EARLY INTERVENTION IN PSYCHOTIC DISORDERS

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EARLY INTERVENTION IN PSYCHOTIC DISORDERS

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EDITORIAL
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Editorial: Early Intervention in Psychotic Disorders

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Editorial on the Research Topic

Early Intervention in Psychotic Disorders

Psychotic disorders such as schizophrenia are often chronic and disabling in a number of domains, including social and occupational functioning. They typically begin in adolescence or early adulthood, and major changes in the psychosocial functioning of patients with schizophrenia spectrum disorders are often evident within the first 3 years of onset, although the decline in functioning tends to plateau thereafter. Intervention during the early stages of these disorders can reduce their ultimate severity. Therefore, the first 3 years of these disorders have been described as a critical period (1), during which the patient's future disease course and prognosis are determined.

Over the last twenty years, the retrospective examination of the psychosis prodrome has been replaced by a prospective approach—referred to as the ultra-high risk (UHR) or clinical high risk (CHR) paradigm, with the aim of effectively identifying people who may be at risk of developing a psychotic disorder and, possibly, preventing its progression (2). Early intervention in psychotic disorders generally has two objectives: to prevent the onset of psychotic disorders in people with prodromal symptoms and to provide effective treatment to people in the early stages of psychotic disorder, with the goals of maximizing recovery and reducing the severity of illness (3).

Over the last three decades, numerous studies have investigated the early stages of psychotic disorders. These studies have provided an opportunity to identify factors associated with prevention and treatment outcomes and offer results suggesting how early intervention in psychosis might be the best way to reduce the social and medical burden of schizophrenia (4). However, scientifically derived data addressing many domains of early intervention in psychotic disorders are needed. For example, further research should be conducted to: identify markers for predicting psychotic conversion in UHR patients; investigate the effectiveness of psychosocial intervention and early intervention services; and understand the clinical course and pathogenesis of psychotic disorders beginning at a very early stage of the illness.

This Research Topic covers studies on biomarkers for early psychosis. Hsieh et al. identified a potential biomarker using auditory event-related potentials for individuals at UHR and in their first episode of psychosis. They observed significant sensory gating deficits and impaired deviance detection in this population. Importantly, antipsychotic medications did not seem to impact the sensory gating deficits, making it a convenient marker for the early stages of the psychotic process. Takahashi et al. examined possible relations between pituitary volume and sociocognitive impairments in patients at UHR and with schizophrenia. They found that these subjects had a significantly larger pituitary volume compared to healthy controls, and identified its negative association with working memory in patients with schizophrenia. Berger et al. reported a secondary analysis of the international NEURAPRO clinical trial of omega-3 fatty acids in UHR patients. Their findings indicated that the severity of attenuated psychotic symptoms, general psychopathology, depressive symptoms, and manic symptoms were associated with several classes of fatty acids, partially consistent with previous reports. These findings highlight the possible relevance of membrane fatty acid levels as biomarkers of psychosis risk and also suggest their possible transdiagnostic significance.

Epidemiological studies to investigate factors associated with UHR of psychosis have facilitated our understanding of the pathogenesis and course of UHR of psychosis. Lee et al. reported that problematic Internet use and negative life experiences were significantly associated with psychotic-like experiences in adolescents. Kim et al. evaluated factors associated with psychosocial function and prognostic factors in patients at UHR and with recent-onset schizophrenia. Factor analysis revealed an intrinsic four-factor structure of social-cognitive bias, reflective self, neurocognition, and pre-reflective self. These four factors were found to be associated with baseline social functioning and prodrome-to-psychosis conversion. Conus et al. conducted a questionnaire survey to explore patterns of urban experience, perception when exposed to stressors, and sensitivity to stimuli in early psychosis patients. Findings indicated that city avoidance and negative perceptions toward an urban environment increased in patients after onset of psychosis, suggesting a lower capacity to benefit from the positive aspects of urban spaces. As city avoidance is thought to influence social relations and the recovery process of early psychosis patients, these findings suggest the development of strategies to help patients in their recovery process. Chan et al. conducted a longitudinal study with a follow-up period of 2 years in adolescents and young adults at UHR of psychosis. Low education level, baseline unemployment, a history of violence, and brief limited intermittent psychotic symptoms predicted transition to psychosis, while male sex predicted persistence of the UHR state, or the development of non-psychotic disorders. The results indicated that use of the current UHR criteria can identify individuals who are at imminent risk of developing not just psychosis, but also those who may develop other mental health disorders. Tan et al. examined the longitudinal trend of subjective quality of life among patients with first-episode psychosis to identify the potential influence of patients' sociodemographic and lifestyle factors. The results indicated that employment was associated with better social relationships and environment, while higher level of educational achievement was associated with improvement of physical health, social relationships, and environment. The results highlighted the need to address educational achievement and employment in the optimization of future early psychosis intervention programs.

Clinical services for the early detection of individuals at clinical high risk of psychosis have been successful in providing psychological interventions and psychosocial support, but the path to vocational recovery has received less attention. Tognin et al. evaluated the presence and quality of educational and employment-focused interventions in the Outreach And Support In South London (OASIS) service, and discussed the path to vocational recovery in these young individuals. They suggested that the focus of early interventions should go beyond alleviating symptoms and move on to the recovery of social and vocational function.

Three review articles discussed cognitive and neurobiological mechanisms in patients at UHR and those with schizophrenia. Yamada et al. performed a systematic review of social cognitive impairment in early psychosis to explore the benefits of early intervention for disturbances of social cognition in psychosis. Allen et al. summarized the significant neurobiological findings in CHR individuals with emergent psychotic symptoms and conversion to psychosis. Delusions were suggested to be related to dysfunction in the medial temporal lobe, particularly the hippocampal–striatal–midbrain network. In addition, disorganized speech and language impairments seemed to be related to lateral temporal dysfunction. Lin et al. reviewed the literature regarding glutamate signal dysfunction, oxidative stress dysregulation, and the links between both in prodromal schizophrenia. Their findings highlighted potential biomarkers related to the *N*-methyl-D-aspartate receptor and oxidative stress regulation.

This Research Topic provides a forum for translational and clinical research conducted in the early stages of psychotic disorders, from the high-risk period to the critical period after the onset of psychosis. Reports published to date have addressed current biological, psychological, and social issues in this field. In addition, they cover the pathogenesis, clinical course, and outcomes of early psychosis. Overall, scientific studies addressing this topic can facilitate our understanding of early psychosis and contribute to the development of effective early intervention strategies.

AUTHOR CONTRIBUTIONS

All authors contributed to the article and approved the submitted version.

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Pituitary Volume and Socio-Cognitive Functions in Individuals at Risk of Psychosis and Patients With Schizophrenia

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Objectives: Increased pituitary volume, which probably reflects hypothalamic-pituitary-adrenal (HPA) hyperactivity, has been reported in patients with schizophrenia and individuals at risk of psychosis. On the basis of potential role of abnormal HPA axis function on cognitive impairments in psychosis, we aimed to examine possible relations between the pituitary volume and socio-cognitive impairments in these subjects.

Methods: This magnetic resonance imaging study examined the pituitary gland volume in 38 subjects with at-risk mental state (ARMS) [of whom 4 (10.5%) exhibited the transition to schizophrenia], 63 patients with schizophrenia, and 61 healthy controls. Social and cognitive functions of the ARMS and schizophrenia groups were assessed using the Brief Assessment of Cognition in Schizophrenia (BACS), the Schizophrenia Cognition Rating Scale (SCoRS), and the Social and Occupational Functioning Assessment Scale (SOFAS).

Results: Both the ARMS and schizophrenia groups had a significantly larger pituitary volume compared to controls. In the schizophrenia group, the pituitary volume was negatively associated with the BACS working memory score. No association was found between the pituitary volume and clinical variables (medication, symptom severity) in either clinical group.

Conclusion: Our findings support the notion of common HPA hyperactivity in the ARMS and schizophrenia groups, but abnormal HPA axis function may contribute differently to cognitive deficits according to the illness stages of schizophrenia.

Keywords: at-risk mental state, schizophrenia, pituitary gland, HPA axis, working memory

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INTRODUCTION

Neuroendocrine studies in schizophrenia (1, 2) and clinical high-risk subjects for developing psychosis [i.e., at-risk mental state; ARMS (3, 4)] (5–7) have reported hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, which mediates the stress response by governing the release of steroids (e.g., cortisol) and also regulates a number of physiological and neurobehavioral

processes (e.g., immunity, fertility, anxiety, and cognitive functioning) (8, 9), implying the role of hormonal dysregulation during the course of psychosis. Previous magnetic resonance imaging (MRI) studies in schizophrenia and related psychoses have generally reported enlarged volume of the pituitary gland, an integral part of the HPA axis, prior to psychosis onset (10, 11), along with ongoing expansion early in the course of schizophrenia (12, 13), which was associated with the emergence of psychosis and the early course of clinical symptoms (14, 15). However, some discrepant findings, such as an even smaller pituitary volume in antipsychotic-naïve schizophrenia patients with recent onset (16) or normal pituitary volume both in patients with first-episode schizophrenia and individuals with ARMS (7), have also been reported. Thus, pituitary findings in schizophrenia and high-risk subjects remain elusive and further studies will be needed to clarify the role of HPA axis abnormality and its relation to clinical characteristics in these subjects.

Cognitive impairments, particularly in memory and executive function, are a core feature of psychosis that exist during first-episode (17, 18) or even before psychosis onset (19, 20), and are also associated with poor functional outcome (21, 22). Previous neuroendocrine studies have demonstrated that these cognitive impairments (especially memory deficits) are at least partly due to abnormal HPA axis function, as indexed by an elevated diurnal cortisol level and/or blunted cortisol awaking response, in both schizophrenia (23, 24) and high-risk individuals (25). However, it is also noted that different mechanisms may contribute to distinct HPA axis abnormalities for vulnerability and onset of psychosis (25) and that the relationship between the HPA axis and memory functioning may differ at different illness stages (26). To our knowledge, it is unknown whether the pituitary volume in schizophrenia, which probably reflects HPA axis functioning, is associated with cognitive function and whether their relations differ during the course of the illness.

The present MRI study aimed to investigate the pituitary volume in individuals with ARMS and patients with schizophrenia in comparison with healthy subjects and to examine whether pituitary volume was related to neurocognitive measures and social functioning in these subjects. On the basis of our previous MRI study in an independent sample of early psychosis (11), as well as the potential role of HPA axis dysregulation in modulating cognitive function in patients with psychosis (24, 25), we predicted enlarged pituitary volume in both the ARMS and schizophrenia groups, which could be partly related to cognitive impairments in these subjects.

MATERIALS AND METHODS

Participants

Thirty-eight individuals with ARMS, 63 schizophrenia patients, and 61 healthy subjects were included in this study. Recruitment strategies for the study participants in our department have been described in detail elsewhere (27, 28).

Briefly, the individuals with ARMS, who had no previous episode of overt psychosis, were recruited from the Consultation Support Service in Toyama (CAST), a specialized clinical setting for young people (aged 15–30 years) at risk for psychosis (29). All subjects were categorized as the attenuated psychotic symptoms (APS) group (4) according to the Japanese version of the CAARMS (30). Comorbid DSM-IV-TR Axis I diagnoses (31) were anxiety disorders ($N = 9$), pervasive developmental disorders ($N = 6$), depressive disorders ($N = 6$), schizotypal personality disorders ($N = 6$), adjustment disorders ($N = 1$), or dissociative disorders ($N = 1$). Four subjects had no axis I diagnosis. They were prospectively followed up regularly at outpatient clinics of the Department of Neuropsychiatry of Toyama University Hospital; four (10.5%) of the ARMS group developed schizophrenia during clinical follow-up (mean follow-up period = 896.1 ± 841.6 days, median = 581.5). Medication status and other clinical data are summarized in **Table 1**. They were also receiving benzodiazepines ($N = 6$), antidepressants ($N = 4$), and/or tandospirone ($N = 1$) at the time of scanning.

The schizophrenia patients fulfilling the DSM-IV-TR criteria (31) were recruited from inpatient and outpatient clinics of Toyama University Hospital. They were diagnosed based on information obtained from a clinical assessment using the Structured Clinical Interview for DSM-IV Axis I Disorders Patient Edition (SCID-I/P) (32), a detailed chart review, as well as the clinical symptoms rated at the time of scanning. Medication and other clinical data are summarized in **Table 1**. At the time of scanning, experienced psychiatrists rated the clinical symptoms of the ARMS and schizophrenia subjects using the Positive and Negative Syndrome Scale (PANSS) (33).

The healthy controls, who were screened for psychiatric illness using the SCID-I Non-patient Edition (32), were recruited from hospital staff, members of the local community, and university students. They were also screened using a questionnaire consisting of 19 items concerning their personal (17 items; including a history of obstetric complications, serious head injury, seizures, neurological illness, impaired thyroid function, hypertension, diabetes, and substance abuse) and family (2 items) histories of illness. Subjects with family history of psychiatric illness among their first-degree relatives were excluded.

All participants in this study were physically healthy at the time of the study and none had a lifetime history of serious head trauma, neurological illness, serious medical or surgical illness, substance abuse, or steroid use. Handedness (34), personal and parental socioeconomic status (SES) (35), and IQ estimated using the Japanese version of the National Adult Reading Test (JART) (36) were also evaluated. None of the participants was pregnant or taking exogenous estrogens at the time of the study, but estrogen levels and menstrual cycle in female subjects were not assessed. Serum prolactin levels at the time of scanning were available for 27 ARMS and 45 schizophrenia subjects. While we previously reported the pituitary volume in early psychosis using 1.5T MRI data (11), this was our first study of the pituitary gland using independent 3T MRI data. This study received approval from the Committee on Medical Ethics of Toyama University (No. 25-7). Written informed consent was obtained from all subjects in accordance with the Declaration of Helsinki. When participants were under the age of 20, written consent was also obtained from the parent/guardian.

TABLE 1 | Demographic/clinical data, socio-cognitive functions, and brain measures in the ARMS, schizophrenia, and control subjects.

	Controls	ARMS	Sz	Group difference
	(*N* = 61)	(*N* = 38)	(*N* = 63)	
Age	25.6 ± 3.2	18.4 ± 3.9	28.0 ± 9.4	$F_{(2,159)} = 27.01$, $p < 0.001$; ARMS < Contols, Sz
Male/female	32/29	24/14	29/34	Chi-square = 2.79, $p = 0.248$
Height (cm)	166.0 ± 8.3	165.3 ± 9.0	163.2 ± 8.4	$F_{(2,159)} = 1.80$, $p = 0.168$
JART-IQ	110.2 ± 5.9	98.0 ± 10.2	99.5 ± 9.7	$F_{(2,159)} = 32.91$, $p < 0.001$; ARMS, Sz < Controls
Handedness (right/mixed/left)	40/15/6	22/12/4	52/9/2	Fisher's exact test, $p = 0.064$
SES	6.3 ± 0.9	3.2 ± 1.4	4.2 ± 1.4	$F_{(2,159)} = 82.61$, $p < 0.001$; ARMS < Sz < Controls
Parental SES	5.9 ± 0.9	4.8 ± 0.9	4.8 ± 1.4	$F_{(2,158)} = 17.86$, $p < 0.001$; ARMS, Sz < Controls
Onset age (years)	–	–	22.4 ± 7.4	–
Illness duration (years)	–	–	5.5 ± 6.0	–
Medication dose (HPD equiv., mg/day)	–	2.0 ± 1.6 (*N* = 11)	11.3 ± 7.8 (*N* = 51)	$F_{(1,59)} = 15.15$, $p < 0.001$; ARMS < Sz
Medication type (atypical/typical/mixed)	–	9/1/1	45/1/5	Fisher's exact test, $p = 0.372$
Duration of medication (years)	–	0.7 ± 1.3 (*N* = 14)	5.2 ± 6.2 (*N* = 53)	$F_{(1,64)} = 0.05$, $p = 0.820$
Serum prolactin level (ng/mL)	–	14.5 ± 13.9 (*N* = 27)	47.6 ± 73.4 (*N* = 45)	$F_{(1,69)} = 5.37$, $p = 0.023$; ARMS < Sz
PANSS positive	–	11.4 ± 3.6	13.9 ± 5.6	$F_{(1,98)} = 5.20$, $p = 0.024$; ARMS < Sz
PANSS negative	–	15.4 ± 6.7	16.3 ± 5.6	$F_{(1,98)} = 3.97$, $p = 0.049$; not significant (*post-hoc* test)
PANSS general	–	30.4 ± 8.1	31.0 ± 9.7	$F_{(1,98)} = 1.38$, $p = 0.243$
SOFAS[a]	–	52.2 ± 10.8	48.2 ± 13.9	$F_{(1,97)} = 4.52$, $p = 0.036$: not significant (*post-hoc* test)
SCoRS global rating score[a]	–	5.4 ± 2.4	5.2 ± 2.5	$F_{(1,97)} = 0.49$, $p = 0.487$
BACS subdomain z-scores				Group x domain interaction, $F_{(5,495)} = 5.64$, $p < 0.001$
Verbal memory	–	−0.9 ± 1.6	−1.3 ± 1.4	$p = 0.933$
Working memory	–	−0.8 ± 1.4	−1.0 ± 1.4	$p = 1.000$
Motor function	–	−0.8 ± 1.4	−1.9 ± 1.5	$p = 0.009$; Sz < ARMS
Verbal fluency	–	−1.0 ± 1.6	−0.8 ± 1.1	$p = 1.000$
Attention and processing speed	–	−0.3 ± 1.3	−1.4 ± 1.5	$p = 0.013$; Sz < ARMS
Executive function	–	−0.5 ± 1.3	−0.8 ± 1.6	$p = 1.000$
Pituitary volume (mm^3)	599 ± 112	687 ± 134	739 ± 150	$F_{(2,154)} = 18.62$, $p < 0.001$; Contols < ARMS, Sz
Intracranial volume (ml)	1,459 ± 126	1,408 ± 127	1,441 ± 149	$F_{(2,158)} = 1.25$, $p = 0.288$[b]
Total gray matter volume (ml)	754 ± 55	749 ± 66	704 ± 102	$F_{(2,154)} = 6.60$, $p = 0.002$; Sz < ARMS, Controls

Values represent Means ± SDs unless otherwise stated.

