotropy in the medial temporal lobe. HC< FEP in mean diffusivity in the hippocampal part of the cingulum bundle.
Kraguljac et al. (19)	2019	42/30	Orientation dispersion index, extracellular free water	Whole brain	HC< FEP in orientation dispersion in the posterior limb of the internal capsule. No group differences in extracellular free water.
Kraguljac et al. (62)	2020	45/66	Fractional anisotropy, mean diffusivity, radial diffusivity, axial diffusivity	Whole brain	HC> FEP in whole brain fractional anisotropy and axial diffusivity.
Resting state fMRI					
Maximo et al. (68)	2019	0/55	Seed based functional connectivity	DMN CEN, SN	Longer duration of untreated psychosis was associated with reduced connectivity in all three networks and with a single cluster of increased connectivity in the CEN.
Briend et al. (70)	2020	40/40	Static and dynamic connectivity (quasi-periodic patterns)	Fronto-parietal network	HC> FEP in static connectivity. The strength of the correlation of quasi-periodic patterns in the quasi-periodic pattern sliding vector was stronger in FEP than in HC, suggesting a greater impact on intrinsic brain activity in FEP. Regressing quasi-periodic patterns from functional scans erased connectivity group differences, suggesting that abnormal connectivity in FEP could result from altered quasi-periodic patterns.
Nelson et al. (71)	2020	41/55	Seed based functional connectivity	Hippocampus	HC< FEP in hippocampus connectivity to the cuneus, precuneus, and lingual gyrus. HC> FEP in hippocampus connectivity to the PCC, parahippocampus, and rostral orbitofrontal cortex.
MRS					
Sivaraman et al. (72)	2018	18/14	Glx, NAA, Cho	Associative striatum	HC< FEP in choline levels, relationship between NAA and Glx is disrupted in patients.
Birur et al. (31)	2020	22/29	Glx, NAA, Cho, Cr	MPFC	No group differences
Nelson et al. (71)	2020	41/55	Glx, NAA	Hippocampus	No group differences
Briend et al. (69)	2020	41/54	Glx	Hippocampus	HC< FEP in Glx in patients with long but not short duration of untreated psychosis.
Multimodal imaging					
Nelson et al. (71)	2020	41/55	Glx, seed based functional connectivity	Hippocampus	Greater hippocampal connectivity was correlated with higher Glx levels in the anterior and posterior DMN in both groups. In the entorhinal and orbitofrontal cortices, higher Glx levels predicted greater connectivity in HC, and the opposite was true in FEP.
Briend et al. (69)	2020	41/54	Glx, subfield volumes	Hippocampus	No associations between Glx and hippocampus subfield volumes in both groups.

CEN, central executive network; Cho, Choline; Cr, Creatine; DMN, default mode network; FEP, first episode psychosis patients; Glx, glutamate+glutamine; HC, healthy control; NAA, N-acetyl-aspartate; SN, salience network.

What Are the Neuroimaging Signatures That Reflect the Core Pathology in Schizophrenia?

There is a growing sense that progressive brain changes occur beyond the first psychotic episode and that illness chronicity may fundamentally affect the brain (66). It is difficult to pinpoint the extent to which abnormalities can be attributed to antipsychotic medication effects or to ongoing disease progression. Studying patients at later illness stages makes it problematic to discern downstream effects of pathology and prior treatment attempts from primary pathology. Even though this patient population is difficult to recruit (67), studying antipsychotic medication-naïve first episode psychosis patients can mitigate these issues. Our group has conducted studies in this population using different imaging modalities in an effort to characterize relevant neural signatures (**Table 3**).

Using structural neuroimaging techniques, we found that a number of alterations are already present in medication-naive patients. Alterations include decreased gyrification in the pre- and post-central gyri, decreased total hippocampus and hippocampus subfield volumes, a trend level decrease in cortical thickness, as well as a decrease in whole brain fractional anisotropy and axial diffusivity (17, 18, 62, 69). Additionally, an increase in mean diffusivity in the hippocampal part of the cingulum, which is often interpreted as evidence of neuroinflammation, is already evident in first episode patients (18). Importantly, the duration of untreated psychosis, which is the time between first onset of psychotic symptoms and the first antipsychotic treatment, seems to be an important modulatory factor for structural integrity, as a longer duration of untreated psychosis is associated with greater gray and white matter alterations (62, 68, 69).

We saw similar results in our functional imaging studies where greater duration of untreated psychosis was associated with greater disruptions in functional connectivity in large-scale brain networks supporting higher order cognition (68). In the overall group of antipsychotic medication-naïve patients, we note that hippocampus connectivity is disrupted. Spatial patterns of dysconnectivity resemble those in unmedicated, chronic schizophrenia patients (71). When examining dynamic connectivity, we found that quasi-periodic patterns had a greater impact of fronto-parietal control network connectivity in first episode patients compared to controls, suggesting that brain network dynamics are already altered in this patient group (70). Taken together, connectivity alterations are clearly already present in medication-naïve patients, which is consistent with the hypothesis that brain network dysconnectivity is a core feature of the illness (73–75).

In magnetic resonance spectroscopy studies, we found elevated choline and a disruption of the relationship between NAA and glutamate in the left striatum, indicating possible mitochondrial, membrane, and glial dysfunction (72). However, we reported no neurometabolite abnormalities in the medial prefrontal cortex or the hippocampus when contrasting antipsychotic medication-naïve first episode patients and controls in the overall group (31, 69). It is important to note that glutamate levels in both areas showed a greater variance in patients compared to controls, suggesting heterogeneity in glutamatergic metabolism in first episode psychosis. When the duration of untreated psychosis is taken into consideration, those with a shorter but not those with a longer duration of untreated psychosis did have an elevation in hippocampal glutamate (69).

Collectively, it is evident that functional and structural abnormalities are already present in patients who are in their early illness stages who have no prior exposure to antipsychotic medications. However, wee did not observe group level alterations in NAA or glutamate which was somewhat unexpected. Interestingly, the variance in measurements was greater in patients compared to controls, suggesting that neurometabolite alterations may only be present in a subset of patients, or become more pronounced as the illness progresses. Importantly, we found the duration of untreated psychosis to be an important mediator, such that a longer interval adversely impacts brain structure and function, underscoring the importance of early intervention efforts in this syndrome.

Can Multimodal Brain Imaging Help Us Better Characterize the Complex Pathophysiology in Schizophrenia?

The field is moving from traditional models of schizophrenia focused on the disruption of a single molecule such as dopamine or glutamate, to models of pathway dysregulation as a means of integrating findings from diverse imaging modalities. An individual component of a pathway in this context can be best understood as part of a highly interactive network that may influence other parts of the network and in turn be regulated by a number of other factors (76). An abnormality may represent a primary etiological factor, but could also be present because of a disruption in modulatory inputs and thus reflect a secondary consequence of a pathophysiological process. It is critical to develop disease models with a degree of complexity that accurately reflect these highly interactive patterns. Multimodal imaging allows investigation of brain dysfunction using a range of techniques within the same individual and to test hypotheses about relationships between biological mechanisms. This approach may reveal details about the pathophysiology that would not be detectable when using one modality alone.

For example, glutamatergic hyperactivity is hypothesized to be a key pathological feature in schizophrenia (77, 78). Glutamate neurotransmitter flux, neuronal firing rate, and the blood oxygen level dependent (BOLD) response are tightly coupled (79, 80), and glutamate plays a role in long-range functional connections (81). In preclinical studies, excess glutamate has been shown to be associated with disorganized neuronal activity (82) and may result in increased synapse turnover as well as axonal or glial injury (83–85). If this premise holds true, multimodal neuroimaging studies should detect relationships between glutamate levels and brain function in healthy subjects that are disrupted in patients with schizophrenia. They also should reveal an association between glutamate excess and structural integrity deficits in patients. Our group has conducted a number of such studies to empirically test the relationship

between glutamate and brain function the impact of glutamate excess on brain structure.

We used several task paradigms and resting state functional MRI to characterize the relationship between glutamate levels and brain function in healthy subjects and schizophrenia spectrum patients. We reported a positive correlation between hippocampal glutamate and inferior frontal activation during a memory retrieval task in controls that was absent in medicated chronic schizophrenia patients (86). The relationship between hippocampal glutamate and the BOLD response in default mode network regions during memory encoding also differed between unmedicated patients and controls (24). Using a Stroop task, we observed a negative correlation between anterior cingulate cortex glutamate and the BOLD response in the posterior cingulate cortex, precuneus, occipital cortex and cerebellum in controls; this correlation was inverted in medicated first-episode psychosis patients (87). Similarly, we noted a correlation between anterior cingulate cortex glutamate and the BOLD response in the salience network and posterior default network during a Stroop task in healthy controls but not unmedicated patients with schizophrenia (22). Using a reward task, we observed an association between the prediction error related BOLD response in the midbrain and substantia nigra glutamate in healthy controls but not medicated patients with chronic schizophrenia. Interestingly, glutamate levels were elevated in patients, suggesting that glutamatergic dysfunction might contribute to abnormal neural prediction error coding (88). At rest, we initially did not detect a relationship between hippocampal glutamate and aberrant hippocampal connectivity to the precuneus in a small group of unmedicated schizophrenia patients (89). However, after expanding the sample size, we did observe that higher glutamate levels were correlated with higher hippocampus resting state connectivity to the anterior default mode network in healthy controls, but the relationship between measures was inverse in first episode psychosis patients (71). Taken together, our studies consistently demonstrated a link between glutamate levels and brain function, regardless of task condition and even in absence of a task in healthy subjects. Importantly, this relationship was consistently found to be altered or absent in patients across paradigms tapping into various aspects of brain function, which implicates that the disruption in this coupling may be a fundamental feature of the illness. Interestingly, a detectable alteration in glutamate levels does not seem to be a necessary element to reach the threshold of a disruption in brain function, suggesting the presence of subtle abnormalities in glutamatergic neurotransmission that may be below the level of detection with magnetic resonance spectroscopy. Our longitudinal studies further demonstrate that the relationship between glutamate and brain function in patients is modulated by antipsychotic drug treatment, suggesting a potential mechanism of antipsychotic drug action (22, 24).