ARMS, at risk mental state; BACS, Brief Assessment of Cognition in Schizophrenia; JART, Japanese version of National Adult Reading Test; HPD, haloperidol; PANSS, Positive and Negative Syndrome Scale; SCoRS, Schizophrenia Cognition Rating Scale; SES, socioeconomic status; SOFAS, Social and Occupational Functioning Assessment Scale; Sz, schizophrenia.

[a] *Data missing for one schizophrenia patient.*

[b] *Age was used as a covariate.*

MRI Acquisition and Data Processing

Magnetic resonance images were obtained by utilizing a 3-T Magnetom Verio (Siemens Medical System, Inc., Erlangen, Germany) with a 12-channel head coil. A three-dimensional magnetization-prepared rapid gradient echo (MPRAGE) sequence yielded 176 contiguous T1-weighted slices of 1.2-mm thickness in the sagittal plane. The imaging parameters were: repetition time = 2,300 ms; echo time = 2.9 ms; flip angle = 9°; field of view = 256 mm; and matrix size = 256 × 256 pixels. The voxel size was 1.0 × 1.0 × 1.2 mm.

The image data were then processed on a Macintosh computer (Apple Inc., California, USA) using Dr. View software (Infocom, Tokyo, Japan) (11, 37, 38). Brain images were realigned in three dimensions to standardize for differences in head tilt during image acquisition and were then reconstructed into entire contiguous coronal images, with a 1-mm thickness, perpendicular to the anterior commissure-posterior commissure line. The signal-intensity histogram distributions from the T1-weighted images across the whole cerebrum were then used to semi-automatically segment the voxels into brain tissue components and cerebrospinal fluid. The intracranial volume (ICV) (i.e., the sum of gray matter, white matter, and CSF volumes) was estimated using SPM 12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) to correct for differences in head size (39); the groups did not significantly differ in their ICV volumes, but the schizophrenia group had a significantly smaller total gray matter volume as compared with other groups (**Table 1**).

Pituitary Measurements

As described in detail elsewhere (11, 37, 38), the volume of the pituitary gland was manually traced on 1.0-mm consecutive coronal slices based on a method used by Garner et al. (40). Briefly, we traced around the usually well-defined borders of the anterior and posterior pituitary: the diaphragma sellae, superiorly; the sphenoid sinus, inferiorly; and the cavernous sinuses, bilaterally (**Figure 1**).

All measurements were carried out by one rater (TT) without knowledge of the subject's identity, gender or diagnosis. Inter- (TT and DS) and intra-rater intraclass correlation coefficients in a subset of 10 randomly selected brains were 0.82 and 0.86, respectively.

Assessment of Socio-Cognitive Functions

Socio-cognitive functions were assessed using the same method as in our previous studies of olfactory functioning (27) and quality of life (28). All of these assessments were administered by an experienced psychologist (YK) at the time of scanning.

Briefly, the cognitive functioning was assessed using the Japanese version (41) of the Brief Assessment of Cognition in Schizophrenia (BACS) (42), which includes six cognitive domains (verbal memory, working memory, motor speed, verbal fluency, attention, and executive function). The primary measure from each test of the BACS was standardized by creating z-scores, whereby the mean score of Japanese healthy controls was set to zero and the standard deviation set to one (43). The study participants were also administered the Schizophrenia Cognition Rating Scale (SCoRS), an interview-based measure of cognitive abilities related to daily-living functioning (44). Based on three different sources (i.e., an interview with the patient, an interview with the caregiver(s), and the interviewer's rating), the rater (interviewer) assigned the SCoRS global rating score (range 1–10, higher ratings indicate greater impairment in daily living skills). Social functioning was assessed using the Social and Occupational Functioning Assessment Scale (SOFAS) (45), which corresponds to the social functioning domains of the Global Assessment of Functioning Scale in the DSM-IV (46). The scores range from 0 to 100, with higher scores indicating better functioning.

Statistical Analysis

Group differences in the demographic data were assessed by using one-way analysis of variance (ANOVA) or chi-square test. Clinical variables and social/cognitive functions were compared using the analysis of covariance (ANCOVA) with age as a covariate, because a significant group difference in age could affect these variables.

Group difference in the absolute pituitary volume was analyzed using ANCOVA with ICV and age as covariates, with diagnosis and gender as between-subject factors. Then, the schizophrenia patients were divided into first-episode (illness duration $\leq$ 12 months, 8 males and 9 females) and chronic (illness duration $\geq$ 36 months, 17 males and 21 females) subgroups; the pituitary volume was compared with the same ANCOVA model but with the subgroups (first-episode, chronic) and gender as between-subject factors. The absolute pituitary volume of neuroleptic-free patients (27 ARMS and 12 schizophrenia patients) and those who were receiving antipsychotic medication (11 ARMS and 51 schizophrenia patients) was also analyzed by ANCOVA. *Post-hoc* Scheffé's tests were carried out to follow up these analyses. The study findings remained essentially the same even when we included medication dose and duration as the covariates.

Spearman's rank correlations were calculated to examine relationships between relative pituitary volume [(absolute volume / ICV) $\times$ 100] and the clinical/socio-cognitive variables. Statistical significance was defined as $p < 0.05$.

RESULTS

Demographic, Clinical and Socio-Cognitive Characteristics

Table 1 shows the sample characteristics of the study participants. The groups did not differ in gender and height, but there were group differences in age, IQ, and parental/personal SES.

The individuals with ARMS were characterized by lower amounts of antipsychotics, less severe positive symptoms, and higher BACS measures compared with the patients with schizophrenia. However, the first-episode and chronic schizophrenia subgroups did not differ in terms of the symptom severity or socio-cognitive measures.

Pituitary Gland Volume

ANCOVA of the pituitary volume demonstrated significant main effects for diagnosis (**Table 1**) and gender ($F = 16.83$; $df = 1, 154$; $p < 0.001$), but no diagnosis-by-gender interaction was found ($F = 2.14$; $df = 2, 154$; $p = 0.122$). *Post-hoc* analyses showed that the schizophrenia ($p < 0.001$) and ARMS ($p = 0.003$) groups had significantly larger pituitary volumes compared to controls (**Figure 2**) and there was a significant gender difference in pituitary size (female > male, $p < 0.001$). The pituitary volume did not differ between the ARMS and schizophrenia groups ($p = 0.247$).

The ARMS individuals who later developed schizophrenia had a comparable pituitary volume ($N = 4$; mean = 691 mm^3, $SD = 58$) with those who did not ($N = 34$; mean = 687 mm^3, $SD = 141$). The first episode (mean = 747 mm^3, $SD = 156$) and chronic (mean = 740 mm^3, $SD = 150$) schizophrenia groups did not significantly differ for pituitary volume (ANCOVA, $F = 0.03$; $df = 1, 49$; $p = 0.863$). The patients treated with antipsychotics (mean = 750 mm^3, $SD = 145$) had a larger pituitary volume than antipsychotic-free patients (mean = 671 mm^3, $SD = 135$) (ANCOVA, $F = 4.56$; $df = 1, 95$; $p = 0.035$), while the pituitary volume in these antipsychotic-free patients was significantly larger than controls (ANCOVA, $F = 8.67$; $df = 1, 94$; $p = 0.004$).

Correlational Analyses

The relative pituitary volume was negatively correlated with age only in healthy controls ($rho = -0.403$, $p = 0.001$). There was no significant relation between the pituitary volume and clinical variables, but the BACS working memory score in schizophrenia was negatively correlated with pituitary volume (**Table 2** and **Figure 3**). This correlation survived Bonferroni's correction for

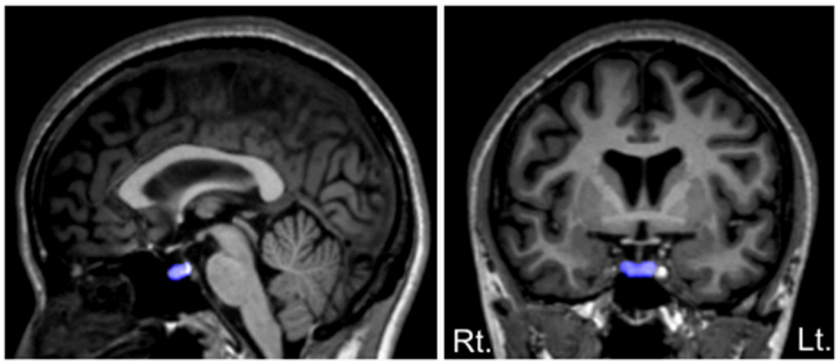

FIGURE 1 | Sagittal **(left)** and coronal **(right)** views of the pituitary gland manually traced in this study. The pituitary stalk was excluded from the tracings, but we included a posterior bright spot, corresponding to the posterior pituitary (the intensity of which is thought to reflect vasopressin concentrations).

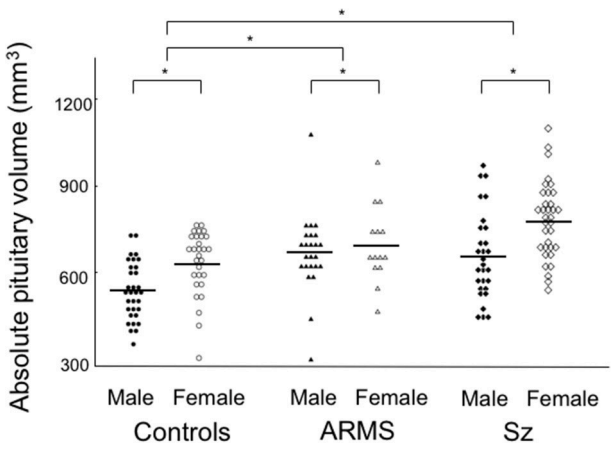

FIGURE 2 | Absolute pituitary gland volume in the subjects with at-risk mental state (ARMS), patients with schizophrenia (Sz), and healthy controls. Horizontal lines indicate mean values. *post-hoc* test: $^*p < 0.01$.

TABLE 2 | Correlations between the pituitary volume and clinical/socio-cognitive variables.

	ARMS		Schizophrenia	
	rho	***p***	***rho***	***p***
Onset age (years)	–	–	−0.17	0.174
Illness duration	–	–	0.02	0.892
Medication dose	0.06	0.730	0.17	0.190
Duration of medication	−0.01	0.967	0.11	0.382
SOFAS	0.15	0.373	−0.16	0.205
PANSS positive	0.13	0.437	0.12	0.349
PANSS negative	0.08	0.627	−0.01	0.971
PANSS general	−0.01	0.952	−0.02	0.852
SCoRS global rating score	−0.07	0.672	0.14	0.276
BACS z-scores				
Verbal memory	0.29	0.081	−0.26	0.037
Working memory	−0.05	0.782	−0.39	0.00176[a]
Motor function	−0.02	0.912	−0.11	0.412
Verbal fluency	0.07	0.660	0.12	0.362
Attention and processing speed	0.25	0.136	−0.10	0.440
Executive function	0.10	0.548	−0.27	0.034

ARMS, at risk mental state; BACS, Brief Assessment of Cognition in Schizophrenia; PANSS, Positive and Negative Syndrome Scale; SCoRS, Schizophrenia Cognition Rating Scale; SOFAS, Social and Occupational Functioning Assessment Scale.

[a] *Significant after Bonferroni's correction for multiple comparisons [28 comparisons; $p < 0.00179$ (0.05/28)].*

multiple comparisons [28 comparisons; $p < 0.00179$ (0.05/28)] (**Table 2**). The correlation between the pituitary volume and working memory, which did not change even when we used Pearson's partial correlation coefficients controlling for age ($r = -0.39$, $p = 0.00177$) or medication dose and duration ($r = -0.39$, $p = 0.00171$), was more evident in first-episode ($rho = -0.56$, $p = 0.020$) than in chronic ($rho = -0.31$, $p = 0.057$) patients. For the validation purpose, we then assessed the independent contribution of all demographic/clinical variables except for other BACS subdomain scores (**Table 1**) to predicting the BACS working memory score in schizophrenia by using stepwise regression analysis; the working memory score was significantly predicted only by the pituitary volume (Beta $= -0.316$, $t = -2.64$, $p = 0.011$) and PANSS negative score (Beta $= -0.269$, $t = -2.24$, $p = 0.029$) (Adjusted $R^2 = 0.185$).

We also examined the possible relation between the relative pituitary volume and serum prolactin levels in a subsample of 72 (27 ARMS and 45 schizophrenia) subjects, which showed a significant positive correlation ($rho = 0.293$, $p = 0.012$). The correlation between the pituitary volume and working memory in schizophrenia was not significant when we used prolactin level as a controlling factor ($rho = -0.23$, $p = 0.122$).

DISCUSSION

To our knowledge, this is the first MRI study to demonstrate a significant correlation between the pituitary volume and cognitive impairments in schizophrenia. In the present study, we replicated our previous finding of enlarged pituitary volume in

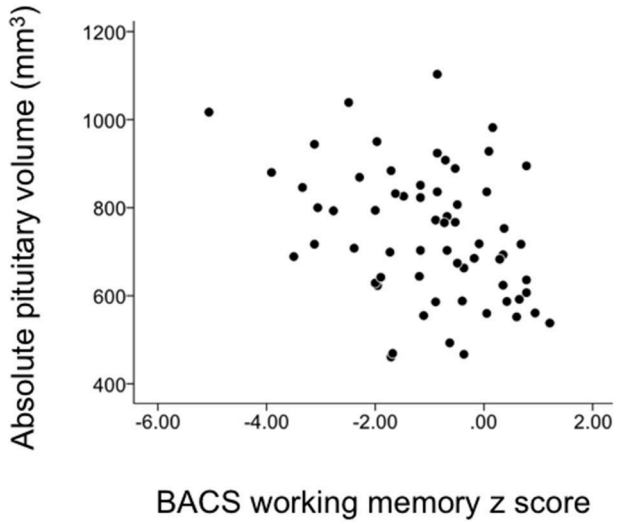

FIGURE 3 | Correlation between the pituitary volume and the Brief Assessment of Cognition in Schizophrenia (BACS) working memory score in schizophrenia patients.

both the ARMS and schizophrenia groups (11) in an independent cohort. The pituitary enlargement was significantly associated with working memory deficits, but not with clinical or other socio-cognitive measures, specifically in schizophrenia patients especially for the first-episode subgroup. These findings may reflect HPA hyperactivity as a possible indicator of vulnerability to psychosis, but also support the potential role of distinct HPA axis abnormalities in the cognitive impairments in different illness stages (25, 26).

Our pituitary findings are generally in line with previous MRI studies in clinical high-risk subjects; the individuals who later develop psychosis may exhibit pituitary expansion prior to psychosis onset (10, 40), but those without psychosis onset also have similar pituitary changes (10, 11). Although some high-risk studies did not replicate these findings (7, 47), probably due to small sample sizes and/or differences in various influencing factors as described below, pituitary expansion reported in psychosis is thought to reflect HPA hyperactivity and a subsequent increase in the size and number of corticotrophs, whereas chronic HPA activation could cause pituitary atrophy by reducing the function of the cells producing other pituitary hormones (15, 48). Thus, the pituitary volume in the course of psychosis likely reflects state-related HPA axis dysregulation, which is associated with illness stages and symptom severity (15), antipsychotic medication (2, 49), demographic characteristics [e.g., age, gender (50, 51)], and other mediating factors. Indeed, the present results supported that the pituitary gland is especially sensitive to prolactin-elevating antipsychotics (12, 52), while the effect of medication alone could not explain pituitary expansion in the antipsychotic-free subsample. On the other hand, despite a significant group difference in the medication status and symptom severity (especially for positive psychotic symptoms), we demonstrated that the pituitary gland was expanded to a similar degree in high-risk subjects as in schizophrenia patients, suggesting that distress related to prodromal symptomatology or impaired role functioning could activate the stress response even without florid psychosis.