We also conducted studies to examine the impact of glutamate (excess) on brain structures. In unmedicated chronic schizophrenia patients, we found that higher hippocampal glutamate was associated with lower hippocampal volumes, suggesting that glutamate related excitotoxicity (neurotransmitter excess related increased synapse turnover) might affect brain structure (90). Our finding is in agreement with a later study that reported a negative relationship between glutamate excess and brain volumes in the caudate nucleus in first episode psychosis patients (91). In contrast, we did not observe a linear relationship between hippocampus subfield volumes and glutamate levels in antipsychotic medication-naïve first episode psychosis patients (69). Interestingly though, those with a longer duration of untreated psychosis showed lower hippocampus subfield volumes. While this discrepancy between our studies at first glance does not support the hypothesis that glutamate impacts brain structures as a fundamental mechanism of the illness, it is possible that the amount of time the brain is exposed to altered glutamate is the key factor in adversely affecting brain structures rather than the amount of glutamate present in the brain at any given time.

As demonstrated with the above examples, multimodal neuroimaging clearly can give important insights into the pathophysiology of the illness, and allows testing of hypotheses about the relationships between biological mechanisms which is not possible with a single imaging modality. However, because different aspects of the pathophysiology are typically assessed at the same time in multimodal imaging, interpretations are limited to discovery of associations but not causality. In other words, it is possible to detect a relationship between two different imaging markers, but it is not feasible to discern if one abnormality is caused by the other or vice versa.

Can Pharmacological Challenge Studies Provide a Framework for the Interpretation of Neuroimaging Findings in Schizophrenia?

A complementary line of research, pharmacological challenge studies, which are designed to model aspects of the pathophysiology, can inform inferences drawn about causality for neuroimaging alterations seen in schizophrenia spectrum patients. Our group has done several pharmacological challenge studies using subanesthetic ketamine, a non-competitive N-methyl-d-aspartate (NMDA) receptor blocker that transiently induces a behavioral phenotype similar to that seen in the illness (92–96), to test the hypothesis that experimentally induced NMDA receptor hypofunction causes changes in brain function and neurochemistry that are comparable to neural signatures observed in schizophrenia.

Early imaging studies testing the effects of a pharmacological challenge found that sub-anesthetic ketamine affects regional cerebral blood flow (rCBF). In response to the drug, an increase in psychosis symptom severity was paralleled by an increase in rCBF in the anterior cingulate cortex, both in healthy controls and medicated patients with schizophrenia (97). In addition to a ketamine related increase in rCBF in the anterior cingulate cortex, a reduction in rCBF was found in the hippocampus, lingual gyrus and fusiform gyrus in a different study of healthy controls (98). Interestingly, kinetic analyses suggest that the ketamine induced rCBF response differs across brain areas (99). Using a MRI based rather than PET based technique to quantify blood flow, our group later reported increased rCBF

in the prefrontal cortex, cingulate cortex caudate, putamen, thalamus and hippocampus, as well as interregional connectivity alterations in areas of the salience network (100). This again suggests systems level, but not uniform, effects of experimentally induced NMDA receptor hypofunction.

In a combined magnetic resonance spectroscopy and resting state functional connectivity study of the hippocampus (101), we reported that experimentally induced NMDA receptor hypofunction resulted in an increase in glutamate that was similar in magnitude to that we saw in unmedicated schizophrenia patients (90). In parallel, we also found a reduction in hippocampal resting state connectivity to the anterior cingulate cortex, medial prefrontal cortex, insula, hippocampus, precuneus, posterior cingulate cortex and lingual gyrus. Spatial patterns of abnormalities here closely resemble those we observed in both unmedicated schizophrenia patients (27, 71) and antipsychotic medication-naïve first episode psychosis patients (71).

Taken together, our findings from ketamine challenge studies lend empirical support to the putative link between NMDA receptor hypofunction, disruption in brain function and glutamate excess and provide a theoretical framework for the interpretation of abnormal brain signatures in schizophrenia in the context of NMDA receptor hypofunction. It is important to note that this type of framework can also be leveraged to test target engagement for putative novel pharmacological agents as recently demonstrated a multi-center proof of mechanism study of pomaglumetad (102), which will ideally translate into accelerated development of novel drugs.

How Can Postmortem Work Provide Context for the Neuroimaging Findings in Schizophrenia?

Postmortem studies reporting abnormalities in γ-Aminobutyric-acid (GABA)ergic interneurons (103, 104) and glutamatergic signaling (105) provided the impetus for the measurement of glutamate and GABA using MR spectroscopy, as well as the measurement of brain oscillations using EEG/MEG. The fast-spiking GABA-interneurons play a fundamental role in controlling of the synchrony of cortical pyramidal neurons by producing rhythmic inhibitory postsynaptic potentials. Consequently, these interneurons appear to be key to the generation of gamma oscillations (106). In a group of first episode psychosis patients scanned using an ultra-high field magnet [7 Tesla (T)] we reported a decrease in glutamate, but not GABA levels, in the anterior cingulate cortex (107). Interestingly, in a larger group of first episode psychosis patients also scanned at 7T, Wang reported both a decrease in anterior cingulate glutamate and GABA levels (108). In the same group of first episode psychosis patients in which we found a glutamate decrease (107), we did not find abnormalities in gamma range oscillations using MEG (109), although others, also in first episode patients, have reported such alterations (110–112). All three of these studies used EEG, and it has been shown that there can be differences in the cortical auditory evoked response between MEG and EEG (113). Inspired by imaging studies reporting decrease in N-acetyl-aspartate, a marker of neuronal integrity, in the anterior cingulate cortex in schizophrenia (114), Roberts (115) used electron microscopy in anterior cingulate cortex postmortem brain samples and identified a decrease in the number of excitatory synaptic connections, as well as a decrease in the number of mitochondria per neuronal somata, suggesting a decrease in cortical efficiency in schizophrenia.

How Does Neuroimaging Inform Our Mechanistic Understanding of the Illness?

Our work has contributed to the extensive efforts in studying the structural and functional neuroanatomy of schizophrenia by mapping relevant neural signatures in psychosis spectrum patients. Our data is congruent with the idea that the brain is fundamentally affected in the illness, where widespread structural gray and white matter involvement, functionally abnormal cortical and subcortical information processing, and neurometabolic dysregulation are present in patients. Importantly, data indicate that pathology is not merely diffusely distributed across the entire brain, rather it appears that certain brain circuits are preferentially affected. The evidence is compelling that many of the subtle abnormalities described in chronic schizophrenia are already evident in first episode psychosis patients, highlighting that these brain signatures are likely to be relevant to the core pathology and not a just be a consequence of other non-specific factors associated with the illness (116). We also demonstrated that these brain circuitry alterations are clinically relevant by showing that these pathological signatures can be leveraged for predicting subsequent response to antipsychotic treatment, further underscoring that they are key features of the illness.

Despite these successes in delineating disease signatures, it remains challenging to identify casual factors leading to these alterations through cross-sectional unimodal mapping alone (117). To gain further insights, our group has leveraged different approaches. First, we used various pharmacological challenges to characterize the effects of active modulation of major neurotransmitter systems on neural signatures. We clearly demonstrated that dopamine D2 receptor blockers alleviate neural abnormalities to some extent, and that experimentally induced NMDA receptor blockage results in alterations that resemble those seen schizophrenia, underscoring the pathophysiological relevance of these neurotransmitter systems. Second, we combined findings from different imaging modalities to gain additional insights into the role of glutamatergic neurotransmission for the modulation of functional brain networks. Our studies consistently demonstrated a disruption in the link between glutamate levels and brain function in patients across paradigms tapping into various aspects of brain function, which implicates that the disruption in this coupling may be a fundamental feature of the illness. Third, postmortem studies can also inform mechanistic understanding. For example, decrease in mitochondrial function observed in schizophrenia postmortem samples (115) suggest abnormalities in brain bioenergetics.

Taken together, it is highly unlikely that the pathogenesis of schizophrenia is uniform (118), it is more plausible that there may be multiple different etiologies that converge to the behavioral phenotype of schizophrenia (119). Our data underscore that mechanistically oriented neuroimaging studies must take non-specific factors such as antipsychotic drug exposure or illness chronicity into consideration when interpreting disease signatures, as a clear characterization of primary pathophysiological processes is an imperative prerequisite for rational drug development and for alleviating disease burden in our patients.

AUTHOR CONTRIBUTIONS

AL and NK wrote the manuscript. Both authors contributed to and approved the final version of this manuscript.

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Abnormal Habituation of the Auditory Event-Related Potential P2 Component in Patients With Schizophrenia

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Auditory event-related potentials (ERP) may serve as diagnostic tools for schizophrenia and inform on the susceptibility for this condition. Particularly, the examination of N1 and P2 components of the auditory ERP may shed light on the impairments of information processing streams in schizophrenia. However, the habituation properties (i.e., decreasing amplitude with the repeated presentation of an auditory stimulus) of these components remain poorly studied compared to other auditory ERPs. Therefore, the current study used a roving paradigm to assess the modulation and habituation of N1 and P2 to simple (pure tones) and complex sounds (human voices and bird songs) in 26 first-episode patients with schizophrenia and 27 healthy participants. To explore the habituation properties of these ERPs, we measured the decrease in amplitude over a train of seven repetitions of the same stimulus (either bird songs or human voices). We observed that, for human voices, N1 and P2 amplitudes decreased linearly from stimulus 1–7, in both groups. Regarding bird songs, only the P2 component showed a decreased amplitude with stimulus presentation, exclusively in the control group. This suggests that patients did not show a fading of neural responses to repeated bird songs, reflecting abnormal habituation to this stimulus. This could reflect the inability to inhibit irrelevant or redundant information at later stages of auditory processing. In turn schizophrenia patients appear to have a preserved auditory processing of human voices.

Keywords: schizophrenia, auditory, EEG, event-related potentials, habituation, N1, P2

INTRODUCTION

The orienting response to novel/rare stimuli is considered a fundamental reaction in living organisms. However, when confronted with the repetition of stimuli in stable and non-threatening conditions, neural responses are expected to fade with repetition, demonstrating that humans tend to adapt to the surrounding environment (1). Auditory event-related potentials (ERP) and early components such as the N1 and P2, allow tracking the time course of neural activity related to auditory processing (2) and respective habituation

(i.e., component amplitudes decrease with successive repetitions) and sensory gating processes (i.e., inhibition of the processing of repeated information).

N1 is a negative component that peaks around 100 ms after the onset of an auditory stimulus and is followed by the P2, a positive component occurring approximately after 200 ms (3). N1 and P2 are sensitive to the exogenous physical properties of the stimuli (4), although they also encompass endogenous characteristics (2, 3). At the exogenous level, early auditory categorical differences have been reported for distinct categories of sounds (e.g., voices and bird songs) such that results suggest a rapid brain discrimination of human voices (5–8). At the endogenous level, N1 also seems to reflect a selective-orienting attention response toward novel/rare stimuli (9, 10), while P2 probably represents a subsequent stage of stimulus recognition toward specific stimuli (e.g., human voices) independently of attentional demands (5–7, 11).

Regarding habituation processes, the N1-like orienting neural responses are likely to decrease in magnitude with the repeated presentation of an auditory stimulus (1, 9). Similarly, P2 also shows habituation and sensory gating properties, especially for the consecutive stimuli repetition with shorter and constant inter-stimulus intervals (1, 4, 12). Nevertheless, the mechanisms underlying ERP adaptation are complex (13) and further investigation is still required in order to unveil their potential clinical applications.

Several studies have focused indeed on the potential of auditory ERP components and habituation properties (e.g., P50 and P300) as diagnostic tools for schizophrenia (14, 15). N1 and P2 can be particularly useful to study the mechanisms underlying the pathophysiology of schizophrenia since they are especially sensitive to early cortical auditory processing (that appears to be affected by this disorder) and seem to arise from temporal lobe generators, which are also affected in schizophrenia (9, 16). More specifically, the ability to filter out irrelevant or repetitive information—as assessed through sensory gating and habituation processes—maps early pre-attentive and later-stages of information processing, respectively (17). Research consistently reports reduced N1 amplitudes in first-episode, as well as chronic schizophrenic patients and first-degree relatives using both simple (18–21) and complex stimuli (22, 23). Conversely, P2 is often examined in the context of the N1/P2 complex, and thus it has been less studied independently. Studies that have examined both components show either smaller P2 amplitudes (19) or no differences in first-episode schizophrenia (using simple stimuli) compared to healthy controls (21), despite systematic reductions in N1. A meta-analysis by Ferreira-Santos et al. (24) reviewed 20 studies on P2 in schizophrenia and showed that patients exhibited smaller amplitudes to standard stimuli and larger amplitudes for target stimuli when compared to controls in oddball tasks. In addition, even if fewer studies have assessed habituation processes for N1 and P2, there is evidence of less attenuation in schizophrenia (25, 26), although a meta-analysis by Rosburg (27) found that patients with schizophrenia display reduced N1 gating due to the initial/novel stimulus—not to effects of repetition/habituation. Such abnormalities extend to the processing of voice stimuli with N1 being smaller to pre-recorded voices (23, 28) and P2 exhibiting larger amplitudes for voices with affective content (29) and no differences in amplitude for neutral content (30) in Schizophrenia.

Studying voice processing in schizophrenia is particularly important since auditory verbal hallucinations and abnormal social cognition represent well-recognized symptoms of this pathology. Also, the study of pre-attentive and later-stages of information processing could help us understand which stages of the auditory cortical information processing are impaired (and which are intact) in schizophrenia, as well as if the type of stimuli (i.e., complex, simple, or social) interferes with this process. Since neurobiological impairments precede the beginning of a full clinical syndrome, it is of extreme relevance to study the N1 and P2 in pre-psychotic and early-psychotic states of schizophrenia (31) to explore deficits underlying genetic susceptibility for schizophrenia (9, 20). For this purpose, the current study assessed the habituation of auditory ERP components in first-episode schizophrenia such that amplitude attenuations at N1 and P2 time-windows were measured in a roving paradigm including both complex sounds (human voices and bird songs) and a target/rare pure sinusoidal tone. In healthy participants, the reviewed literature indicates that (a) N1 increases for rare stimuli vs. frequent stimuli (9, 10), (b) P2 is particularly responsive to human voices vs. bird sounds (5), and (c) both components decrease as a function of repetition/habituation (1, 4, 12, 32). Inversely, we hypothesized that patients with schizophrenia would show: (H1) a diminished N1 amplitude for target stimuli—pure tones (9); (H2) a diminished P2 to human voices, considering P2 specificity to voices (5) and deficits in voice processing in schizophrenia (33); and (H3) reduced habituation of N1 and P2 when compared to controls (25), considering deficits reported in sensory gating in early ERP components in schizophrenia (34).

METHOD

Participants

Twenty-seven first-episode patients diagnosed with schizophrenia were originally recruited, but one was excluded due to excessive noise in EEG recordings. Thus, the clinical group included 26 participants (8 female; 2 left-handed), with a mean age of 27.88 years ($SD = 11.94$) and a mean education of 11.73 years ($SD = 2.69$). All patients were medicated with second generation antipsychotics corresponding to, on average, 12.63 mg of olanzapine equivalents ($SD = 5.01$). Mean illness duration was 15.11 months ($SD = 8.01$). The control group included 27 healthy individuals (seven female; two left-handed), with a mean age of 27.56 years ($SD = 7.79$) and a mean education of 13.67 years ($SD = 2.26$). All participants reported being free from head injuries, other neurological disorders, learning disabilities, or substance abuse, and all disclosed having normal hearing. There were statistically significant differences between groups for education ($p = 0.006$) but not for age ($p = 0.897$). Although education varied between groups, all participants in the patient group had completed at least compulsory school (9 years), except for one who completed 8 years. All participants signed the informed consent before the beginning of the experiment.

Stimuli and Procedures

The selection of auditory stimulus for the task was based on a preliminary validation study (for more details see section Validation study of the auditory stimuli in the **Supplementary Material**). Using a modified version of the roving standard frequency paradigm (35), auditory stimuli (i.e., bird songs, voices, and the pure tone) were delivered via headphones and E-Prime 2.0 (Psychology Software Tools, Pittsburgh, PA) with an intensity of 90 dB SPL.

The protocol included 16 complex auditory stimuli (i.e., eight bird songs and eight non-speech human voices) with a duration of 200 ms each (10 ms rise and fall times). The complex sounds were presented in fixed trains composed of seven repetitions of the same sound with an inter-stimulus interval of 1,000 ms. Each train was randomly repeated 5 times during the protocol, resulting in a total of 80 blocks. The target tone was randomly presented 40 times during the entire protocol (i.e., probability of ∼7%) and only appeared between trains (**Figure 1**). This target consisted of a 1,000 Hz pure tone with 70 ms duration (10 ms rise and fall times). During the task, a black screen with a fixation point was presented. Behavioral data was collected on the target tone with the main purpose of maintaining participants' attention and avoiding sleepiness and fatigue (which could impair EEG data quality due to alpha activity). Thus, participants were asked to pay attention and rapidly identify when the target tone was presented by pressing a button (i.e., in a SRBOX display; E-Prime).

EEG Data Collection and Pre-processing

EEG data were recorded with a digitizing rate of 500 Hz from 128 channels (Hydrocel Geodesic Sensor Net, NetAmps 300 amplifier, NetStation 4.2. software—Electrical Geodesics Inc.). The electrodes were referenced to the vertex (Cz) during recording and re-referenced offline to the average reference. Impedances were kept below 50 kΩ for all electrodes (high input impedance system). Data was pre-processed using EEGLAB (v11.4.2.2b) (36, 37) and custom MATLAB scripts. Continuous EEG records were downsampled to 250 Hz and band-pass filtered (0.2–30 Hz) and submitted to an Independent Components Analysis (ICA) decomposition after interpolation of bad channels (maximum of 10% per record). Correction of eye blink artifacts was carried out semi-automatically using the CORRMAP EEGLAB plug-in (38). We used a correlation threshold of 0.80 to identify the artifactual ICs and then subtracted their activity from the EEG data. Pre- and post-subtraction EEG traces were visually inspected to ensure that signals were not altered outside the time windows of eye blinks. EEG records were segmented into 1,000 ms epochs (−200 to 800 ms in peri-stimulus time). Epochs with voltages below −100 or above 100 μV were automatically rejected and all segments were subjected to visual inspection and manual artifact rejection. Finally, all epochs were baseline corrected (200 ms pre-stimulus) and averaged by condition for each participant.

ERP Analysis

Grand-averaged ERPs were computed and visually inspected to ensure that the expected ERP morphology was present. We analyzed frontal scalp regions in the left (i.e., FC5 cluster: E24, E27, E28, E29, E34, and E35) and right hemispheres (i.e., FC6 cluster: E110, E111, E116, E123, E124, and E117), where the frontotemporal positivity to voices has been shown to be maximal (5). Time-windows for the N1 and P2 components were based on the visual inspection of the grand-averages and on the typical settings described in the literature on auditory ERPs. Therefore, peak amplitudes were quantified as the minimum voltage in the 80–200 ms post-stimulus presentation time-window for N1 and as the maximum voltage in the 200–300 ms time-window for P2. Peaks were extracted for each participant at each channel and then averaged per train position (i.e., 1–7, for bird songs and voices) and stimulus type (i.e., bird songs, vocalization, and pure tone).

Statistical Analysis

For the analysis of behavioral data on the target detection task, responses were divided according to the sound (i.e., bird songs or voices) that was presented previous to the target (i.e., pure tone) and submitted to paired-sample *t*-tests to assess possible differences in reaction times (RTs). Additionally, independent samples *t*-tests were performed to assess group differences (i.e., patients vs. controls) in RTs (ms) and accuracy (percentage of times the target tone was correctly identified).

For neural data, separate Mixed Repeated Measure ANOVAs were conducted for N1 and P2. Pure tones (H1) were analyzed by hemisphere (within-participants factor: left, right) and group (between-participants factor: controls, patients). To replicate the conditions from previous studies that did not analyze the seven positions in the train (5), we explored group differences in the processing of complex stimulus (H2) only for the first stimulus of the train (within-participants factors: hemisphere—left, right, and stimulus category—bird songs, human voices). Finally, to explore the habituation properties of these ERPs for bird and human voices stimuli, we measured the decrease in amplitude across stimulus repetition in each train from S1 to S7 using linear contrasts (H3). As such this model entered with between groups and within-participants factors (train sequence—stimuli repetition from 1 to 7; stimulus category—voices, bird songs; hemisphere—left, right). All the pairwise comparisons were corrected for multiple comparisons using the Bonferroni Correction, and effect sizes were calculated (i.e., partial eta squared and Cohen's *d*).