One major finding of this study was that pituitary expansion in schizophrenia significantly correlated with working memory deficits, while such a correlation was not observed in the ARMS group. Consistent with previous studies (19, 20), the schizophrenia patients showed global cognitive deficits, with those for some domains (e.g., attention and processing speed) being more severe compared to high-risk subjects. Among these deficits, working memory impairment, which exists prior to the onset of psychosis (19, 20), is considered a central cognitive impairment in schizophrenia that is associated with a range of clinical characteristics [e.g., both positive (53) and negative (54) symptomatology and social deficits (55)]. While candidate neural circuits for working memory dysfunction in schizophrenia include the frontal-striatal-thalamic systems, particularly those involving the dorsolateral prefrontal cortex (54, 56), there is also neuroendocrine evidence that abnormal HPA axis function (i.e., flattened diurnal cortisol slope) is associated with working memory deficits in the early stages of psychosis (57) and that higher levels of dehydroepiandosterone (DHEA), an HPA-related hormone that counteracts the negative effects of cortisol in the brain (58), are associated with better working memory performance in schizophrenia (59). However, it is also suggested that each of the working memory components (e.g., the temporary systems and central executive system) may be differently impaired in psychosis (60) and that cortisol is linked with memory function in two different ways: (1) directly, by acutely disrupting working memory and short-term recall, and (2) indirectly, through the effects of persistent cortisol elevation on hippocampal integrity (23). Thus, the relation between the HPA axis dysregulation and memory deficits in psychosis is complex and may differ according to illness stages (26). Our findings of a significant relation between pituitary expansion and working memory impairment, especially in first-episode schizophrenia, but not in ARMS individuals, may reflect acute HPA hyperactivity that emerges only proximally to psychosis onset (25).

We note several limitations in this study. First, the sample size of our ARMS cohort (especially those who developed psychosis) was relatively small and their clinical follow-up periods were short (<12 months) for a substantial number of cases ($N = 14$). We therefore could not reliably examine the relationship between the pituitary volume or cognitive measures and later transition into psychosis. In addition, the ARMS group in this study was younger than the other groups. Although we statistically controlled for age differences, pituitary findings and their relation to clinical characteristics should be further tested in a larger, well-defined high-risk cohort in comparison with age-matched controls. Second, we did not assess pituitary function in this study. Although our findings regarding pituitary expansion are thought to reflect HPA axis dysregulation, a recent study of multiple measures of HPA axis function (7) did not find any association between the pituitary volume and cortical measures in high-risk and first-episode schizophrenia patients. The present

study replicated the gender difference in the pituitary volume (female > male), probably due to different endogenous estrogen levels (51), but we did not assess estrogen levels. Thus, further assessment of both pituitary volume and hormonal levels (e.g., cortisol, DHEA, and estrogen) will be needed. Third, we did not assess other brain regions closely associated with memory function (e.g., hippocampus), representing a major limitation of the study. In this study, the correlation between the pituitary volume and working memory remained essentially the same even when controlling for total gray matter volume ($r = -0.38$, $p = 0.002$), suggesting no major contribution of gray matter changes to the pituitary-cognition relationship. However, future studies should conduct more comprehensive assessment to investigate potential neural underpinnings of working memory deficits in schizophrenia. Finally, most schizophrenia patients and 11 high-risk subjects were receiving antipsychotics at the time of the study, which could have affected both pituitary volume (2) and cognitive function (61). Although we did not find a direct relation between the medication (dose, duration) and pituitary volume, BACS subscale scores, or their relationships for either the ARMS or schizophrenia groups, our results suggested that serum prolactin level could be a confounding factor for our main findings. While schizophrenia patients frequently show hyperprolactinemia as a consequence of antipsychotic treatment, several studies have reported an elevated prolactin level and its relation to cognitive function independent of medication (62). Thus, possible role of prolactin on the relation between the pituitary volume and cognitive impairments should be further tested in an antipsychotic-naïve cohort.

In summary, the present study demonstrated that clinical high-risk subjects for psychosis exhibit enlargement of the pituitary gland similar to that observed in established schizophrenia, possibly reflecting a common vulnerability. On the other hand, our findings demonstrated that the pituitary volume may be specifically associated with working memory deficits during the first-episode of schizophrenia. These findings may support the potential role of distinct HPA axis abnormalities that contribute to the cognitive impairments in different illness stages, but future studies should also examine hormone levels to understand the role of HPA functioning during the course of psychosis.

AUTHOR CONTRIBUTIONS

MS, YH, and TT conceived the idea and methodology of the study. TT conducted the statistical analyses and wrote the manuscript. SN, DS, MN, and YN recruited subjects and were involved in clinical and diagnostic assessments. TT, DS, and MK analyzed the MRI data. YK assessed the socio-cognitive functions of the study participants. KN provided technical support for MRI scanning and data processing. AF, YN, and MN managed the MRI and clinical data. MS, YH, and YT contributed to the writing and editing of the manuscript. All authors contributed to and have approved the final manuscript.

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Two-Year Clinical and Functional Outcomes of an Asian Cohort at Ultra-High Risk of Psychosis

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Background: To determine the 2-year clinical and functional outcomes of an Asian cohort at ultra-high risk (UHR) of psychosis.

Method: This was a longitudinal study with a follow-up period of 2 years on 255 help-seeking adolescents and young adults at UHR of psychosis managed by a multi-disciplinary mental health team in Singapore. Clients received case management, psychosocial, and pharmacological treatment as appropriate. Data comprising symptom and functional outcomes were collected over the observation period by trained clinicians and psychiatrists.

Results: The 2-year psychosis transition rate was 16.9%, with a median time to transition of 168 days. After 2 years, 14.5% of the subjects had persistent at-risk symptoms while 7.5% developed other non-psychotic psychiatric disorders. 38.4% of the cohort had recovered and was discharged from mental health services. The entire cohort's functioning improved as reflected by an increase in the score of the Social and Occupational Functioning Assessment Scale during the follow-up period. Predictors to psychosis transition included low education level, baseline unemployment, a history of violence, and brief limited intermittent psychotic symptoms, while male gender predicted the persistence of UHR state, or the development of non-psychotic disorders.

Conclusion: Use of the current UHR criteria allows us to identify individuals who are at imminent risk of developing not just psychosis, but also those who may develop other mental health disorders. Future research should include identifying the needs of those who do not transition to psychosis, while continuing to refine on ways to improve the UHR prediction algorithm for psychosis.

Keywords: psychosis, ultra-high risk for psychosis, schizophrenia, outcome, treatment

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INTRODUCTION

Schizophrenia and related psychotic disorders impose significant social and economic burden on the patients and the society, with the World Health Organization estimating that the direct costs associated with schizophrenia to be about 2% of total health care expenditure (1).

Detecting and managing persons at Ultra High-Risk (UHR) for psychosis was identified as a potential way to recognize persons at increased risk of developing a psychotic disorder. It is presumed that with early identification and management, mental healthcare providers will be able

to offer treatment to prevent the development of mental health disorders that may follow the prodromal phase.

However, there are significant variations in the psychosis transition rates reported across studies (2–8) which may be affected by factors such as study design, subject characteristics and follow-up duration. It also appears that the psychosis transition rate has been in the decline over the years (7, 9). Regardless, the common finding is that majority of UHR individuals do not develop a psychotic disorder (6, 10–14). This has important implications regarding patient education, treatment provision, and service planning.

Singapore is an island nation in South-East Asia with a population of 5.61 million persons (2017). This is a naturalistic study reporting on the 2-year symptom and functional outcomes of 255 help-seeking UHR individuals in Singapore. These individuals were managed by a multi-disciplinary team under the Support for Wellness Achievement Program (SWAP) which was established in 2008 and is based in the Institute of Mental Health, the only tertiary psychiatric hospital in Singapore. SWAP provides a comprehensive and integrated management program for UHR individuals aged between 16 and 30. Suitable patients are managed by the healthcare team for a maximum of 2 years. The period of care varies depending on the need and desire of the young persons and their families. Our multi-disciplinary team includes psychiatrists, case managers, psychologists, social workers, and occupational therapists. Details of the SWAP service have been described in an earlier article by Rao et al. (15)

METHODS

Sample

This study included individuals accepted into SWAP between January 2008 and June 2014. They were assessed by trained psychiatrists, with their UHR status determined using the Comprehensive Assessment of At-Risk Mental State (CAARMS) scale at baseline. The subjects were aged between 16 and 30 years at intake and assessed to be in a prodromal state. Exclusion criteria included a previous episode of DSM-IV psychotic disorder, the presence of organic brain disease, serious developmental disorder, and physical and neurological illnesses that could cause psychosis.

All data was collected at the Institute of Mental Health and its satellite clinics in Singapore. Data was captured in a clinical database and anonymized before the analysis. The study protocol was approved by the Domain Specific Review Board of the National Healthcare Group.

Assessment

Structured clinical and psychosocial assessments were conducted for patients at regular intervals. Diagnoses were confirmed by trained psychiatrists using the Structured Clinical Interviews for Diagnostic and Statistical Manual for Mental Disorders-4th Edition (SCID-I) (16). CAARMS was administered by trained case managers.

The level of functioning was measured using the Social and Occupational Functioning Assessment Scale (SOFAS) (17) and a survey of their vocational status.

SCID-I–The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) is a semi-structured interview for making the major DSM-IV Axis I diagnoses. The instrument is administered by a trained psychiatrist at baseline, 1 year, and 2 years.

SOFAS–The SOFAS is a scale that measures the individual's level of social and occupational functioning. It differs from the Global Assessment of Functioning in that it is not directly influenced by the overall severity of the individual's psychological symptoms. The SOFAS is used to rate current functioning and is rated on a scale of 0–100, which is done at baseline, 6 months, 1 year, and 2 years.

CAARMS–The Comprehensive Assessment of At-Risk Mental State (CAARMS) is a semi structured interview used to evaluate if an individual meets the UHR criteria. The positive symptom subscale was used, which assesses four symptom domains: unusual thought content, non-bizarre ideas, perceptual abnormalities, and disorganized speech. Each symptom was rated for the maximum intensity, frequency and duration, pattern, and related distress over the past 1 year. The 3 main criteria for UHR include the presence of (1) Brief Limited Intermittent Psychosis (BLIPS, with history of psychotic symptoms that resolved spontaneously within 1 week) (2) Attenuated Psychosis Syndrome (APS, having experienced subthreshold psychotic symptoms) or (3) Vulnerability group (Functional decline in a person with first degree family member suffering from psychosis). CAARMS is a widely used instrument in both Asian and Western centers (12, 18–20). CAARMS was done by trained case managers in person or by phone, and was administered at baseline, 1 year, and 2 years.

Violence was measured using self-reported information and family report. A positive answer from either the subject or their family was treated as positive for violence. These data were collected at baseline, 6 months, 1 year, and 2 years.

All measures were administered by trained clinicians. Clinical consensus was reached between psychiatrists in the study team if necessary.

Outcomes

The primary outcome of the study was the transition to a primary psychotic disorder over the 2-year follow-up period. Secondary outcomes include the persistence of UHR state, the development of a non-psychotic psychiatric disorder, and the level of functioning at 2 years.

Statistical Analysis

All statistical analyses were performed using STATA version 13. Descriptive statistics were computed for the basic demographic and clinical variables. Mean and standard deviations (SD) were calculated for continuous variables and frequencies and percentages for categorical variables. Differences between variables at baseline and last visits at 24 months were tested by paired *t*-test and Wilcoxon signed-rank test for normal and non-normal continuous variable whenever appropriate. Cox proportional hazards regression model was used to identify variables associated with conversion to psychosis.

Multinomial logistic regression analyses were also used to predict persistence of ARMS and the development of psychotic disorder at year 2 follow-up. Level of significance was set at $p < 0.05$.

RESULTS

Participants

A total of 343 patients were accepted into SWAP during the study period. Data from 255 patients was available for baseline analysis. The sample consisted of 173 males (67.8%) and 82 females (32.2%) with a mean age of 20.8 years (SD 3.3). There were 199 (78.0%) Chinese, 28 (11.0%) Malays, 23 (9.0%) Indians with the rest (2%) being Eurasians or others (**Table 1**). The study population was reflective of the racial distribution of the general population in Singapore (21).

TABLE 1 | Baseline sociodemographic and clinical characteristics of the sample.

	Mean	SD
Age, year	20.8	3.3
	n	%
GENDER		
Male	173	67.8
Female	82	32.2
RACE		
Chinese	199	78.0
Malay	28	11.0
Indian	23	9.0
Others	5	2
MARITAL STATUS		
Single/Never married	246	97.2
Married	6	2.4
Separated	1	0.4
EDUCATION		
Primary and below	27	10.6
Secondary	115	45.3
Tertiary	112	44.1
EMPLOYMENT STATUS		
Employed	113	44.3
Unemployed	25	10.1
Economically inactive	110	44.3
CAARMS GROUP		
CAARMS-APS[a] (%)	153	60.0
CAARMS-Vulnerable[b] (%)	54	21.2
CAARMS-BLIPS[c] (%)	7	2.7
Current smoker	47	18.7
Past suicide attempt at baseline	30	11.8
Past aggression or violence	71	28.0
1st degree family history of psychiatric illness	95	37.9
Past contact with the police	24	9.5

CAARMS, The Comprehensive Assessment of At-Risk Mental State; [a]CAARMS-Vulnerable, Vulnerable group; [b]CAARMS-APS, Attenuated psychotic symptom group; [c]CAARMS-BLIPS, Brief limited intermittent psychotic symptoms group.

Symptom Outcomes

At baseline, 153 (60.0%) fulfilled the criteria for APS, 54 (21.2%) for the vulnerable group and 7 (2.7%) for BLIPS. The remaining patients (16.1%) either did not fall into any specific subgroup but were determined to be in a prodromal state based on clinical decision or they fulfilled the criteria for more than 1 UHR group.

Over the 2-year follow-up period, 43 patients (16.9%) developed a psychotic disorder with a median time to transition of 168 days (**Figure 1**).

Thirty-seven patients (14.5%) continued to meet the criteria for UHR at 2 years. Nineteen (7.5%) required psychiatric care with other services but did not develop a psychotic disorder. Ninety-eight patients (38.4%) were discharged without the need for further psychiatric follow-up. One patient (0.4%) had defaulted during the follow-up period, and the 2-year data was not available for 56 (22.0%) of the patients.

Predictors of Transition to Psychosis, Persistence of UHR Characteristics and Other Psychiatric Symptoms

Using the Cox regression model, a primary or lower education level (<6 years of formal education) ($p = 0.047$), the presence of history of violence ($p = 0.003$), unemployment at baseline (vs. employed) ($p = 0.004$), and BLIPS ($p = 0.018$) predicted the development of a psychotic disorder (**Table 2**).

Further comparisons between subjects who had developed psychotic disorders, persistence of UHR or developed non-psychotic psychiatric disorders, and discharged without the need for further psychiatric follow-up using the multinomial logistic regression model, we found that male gender (vs. female) ($p = 0.024$) was significantly more likely to have persistent UHR or the development of a non-psychotic psychiatric disorder than discharged without the need for further psychiatric follow-up (**Table 3**).

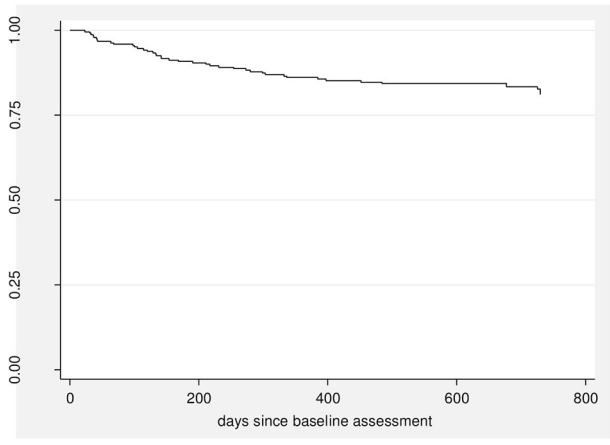

FIGURE 1 | Kaplan-Meier estimates of the risk of developing psychotic disorder.

TABLE 2 | Predictors of transition to psychosis.

	Hazard risk	95% confidence interval		*P*-value
Age	1.1	1.0	1.2	0.180
GENDER				
Male	Reference.			
Female	1.4	0.7	2.9	0.377
RACE				
Chinese	Reference			
Malay	0.8	0.3	2.2	0.643
Indian	.	.	.	.
Others	.	.	.	.
MARITAL STATUS				
Never married	Reference			
Single	3.2	0.5	20.0	0.213
Separated	.	.	.	.
Education				
Primary or lower	2.6	1.0	6.6	0.047
Secondary	Reference			
Tertiary	1.0	0.4	2.3	1.000
EMPLOYMENT STATUS				
Employed	Reference			
Unemployment	4.2	1.6	10.7	0.003
Student	1.2	0.5	2.8	0.683
FAMILY HISTORY WITH MENTAL ILLNESS				
No	Reference			
Yes	1.7	0.8	3.7	0.153
SUICIDE ATTEMPT				
No	Reference			
Yes	0.6	0.2	2.0	0.393
VIOLENCE				
No	Reference			
Yes	2.9	1.5	5.8	0.002
POLICE CONTACT				
No	Reference			
Yes	1.6	0.5	5.0	0.420
CAARMS-VULNERABLE[a]				
No	Reference			
Yes	0.6	0.2	1.4	0.202
CAARMS-APS[b]				
No	Reference			
Yes	1.1	0.6	2.2	0.787
CAARMS-BLIPS[c]				
No	Reference			
Yes	6.5	1.4	30.6	0.018

. = Not estimated due to small sample size.

CAARMS, The Comprehensive Assessment of At-Risk Mental State; [a]CAARMS-Vulnerable, Vulnerable group; [b]CAARMS-APS, Attenuated psychotic symptom group; [c]CAARMS-BLIPS, Brief limited intermittent psychotic symptoms group.

Functional Recovery

The mean SOFAS score at baseline was 53.4 (SD = 10.1), indicating a serious impairment of functioning on initial presentation. Over the 2-year follow-up period, the cohort showed a significant improvement in SOFAS score ($p < 0.001$) which improved to 69.8 ($SD = 13.4$) at 2 years.