RESULTS

Behavioral Results: Target/ Pure-Tone Detection

RTs were significantly longer for targets following the presentation of human voices ($M = 423.70$, $SD = 93.78$) compared to targets following bird songs ($M = 392.60$, $SD = 80.15$), $t_{(50)} = -5.26$, $p < 0.001$, $d = 0.737$. For targets following the presentation of bird songs, patients had significantly longer RTs ($M = 419.14$, $SD = 80.85$) compared to controls ($M = 364.98$, $SD = 70.2$), $t_{(49)} = 2.54$, $p = 0.014$, $d = 0.713$. Patients also had significantly longer RTs for targets following human

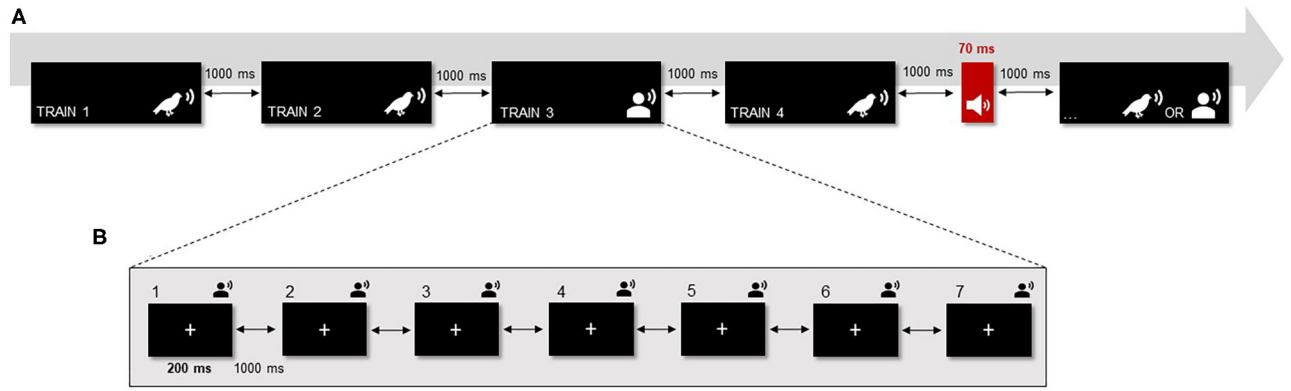

FIGURE 1 | Modified version of the roving standard frequency paradigm (Baldeweg et al., 2004). **(A)** There were 16 complex auditory stimuli divided into two categories: eight bird songs and eight human voices (non-speech voices). Each complex sound was presented in trains composed of seven repetitions of the same sound (ISI = 1,000 ms). Each train was randomly repeated five times during the protocol, resulting in a total of 80 blocks. Additionally, a target tone (i.e., a pure tone with duration of 70 ms) was randomly presented 40 times in between the trains of complex sounds. **(B)** Within the trains, each sound was presented for 200 ms (ISI = 1,000 ms) while a black screen with a fixation point was displayed.

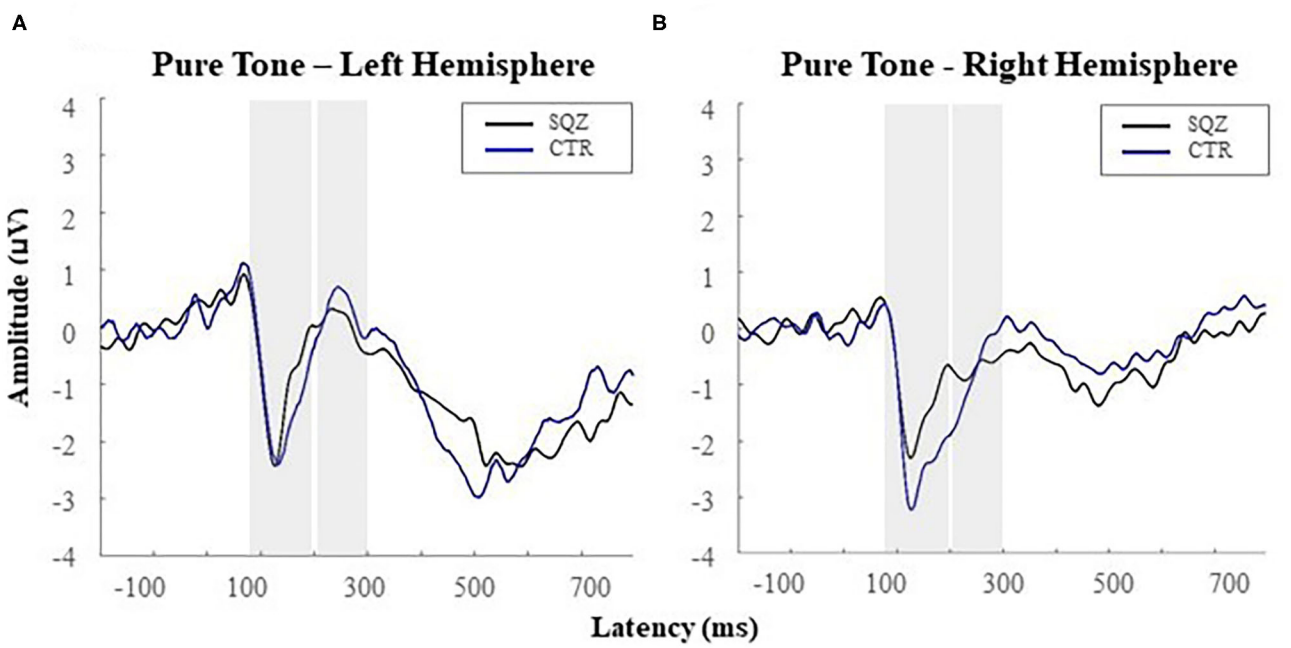

FIGURE 2 | Auditory event-related potentials [i.e., N1 (80–200 ms); P2 (200–300 ms)] for the pure tone (i.e., the target tone) in patients with schizophrenia (SQZ) and healthy controls (CTR): **(A)** in the left hemisphere (i.e., cluster FC5) and **(B)** in the right hemisphere (i.e., cluster FC6).

voices ($M = 461.95$, $SD = 92.71$) compared to controls ($M = 383.92$, $SD = 78.32$), $t_{(49)} = 3.24$, $p = 0.002$, $d = 0.909$.

The differences in accuracy between patients ($M = 96.50\%$, $SD = 7.01$) and controls ($M = 99.19\%$, $SD = 2.19$) were not statistically different, $t_{(51)} = -1.87$, $p = 0.067$, $d = 0.518$.

H1: Category— Simple Sound (Pure Tones—Target Stimuli)

At the N1 time-window, a significant hemisphere*group interaction was found, $F_{(1,51)} = 4.52$, $p = 0.038$, $\eta^2_p = 0.081$, revealing lower N1 amplitudes in patients ($M = -3.02$, $SD = 1.48$) compared to controls ($M = -4.42$, $SD = 1.87$) in the right hemisphere, $t_{(51)} = -3.01$, $p = 0.024$, $d = 0.83$ (see **Figure 2**). No other significant effects were found for the N1.

For P2, a significant effect was found for hemisphere, $F_{(1,51)} = 5.35$, $p = 0.025$, $\eta^2_p = 0.095$, indicating higher amplitudes for the left ($M = 1.82$, $SD = 1.89$) comparing to the right hemisphere ($M = 1.02$, $SD = 2.12$), $t_{(52)} = 2.34$, $p = 0.023$, $d = 0.31$, for both groups. No other significant effects were found for the P2.

All descriptive statistics of peak amplitudes and results of the separate Mixed Repeated Measure ANOVAs for N1 and P2 can be found in the **Supplementary Tables 1, 2**).

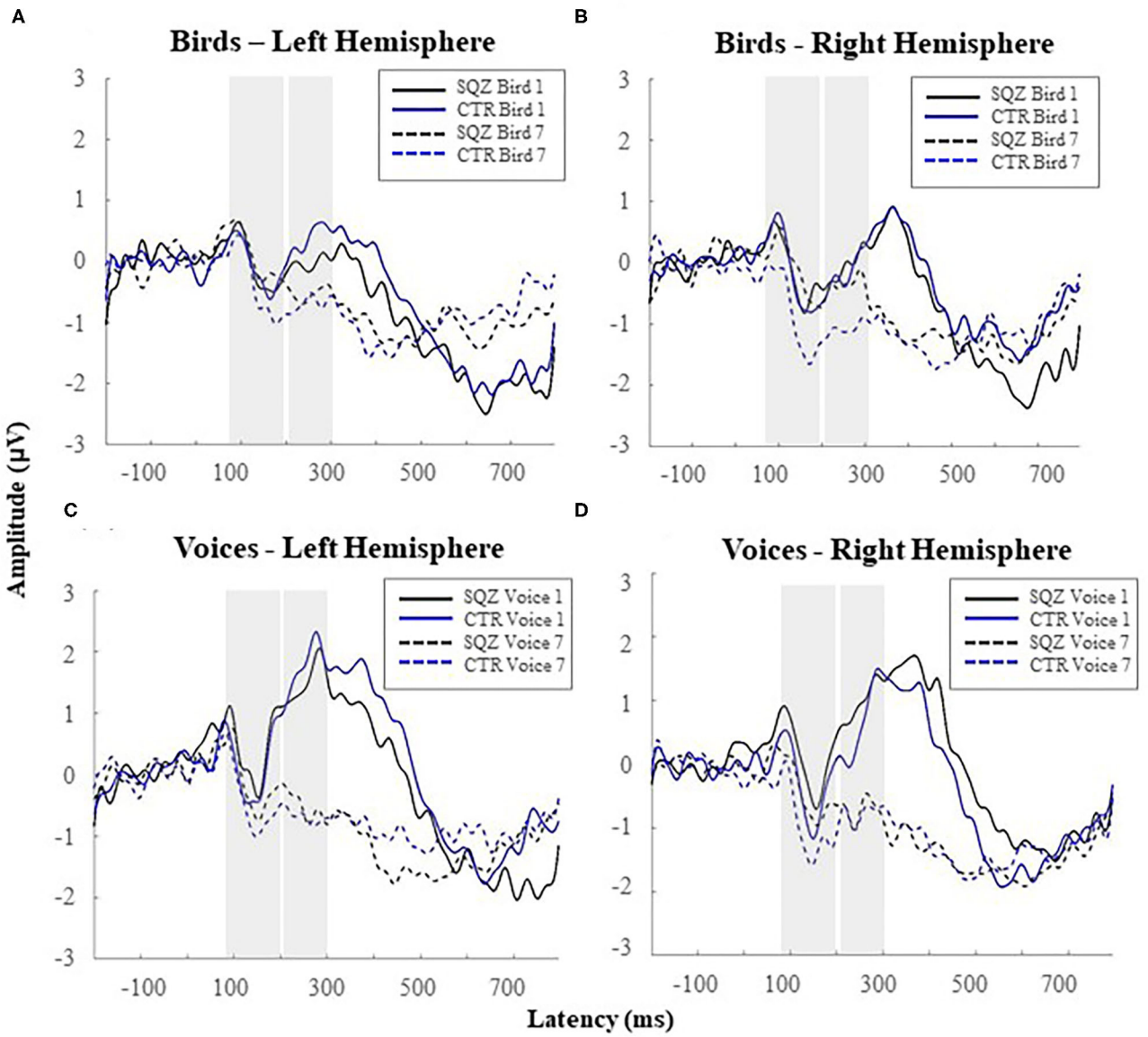

FIGURE 3 | Auditory event-related potentials [i.e., N1 (80–200 ms); P2 (200–300 ms)] for complex sounds in patients with schizophrenia (SQZ) and healthy controls (CTR): **(A)** for bird songs in the left hemisphere (i.e., cluster FC5) and **(B)** right hemisphere (i.e., cluster FC6); and **(C)** for human voices in the left hemisphere (i.e., cluster FC5) and **(D)** the right hemisphere (i.e., cluster FC6).

H2: Category—Complex Sounds (Voices vs. Bird Songs)

There were no main effects of stimulus category, nor category*group or category*group*hemisphere interactions on N1 amplitude (see also **Supplementary Table 3**).

A main effect of category was found on P2 amplitude, $F_{(1,51)} = 78.63$, $p < 0.001$, $\eta^2_p = 0.607$, indicating that voices elicited increased P2 amplitude (see **Figure 3**) than bird songs for both groups (all $p < 0.036$). No group or hemisphere*group interactions were found (see also **Supplementary Table 4**).

H3: Habituation Effects

For N1, we found a significant linear contrast effect of order for human voices, $F_{(1,51)} = 10.00$, $p = 0.003$, $\eta^2_p = 0.164$, but not for bird songs $F_{(1,51)} = 1.75$, $p = 0.192$, $\eta^2_p = 0.033$. No further effects were observed.

For P2, we found a significant linear contrast effect of order in bird songs $F_{(1,51)} = 21.71$, $p < 0.001$, $\eta^2_p = 0.299$, and voices, $F_{(1,51)} = 81.10$, $p < 0.001$, $\eta^2_p = 0.614$. Also, a significant interaction order*group was found in P2 for bird songs, $F_{(1,51)} = 4.21$, $p < 0.045$, $\eta^2_p = 0.760$ [vs. human voices, $F_{(1,51)} = 0.294$, $p = 0.590$, $\eta^2_p = 0.006$], independently of the hemisphere,

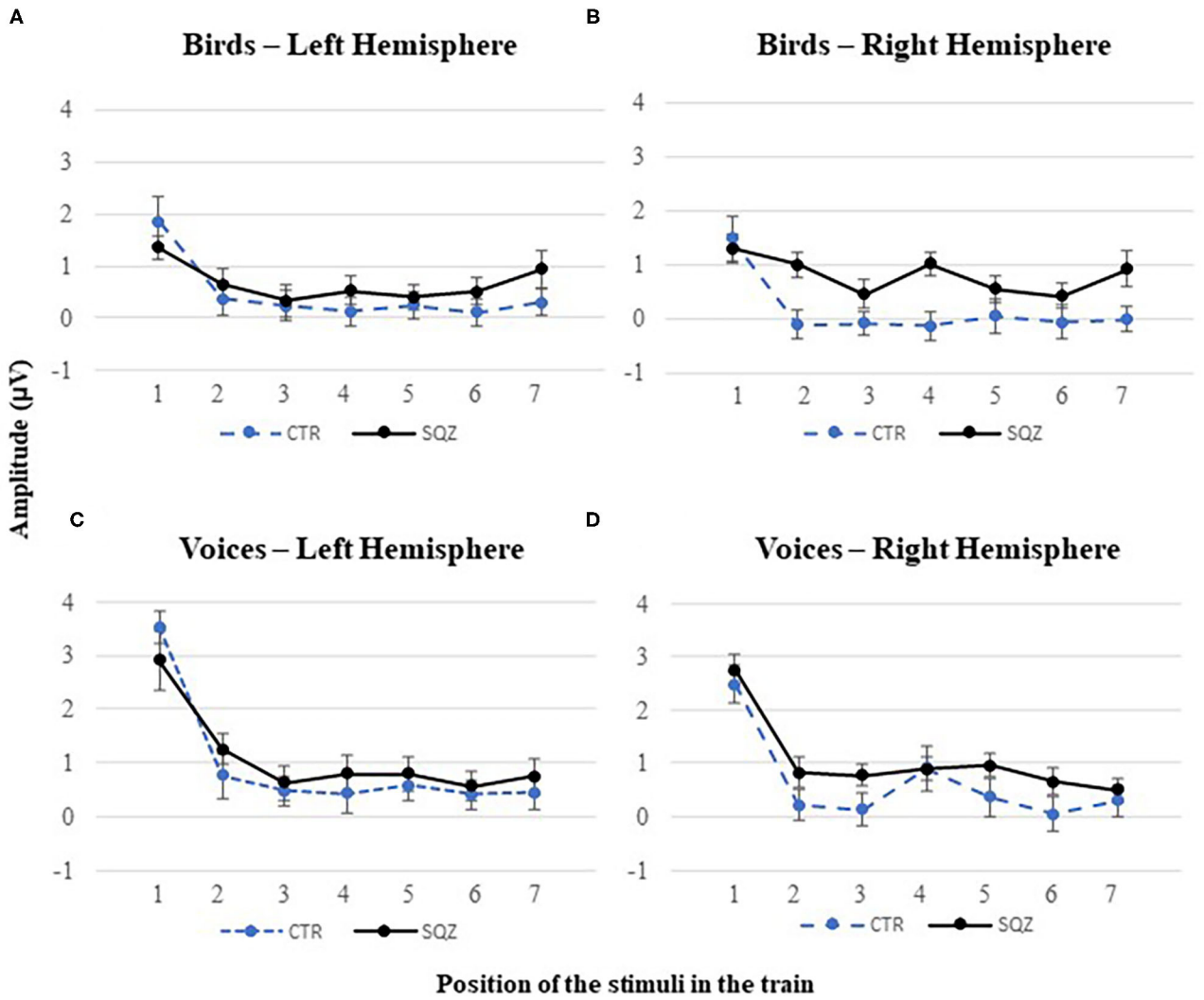

FIGURE 4 | P2 habituation effect in patients with schizophrenia (SQZ) and healthy controls (CTR) for complex sounds. P2 peak amplitudes to each position of the stimuli in the train for: **(A)** bird songs in the left hemisphere (i.e., cluster FC5) and **(B)** the right hemisphere (i.e., cluster FC6); and **(C)** human voices in the left hemisphere (i.e., cluster FC5) and **(D)** the right hemisphere (i.e., cluster FC6), for each position in the train.

$F_{(1,51)} = 1.02$, $p = 0.319$, $\eta^2_p = 0.020$. This finding (see **Figures 3**, **4**) represents a gradual decrease in P2 amplitude for controls from Bird1 to Bird7 at both hemispheres (Bird1: $M_{FC5} = 1.85$, $SD = 2.44$, $M_{FC6} = 1.49$, $SD = 2.21$; Bird7: $M_{FC5} = 0.30$, $SD = 1.38$, $M_{FC6} = -0.01$, $SD = 1.31$, both $ps < 0.040$). This habituation effect on birds was not observed in patients (Bird1: $M_{FC5} = 1.35$, $SD = 1.19$, $M_{FC6} = 1.31$, $SD = 1.41$; Bird7: $M_{FC5} = 0.94$, $SD = 0.86$, $M_{FC6} = -0.92$, $SD = 1.75$, all $ps > 0.820$).

DISCUSSION

The habituation of the auditory N1 and P2 components of the ERPs remains largely unexplored in schizophrenia, especially when compared with the body of research directed to P50 and P300 components. The current work intended to expand the knowledge on these components. For this purpose, N1 and P2 amplitudes were measured in a roving paradigm. Our hypotheses considered not only the habituation properties of N1 and P2, but also the different modulations induced by distinct stimulus categories. Supporting H1, we found a diminished N1 amplitude for pure tones in patients at the right frontotemporal region. In turn, H2 was not confirmed since human voices elicited higher P2 amplitudes than bird song at frontotemporal locations for both groups. Finally, H3 was partially verified, since habituation effects were moderated by group differences in P2, but not in N1 and only for bird songs. Our results showed that human voices (but not bird songs) specifically elicited a pattern of habituation in N1 in both groups. However, P2 amplitudes faded with train repetitions of bird songs only in the control group, while habituation effects to human voices were present in both groups.