Whitehorn et al. defined functional recovery in a cohort of patients suffering from psychosis as SOFAS score >60 (22). Using this criterion, 70.1% of our patients were able to attain functional recovery at 2 years. The rates of functional recovery were slightly higher in those with persistent UHR (74.1%) than those with a non-psychotic psychiatric disorder (50%) and those who experienced full symptom remission (69.4%). The difference was however non-statistically significant ($p = 0.737$).

DISCUSSION

UHR states are conceptualized as clinical syndromes where individuals are at elevated risk of developing psychotic disorders. But studies have shown that UHR states can take on several possible clinical trajectories (11, 23–25), ranging from complete remission of all psychiatric symptoms, to the persistence of UHR states, to the development of psychotic, and non-psychotic psychiatric conditions. This highlights the importance of maintaining flexibility of mental health services in supporting young UHR individuals whose clinical symptoms may evolve over time.

Functional decline and the emergence of subthreshold psychiatric symptoms often precede the development of psychotic disorders such as schizophrenia (5, 26) (Addington and Heinssen, Prediction and prevention of psychosis in youth at clinical high risk., (27), and one of the functions of identifying UHR individuals in this "pre-illness" stage is so that evidence-based treatment can be instituted. This brings about the possibility of reducing the individual's risk of developing any psychiatric disorder, improving their mental well-being and functional outcomes.

Psychosis Transition

This study examines the symptom and functional outcomes of help-seeking UHR individuals in an Asian population. The primary finding was that based on the current UHR criteria, the cumulative conversion rate to a primary psychotic disorder after 2 years was 16.9%, with a median duration to transition of about 5 months. In a meta-analysis involving 2,500 UHR individuals, Fusar-Poli et al. found a 29% transition rate (95% CI, 27.3–31.1%) within 31 months following first clinical presentation (23), and specifically, the transition risk at 24 months was 29.1% (23). This shows that transition rate in our cohort was low compared to that reported in other studies examining the short to medium term development of psychotic disorder in UHR individuals.

Transition rates vary between studies and factors influencing the observed rates include differences in study methodology, risk criteria, sample characteristics, duration of follow-up, and treatment. In addition, it has been observed that the rate of psychosis transition has reduced over the recent years. Yung et al. reported a reduction in the 12-month transition rate from 50 to 12% between 1995 and 2000 (9), which was not accounted for by differences in levels of pre-morbid functioning or severity of psychiatric symptoms. A possible explanation was the decrease in the duration of symptoms experienced by the patients before they received medical attention. This early detection allowed for the

TABLE 3 | Difference in sociodemographic and clinical characteristics between the three groups (transitioned, persistent ARMS / other disorders and recovered).

	Persistence of ARMS features vs. Recovered				Developed psychotic disorders vs. Recovered			
	Odds ratio	95% confidence interval		*P*-value	Odds ratio	95% confidence interval		*P*-value
Age	1.02	0.9	1.2	0.806	1.1	0.9	1.3	0.156
GENDER								
Male	Reference.				Reference.			
Female	0.3	0.1	0.8	0.024	0.9	0.4	2.1	0.747
RACE								
Chinese	Reference				Reference			
Malay	1.2	0.3	4.2	0.793	0.9	0.3	2.9	0.776
Indian	1.4	0.3	6.3	0.643	.	.	.	.
Others	1.4	0.2	15.5	0.78	.	.	.	.
MARITAL STATUS								
Single/Never married	Reference				Reference			
Married	8.1	0.3	225.2	0.216	6.8	0.4	115.0	0.184
EDUCATION								
Lower	.	.	.	.	2.8	0.9	9.3	0.087
Secondary	Reference				Reference			
Tertiary	0.8	0.3	2.2	0.728	1.03	0.4	2.7	0.951
EMPLOYMENT STATUS								
Employed	Reference				Reference			
Unemployment	3.1	0.7	13.1	0.133	7.5	2.1	27.2	0.002
Student	1.1	0.4	3.1	0.853	1.6	0.6	4.3	0.354
Smoking (Yes vs. No)	0.9	0.3	3.1	0.913	0.5	0.1	1.5	0.202
FAMILY HISTORY WITH MENTAL ILLNESS								
No	Reference				Reference			
Yes	1.4	0.5	3.8	0.453	1.7	0.7	4.3	0.238
SUICIDE ATTEMPT								
No	Reference				Reference			
Yes	2.0	0.6	6.6	0.244	0.8	0.2	4.1	0.990
VIOLENCE								
No	Reference				Reference			
Yes	1.1	0.4	3.0	0.843	2.9	1.2	6.9	0.014
POLICE CONTACT								
No	Reference				Reference			
Yes	0.1	0.01	1.5	0.104	1.01	0.2	4.1	0.990
CAARMS-VULNERABLE[a]								
No					Reference			
Yes	1.7	0.5	5.1	0.379	0.7	0.2	2.2	0.576
CAARMS-APS[b]								
No					Reference			
Yes	1.6	0.7	3.8	0.254	1.5	0.7	3.4	0.312
CAARMS-BLIPS[c]								
No					Reference			
Yes	.	.	.	.	6.0	0.8	46.7	0.088

. = Not estimated due to small sample size.

CAARMS, The Comprehensive Assessment of At-Risk Mental State; [a] CAARMS-Vulnerable, Vulnerable group; [b] CAARMS-APS, Attenuated psychotic symptom group; [c] CAARMS-BLIPS, Brief limited intermittent psychotic symptoms group.

early identification of UHR individuals so that effective treatment could be instituted, reducing the rate of transition to psychosis.

The age of onset of psychotic disorders such as schizophrenia varies between studies. This variation can be attributed to the use of differing symptom criteria in determining the onset of the illness as well as the reliability of patient-reported or family-observed onset of behavioral changes (28, 29). The consensus on the age of onset of schizophrenia is that the incidence peaks

before the age of 25 in men and between 25 and 35 for women (30). The mean age of our study population was 20.8 years. This suggests that a proportion of persons under our care may not have lived past the peak age of psychosis onset, contributing to the low transition rate. From a population perspective, illicit drug use is less common in Singapore (31, 32) and those who have an active substance use disorder have been excluded from SWAP and could have contributed to the low observed transition rate.

In addition, case management offered by SWAP may have been responsible for the low transition rate. In a double-blind, placebo-controlled trial, cognitive-behavioral case management (33) was found to be effective in reducing the 6-month conversion rate to psychosis. Our case managers are trained in providing psychological support while the team psychologists manage individuals requiring more in-depth structured therapies. This ensures that treatments with lower risk of adverse effects are made available to the UHR population, while at the same time providing benefits to those in need.

Predictors of Transition

We found that significant predictors of transition were unemployment at baseline and having a history of violence. These factors are consistent with findings from previous research (5, 9, 23, 34, 35).

The relationship between violent behavior and psychotic disorders is complex and can be influenced by factors related to the illness as well as those associated with the person's socio-occupational state (36). Some examples of these factors are impulsivity, severity of the psychotic symptoms, unemployment, and housing status. We hypothesize that UHR individuals who are at the highest risk of transition exhibit elevated levels of impulsivity, a trait found in persons suffering from both early psychosis and those with longer duration of illness (37, 38). This impulsivity could have led to the increased rates of violence (37, 38) observed in the study.

It has been reported that those experiencing BLIPS are at increased risk of developing psychotic disorders (24, 39), which is consistent with findings from our study. This suggest that BLIPS may fall along the psychosis spectrum of disorders and that treatments, including the use of antipsychotics, should be considered in the earlier illness course for someone experiencing BLIPS. In our sample, we did not find those in the CAARMS—APS group were at elevated risk of transitioning to psychosis as compared to subjects in the CAARMS—Vulnerable group.

Secondary Outcomes

The secondary aim of this study was to examine the outcomes of UHR individuals who did not develop a psychotic disorder. A significant proportion of our study population (24.0%) continued to experience persistent prodromal psychotic symptoms while 13.4% developed a non-psychotic psychiatric disorder requiring further attention. This highlights the fact that a significant proportion of UHR individuals are at risk of developing other psychiatric disorders or may continue to experience ongoing subthreshold symptoms. Hence treatment in these individuals should not merely focus on prevention of psychotic disorders but also address the myriad of other psychiatric symptoms and maladaptive coping that these individuals often exhibit.

Unemployment at baseline again predicted either the persistence of prodromal symptoms or the development of other non-psychotic psychiatric condition (40). UHR individuals often experience difficulties in their academic and occupational performance. This is consistent with the findings from our cohort where the mean baseline SOFAS score was 50.3, which indicates that many of them experienced serious challenges socio-occupational functioning. However, it is of interest to note that the proportion of individuals actively engaged in education or work remained high. This may be explained by the economic situation in Singapore.

Since 2003, Singapore has mandated compulsory primary education between the age of 6 and 15 years (41). In addition, there is a wide-range of options in higher education offered by the Singaporean government and private institutions. These would have contributed to the high proportion of the study cohort being engaged in education at baseline and at 2 years.

Furthermore, the unemployment rate in Singapore stands at a low of 2.2% in 2017, and there continues to be a large demand for both skilled and unskilled workers in the country. This is likely to be at least partially responsible for the low employment rate as seen in the study cohort.

There was significant improvement in SOFAS score to 69.8 after 2 years, reflecting an improvement in psychiatric symptoms and better psychosocial well-being from the multi-disciplinary services offered by SWAP. We did not identify any factor at baseline that could predict the 2-year functional outcomes of the cohort.

Strengths and Weaknesses

The strengths of this study are the large sample size, a low dropout rate and the clearly defined criteria for UHR state from a single study site. The limitations include (1) A proportion of subjects who were accepted into SWAP during the recruitment time-frame did not have a baseline CAARMS assessment performed and were excluded from analysis. This may have included individuals with clinical characteristics not fitting the UHR state and which could have confounded the study's findings. (2) We did not capture the diagnosis individuals who developed a non-psychotic disorder. The information would have been useful in characterizing the clinical outcomes of UHR individuals. (3) Pharmacological and non-pharmacological treatment received by the subjects were not available in detail as the information was not universally collected and may have an influence on the subjects' symptom and functional outcomes.

CONCLUSION

Research and ideas involving UHR states have evolved over time. The use of clinical criteria allows us to prospectively identify individuals at increased imminent risk for psychosis relative to the general population. Moreover, we know that a significant proportion of these individuals will have a persistence

of prodromal symptoms and may go on to develop other psychiatric disorders. Many of them will experience significant functional impairments. These individuals are likely adolescents and young adults and should be monitored regularly. Adequately addressing the needs for these individuals through a multi-disciplinary management approach may allow us to delay or even prevent the onset of more serious mental health conditions. From the results of this study, we note that those with poorer baseline functioning are at increased risk of having persistent psychiatric symptoms, and mental health services should be tailored to the needs of these individuals.

The association between low education level and an increased rate of transition indicates that it is important for mental healthcare services to allocate increased resources and attention to young persons with lower academic achievements and/or are not employed on entry into mental health service, and to consider extending the duration of care for those who may not have transited by the end of the service period, which generally range between 1 and 3 years.

Future research should include the evaluation of other risk factors that can further refine the predictive accuracy of UHR states and may include the use of biological assays in risk calculations. We should also develop therapies that may prevent the onset of both psychotic and non-psychotic disorders and to improve the functional outcomes of these young persons.

AUTHOR CONTRIBUTIONS

CC responsible for data collection, data analysis and writing up of the manuscript. SV, MS, and EA preparation of the study protocol, data analysis, and writing of the manuscript. ST and LL preparation of the study protocol, writing of the manuscript.

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Trends in Subjective Quality of Life Among Patients With First Episode Psychosis—A 1 Year Longitudinal Study

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Quality of life (QoL) is often used as an outcome assessment in programs treating patients with first-episode psychosis (FEP). The aim of this study was to examine the longitudinal trend of subjective QoL among patients with FEP and identify the potential influence of patients' social-demographic/lifestyle factors on the trend of QoL. Two hundred and eighty subjects participated in the study. Patient's demographics and subjective QoL were collected at baseline, 6 months and 1 year follow-up. Data were analyzed with a fixed-effect general linear regression model. Subjective QoL demonstrated significant trends of improvement in all four subdomains (physical health, psychological health, social relationships, and environment). Compared with unemployed participants, employed participants were significantly associated with better social relationships ($p = 0.005$) and environment ($p = 0.029$) after adjusting for age and gender. Moderation analysis demonstrated a significant improvement of physical health, social relationships, and environment for participants with a higher level of educational achievement, but not for participants with a lower level of educational achievement. Our results indicate that patients with FEP experienced significant improvement in subjective QoL over a 1 year period. Being employed was associated with overall better social relationships and environment among patients with FEP and higher educational achievement was associated with improvement of physical health, social relationship, and environment. Hence, educational achievement and employment could be considered for future optimization of early psychosis intervention programs.

Keywords: first episode psychosis, subjective Quality of Life, educational achievement, employment, longitudinal study

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INTRODUCTION

The World Health Organization (WHO) has defined QoL as individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns (1). In accordance with the definition of health by WHO, subjective Quality of Life (QoL) covers physical, emotional, mental, social, and behavioral components of well-being and function as perceived by each individual (2). Subjective

QoL was recommended as a valuable outcome assessment in programs treating patients with schizophrenia (3, 4), and patients with first episode psychosis (FEP) (5). Early treatment of patients with psychotic symptoms can result in a significant reduction of morbidity, suicide rate, improved subjective QoL, and functional recovery (5–9). Although studies have suggested a significant improvement in objective QoL over the 1st year in the treatment of patients with FEP (10), there is still a lack of conclusive evidence concerning the course of subjective QoL. Few existing studies suggest that subjective QoL does not appear to improve over time and that it remains stable both during short (11) and long periods of follow-up (12), while other studies demonstrated an improvement of subjective QoL over the years of follow-up (13, 14). Moreover, among patients with FEP, the associations between clinical characteristics, such as psychotic and cognitive symptoms, and subjective QoL have been inconsistently reported. Symptomatic remitters of positive and psychotic symptoms were reported to be associated with higher levels of subjective life satisfaction and functioning (15, 16). Severe positive and negative symptoms were strongly related to poor QoL among outpatients with schizophrenia (13, 17), while QoL was also reported to be correlated with both psychotic and negative symptoms to a minor extent (18). These inconclusive findings were most probably due to the heterogeneity of study design, patient setting, methods of recruitment, premorbid adjustment, varying instruments that were used for assessment of QoL and different approaches of statistical analysis.

The factors influencing QoL of patients with FEP remains unclear. Higher depressive symptoms and lower daily activities had a negative effect on subjective QoL and this independent effect diminished over time (13). Educational achievement in patients with chronic schizophrenia was reported to be either positively (19) or negatively (20) associated with subjective QoL, which was influenced by the individual's cognitive difficulties, personal adaptive skills, resilience as well as environmental-social factors and support. For patients with psychiatric disabilities, employment plays an essential role in providing financial gains, social contacts, and support, as well as a sense of personal achievement (21). Being employed was associated with better health related QoL for patients with chronic schizophrenia (22–24). Results from the NAVIGATE study indicated that, compared with usual community care, comprehensive care improved the subjective QoL, and psychopathology among patients with FEP (25). Secondary analysis of data from the NAVIGATE study showed that a program with supported employment and education (SSE) was associated with improvement in work or school participation among patients with FEP (26). However, the influence of SSE on participants' subjective QoL remains unclear.

PURPOSE OF STUDY

The primary goal of the current study was to examine the trend of subjective QoL among patients with FEP over 1 year of treatment in the early psychosis intervention program (EPIP). We further aimed to identify the potential association of significant confounders including educational achievement and employment, with the trend of subjective QoL.

METHODS

Sample

This single center cohort study enrolled outpatients with FEP diagnosed at the Institute of Mental Health, Singapore, which is the de facto national mental health institute of the country and a tertiary treatment center that serves the entire population of Singapore. FEP was defined as the first episode of psychotic disorder with no prior or minimal treatment (<12 weeks of antipsychotic medication) (27). The recruitment for the current study started in Feburary 2014 and ended in October 2016, with the last follow-up conducted on October 2017. The inclusion criteria for the participants were: (i) aged between 16 and 40 years and (ii) no history of major medical or neurological illness. Ethical approval to conduct the study was obtained from the National Healthcare Group Domain Specific Review Board. All participants provided written informed consent. Parental consent was obtained for participants who were below the age of 21 years. The EPIP in Singapore was implemented to provide universal and indicated prevention for patients with FEP, with the primary goals of improving clinical outcomes and QoL, as well as reducing the cost and burden of care for their families and the general public. The program comprises several initiatives. (1). Education of the general public with the major goal of reducing the duration of untreated psychosis (DUP). (2). Networking with primary healthcare providers. (3). Providing decentralized and accessible services. (4). Tertiary prevention aimed at reducing mortality, morbidity and the progression of the illness, provided by a multidisciplinary team (psychiatrists, case managers, psychologists, social workers, occupational therapists, pharmacologists, and nurses). The details of the EPIP in Singapore have been described in previous articles (27, 28).

Measures

Baseline assessment included data on participants' social demographics and clinical history. Severity of symptoms was assessed using the Positive and Negative Syndrome Scale (PANSS) for schizophrenia (29) while functioning was assessed with the Global Assessment of Functioning (GAF) score (30). These ratings were performed by psychiatrists who were trained in the use of the rating instruments (9). The inter-rater reliability for PANSS in our sample was 0.94. PANSS, GAF score, prescription of antipsychotics, antidepressants, and mood stabilizers were collected from medical records.