The results concerning H1-Pure tones—resemble previous findings from oddball tasks, since patients with schizophrenia seem to have difficulties in allocating attention to target/relevant auditory stimuli, as reflected in the attenuation of the N1

component (9). However, for H2 we found no evidence that deficits in voice processing in schizophrenia would lead to a diminished P2. Notwithstanding, our results support previous literature that reported higher P2 amplitudes elicited by human voices compared to bird songs at Frontocentral locations (5, 7, 11), but these results did not interact with group. In other words, patients showed similar response amplitudes as controls in the initial discrimination of human voices, despite the literature describing abnormalities in P2 modulation for this group (24, 25). It may be the case that the P2 reflects an early preference for human voice processing that goes in line with the social nature of the human brain and the priority given to social cues within the species (6, 7). Although there have been descriptions of abnormalities regarding voice processing when negative emotional content is added (29), no differences have been found for non-semantic speech and neutral voice sounds (28, 30), suggesting that early stages of voice processing might be unaffected in early schizophrenia.

Taking together H1 and H2, N1 seems to mirror an orienting response toward target/simple stimuli that is impaired in schizophrenia, while P2 is likely to index more specific, elaborated categorization processes of complex sounds that are not necessarily impaired in schizophrenia. Given the differences in functional significance, these findings further unveil that the current experimental manipulation led to the dissociation of N1 and P2 amplitude, which is also reflected in habituation processes.

Furthermore, our results provide evidence that both N1 and P2 are habituating components (1, 13), notwithstanding that habituation effects are category dependent for N1. Interestingly, habituation effects were moderated by group differences in P2, but not in N1. This partially contradicts H3, as we expected a general dysfunction in habituation processes at both time-windows and stimuli in patients (25). Importantly, this effect was specific to birds and not voices, with patients showing the expected pattern of non-habituation for birds in P2. Patterns of abnormal habituation have been found for this component in schizophrenia using simple stimuli (25), and the same seems to be the case for bird songs [complex non-vocal stimuli. The specificity regarding auditory processing of the human voice may help to understand this differential effect. The early positivity that occurs around the P2 time-window has been described as sensitive to voices with increased amplitudes for these stimuli when compared with other sound categories (5). Our results corroborate these findings i.e., human voices elicited higher P2 amplitudes than bird songs for both groups]. In fact, the preference for sensory information of conspecifics is observable on the visual N170 and its increased amplitudes for faces when compared with objects (39, 40). Thus, it is possible that both auditory and visual preference for conspecific stimuli plays a relevant role in social information processing (41). From the available evidence on this matter, one study by Williams et al. (42) analyzed the habituation of brain activations in response to faces in schizophrenia. No habituation was found in several brain regions of patients (e.g., primary visual cortex and hippocampus), but when looking at the putative generator of the N170—the Fusiform Face Area (43)—patients and controls showed a similar pattern of habituation to faces. It remains plausible therefore that conspecific signals (such as voice and faces) are processed by specialized brain modules that are somewhat independent of other stimulus categories, considering how crucial it is for communication and social interactions. Developmental studies highlight indeed that preference for voices emerges early, with habituation to human voices (vs. environmental stimuli) being observable in preschoolers (44). Additionally, brain regions responsible for voice processing are thought to maturate during the 1st year of life (45), whereas P2 modulations by stimulus category and habituation are mature in 5-year-old toddlers (46, 47). So, it is possible that voice processing specializes much earlier than the onset of schizophrenia symptoms and possibly explaining how first-episode patients exhibit normal patterns of brain response to neutral non-speech human voices.

Limitations of this study comprise the absence of a formal assessment of mental and hearing abilities and the inclusion of groups on antipsychotic medication, making it impossible to dissociate the effects of the medication from the abnormalities found, as it has been previously suggested [e.g., (48)]. Also, only mid-latency ERP components were studied, not allowing us to investigate later stages of the auditory processing. Future research should consider additional stages of voice processing and investigate more nuanced associations with schizophrenia symptoms, such as hallucinations, as possible predictive factors of impairment [see e.g., (33)]. Nonetheless, regarding abnormal habituation for bird songs, it is important that future research uses other stimuli to understand if this pattern of habituation is generalized for non-voices or specific for bird songs. In addition, our results show that preference for human voices seems to be unaffected in early diagnosed schizophrenia patients. The investigation of abnormal patterns of brain activity in patients with schizophrenia, such as the ones found in the current work, allows researchers to better understand the impairments and symptoms of this pathology. More specifically, the ability to filter out irrelevant or repetitive information in early and later stages of information processing. This growing knowledge may be crucial for the future development of neurobiologically-informed early-diagnosis, assessment, and treatment for schizophrenia.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, Prune Mazer, upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Local Ethics committee of the Faculty of Psychology and Educational Sciences of the University of Porto. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FF-S, PA, TP, FB, and JM-T conceptualized the study: CC-R, TP, and CS collected the data: PM, IM, RP, FF-S, and TP analyzed

the data: PM, IM, RP, and TP drafted the manuscript. All authors revised the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.630406/full#supplementary-material

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The Effects of Antipsychotic Treatment on the Brain of Patients With First-Episode Schizophrenia: A Selective Review of Longitudinal MRI Studies

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A large number of neuroimaging studies have detected brain abnormalities in first-episode schizophrenia both before and after treatment, but it remains unclear how these abnormalities reflect the effects of antipsychotic treatment on the brain. To summarize the findings in this regard and provide potential directions for future work, we reviewed longitudinal structural and functional imaging studies in patients with first-episode schizophrenia before and after antipsychotic treatment. A total of 36 neuroimaging studies was included, involving 21 structural imaging studies and 15 functional imaging studies. Both anatomical and functional brain changes in patients after treatment were consistently observed in the frontal and temporal lobes, basal ganglia, limbic system and several key components within the default mode network (DMN). Alterations in these regions were affected by factors such as antipsychotic type, course of treatment, and duration of untreated psychosis (DUP). Over all we showed that: (a) The striatum and DMN were core target regions of treatment in schizophrenia, and their changes were related to different antipsychotics; (b) The gray matter of frontal and temporal lobes tended to reduce after long-term treatment; and (c) Longer DUP was accompanied with faster hippocampal atrophy after initial treatment, which was also associated with poorer outcome. These findings are in accordance with previous notions but should be interpreted with caution. Future studies are needed to clarify the effects of different antipsychotics in multiple conditions and to identify imaging or other biomarkers that may predict antipsychotic treatment response. With such progress, it may help choose effective pharmacological interventional strategies for individuals experiencing recent-onset schizophrenia.

Keywords: first-episode schizophrenia, antipsychotics, treatment response, longitudinal, magnetic resonance imaging

INTRODUCTION

Schizophrenia is a chronic and severe psychotic disorder that affects approximately 1% of the population, and has a profound impact on individuals who have been affected (1). The core features of this disorder are positive symptoms (delusions and hallucinations), negative symptoms (apathy, loss of emotional expression) and cognitive impairments (2). Antipsychotics, which exert effects on eliminating these symptoms by interacting with the dopamine D2 receptors in the brain (3), have been the mainstream treatment for schizophrenia since the 1950s (4). However, in spite of development and administration for decades, the usage of antipsychotic drugs as the first choice for schizophrenia patients has been of sustain controversy. The reasons include: (1) low effectiveness for whole population-about 30% of first episode patients, as well as over 50% of patients with multiple episodes, did not respond to conventional antipsychotic treatment (5); (2) many side effects-specifically, first-generation (conventional) agents (FGAs) appear to have high efficacy in reducing positive symptoms but are accompanied with serious side effects, such as acute extrapyramidal side effects (EPS) and tardive dyskinesia (TD) (6), although these effects are shown to be attenuated by second-generation (atypical) agents (SGAs) (2); and (3) effects with unpredictable outcomes-it was found that patients exposed to antipsychotics appeared to have cell loss in brain and smaller brain volume (7–9), and what these changes might cause remains uncertain. Therefore, determining the effects of different antipsychotics on the brain is important to elucidate the efficacy and side effects of the drugs simultaneously, and to justify the administration of antipsychotics (10, 11).

The magnetic resonance imaging (MRI) provides an important alternative to examine how the antipsychotic treatment affects human brain *in vivo*. In previous work, using different imaging techniques and analytic algorithms, both structural and functional brain alterations were identified in response to antipsychotics in patients with schizophrenia, mainly involving the fronto-temporal brain regions (12), basal ganglia (13), limbic system, (14–16) and several key components within the default mode network (DMN) (17). However, the findings thus far have been inconsistent. While the discrepancy in previous findings might attribute to heterogeneity in sample size, patient ethnics, illness course, and analytic approaches, several other important factors were also showing great impacts on the brain changes, including different types of drug administered, duration of untreated illness, and follow-up time (the time period that the patients were treated). As a result, it is necessary to summarize findings between brain alterations and antipsychotic treatment, and to identify factors that might bias the effects. This is essential before validating the findings in larger samples with unified analytic methodology.

In such efforts, reviewing studies that have included patients with untreated schizophrenia and collected brain imaging data before and after treatment is preferable. However, given long-standing and almost universal treatment with antipsychotic medications right after illness onset especially in the Western countries, a great number of previous studies enrolled patients who had already taken antipsychotics for a period of time (8). From the research perspective, never-treated schizophrenia patients should be included at baseline to precisely identify the treatment effects of antipsychotics on the brain. Furthermore, patients with first-episode schizophrenia display a greater sensitivity, or respond easily, to antipsychotic treatment in reducing psychotic symptoms than those who with multiple episodes (5, 6, 18). Therefore, studies with antipsychotic-naïve patients with first-episode schizophrenia are especially important as a starting point for evaluating the brain alterations after the administration of antipsychotics, to better specify the anatomical and functional changes that are associated with treatment (19). With this in mind, over the past decade, our group has collected imaging and clinical data from a large sample of antipsychotic-naïve patients with first-episode schizophrenia and longitudinally followed these patients after treatment. We found that the gray matter volume in the hippocampus was reduced after 6 weeks of antipsychotic treatment in a dose-related manner (14), and the abnormal regional activities in the orbitofrontal cortex and occipital gyrus were partly normalized after 1-year treatment (20). These findings added importance evidence in this aspect, however, our patients were followed just for 1 year and findings from different centers varied a lot as noted above. Thus, the brain changes in response to antipsychotics remain uncertain and require further exploration and generalization.