Hazardous alcohol use was estimated using the Alcohol Use Disorders Identification Test (AUDIT, self report version), which is a brief, 10 item inventory developed by the World Health Organization (WHO). Responses to the ten AUDIT questions were assigned a score between 0 and 4, based on the frequency of the circumstance or activity described. Scores of 8 or higher suggest a possibility of hazardous alcohol use, and a need for further monitoring or assessment (31). AUDIT has been used

among patients with FEP in Singapore to measure hazardous alcohol use (32).

The WHOQOL-BREF is a 26 item questionnaire that is designed to measure an individual's perception of QoL over the past 1 month (33). The WHOQOL-BREF consists of 4 domains: physical health, psychological health, social relationships, and environment. All items are constructed on variations of a 5-point Likert scale, with scores from 1 to 5, enquiring on "how much," "how completely," "how often," "how good," or "how satisfied" the individual felt. Scores for the 4 domains were calculated by taking the mean of all items within the domain and multiplying by 4 and transforming it to a 0–20 scale. Domain scores were not scored when more than 20% of the items were missing. It was also not calculated when more than 2 items were missing from the domain. This is, with the exception of domain 3 (social relationship), where it is unacceptable if one item is missing (34). This instrument has been validated in patients with schizophrenia, reporting good internal consistency for total WHOQOL-BREF score and being adequate for the 4 domains (35). In our current study, QoL of participants was assessed at baseline, 6 months and 1 year follow-up.

For statistical analysis, patient characteristics were regrouped. Educational achievement, "Low" included those with General Certificate of Education (GCE) "O" level (or equivalent) and lower qualifications; "High" included those with higher than GCE "O" level qualifications. Participant's employment status was self-reported by answering the question "What was your main working status over the past 1 year." Participants with the answer "full-time/part-time employment," "on national service," and "student" were grouped as "Employed." Those who answered, "home maker/house wife" or "jobless" were grouped as "Unemployed." "Unmarried" referred to participants who were never married, separated, divorced or widowed. "Married" referred to participants who were currently married. "Housing type" was defined as the current housing condition regardless of whether it was self-owned or rented. "Economic house" referred to all government developed housing and "Private house" referred to all private housing developments including condominium, terrace houses and bungalows. Baseline data on smoking was collected by asking participants if they were smokers with the additional options of "ex-smoker," "never smoked," or "currently smoking." Participants who answered "ex-smoker" and "never smoked" were grouped as "non-smokers." Participants who answered that they were "currently smoking" were grouped as "current smokers."

Two hundred and eighty patients were consecutively enrolled in this study and 81 of them completed the assessments at all three time points.

Data Analysis

All statistical analyses were performed with SPSS (*IBM, v.25*). We used descriptive statistics to establish the socio-demographic and clinical characteristics of the study cohort. Numerical variables were presented as mean ± standard deviation (SD) for variables with normal distribution and median (interquartile range, IQR) for variables with skewed distribution. Categorical variables were presented as count (percentage, %). Comparison analysis between the participants who presented and those who were lost to follow-up at either the 6 months or 1 year visit were performed with *t*-test, chi-square test, or Mann-Whitney *U*-tests to determine the differences in socio-demographic and clinical characteristics. The actual mean scores of QoL collected at baseline, 6 months follow-up and 1 year follow-up were compared with Analysis of Variance (ANOVA) with a *post-hoc Bonferroni* test and the actual mean score of PANSS or GAF scale collected at baseline and 1 year follow-up were compared with a paired *t*-test.

The association of participant educational achievement and employment status with the course of QoL was analyzed by the fixed-effect linear mixed regression model (LMM). LMM with repeated measurement was used to estimate the within-subject trend of QoL, PANSS score, GAF score, and the moderation (interaction) between participant's social demographics and the course of QoL. In the mixed regression model, QoL score was treated as a dependent variable. Patients' characteristics and index for repeated measurement were treated as independent variables. Interaction terms which were built between social-demographic/lifestyle factors and index of repeated measurement were included into the adjusted LMM model, providing the *p*-value for the interaction terms were <0.05 before adjustment. The interaction term between educational achievement and the trend of QoL was included in the final model as the interaction was statistically significant. Mean values of subgroup QoL score at various time points were estimated by treating the index of repeated measurements as a categorical variable in the regression model and the estimated mean scores were exported into an Excel document for plotting. The repeated covariance type for LMM was set at AR(1) to achieve lowest value of Akaike information criterion (AIC) and Bayesian information criterion (BIC). Statistical significance was accepted at the ≤ 0.05 level for all tests.

RESULTS

Of the 280 patients who were included in the study, 136 completed the 6 months follow-up and 129 completed the 1 year follow-up. Participants' baseline demographics and clinical characteristics are shown in **Table 1**. 91.2% of the participants were patients diagnosed with schizophrenia and related psychosis and 8.2% were patients diagnosed with mood disorder with psychotic symptoms. At 6 months, Chinese patients (79.4%) were more likely to continue with the study follow-up compared with patients in other ethnic groups ($p = 0.024$, **Table 1**). Patients who were Singaporeans (97.8%) were more likely to continue with the study follow-up compared with foreigners ($p = 0.015$). At 1 year, unmarried patients (92.2%) were more likely to participate in the study compared with married participants ($p = 0.038$).

Participants reported improved QoL in all four subdomains over the 1 year period (**Figure 1A**). In domain 1 (physical health), the estimated mean score of QoL improved from 14.31 ± 0.28 to 14.96 ± 0.28 (**Figure 1B**). Overall *p*-value for this trend of QoL was 0.036. In domain 2 (psychological health),

TABLE 1 | Comparison of patient characteristics of those with and without 6 months and 1 year follow up.

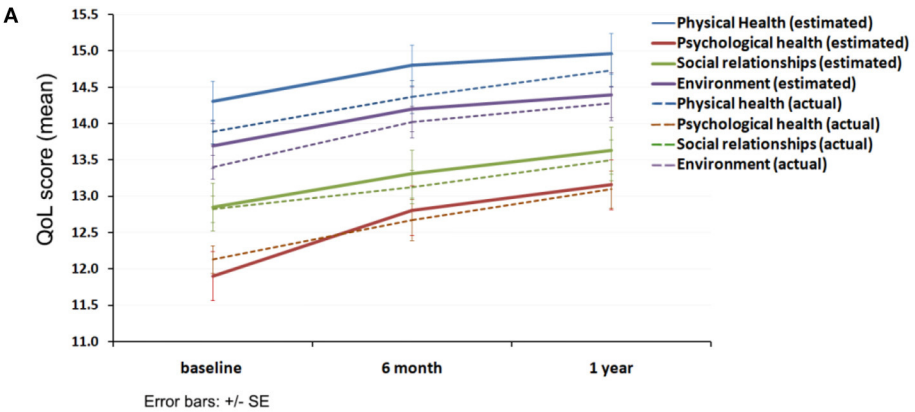
Patient characteristics	Baseline ($n = 280$)	6M with follow up ($n = 136$)	6M without follow up ($n = 144$)	*p*-value	1 year with follow up ($n = 151$)	1 year without follow up ($n = 129$)	*p*-value
Age, years, mean ± SD	25.76 ± 6.23	25.24 ± 5.80	26.26 ± 6.61	0.174	25.03 ± 5.97	26.39 ± 6.41	0.067
Sex, no. (%)				0.234			0.561
Male	142 (50.7)	64 (47.1)	78 (54.2)		79 (52.3)	63 (48.8)	
Female	138 (49.3)	72 (52.9)	66 (45.8)		72 (47.7)	66 (51.2)	
Ethnicity, no. (%)				0.024[a]			0.227
Chinese	200 (71.4)	108 (79.4)	92 (63.9)		107 (70.9)	93 (72.1)	
Malay	41 (14.6)	13 (9.6)	28 (19.4)		19 (12.6)	22 (17.1)	
Indian	25 (8.9)	11 (8.1)	14 (9.7)		18 (11.9)	7 (5.4)	
Others	14 (5.0)	4 (2.9)	10 (6.9)		7 (4.6)	7 (5.4)	
Nationality, no. (%)				0.015[a]			0.123
Singaporean	262 (93.6)	133 (97.8)	129 (89.6)		138 (91.4)	124 (96.1)	
Permanent resident	14 (5.0)	3 (2.2)	11 (7.6)		9 (6.0)	5 (3.9)	
Others	4 (1.4)	0 (0.0)	4 (2.8)		4 (2.6)	0 (0.0)	
Marital Status, no. (%)				0.851			0.038[a]
No	246 (87.9)	120 (88.2)	126 (87.5)		127 (84.1)	119 (92.2)	
Yes	34 (12.1)	16 (11.8)	18 (12.5)		24 (15.9)	10 (7.8)	
Children, no. (%)				0.392			0.162
Without children	253 (90.4)	125 (91.9)	128 (88.9)		133 (88.1)	120 (93.0)	
With children	27 (9.6)	11 (8.1)	16 (11.1)		18 (11.9)	9 (7.0)	
Educational achievement, no. (%)				0.915			0.224
Low	77 (27.5)	37 (27.2)	40 (27.8)		37 (24.5)	40 (31.0)	
High	203 (72.5)	99 (72.8)	104 (72.2)		114 (75.5)	89 (69.0)	
Father education, no. (%)				0.259			0.557
Low	197 (70.4)	97 (67.4)	100 (73.5)		47 (31.1)	36 (27.9)	
High	83 (29.6)	47 (32.6)	36 (26.5)		104 (68.9)	93 (72.1)	
Mother education, no. (%)				0.882			0.321
Low	207 (73.9)	100 (74.3)	107 (74.3)		108 (71.5)	99 (76.7)	
High	73 (26.1)	36 (26.5)	37 (25.7)		43 (28.5)	30 (23.3)	
House own[b], no. (%)				0.756			0.395
Private	26 (10)	12 (9.4)	14 (10.5)		16 (11.4)	10 (8.3)	
Economic	235 (90)	116 (90.6)	119 (89.5)		124 (88.6)	111 (91.7)	
Employment status[b], no. (%)				0.906			0.378
Unemployed	181 (66.1)	87 (66.4)	94 (65.7)		93 (63.7)	88 (68.8)	
Employed	93 (33.9)	44 (33.6)	49 (34.3)		53 (36.3)	40 (31.3)	
Smoking status, no. (%)				0.621			0.114
Ex or never smoker	168 (60.0)	83 (61.0)	92 (63.9)		88 (58.3)	87 (67.4)	
Current smoker	112 (40.0)	53 (39.0)	52 (36.1)		63 (41.7)	42 (32.6)	
Alcohol, no. (%)				0.369			0.570
No hazardous use	244 (87.1)	116 (85.3)	128 (88.9)		130 (86.1)	114 (88.4)	
With hazardous use	36 (12.9)	20 (14.7)	16 (11.1)		21 (13.9)	15 (11.6)	
Diagnosis,[b] no. (%)							
Schizophrenia and related Psychosis	212 (75.7)	113 (83.1)	99 (68.8)	0.489	116 (63.6)	96 (74.4)	0.078
Mood disorder with Psychotic symptoms	23 (8.2)	14 (10.3)	9 (6.2)		17 (11.3)	6 (4.7)	
PANSS_P[b], mean ± SD	21.89 ± 5.99	22.11 ± 6.12	21.71 ± 5.91	0.613	22.27 ± 6.19	21.60 ± 5.85	0.400
PANSS_N[b], mean ± SD	15.76 ± 8.73	15.72 ± 8.60	15.78 ± 8.88	0.957	16.32 ± 8.61	15.32 ± 8.84	0.382
PANSS_GPS[b], mean ± SD	38.16 ± 11.35	38.42 ± 10.48	37.94 ± 12.06	0.744	39.35 ± 10.74	37.24 ± 11.75	0.151
GAF_S[b], mean ± SD	44.57 ± 12.21	43.50 ± 12.15	45.47 ± 12.23	0.218	43.56 ± 12.25	45.34 ± 12.17	0.267
GAF_D[b], mean ± SD	46.57 ± 11.60	45.58 ± 11.39	47.39 ± 11.75	0.232	46.15 ± 11.82	46.89 ± 11.46	0.628
No. of antipsychotics, median (IQR)	1 (0)	1 (0)	1 (0)	0.777	1 (0)	1 (0)	0.880

(Continued)

TABLE 1 | Continued

Patient characteristics	Baseline ($n = 280$)	6M with follow up ($n = 136$)	6M without follow up ($n = 144$)	p-value	1 year with follow up ($n = 151$)	1 year without follow up ($n = 129$)	p-value
No. of antidepressants, median (IQR)	0 (1)	0 (1)	0 (1)	0.651	0 (1)	0 (1)	0.692
No. of mood stabilizers, median (IQR)	0 (0)	0 (0)	0 (0)	0.097	0 (0)	0 (0)	0.175
DUP[b], days, mean ± SD	13.55 ± 21.69	13.28 ± 20.37	13.79 ± 22.85	0.856	12.41 ± 20.60	14.43 ± 22.53	0.475

[a] $p < 0.05$.
[b] *Data may not sum to total due to missing values.*
SD, Standard deviation; IQR, Interquartile range; PANSS_P, Positive and negative syndrome scale_ positive; PANSS_N, Positive and negative syndrome scale _negative; PANSS_GPS, Positive and negative syndrome scale _general psychopathology scale; GAF_S, Global assessment of functioning_symptoms; GAF_D, Global assessment of functioning_disabilities; DUP, Duration of untreated psychosis.



B

		QoL score (mean±SE)			
		Baseine	6 month	1 year	P value (within-subject effect)
Physical health	Estimated	14.31±0.28	14.80±0.28	14.96±0.28	0.036
	Actual	13.89±0.16	14.37±0.22	14.73±0.23	0.009
Psychological health	Estimated	11.90±0.34	12.80±0.34	13.16±0.34	0.001
	Actual	12.13±0.19	12.67±0.28	13.09±0.26	0.012
Social relationships	Estimated	12.85±0.33	13.31±0.33	13.63±0.33	0.040
	Actual	12.82±0.18	13.13±0.23	13.50±0.28	0.104
Environment	Estimated	13.69±0.31	14.20±0.31	14.40±0.31	0.031
	Actual	13.40±0.17	14.02±0.22	14.28±0.23	0.004

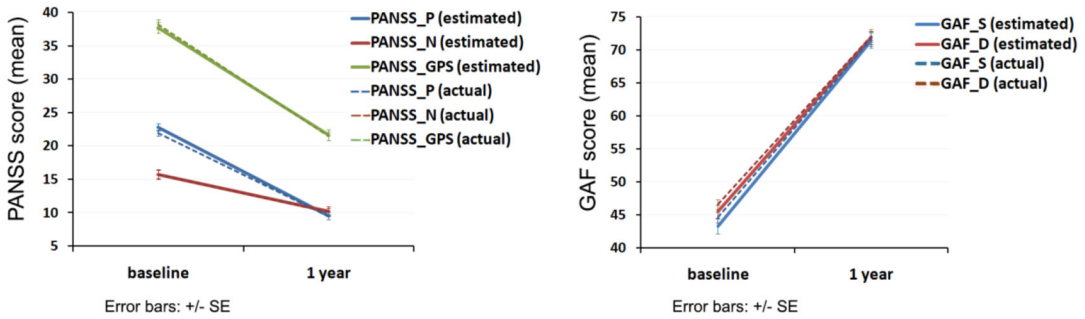
FIGURE 1 | QoL of the participants. **(A)** Trends of subjective QoL over 1 year follow-up period; **(B)** Subdomain QoL score at baseline, 6 months and 1 year.

the estimated mean score of QoL significantly increased from 11.9 ± 0.34 to 13.16 ± 0.34 ($p < 0.001$). In domain 3 (social relationships), the estimated mean score of QoL improved from 12.85 ± 0.33 to 13.63 ± 0.33, with an overall p-value of 0.04. In domain 4 (environment), the estimated mean score of QoL improved from 13.69 ± 0.31 to 14.4 ± 0.31. P-value for the trend of QoL was 0.031. The actual mean score of QoL showed similar trends to the estimated mean score with $p <$ 0.05 for subdomains of physical health, psychological health and environment.

Clinical assessments demonstrated an overall reduction in psychotic symptoms and improvement in function as indexed by PANSS and GAF scores, respectively (**Figure 2A**). PANSS score decreased by about 58.3% for positive symptoms (within-subject $p < 0.001$, **Figure 2B**); 35.1% for negative symptoms ($p < 0.001$) and 42.6% for general psychopathology ($p < 0.001$) over the 1 year follow up. GAF score increased by about 65.1% for the assessment of symptoms ($p < 0.001$) and increased by about 58.1% for the assessment of disabilities ($p < 0.001$). Actual mean score of PANSS and GAF showed similar trends to the estimated score with $p < 0.001$ for all subcategories.