When interpreting the treatment effects, it is noteworthy that the treatment effects could not be easily explained by the brain changes before and after treatment. The model associated with illness progression also needs to be taken into consideration since the relative contribution of both models (antipsychotic drug vs. illness progression) to different brain changes remains to be clarified. Neuroimaging studies have revealed progressive brain changes since first-episode schizophrenia and provided evidence that brain changes might represent an ongoing pathophysiological process (21, 22). Under this circumstance, taking the dynamics of brain structure and function within the illness itself into consideration is necessary in studies with longitudinal designs when brain changes along the treatment are assessed (22). Findings from these longitudinal designs should be interpreted with caution, as they are not necessarily representative of a causal effect of treatment but may involve progressive pathological changes along the illness duration, especially for patients who were followed for a long time.

In the current review, therefore, we attempted to identify and summarize longitudinal neuroimaging studies providing evidence for a relationship between antipsychotic medications and brain changes in patients with first-episode schizophrenia. For a better characterization, we focused our attention chiefly on studies with patients who had never received any antipsychotics (drug-naïve), rather than patients who had been free of effects of antipsychotic medication for a period of time before admission (drug-free).

MATERIALS AND METHODS

Searching Procedures

This review was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. We searched for publications in PubMed and Embase from Jan 1st, 2000 to the present. The key words

used in the literature search were "first episode" or "first-episode" and "schizophrenia" and "antipsychotic treatment" or "antipsychotics" or "antipsychotic drug" or "antipsychotic medication" and "magnetic resonance imaging" or "MRI" or "diffusion tensor imaging" or "DTI" and "longitudinal." We also limited the search to articles that were written in English, and manually checked the reference lists of the retrieved articles for additional relevant studies.

Studies were included based on the following criteria: (a) peer-reviewed original literature, (b) longitudinal MRI studies, (c) examining the effects of antipsychotic treatment on the brain, (d) drug-naïve or drug-naïve/drug-free patients, and (e) first-episode schizophrenia patients. Studies were excluded for any of the following reasons: (a) they were case reports, editorials, comments, reviews or meta-analyses, (b) MRI was not used as the main method to investigate the neural basis of schizophrenia, (c) the effects of antipsychotic treatment on brain changes of patients were not described, (d) patients had received antipsychotic medication at the baseline assessment, or (e) patients studied had disorders other than schizophrenia, such as bipolar disorder, depression, brief psychotic disorder, delusional disorder or psychotic disorder not otherwise specified.

Notably, to better specify the brain changes associated with anatomy and function, respectively, we stratified the included studies into those were of structural imaging study and functional imaging study (**Figure 1**). In structural imaging studies, high-resolution 3D T1-weighted imaging and diffusion tensor imaging were collected, and structural parameters for gray matter (gray matter volume, cortical thickness, surface area, and etc.) and white matter [fractional anisotropy (FA), mean diffusion (MD) and etc.] were assessed. In functional imaging studies, resting-state or task-based functional MRI data was acquired, and imaging measures of regional activity, functional connectivity between regions, and brain networks were calculated.

Quality Assessment of Selected Studies

The quality of each included study was evaluated with Newcastle Ottawa Scale (23), which contains 3 categories: 4 items for patients selection, 1 item for study comparability and 3 items for outcomes assessment. The score is classified into 3 scales: 7–9 defined as good, 5–6 is fair quality, and 0–4 is poor quality. Of note, this checklist was just used to assess the quality of the included studies in our review, without criticizing the work itself or investigators.

RESULTS

A flowchart of the selection procedure with strict inclusion and exclusion criteria is shown in **Figure 1**. Among the 85 studies that were found according to our searching strategy, 19 (14, 15, 20, 24–39) of them met the inclusion criteria and were enrolled. Additional 17 (16, 17, 40–54) studies were found in other sources: five studies (50–54) came from a review (55), 4 studies (16, 46–48) came from another review (19), the co-author of 3 studies (40, 43, 45), 2 studies (17, 41) and one study (42) came from three research centers, respectively, which were same as the included studies through our searching strategy, one study (44) came from our group and one study (49) came from a reference list of a included study (37). All additional studies included 9 structural studies (16, 44, 48–54) and 8 functional studies (17, 40–43, 45–47). Finally, a total of 36 longitudinal studies was included in this review with good quality (mean score = 8.78) (**Supplementary Table 1**), including 21 studies (14–16, 27–30, 32, 33, 35–37, 39, 44, 48–54) on brain structure and 15 studies (17, 20, 24–26, 31, 34, 38, 40–43, 45–47) on brain function (**Figure 1**).

In 10 studies patients were treated with both FGAs and SGAs after baseline MRI scan (14, 15, 20, 28, 37, 39, 47–49, 52). Other 24 studies observed brain changes after treatment with SGAs (16, 17, 24–27, 30–36, 38, 40, 41, 43–46, 50, 51, 53, 54). Only two studies had no clear information of medication (29, 42). Most first-episode schizophrenia patients were in their 20 s (mean age) with illness duration <3 years, except one study with over 3 years (48). At the baseline scan, 34 studies recruited patients who had been drug-naïve (14–17, 20, 24–33, 35–44, 46–54), and the other two studies had mixed sample with both drug-naïve and drug-free patients (34, 45). The periods of follow-up ranged from 1 week to 4 years. To facilitate the discussion, the time period of antipsychotic treatment was divided into 3 phases as indicated in a previous work (56). In particular, the short-term phase was defined as the period of acute and intense psychosis, and typically <1 year. The mid-term phase was defined as the 2- to 3-year period after the acute phase, and the long-term phase was defined as the period from 3 years onward (56).

Structural Imaging Studies

Among structural MRI studies, 17 studies investigated gray matter volume alterations (14–16, 27–30, 35, 36, 39, 48–54). In particular, four studies used Diffusion Tensor Imaging (DTI) to assess the white matter microstructure (32, 33, 37, 44). Structural changes in the brain of patients with first-episode schizophrenia before and after treatment have been frequently reported in the frontal and temporal gyrus, basal ganglia and limbic system. These brain alterations were associated with symptom improvements, also influenced by antipsychotic dose. However, the effects of antipsychotics on the brain anatomy were inconsistent. Specifically, the gray matter volume in the frontal and temporal regions decreased after mid-term and long-term treatment (39, 48) but increased after short-term following-up (30, 49, 50). One of these studies observed that greater volume of the prefrontal cortex was associated with improvement in negative symptoms (30). Regarding the striatum, amisulpride monotherapy induced hypertrophy of the structure (27) but quetiapine monotherapy caused hypotrophy (16). In these two studies, it was showed that the reductions in positive symptoms were associated with striatal volume increases after the administration of antipsychotics (27), while striatal volume loss was related to low quetiapine dose (16). As to the subregions of striatum, such as the caudate and putamen, their gray matter consistently increased in patients after antipsychotic treatment (15, 49, 53, 54). Interestingly, there was a significant sex effect on the relationship between atypical neuroleptic exposure and changes in the structure of the caudate over time (54). In women, greater amount of drug exposure was associated with

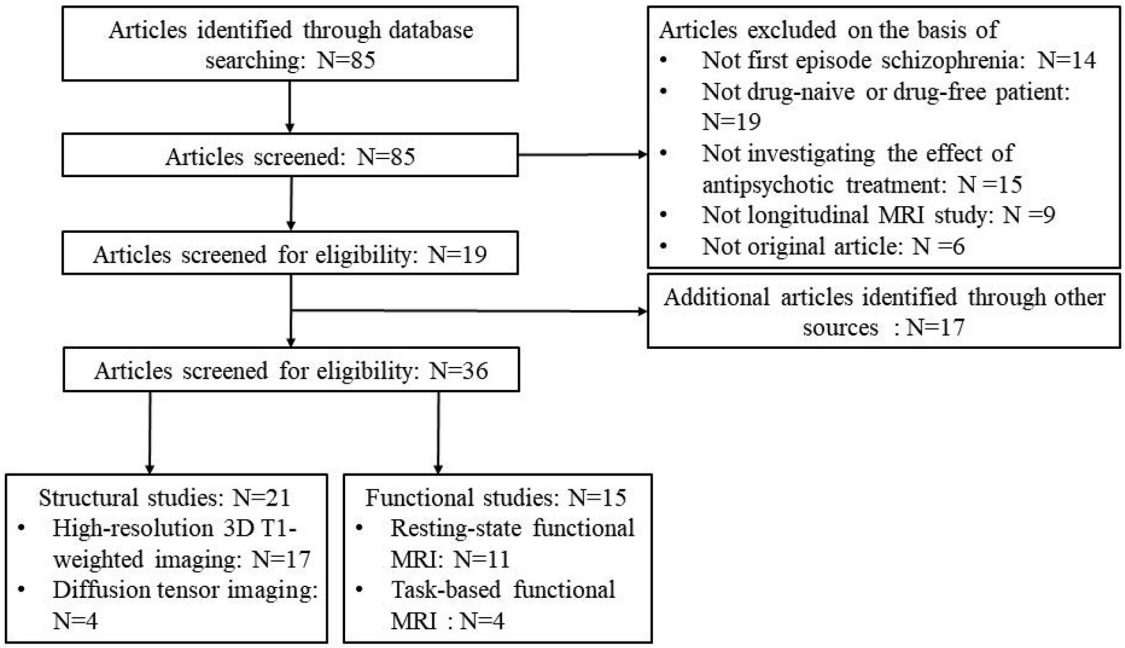

FIGURE 1 | Flowchart of the article search and selection procedure for this review.

less enlargement of the caudate, with the opposite observed in men. The volume of the anterior cingulate cortex (ACC) was decreased in patients treated with mixed FGAs and SGAs (28) or SGAs (52) but increased with FGAs (52). The increased ACC volume was correlated with greater psychotic symptom improvements (52). In addition, most studies showed reduced gray matter volume in the hippocampus over time (14, 16, 29, 35), and the changes altered in a dose-related manner (14, 16). One study observed progressive gray matter increase in the amygdala-hippocampal cluster that was related to drug plasma levels (36). Despite the limited number of DTI studies, two studies (37, 44) reported widespread white matter integrity deficits in patients after treatment, while another study revealed that lower fractional anisotropy (FA) was normalized in patients treated with amisulpride monotherapy (33). A graph-based study for anatomical brain networks showed deficits of topological parameters in the limbic system were normalized along with reductions in positive symptoms after 8 weeks of risperidone monotherapy (32).