Regression analysis showed no significant association between participant's educational achievement and overall QoL both before and after adjustment (**Table 2**). Compared with patients

A



B

		Scores (mean±SE)			
		Baseline	**1 year**	**Change %**	**P value (within-subject effect)**
PANSS_P	Estimated	22.82±0.50	9.52±0.50	58.3%	<0.001
	Actual	21.89±0.39	9.43±0.39	56.9%	<0.001
PANSS_N	Estimated	15.74±0.72	10.21±0.72	35.1%	<0.001
	Actual	15.76±0.57	10.11±0.54	35.9%	<0.001
PANSS_GPS	Estimated	37.71±0.84	21.65±0.84	42.6%	<0.001
	Actual	38.16±0.74	21.44±0.65	43.8%	<0.001
GAF_S	Estimated	43.25±1.11	71.39±1.11	65.1%	<0.001
	Actual	44.57±0.79	71.63±1.06	60.7%	<0.001
GAF_D	Estimated	45.46±0.99	71.86±0.99	58.1%	<0.001
	Actual	46.57±0.75	72.09±0.96	54.8%	<0.001

FIGURE 2 | Clinical assessment of participant's psychotic symptoms and function. **(A)** Change of PANSS and GAF score over 1 year; **(B)** PANSS and GAF score at baseline and 1 year. PANSS_P, Positive and negative syndrome scale_ positive; PANSS_N, Positive and negative syndrome scale_negative; PANSS_GPS, Positive and negative syndrome scale_general psychopathology scale; GAF_S, Global assessment of functioning_symptoms; GAF_D, Global assessment of functioning_disabilities.

who were unemployed, patients who were employed were associated with better social relationships [adjusted B: 1.73, 95% CI: 0.55–2.93, $p = 0.005$] and environment [adjusted B: 1.29, 95% CI: 0.13–2.44, $p = 0.029$) (**Table 2**).

Moderation analysis identified a continuous and significant improvement of physical health (domain 1, **Figure 3A**), social relationships (domain 3, **Figure 3B**) and environment (domain 4, **Figure 3C**) over a 1 year period for participants with higher level of educational achievement, but not for participants with a lower level of educational achievement ($p = 0.006$, 0.037 and 0.015, respectively). The moderation relationship between educational achievement and psychological health was borderline ($p = 0.09$) and there was no significant moderation relationship between employment status and the four subdomains of QoL.

DISCUSSION

In the present study, patients with FEP demonstrated a significant improvement of psychotic symptoms, general functioning and subjective QoL during the 1 year follow-up period. To our best knowledge, this study is among the first few studies that have examined the temporal development of subjective QoL among patients with FEP using a model of repeated measurements with multiple time points of assessment.

Although there have been many studies on the determinants of QoL among patients with mental disorders (36, 37), there is a lack of consensus as to how QoL should be defined and measured. For patients with schizophrenia, the validity of subjective QoL might be limited by a self-reporting scale (2) and could have been influenced by several factors including patients' persistent psychotic symptoms, self-esteem, adaptation to adverse circumstances (38), presence of cognitive deficits and lack of insight (20, 36). However, some studies have demonstrated the convergent validity of QoL assessed by a patient's self-report and that assessed objectively by clinicians (39). Patients with schizophrenia were able to report their feelings, experiences, and social functions accurately (37, 40, 41), showing that the QoL of patients with psychosis can be assessed subjectively.

Our study allows the testing of potential factors influencing the trend of QoL over time. The literature on the relationship between QoL and education in schizopherenia is inconclusive. In some studies, patients with a higher level of education reported worse QoL compared to patients with lower levels of education (20). While, others demonstrated that in patients with schizophrenia, higher educational achievement was correlated with better social functioning and greater satistifaction with life (42). In the current study, we found no evidence of

TABLE 2 | Association of participant's educational achievement or employment status with overall subjective QoL during follow-up period.

Variable	Outcome	Before adjustment				After adjustment[a]			
			95% CI				95% CI		
		B	Lower bound	Upper bound	*p*-value	B	Lower bound	Upper bound	*p*-value
Education (high vs. low)	Physical health	0.13	−0.93	1.18	0.813	0.44	−0.65	1.52	0.427
	Psychological health	−0.68	−1.96	0.61	0.297	−0.50	−1.83	0.84	0.461
	Social relationships	0.04	−1.18	1.25	0.952	0.43	−0.81	1.68	0.491
	Environment	0.35	−0.82	1.53	0.552	0.89	−0.27	2.05	1.131
Employment (employed vs. unemployed)	Physical health	0.51	−0.47	1.48	0.305	0.32	−0.76	1.40	0.555
	Psychological health	0.52	−0.71	1.76	0.404	0.64	−0.70	1.99	0.344
	Social relationships	1.74	0.66	2.82	0.002	1.73	0.55	2.93	0.005
	Environment	1.41	0.33	2.49	0.011	1.29	0.13	2.44	0.029

[a]*Adjusted for age and gender.*
CI, Confidence interval; B, Beta coefficient.

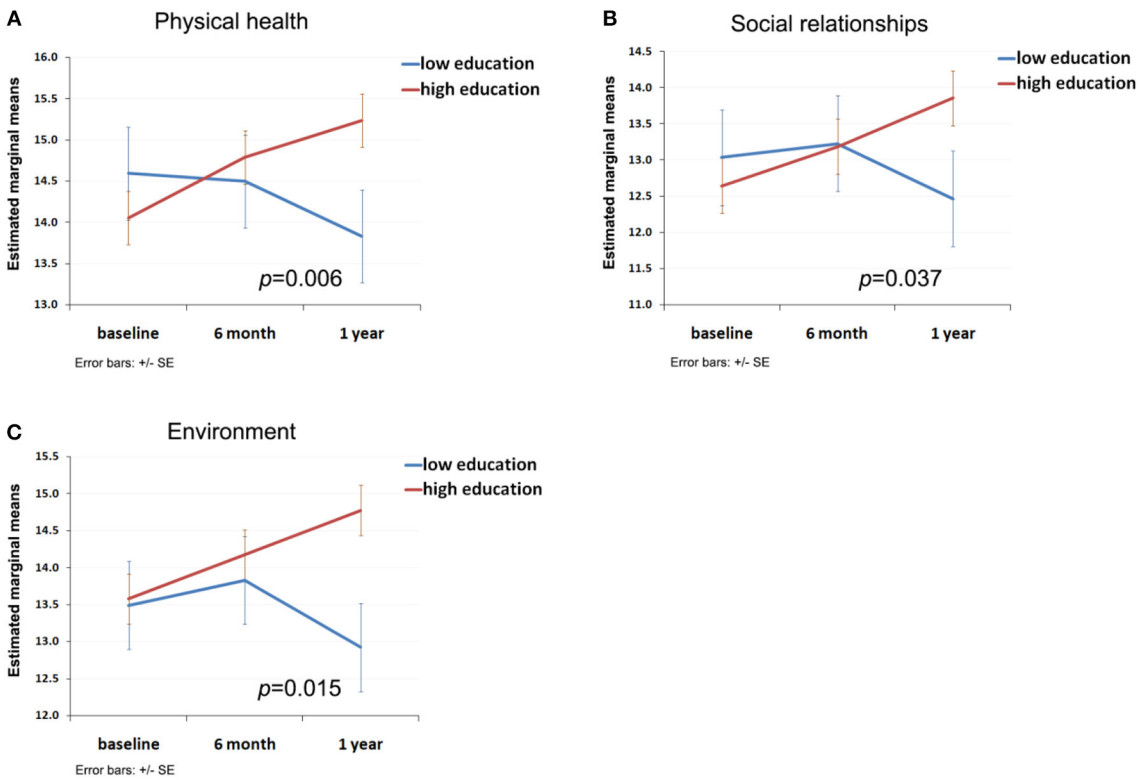


FIGURE 3 | Moderation effect of participant's educational achievement on the trend of subjective QoL. **(A)** Moderation curve of educational achievement with trend of physical health; **(B)** Moderation curve of educational achievement with trend of social relationships; **(C)** Moderation curve of educational achievement with trend of environment.

significant association between participants' educational level and overall QoL. However, compared to participants with lower educational achievement, participants with higher educational achievement were more likely to report worse physical health and social relationships at baseline, which is possibly due to the higher social demands and expectations among this group of patients.

The results of the associations between employment and overall QoL in this study appear to be consistent with previous studies in the literature. Patients who were employed were likely to be associated with better health-related QoL compared with patients who were unemployed (43). The association may be explained by the better self-esteem among patients with employment, which was described as a mediating factor between being employed and QoL (44), and having a larger social network due to being employed (45). The causal relationship between employment and QoL remains unclear and it is possible that the participants with higher QoL were more likely to be employed.

During the 1 year follow-up period, compared to patients with a relatively lower level of educational achievement, patients with a higher level of educational achievement demonstrated a continuous and significant improvement of QoL in almost all four subdomains (physical health, social relationships, environment support, and psychological health). This pattern was similarly reported in a previous study which showed that graduates were more resilient in the face of adversities, and stressful circumstances such as divorce and ill-health as compared to non-graduates (46). Across three measures of well-being—life satisfaction, happiness and worthwhileness—graduates reported greater well-being even when confronting challenging life events, although graduates tended to be more anxious than non-graduates when in good health. Hence, it is reasonable for us to speculate that higher level of education may benefit patients with mental health disorders, especially when confronting episodes of psychosis. Indeed, students with successful post-secondary level of school education have been found to be able to continuously develop coping strategies to overcome cognitive difficulties while they are suffering from early episodes of psychosis (47).

We observed no moderation effect of employment status with the trend of QoL although being employed was associated with, overall, better social relationships and environment. Compared with patients who were unemployed, patients who were employed may have better financial resources to support the treatment, respond better to the treatment with regards to medication/therapy adherence, and enjoy better co-operation with their primary attendants and other care-givers. Participants being employed may have better social relationships or resources to start with, and these resources in turn may help them to have a better QoL at both baseline and during the follow-up period.

It has been reported that there is higher school dropout (15, 48) as well as unemployment (49–52) among young adults with schizophrenia after the first episode of their illness than in the general population. Young adults with FEP have been observed to frequently disregard the suggestions from service providers and fail to return to school (53). Many young patients develop psychosis which can interfere with their ability to fulfill their occupational goals. Findings from the Singapore Mental Health Study in 2010 revealed that the rate of unemployment among those with common mental illnesses was 11.1% which was significantly higher than the 6.7% rate of unemployment in those without mental illness. The data also showed that the rate of mental illness in people who were unemployed was twice as high as compared to those who were employed (5.3 vs. 2.3%) (54). Singapore has a multi-racial culture, influenced by South Asian, East Asian, and Eurasian cultures. Singapore has a high standard of living and low unemployment rates. Meritocracy is valued in Singapore and this results in promoting competitiveness for job and prestige in the society (55, 56). Employment and education are therefore highly valued in Singapore and being employed may thus contribute fundamentally to their QoL. Our study emphasizes the influential role of education and employment on the subjective QoL among patients with FEP.

We observed a significant amelioration of overall positive symptoms, negative symptoms and general pathological symptoms as well as a significant improvement of general functioning among our participants over the follow-up period which was possibly caused by the early treatment of psychosis or reasons that we didn't explore in this study. We observed no association of participants' educational achievement and employment status with the overall change of psychiatric symptoms and clinical assessment of general functioning. Nor did we find any interaction relationship between participants' educational achievement and employment status and the change of psychiatric symptoms and general functioning. Hence for patients with FEP, the association and moderation role of patients' educational achievement and employment status on the severity of clinical symptoms and clinical assessment of general functioning was not identified in our model. We were not able to conduct a trend analysis of changes in PANSS and GAF scores in this study as data was available for only two time points (baseline and 1 year). We analyzed the association between the 1 year change of PANSS and GAF score with the change of QoL using generalized linear regression. No significant associations were observed which was in line with previous findings that after comprehensive treatment, subjective QoL among patients with FEP was correlated with both psychotic and negative symptoms, but only to a minor extent (16). Future studies should consider incorporating measures of both socio-demographic and clinical correlates (e.g., medications and psychotherapy) over time to conduct a more robust trend analysis of QoL both in patients with FEP as well as other illnesses to ensure a better understanding of modifiable factors.

In summary, the main strength of our study is the repeated measurements at multiple time points that were used to examine the trend of QoL among those with FEP. The local setting, self-reporting nature of study involving patients with psychosis, and potential bias due to the selective loss of follow-up may limit the generalization of current findings to a global population. We have identified the positive association of employment status with QoL and the moderation effects of educational achievement on the trend of QoL, which could also have been pre-conditioned by other confounders that we didn't explore in this study. Although this secondary analysis should be interpreted cautiously and considered exploratory, our study suggests that it is important for patients with FEP to have age appropriate roles i.e., they return to school or employment as early as possible.

AUTHOR CONTRIBUTIONS

XT, SV, CT, SC, and MS contributed conception and design of the study. SS, PS, and BC contributed to data collection. XT and MS organized the database and wrote the first draft of the manuscript. All authors contributed manuscript revision, and approved the submitted version.

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REVIEW
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Early Identification and Intervention of Schizophrenia: Insight From Hypotheses of Glutamate Dysfunction and Oxidative Stress

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Schizophrenia is a severe mental disorder which leads to functional deterioration. Early detection and intervention are vital for better prognosis. However, the diagnosis of schizophrenia still depends on clinical observation to date. Without reliable biomarkers, schizophrenia is difficult to detect in its early phase. Further, there is no approved medication for prodromal schizophrenia because current antipsychotics fail to show satisfactory efficacy and safety. Therefore, to develop an effective early diagnostic and therapeutic approach for schizophrenia, especially in its prodromal phase, is crucial. Glutamate signaling dysfunction and dysregulation of oxidative stress have been considered to play important roles in schizophrenic prodrome. The N-methyl-D-aspartate receptor (NMDAR) is one of three types of ionotropic glutamate receptors. In this article, we reviewed literature regarding NMDAR hypofunction, oxidative stress, and the linkage between both in prodromal schizophrenia. The efficacy of NMDAR enhancers such as D-amino acid oxidase inhibitor was addressed. Finally, we highlighted potential biomarkers related to NMDAR and oxidative stress regulation, and therefore suggested the strategies of early detection and intervention of prodromal schizophrenia. Future larger-scale studies combining biomarkers and novel drug development for early psychosis are warranted.

Keywords: glutamate, N-methyl-D-aspartate receptor, oxidative stress, early psychosis, schizophrenia, prodrome, biomarker

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INTRODUCTION

Schizophrenia is a high-morbidity and high-mortality brain disorder. Globally 1% population suffered from this disorder. The common symptoms of schizophrenic patients include hallucination, delusion, disorganized thought and behavior, and negative symptoms. Clinical manifestation of schizophrenia consists of three domains: positive symptoms (such as hallucinations or delusions), negative symptoms (such as flattening affect or social withdrawal), and cognitive deficits (such as impaired memory, attention, and executive functions) (1–4). Among them, cognitive function impairments are considered to be core symptoms of schizophrenia, starting from its prodromal phase, while psychotic symptoms have not yet been vivid

(5–9). Cognitive deterioration appears at an earlier age in schizophrenia patients (10, 11). The deterioration of cognitive function in patients with schizophrenia will lead to impairment of self-care, social, and occupational function (12). Therefore, the social impact of schizophrenia is very high. Current antipsychotics have limited, if any, efficacy for cognitive function.

The etiology of schizophrenia remains unclear. Oxidative stress and glutamate-related dysfunction, potentiating each other in a vicious circle, are interdependently involved in the pathogenesis of schizophrenia (13, 14). Adolescence or early adulthood is the critical period when schizophrenia typically arises, while glutamate is the main excitatory neurotransmitter that mediates puberty (15). Oxidative stress and genetic/environmental factors converge during neurodevelopment, leading to the impairment of neural connectivity and synchronization, as well as to cognitive deficits in early psychosis patients (16).

This review highlights a recent development surrounding N-methyl-D-aspartate receptor (NMDAR) modulators and antioxidants, paving the way for biomarker guided early detection and intervention of high-risk individuals (17).

IMPORTANCE OF EARLY DETECTION AND INTERVENTION OF SCHIZOPHRENIA

Most individuals experience a period of prodromal symptoms prior to the diagnosis of schizophrenia (18). Before full-blown psychotic symptoms appear, individuals may experience changes in cognition, behavior, and function (19). Therefore, it is crucial to identify populations at high risk of schizophrenia to initiate early intervention (20). Improved diagnostic tools, the advent of atypical antipsychotic and the development of phase-specific psychosocial treatments have made intervention research in people at prodrome or ultra-high risk or people with attenuated psychosis syndrome for developing schizophrenia possible (21).

Antipsychotic medications, however, have not yet been approved for such populations, mainly because prolonged exposure to antipsychotic medication has been associated with various side effects such as weight gain, metabolic syndrome and hyperlipidemia (22, 23). First-generation antipsychotics, which block the majority of D2 dopamine receptors in the putamen (24, 25), mainly exert effects on positive symptoms and generate numerous intolerable side effects such as parkinsonism (including tremor, rigidity, bradykinesia), akathisia, dystonia, and prolactinemia (26). Newer atypical antipsychotics targeting both dopamine D2 and serotonin 5HT2 receptors (24, 26, 27) have been suggested to be superior to conventional agents in terms of efficacy for positive symptoms and perhaps negative symptoms (28–30). Despite this, there were a considerable percentage of patients resistant or only partially responsive to available medications (31). Moreover, side-effect profiles of second-generation antipsychotics, including obesity, diabetes mellitus, hyperlipidemia, metabolic syndrome, and sudden cardiac death, limit their clinical use (32–34). A substantial portion of schizophrenia patients refuse or cannot tolerate antipsychotics due to poor response and/or side effects (24). Further, long-term antipsychotics use is associated with cognitive impairment (35).