Functional Imaging Studies

Among functional MRI studies, six of them measured regional activities of brain regions (24, 31, 34, 38, 43, 46), including those at resting-state and task-based conditions. Seven studies calculated functional connectivity between regions within the brain (17, 25, 26, 40–42, 45), and two studies involved both functional measures mentioned above (20, 47). Antipsychotics could manifest acute effects on brain function after a very short period of antipsychotic treatment, as reported in studies where patients were treated for only 1 week (40, 43). However, the findings are diverse, different patterns of functional changes were showed that might relate to different mechanisms or pathological processes. Several studies have reported that brain abnormalities at baseline, mostly involving the frontal, parietal, and temporal cortices, basal ganglia and limbic system, were normalized or reduced after being treated (17, 20, 24–26, 34, 38, 40, 41, 43, 47). These dynamic changes in abnormal brain activation with symptom improvements were observed after treatment, which may indirectly represent the beneficial effects of antipsychotics. However, the normalization of dysfunction observed before treatment did not occur in all brain regions or networks in first-episode patients after treatment. The dysfunction might be stable in brain regions over time, mainly including the caudate, putamen and dorsolateral prefrontal cortex (DLPFC) (31, 34, 42, 46). Additionally, the DLPFC was unimpaired prior to treatment but showed significantly reduced activation after treatment, suggesting that antipsychotics may have adverse effects on brain function (34).

DISCUSSION

The present review article summarized the effects of antipsychotics on brain structure and function in patients with first-episode schizophrenia. The longitudinal brain changes in relation to antipsychotic treatment remain inconclusive, as inconsistency was shown among results from different studies which may be attributable to differences in the study design. Moreover, the common brain regions were frequently reported. Specifically, basal ganglia function, especially striatum, as fundamental of dysregulated dopaminergic modulation is underlying the symptoms of schizophrenia, which is affected

by antipsychotic treatments (57). Disrupted DMN plays an important role in the pathogenesis of schizophrenia, and the network are plastic as well as can respond to effective medications (58). Here, we discuss three main factors and their potential effects on the results, namely, the type of drugs, the follow-up period and the duration of untreated psychosis (DUP).

Effects of Different Types of Antipsychotics

The different profiles of affinity for dopamine D2 receptors of FGAs and SGAs may result in different brain changes. FGAs have affinity for dopamine D2 receptors, which are highly expressed in the basal ganglia (59). However, SGAs have a favorable ratio of serotonin 5-HT2A to D2 antagonism, therefore, the findings of treatment effects on the brain have been inconsistent. Specifically, in a functional MRI study (31), patients with risperidone monotherapy showed increased synchronous neural activity in the putamen, while greater increase in activation in the putamen related to less improvement in positive symptoms. In contrast, another study (43) with olanzapine monotherapy reported decreased synchronous neural activity in the putamen, and the activation reduction in the putamen was positively related to improvements in positive symptoms. Besides putamen, the volumes of caudate nuclei and accumbens were found to be increased in patients with risperidone monotherapy, but striatal reductions were observed in patients with quetiapine monotherapy (16, 53). The putamen, caudate nuclei and accumbens are parts of the striatum with rich dopamine receptors, which are recognized as antipsychotic treatment targets for schizophrenia (15). Regarding pharmacological mechanisms, risperidone has high affinity for both 5-HT2A and dopamine D2 receptors (60). Meanwhile, olanzapine has high affinity for the 5-HT2A receptor and moderate affinity for the D2 receptor (61). The differences in therapeutic targets between olanzapine and risperidone may cause opposite findings in the above studies.

Inconsistent findings were also shown in first-episode schizophrenia after SGAs at the network level (17, 45). Specifically, the functional connectivity between the posterior cingulate cortex (PCC) and precuneus (PCUN) was found either increased (45), or decreased (17) in patients before treatment in different studies, but such changes were found to be normalized or reversed in different directionality after treatment in tandem with the improvement in symptoms, i.e., the pre-treatment increased/decreased functional connectivity was decreased/increased after treatment (17, 45). Both PCC and PCUN are central nodes for the default-mode system (62), and are considered to be closely related to functions of self-awareness, self-centered mental imagery, and extraction of episodic memory (63). The DMN was a network circuit, in which the abnormalities were commonly thought to be associated with the core model of the psychopathology of schizophrenia (64). The antipsychotics appear to exert the therapeutic effects greatly in fixing the changes in DMN, which could happen universally after initiation of antipsychotics in schizophrenia patients.

Notably, different drugs might be administered simultaneously in clinical practice for those who with first-episode schizophrenia. In this situation, the structural and functional brain changes observed might represent combining effects of differential antipsychotics. The explanation of effects from different drugs could be difficult. In our review, most patients in the included studies were treated with multiple antipsychotics. Among these studies, consistent findings of reduced volumes in the hippocampus (14, 16, 29) and ACC (28, 52) were observed. In particular, increased FGA exposure was correlated with increased ACC volume, and increased SGA exposure was related to decreased ACC volume over time (52). Other studies did not find the same pattern, but they only focused on regions within dopaminergic projections. While changes or associations could be observed in these studies, the complicated interactions between drugs or also with other factors make it hard to determine where the observed effects come from.

Effects of Follow-Up Periods

The follow-up periods in the reviewed studies ranged from 1 week to 4 years, including 31 short-term studies, four mid-term studies and only one long-term study according to the abovementioned definition. Short-term follow-up studies with different antipsychotic treatments reported robust brain structural and functional changes in first-episode schizophrenia, mainly involving the fronto-temporal cortex, basal ganglia, limbic system and several key components in the DMN. There are relatively fewer mid-term and long-term follow-up studies, and these studies revealed gray matter loss in the frontal and temporal gyri (39, 48) and whole brain volume (8, 65). A longer follow-up or treatment exposure was associated with a greater decrease in brain volumes, and greater intensity of antipsychotic treatment was associated with brain volume reduction (65).

In a recent functional brain network study (66), it was investigated that whether functional alterations in the brain were different after long-term treatment in schizophrenia patients with or without prior antipsychotic treatment. Long-term treatment may protect the functions of the amygdala, hippocampus, and striatum. Although this cross-sectional study should be interpreted with caution, it provided some new insights into the clinical benefit of long-term treatment, particularly in disease-related regions. In addition, compared to the structural changes associated with hippocampal deficits in patients receiving short-term treatment, a study identified advantageous effects of long-term antipsychotic treatment in hippocampal subfields (67). Furthermore, white matter microstructure abnormalities in the corpus callosum were investigated in patients with first-episode schizophrenia after acute antipsychotic treatment (44), while one of our previous studies showed that long-term antipsychotic treatment may also exert positive effects on the integrity of the corpus callosum (68). It has also been postulated that longer antipsychotic treatment may be associated with more adverse effects, such as weight gain, metabolic disturbance or insufficient adherence (69). However, the effects observed above come from a cross-sectional study, and longitudinal studies are needed to confirm this phenomenon and elucidate the causes.

Effects of the DUP

DUP is defined as the time from emergence of psychotic symptoms until treatment with antipsychotics, which usually

ranges from 8 to 48 weeks. The DUP has been shown to be positively associated with worse treatment responses (70). Therefore, patients with first-episode schizophrenia are recommended to take appropriate antipsychotics as soon as possible (71). In a structural study (72), smaller hippocampal gray matter volume was associated with worse cognitive performance, which might be mediated though the dopamine pathway (73). Specifically, longer DUP was significantly associated with smaller whole hippocampal volume (74). Another study (75) observed a positive association between longer DUP and accelerated hippocampal atrophy during initial treatment. These findings together may suggest that impairments in brain structures are associated with both poorer outcomes in schizophrenia and longer DUP. Therefore, reducing the DUP and providing early pharmacological intervention is critical to preventing structural deficits and improving clinical outcomes (74).

In this review, most studies employed young adults with DUP of <1 year. One functional study suggested that longer DUP led to more severe disruptions in functional connectivity in the sensory-motor network, which may subsequently result in difficulties in the treatment of positive symptoms (42). However, none of the included functional studies analyzed patients with long DUP (>2 years). One cross-sectional study (76) compared two cohorts with different DUPs (2 weeks to 2 years) and found that longer DUP was correlated with worse treatment responses and overall decreased functional connectivity between striatal nodes and specific regions within frontal and parietal cortices. Based on these results, the antipsychotics exerted different effects that might be related to different DUPs on patients as revealed by functional changes in the brain. However, the interpretation of these results should consider the heterogeneity of patients between cohorts.

POTENTIAL LIMITATIONS

There are some limitations that need to be noted. First, longitudinal studies investigating the long-term effects of antipsychotic treatment on brain are difficult, and therefore only few longitudinal imaging studies have been conducted to date. Second, the studies included in this review were published with a range of 20 years, therefore different imaging techniques and analyses were used which may influence the results. Third, our review only focused on treatment effects related to type of drugs, follow-up periods, and the DUP. Other variables or factors that may potentially relate to the treatment effect were not discussed due to limited number of studies, such as a history of substance abuse. Fourth, The site effects may to certain degree account for the variability between studies.

FUTURE DIRECTIONS

While conducting longitudinal studies is essential to evaluating medication effects, general effects of antipsychotic medication should be performed in studies controlling factors such as antipsychotic type, DUP, and follow-up period, and the generalization of the findings should be tested in independent datasets. In addition, specific effects associated with different follow-up periods, variable DUP and other factors should also be examined, preferably at the individual level in order to promote individualized medications.

CONCLUSION

To sum up, several brain regions in patients with first-episode schizophrenia are consistently reported and related to the effects of antipsychotics, including the frontal and temporal lobes, basal ganglia, limbic system, and some key components within the DMN. However, the specific anatomical and functional changes in these regions differ between different types of antipsychotics, follow-up periods and DUPs. Future studies with larger and more homogeneous patient samples are needed to clarify the effects of different antipsychotics in various conditions, which might help to develop pharmacological and interventional strategies for individuals experiencing recent-onset schizophrenia.

AUTHOR CONTRIBUTIONS

SL and WZ contributed to the conception and design of the study, as well as the supervision of all the work of this review. CY, JT, and NL contributed to literature searching and drafting of the manuscript. All authors made critical revision of the manuscript for important intellectual content and gave final approval of the version to be submitted.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.593703/full#supplementary-material

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Conflict of Interest: WZ consulted to VeraSci.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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