Most prodromal patients receive no or very brief, if any, antipsychotic treatment, due to safety concerns (36). To date, there is neither approved medication for prodromal schizophrenia, nor reliable outcome predictor for its conversion to full-blown schizophrenia. Therefore, developing early diagnosis and intervention strategy is very important.

THE GLUTAMATE HYPOTHESIS OF SCHIZOPHRENIA

In addition to dopaminergic neurotransmission, glutamatergic neurotransmission has gained more attentions lately as the key deficit of schizophrenia (37–44). Glutamate has two major receptor families: (1) ionotropic receptors, consisting of N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate receptor subtypes, and (2) metabotropic receptors (mGluRs), which are G-protein-coupled receptors.

While glutamatergic outputs appear widespread over the corticolimbic system, disinhibition of the glutamatergic output from the subiculum to the ventral tegmental area leads to the hyperdopaminergic state with treatment of NMDA receptor (NMDAR) antagonists (45).

HYPOFUNCTION OF NMDAR-MEDIATED NEUROTRANSMISSION IN SCHIZOPHRENIA

NMDAR, a heteromeric ion channel, formed from a number of subunits (NR1, NR2ANR2D, NR3A, and NR3B), plays an important role in neurocognition. NMDAR antagonists, such as phencyclidine (PCP) and ketamine, induce psychosis which resembles schizophrenia more closely than the amphetamine/dopamine agonist do (46). The former causes not only positive symptoms, but also negative symptoms and cognitive deficits associated with schizophrenia. Moreover, glycine transporter inhibitors could reverse ketamine-induced effects (37, 47–50). Decreases in NMDAR density were found in post-mortem tissue from schizophrenic patients (51). The above evidence suggests that NMDAR dysfunction may be a critical deficit in schizophrenia (40, 43, 44, 52). Modulation of NMDAR has been proposed as a possible therapy for schizophrenia, including its prodrome (26, 37, 48, 53–56).

ABNORMAL PLASTICITY OF AMPA AND KAINATE RECEPTORS IN SCHIZOPHRENIA

While some glutamatergic synapses have only AMPA receptors (AMPARs) or only NMDARs, most have both receptors. NMDAR modulators may regulate not only NMDARs but also AMPARs (57). Similar to NMDARs, AMPARs modulate fast glutamate transmission, neuronal circuit remodeling

and higher order cognitive functions such as learning and memory; and abnormalities of AMPAR trafficking contribute to dysfunction in brain diseases such as schizophrenia (58). AMPAR subunits (GluR1-4) assemble to form AMPAR complexes in the lumen of the endoplasmic reticulum. Recently, the possibility of AMPAR dysfunction has been proposed to explain abnormalities in glutamate neurotransmission associated with the pathophysiology of schizophrenia (59). Topiramate, an antiepileptic drug with AMPAR antagonist activity has been demonstrated to improve schizophrenia as an adjunctive therapy; however, its efficacy may occur via GABA neurotransmission, as AMPAR antagonism occurs only at high concentrations (60, 61). Beneficial effects of CX516 and minocycline on cognitive domains appeared insignificant with rigorous statistical analyses (62). Newer AMPAR modulators such as UoS12258 which may possess precognitive properties deserve further studies (63).

Studies of kainate receptors (KARs) met difficulties because of the lack of specific activators or blockers for the receptors. First, kainate can also activate AMPARs. Second, AMPA, activates many KARs too (64).

ROLE OF THE MGLUR ALLOSTERIC MODULATION IN SCHIZOPHRENIA

The mGluRs, consisting of eight subtypes, provide a wide range of targets to modulate NMDAR function as well as glutamate release. Preclinical studies demonstrated that activation of the mGluR2/3 down-regulated the excessive dopamine release caused by treatment with NMDAR antagonists (65). A clinical trial showed that an mGluR2/3 agonist, which down-regulates disinhibited glutamate release, exhibited antipsychotic properties (66). There have also been advances in the discovery of highly selective positive allosteric modulators (PAMs) of mGluR2 and mGluR5 for the treatment of schizophrenia (67). The mGluR5 PAMs counter aberrant neuronal activity generated by NMDAR antagonists in the prefrontal cortex (68). Recently, more subtype-selective allosteric modulators for various mGluRs instill hopes of better or alternative treatments for (subgroups of) schizophrenia (69).

OXIDATIVE STRESS IN SCHIZOPHRENIA

Current evidence supports that increased oxidative stress-induced cellular damage of macromolecules may play a role in schizophrenia, and schizophrenia patients have abnormal antioxidant defenses as observed in their peripheral blood (70–72), CSF (73), and postmortem brain tissues (74, 75). Evidence from genetic studies also suggests that schizophrenia patients may have a reduced ability to mount an adequate antioxidant defense (76).

The failure of antioxidant defenses to protect against free-radical generation damages cell membranes, impacts on neurotransmission and, ultimately, leads to phenotypes of schizophrenia (75). Important free radicals include hydrogen peroxide, the hydroxyl radical, nitric oxide (NO), and the superoxide radical. In the rate-limiting step of purine catabolism, xanthine oxidase catalyzes the conversion of xanthine to uric acid, an important antioxidant, and generates superoxide radicals. Superoxide dismutase catalyzes the conversion of superoxide radicals to hydrogen peroxide. Both catalase and glutathione peroxidase converts hydrogen peroxide to water and oxygen. Reduced glutathione is oxidized by glutathione peroxidase to oxidized glutathione. Glutathione peroxidase also converts nitrate (a by-product of NO radicals) to nitrite. Nitrite is often used as a marker for NO activity. Hydroxyl radicals, produced from both hydrogen peroxide and NO, promote apoptosis, DNA damage, protein carbonylation, and lipid peroxidation. Vitamin E, also acting as an antioxidant, can inhibit lipid peroxidation. Thiobarbituric acid reactive substances (TBARS) and malondialdehyde (MDA) are important end products of lipid peroxidation (77).

MODULATION OF OXIDATIVE STRESS IN PATIENTS WITH SCHIZOPHRENIA

Clinical trials also support an association between oxidative stress and schizophrenia. Treatment with the antioxidant N-acetylcysteine significantly reduced psychopathology in schizophrenia (78). Nevertheless, N-acetylcysteine may not represent an optimal antioxidant therapy, as its principal modus operandi, the supply of increased cysteine for glutathione biosynthesis, is of limited help unless the brain can use it to produce, recycle and utilize glutathione (13). Another important study also found that supplementation with fish oil significantly reduced the progression to first-episode psychosis in subjects with prodromal symptoms (79). However, many subjects in the study also carried severe depressive symptoms, hampering the conclusion of the study. Anyhow, these findings suggest that oxidative stress levels may be a biomarker of schizophrenia risk and response to adjunctive antioxidant treatment.

LINKING OXIDATIVE STRESS AND NMDAR HYPOFUNCTION IN SCHIZOPHRENIA PATHOGENESIS

Molecular, genetic and pathological evidence suggests that not only oxidative stress but also NMDAR hypofunction contribute to schizophrenia pathophysiology. Evidence now suggests that these factors are mechanistically interdependent and contribute to a common schizophrenia-associated pathology (13, 14).

There are clear similarities between the impact of developmental NMDAR hypofunction and that of oxidative stress on the adult rodent: both cause similar behavioral and cognitive disturbances. Increasing evidence suggests that NMDAR hypofunction and oxidative stress may be reciprocally linked (13, 14, 80). The NMDAR is regulated by redox state: both GRIN1 and GRIN2A possess pairs of reduction-oxidation reaction (redox)-sensitive cysteine residues whose disulfide bond formation decreases NMDAR currents (80), while an overlapping group of cysteine residues are subject to inhibitory S-nitrosylation, which facilitates disulfide bond formation (80, 81).

Recently, it has been shown that changes in intracellular redox status can also modulate NMDAR activity in a manner that is relevant to age-dependent cognitive decline (82). Age-associated shifts in intracellular redox state to a pro-oxidizing environment have been linked to reduced NMDAR activity via the redox regulation of calcium/calmodulin-dependent protein kinase type II (CaMKII), and can be rescued by intracellular glutathione (83).

Whether NMDAR-related dysfunction may influence the modulation of oxidative stress and whether the modulation of oxidative stress can alter NMDAR-related neurotransmission both also deserve further studies.

SEARCHING FOR DIAGNOSTIC AND THERAPEUTIC BIOMARKERS OF SCHIZOPHRENIA

At present, the diagnosis and treatment response of schizophrenia rely on clinical manifestation. There have been lots of post-mortem brain studies (84). However, RNA expressions may be affected by many factors under post-mortem condition. Therefore, it's needed to establish peripheral, accessible biological markers for mental illness (85). Lymphocytes or white cells have been suggested to be a neural probe because numerous studies showed similarities between receptor expression and mechanisms of transduction processes of cells in the nervous system (e.g., neurons and glia) and lymphocytes (86). Blood-derived RNA has become a convenient alternative to traditional tissue biopsy-derived RNA (87).

Several potential markers have been reported. Hashimoto et al reported that serum levels of D-serine were lower in schizophrenic patients than in healthy subjects (88). Besides, the expression of apolipoprotein D was increased in the plasma and brains of individuals with schizophrenia (89). S100B is a calcium-binding protein produced by astroglial cells. It has also been reported that schizophrenic patients, compared with healthy subjects, have higher DRD3 mRNA levels (85) and lower AKT1 protein levels (90) in peripheral lymphocytes. Adrenomedullin mRNA levels in lymphoblastoid cell lines of male schizophrenia patients was higher than in controls (91). Via microarray technique, six genes were suggested to be biomarkers of schizophrenia (92). Another study demonstrated that mRNA expression of eight biomarkers could be discriminated between schizophrenia, bipolar disorder, and controls (87). However, developing more suitable biomarkers for schizophrenia in future studies is warranted because there exists a large overlap between patients and controls in present biomarker studies.

NMDAR- AND OXIDATIVE-RELATED BIOMARKERS OF SCHIZOPHRENIA

NMDAR-related markers are scanty. Lin et al found that the G72 (D-amino acid oxidase activator, DAOA) protein level in plasma was much higher in patients with schizophrenia than in healthy controls (93). G72, functioning as a D-amino acid oxidase (DAAO) activator (DAOA), exists exclusively in 4 primates including humans. The study suggests that peripheral G72 concentration may be characteristic of schizophrenia. The finding has been replicated independently (94). G72 is a huge protein. Its longest protein is called LG72 and consists of 153 amino acids. Its complex interactions deserve intensive study to elucidate the pathogenesis and pathophysiology of schizophrenia (95). Liquid chromatography-mass spectrometry (LC-MS)-based proteomics and metabolomics that have been used to discover protein and metabolite markers in clinical diseases may be helpful to elucidate the function of G72 and its interaction with other proteins.

A previous study also found that mRNA expression levels of *SLC7A11* and *SLC3A2* were lower in patients with schizophrenia than healthy individuals (96). SLC3A2 and SLC7A11 are two subunits of the cystine/glutamate antiporter system x_c^- which plays a critical role in the regulation of glutamate release. DAAO is responsible for degrading D-serine and other D-amino acids (97). A recent study found that its level in peripheral blood was higher with cognitive aging (98). Serine hydroxyl-methyltransferase 2 (SHMT2) is an isoenzyme that catalyzes the reversible conversion of serine and tetrahydrofolate (THF) to glycine and methylene THF. Phosphoserine aminotransferase 1 (PSAT1) is required for the phosphorylated pathway of L-serine biosynthesis. Uptake of D-serine and L-serine into neurons and astrocytes is predominantly mediated by the serine transporter (ASCT1) subtype. The aforementioned genes/proteins that can regulate glutamate release and NMDAR function may be implicated in the pathogenesis of schizophrenia. Further, a recent study suggests that altered NMDAR signaling and parameters may have the potential to be used to detect vulnerability toward schizophrenia in individuals early in the disease process and thereby enable early intervention in a subgroup of patients (17).

Patients with schizophrenia also exhibit abnormal blood oxidative stress parameters, including total antioxidant status, glutathione peroxidase, catalase, superoxide dismutase, and nitrite (71, 77). It has been suggested that oxidative stress may serve as a potential biomarker in the etiopathophysiology, clinical course (including predicting conversion of high-risk symptoms to psychosis), symptomatology, cognitive function, and treatment response by antioxidants in patients with schizophrenia (16, 77, 99–101).

MISMATCH NEGATIVITY AS AN OBJECTIVE MEASUREMENT FOR NMDA FUNCTION AND A BIOMARKER FOR SCHIZOPHRENIA

Mismatch negativity (MMN) has been proven to be related to NMDAR and has been shown to be reduced in schizophrenia. Previous studies have successfully established a method to generate reliable MMNs and have demonstrated the involvement of the NMDAR in the genesis of MMN (102, 103). Computational model was created to explain the observed functional MRI (fMRI) time-series data by using a state-space model (104), and has been used to model the

evoked components as measured by electroencephalography (EEG) or magnetoencephalography (MEG), that has been used to study the production mechanisms of MMN and P300 (103).

Building a computational model for MMN may be helpful for exploring the network of MMN in schizophrenia and its treatment by the NMDAR enhancers such as D-serine (105). Longitudinal studies have also shown that MMN recordings can assist in predicting the conversion from the prodromal phase to psychosis (106).

DAAO INHIBITION FOR SCHIZOPHRENIA

D-serine is more potent than other NMDAR co-agonists as the neurotransmitter for the glycine-site of the NMDAR (107). DAAO, a flavoenzyme of peroxisomes existing in the brain, kidney and liver of mammals, is responsible for degrading D-serine, D-alanine, and other D-amino acids. Therefore, one of the avenues to enhance NMDAR function is via inhibiting DAAO activity.

Sodium benzoate, a DAAO inhibitor, can elevate synaptic concentrations of D-amino acids, like D-serine and D-alanine, and thereby enhance NMDA neurotransmission. Previous clinical trials have studied the potential of sodium benzoate as an adjuvant therapy for schizophrenia. The first clinical trial suggested that sodium benzoate is beneficial in improving the clinical symptoms including positive and negative symptoms, cognitive and global functioning and quality of life in patients with chronic schizophrenia (40). The effect size of sodium benzoate treatment for Positive and Negative Syndrome Scale (PANSS) total score from baseline to endpoint was 1.76, which was much higher than the effect size (0.51) of sarcosine adjuvant therapy for the PANSS total score in patients with chronic schizophrenia (108).

GLUTAMATERGIC MODULATORS IN PATIENTS WITH PERSISTENT PSYCHOTIC SYMPTOMS

Only a minority of patients with first-onset schizophrenia return to their original level of functioning. Among individuals who respond poorly to antipsychotics (which are principally dopamine antagonists), their glutamatergic/NMDAR dysfunction may lead to failures by the treatment. While second- and third-generation antipsychotics are increasingly used, therapy for refractory schizophrenia remains a great challenge. Even with the treatment of clozapine (the last-line therapy for schizophrenia), a substantial portion of patients still suffer from persistent psychotic symptoms. However, after many clinical trials with various agents, including diverse glutamatergic modulators, there is no convincing evidence to demonstrate the efficacy of adjuvant therapy for clozapine-resistant patients (109). In a recent study, sodium benzoate even showed a beneficial effect on positive and negative symptoms and quality of life with the dose of 2 g/day in patients with clozapine-resistant schizophrenia (43).

STRATEGIES OF EARLY DETECTION AND INTERVENTION OF PRODROMAL SCHIZOPHRENIA

The prodromal phase of schizophrenic disorders has been recognized since the Nineteenth century (110). Recently, the Criteria of Prodromal Syndromes (COPS) diagnostic criteria have been applied; there are three operationally defined prodromal syndromes: attenuated positive psychotic symptom syndrome, brief intermittent psychotic syndrome, and genetic risk and recent functional decline syndrome (18, 111, 112). The PRIME prodromal research team in Yale University has also developed a semi-structured interview called the Structured Interview for Prodromal syndromes (SIPS) (113). The SIPS is utilized to rate presenting symptomatology and to determine if COPS criteria are met. The Scale of Prodromal Symptoms (SOPS) (114), embedded in SIPS, is a 19-item scale designed to measure the severity of prodromal symptoms. The SOPS contains four subscales: five positive, six negative, four disorganization, and four general symptom items. The detection and intervention of young people in the prodromal phase is a newly developed area in psychiatry (115), and the ethical considerations about treatment options must be treated with sensitivity (116).

Standard guidelines have been used in our previous studies aiming to establish or examine prodromal or ultra-high-risk (UHR) (112), clinical high risk (117), and 5 at-risk mental state (118). Recently, objective strategies have been emphasized for screening prodromal illness in many studies. The fMRI with magnetic resonance spectroscopy (MRS) is one of those that identify early stage of mental illness. Individuals with prodromal symptoms demonstrated smaller differential activation in frontal regions in fMRI data (119).

The possibility of treatment intervention during the prodromal phase has a history almost as long as it was first identified (120). Both typical and atypical antipsychotics, including risperidone and olanzapine, have been utilized to reduce prodromal symptoms or the risk of progression to schizophrenia (121–123). However, safety and side effect concerns exist; and it remains unclear whether the benefits of antipsychotic treatments outweigh the risks (116).

Therefore, there is an urgent need to develop safer interventions for schizophrenic prodrome. D-serine (124) and fish oil (79) have been demonstrated to be beneficial as treatment of prodromal schizophrenia. Other antioxidants such as glucoraphanin have also shown potential in preventing the onset of psychosis in the adult offspring after maternal immune activation (125). Future trials with glutamate modulators or antioxidants in early psychosis and even prodromal schizophrenia should consider biomarker-guided treatment (16).

SUMMARY

It is generally recognized that intervention of early psychosis and prevention the progression of schizophrenic prodrome to full-blown schizophrenia is essential, in order to avoid subsequent

functional deterioration. Current antipsychotic medications have not yet been approved for such populations mainly due to the lack of overt efficacy and various side effects including metabolic syndrome and hyperprolactinemia. Therefore, developing novel antipsychotic drugs with better efficacy and safety is critical. Compounds that can enhance the NMDAR have shown encouraging efficacies with favorable safety profiles in clinical trials for patients with schizophrenia. It will be valuable to test whether NMDAR enhancers are beneficial for patients with earlier phases of psychosis.

Identifying high risk populations who are prone to develop full-blown psychosis would be very helpful to apply early an intervention strategy to those people who are in need. It is important to search for biomarkers representing the pathophysiology of schizophrenia and more importantly, the biological changes in the process of early psychosis. In addition to dopamine hypothesis, dysfunction of glutamate signaling, and dysregulation of oxidative stress have been considered to play important roles in early psychosis and schizophrenic prodrome. It will be interesting to search for potential biomarkers that are related to glutamate and oxidative stress modulations via blood-based or brain imaging approaches.

Combining biomarkers and novel drug development for early psychosis is critical in future studies. Notably, the intervention that can both treat early psychosis and serve as the biomarker might have more potential to reach the goal.

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All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Auditory Event-Related Potentials in Antipsychotic-Free Subjects With Ultra-High-Risk State and First-Episode Psychosis

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Background: Auditory event-related potentials (ERPs) have been utilized to study defective information processing of patients with schizophrenia. To delineate the pathophysiological processes from pre-psychotic state to first-episode psychosis, a study on subjects from ultra-high-risk (UHR) state to first-episode psychosis, ideally in an antipsychotic-free condition, can add important information to our understanding.

Methods: Patients with UHR state or at their first-episode psychosis (FEP) who were drug-naive or only have been temporarily treated with antipsychotics were assessed by auditory ERPs measurement, including P50/N100 (sensory gating) and duration mismatch negativity (MMN; deviance detection). A group of age-matched healthy subjects served as their controls.

Results: A total of 42 patients (23 UHR and 19 FEP) and 120 control subjects were recruited, including 21 pure drug-naive and 21 with very short exposure to antipsychotics. Collapsing FEP and UHR as a patient group, they exhibited significant sensory deficits manifested as larger P50 S2 amplitude, larger N100 ratio, and smaller N100 difference, and significantly less deviance detection response revealed by MMN. Such differences were less significant when treating FEP and UHR separately for comparisons. Comparisons of ERP results between drug-naive subjects and antipsychotic-short-exposure subjects revealed no significant difference in any P50/N100 and MMN parameter.

Conclusion: Our study is one of the few studies focused on drug-naive or minimally treated patients at pre- or early-psychotic states. Our results exhibited impaired performance in sensory gating and deviance detection shown by certain parameters. A longitudinal study with larger sample sizes will be helpful to provide more evidence to elucidate the role of antipsychotics on an individual's neurophysiological performance at different stages of psychosis.

Keywords: event-related potentials, first-episode psychosis, mismatch negativity, N100, P50, schizophrenia, ultra-high risk

INTRODUCTION

Neuroscience tools have been widely employed in schizophrenia research in recent decades (1–3). Neurobiological impairments precede the onset of a full clinical syndrome. Therefore, we can delineate psychopathological progresses by careful assessment throughout the pre-psychotic and early-psychotic states (4). Among the various neuroimaging methods, auditory event-related potentials (ERPs) have been utilized to study normal versus defective information processing of neuropsychiatric disorders, such as schizophrenia (1, 3, 5). Successful processing of sensory inputs requires two kinds of ability: sensory gating, the ability to inhibit intrinsic responses to redundant stimuli, and deviance detection, the ability to facilitate responses to less frequent salient stimuli (6). Using ERP components as measuring instruments, P50/N100 suppression represents the extent of inhibitory failure (impaired sensory gating), while MMN (mismatch negativity) indicates the magnitude of impaired deviance detection. Both processes are thought to be "pre-attentive" (passive, not demanding on subject's active attention) and have been found to be impaired in patients with schizophrenia (3, 5, 7). Evidence suggests that auditory P50, N100, and MMN could be candidate endophenotypes of schizophrenia with intermediate relationship to susceptible genes of schizophrenia (3, 6, 8), serve as potential biomarkers to specify the progress of illness (9–12), and even help to predict if a subject would convert to full-blown psychosis (13).

As most neurobiological studies of schizophrenia were conducted in chronic patients, the possible negative impact brought by long duration of illness and long-term use of antipsychotics on brain neurochemistry and possibly on brain morphology (14) could be confounders and make it difficult to interpret those neurobiological findings (15–17). Similarly, even though P50 suppression and MMN has been regarded as endophenotypes for schizophrenia (6, 18, 19), the findings of duration MMN deficits were absent in a few studies focused on subjects at their first-episode psychosis (FEP) (7, 20–23), as well as there are studies that failed to reveal P50/N100 sensory gating deficits in this population (24, 25). However, in the studies including first-episode psychosis, whether patients were drug-free, continuing antipsychotics, or temporarily holding off antipsychotics was not all well controlled during assessment of ERPs. Ignoring such a difference in medication status may lead to confusing results (26), while administration of antipsychotics have been shown to influence ERP results, although the direction and extent of impact were diverse in different antipsychotics (27–32).

To circumvent the impact of long duration of illness and use of antipsychotics, examining subjects with drug naivety is an ideal approach. In schizophrenia research, attention has been directed towards the early state or even "pre-psychotic" state of full-blown psychosis. A lot of studies have been focused on this critical period, not only for identifying factors predicting conversion to psychosis or how to modify the trajectories of psychosis (33), but also for disentangling the complex pathogenesis of schizophrenia-related psychosis (34). The ultra-high risk (UHR), also known as late prodrome, model depicting a group of subjects who had subthreshold psychotic symptoms yet not developed full-blown psychosis (35), has been transformed into an attenuated psychosis syndrome in the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*, Section III, as a category in need of more investigations (36). Furthermore, theoretically, Keshavan et al. pushed the model back to the beginning in the course of psychosis and named an early prodromal state with non-specific symptoms and/or basic symptoms as the "early/broadly defined at-risk mental states" (E-BARS) (37) to capture all possible features that happened during the formation of psychosis.

Our research team has started a prospective study on the psychopathological progress of the pre-psychotic state (the SOPRES study) in 2006 (38). We have recruited subjects at a gradient of clinical severities spanning from the E-BARS to UHR and FEP, together with a group of normal controls. Our ERP results of this cohort revealed a gradient of P50/N100 sensory-gating deficits across different levels of clinical severity (likely a state marker), while impaired deviance detection exhibited by duration MMNs was already detectable in people at pre-psychotic states and not much different from that in FEP (likely a trait marker) (39). But like most previous studies, the SOPRES did not control a patient's medication status. In 2008, we initiated an open-label drug trial on UHR and first-episode psychosis, focused on those who were drug-naive or have only received a short period of antipsychotic treatment (40). The baseline assessment of this sample allows us to examine to what extent the auditory ERP components (P50/MMN/N100) will be different between subjects with UHR state and patients at first-episode psychosis, spared from the influence of antipsychotics, and compared to a large group of healthy controls.

METHODS

Subjects

This study was approved by the Institutional Review Board of the National Taiwan University Hospital. Written informed consent was received from all participants, including written assent given by minors with informed consent from their parents. Subjects were those who participated in a 4-week open-label clinical trial using flexible dose of aripiprazole on patients with UHR state or at their first-episode psychosis between July 2008 and June 2016. Details of the clinical trial procedures have been addressed in our previous publication (40), and the definition of clinical cases is briefed below. The controls were recruited by responding to ads of various studies conducted by our schizophrenia research team with the prerequisite of having no lifetime or current psychiatric diagnosis or family history of psychotic disorders. Those who had a psychotic episode for more than 1 year, a mood episode, current use of psychoactive substance, a history of central nervous system illness or traumatic brain injury, an IQ below 70, and pregnancy were excluded from recruitment.

Definition of Clinical Cases

The FEP subjects were those who developed full-blown psychosis that met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) criteria for schizophrenia or schizophreniform disorder within the recent 1 year. The UHR subjects presented subthreshold psychotic symptoms meeting the

comprehensive assessment of at-risk mental status criteria (41) either with attenuated psychotic symptoms or with brief limited intermittent psychotic symptoms. Subjects have never received antipsychotic treatment before were designated as the "drug-naive" group. Subjects reported to have received a known antipsychotic or psychotropic agent that exerted an effect or adverse event very likely to be associated with antipsychotics for a total of less than 3 months were designated as the "antipsychotic-short-exposure" group.

The antipsychotic-short-exposure group was asked to remain antipsychotic-free for at least 1 week before baseline assessments. Patient's clinical severity was assessed by a Mandarin version of the Positive and Negative Syndrome Scale (PANSS) for schizophrenia and received ERP studies at baseline and 4 weeks after completing treatment with aripiprazole. In this paper, we focused on their baseline ERP results that were not affected by antipsychotic treatment.

Testing Environment

Before ERP recording, audiometry testing was used to exclude subjects who could not detect 40-dB sound pressure level tones at 500, 1,000, and 6,000 Hz presented to either ear. The standard procedures for auditory P50/N100 and MMN paradigm were based on established protocols (42–45). The participants had not smoked for at least 1 h before sessions (46) and were asked to lie down in supine position in a comfortable recliner in a sound-attenuating, electrically shielded booth and instructed to relax with his/her eyes open and to focus on a fixation point (P50 and N100 session) or a cartoon running with no sound on the video monitor (MMN session). There were no tasks performed during the test. During the testing, electroencephalography and stimuli would be recorded continuously, and subjects were closely observed through a video monitor. They would be monitored visually and by electroencephalography (EEG) for signs of sleep or slow wave activity, which, if present, prompted the experimenter to speak briefly with the subject.

The EEG signals were recorded with a Quik-Cap (Compumedics Neuroscan, El Paso, TX, USA) from 32 scalp locations. According to the Quik-Cap website, all electrodes were placed according to the International 10–20 electrode placement standard. Electrodes placed at the tip of the nose and at Fpz served as the reference and ground, respectively. Four additional electrodes were located above and below the left eye and at the outer canthi of both eyes to monitor blinks and eye movements. All electrode impedances were kept below 5 kΩ prior to recording.

Stimuli Session and ERP Recording

The auditory stimuli were generated by a Neuroscan STIM system, and data were recorded on a Neuroscan ACQUIRE system (Compumedics Neuroscan, El Paso, TX, USA). Stimuli were digitized at a rate of 1 kHz, and an online band-pass filter at 0.5–100 Hz, without 60-Hz notch filter, was applied. Auditory stimuli were presented to the subjects binaurally *via* foam insert earphones in two consecutive sessions, i.e., the session of paired-click paradigm for P50/N100 followed by the duration MMN session.

Online averaging was used to monitor the number of trials free from gross artifacts (defined as activities exceeding ±100 μV in the −100 to 500 ms time window following stimuli). Regarding the paired-click P50/N100 paradigm, paired auditory clicks (1 ms, 85 dB) were presented every 8–12 s through the whole test session (average: 10 s), with a 500-ms interstimulus interval (47, 48). The paired-click P50/N100 session was terminated when a minimum of 120 artifact-free trials had been obtained, which took about 30 min. For the duration MMN paradigm, pure tone stimuli (1 kHz, 85-dB SPL, 5-ms rise/fall) were generated by the Neuroscan STIM system. The auditory stimuli consisted of standard stimuli (90%, 50-ms duration) and deviant stimuli (10%, 100-ms duration) delivered in a pseudo-random order with the constraint that deviant stimuli could not be repeated back to back. The cartoon soundtrack was turned off and replaced by the experimental auditory stimuli that were presented at a fixed 500-ms onset-to-onset asynchrony. The MMN session was continued until a minimum of 225 artifact-free deviant trials had been collected online, which took approximately 30 min.

Offline Data Processing

Details regarding offline signal analysis, using Neuroscan Edit 4.5 software (Compumedics Neuroscan, El Paso, TX, USA), were followed as our previous publications (39, 44, 49). All data were processed by researchers who were blind to the subject's group (50). Semi-automated procedures using the Tool Command batch processing language (TCL) began with electrooculography (EOG) artifact reduction through a built-in pattern-recognition algorithm (51). For P50/N100, the data were epoched for the time window from −100 to 923 ms of the first click, covering both S1 and S2 in the same epoch. All epochs containing activities exceeding ±50 μV were excluded. To prevent temporal aliasing, epochs were averaged and digitally band-pass-filtered (10 to 50 Hz for P50, 1 to 50 Hz for N100) in the frequency domain. Trials with artifacts were manually rejected. By using preset intervals, peaks and preceding troughs were then automatically detected at the Cz electrode. The P50 peak was defined as the largest positive deflection between 45- and 75-ms poststimulus, and its amplitude was assessed as the difference between this peak and the preceding negative trough (not earlier than 30-ms poststimulus). The N100 component was identified as the most negative deflection within 80- to 150-ms poststimulus, and N100 amplitude was defined as the absolute difference between the N100 peak and the preceding positive trough. P50 and N100 parameters included the S1 amplitude, S2 amplitude, amplitude difference (S1 − S2), and P50/N100 gating ratio (S2/S1). A maximum gating ratio of 2 was used to prevent outliers from disproportionately affecting the group means (39, 44, 52).

For duration MMN analysis, each subject's continuous data file to 500-ms poststimulus. EEG responses to standard and deviant stimuli were separately averaged to create a standard ERP and a deviant ERP, and both were low-pass filtered at 20 Hz (0-phase shift and 24-dB/octave roll-off) to remove any residual high-frequency artifacts. MMN waveforms were generated by subtracting the standard ERP from the deviant ERP. MMN indices were measured as the mean voltage from 135 to 205 ms of the Fz electrode (18, 39, 53–55).

Statistical Analysis

Statistical analyses were performed using SPSS v16.0 software (SPSS, Chicago, IL). For demographic characteristics and ERP parameters, the results are presented in means and standard deviations (±SD). Chi-square tests were used for categorical variables. Putting subjects with UHR state and first-episode psychosis together as a patient group, we compare control vs. patient group in demographics and ERP results. In addition, comparison between controls, UHR, and FEP groups with analysis of variance (ANOVA) was performed, and we also calculated comparison between control/drug-naive/antipsychotic-short-exposure groups. All *post hoc* comparisons were made using the Scheffe test. Statistical significance was set at $p < 0.05$. Cohen's *d* effect size was calculated for all ERP parameters.

RESULTS

A total of 42 patients (19 FEP and 23 UHR) and 120 control subjects were recruited. Among them, 21 patients endorsed pure drug naivety (7 FEP and 14 UHR), and the other 21 patients (12 FEP and 9 UHR) have only been exposed to antipsychotics for no longer than 3 months. Indeed, the majority of these 21 short-exposure patients took antipsychotics at a low dose level no longer than 4 weeks and they could endure a washout period of 1 week prior to receiving ERP assessment with no apparent worsening of symptoms. Both paired-click P50/N100 paradigm and duration MMN paradigm took about 30 min in duration. Although all 42 patients had ERP recorded, 9 patients (3 UHR/6 FEP) could not finish the P50/N100 paradigm, while 8 patients (5 UHR/3 FEP) could not tolerate duration MMN paradigm, yielding the numbers of subjects with data available for further analysis to be 33 and 34 for P50/N100 and MMN, respectively.

Demographic and Clinical Characteristics

In **Table 1**, UHR and FEP were treated collectively as a patient group to compare with the control group, while in **Table 2**, UHR and FEP were examined separately for any difference between these two groups. There were no statistical differences in age and gender when the patient group is compared to the control group, although the UHR group was significantly younger than the FEP group (23.64 ± 5.08 vs. 28.45 ± 8.33, $p = 0.022$). The controls had 1.6 years more in education and reported much lower amount of smoking compared to the patient group, while there was no difference in these two variables between the UHR and FEP groups. In terms of clinical severity shown by PANSS scores, the UHR patients only exhibited lower scores in positive symptom subscales than the FEP patients (15.0 ± 2.9 vs. 19.4 ± 4.6, $p < 0.001$), while their scores in negative symptoms and general symptoms subscales were comparable to each other.

Comparisons of Event-Related Potentials

Also presented in **Table 1**, the patient group had a smaller magnitude in MMN, a larger P50 S2 amplitude, a larger N100 amplitude ratio, and a smaller N100 difference compared to the control group. However, as detailed in **Table 2**, the patient

TABLE 1 | Demographics and ERP results of control and patient groups (SD in parentheses).[a]

	Control	Patients	Statistics	Effect size (Cohen's *d*)
	n = 120	*n* = 42		
Age	26.63 (5.09)	25.82 (7.08)	0.424	
Male gender (%)[b]	63 (52.5%)	21 (50%)	$\chi^2 = 0.08$, $p = 0.78$	
Education (years)	15.62 (1.88)	14.00 (2.51)	<0.001**	
Smoking PPD	0.03 (0.1)	0.15 (0.4)	0.035*	
PANSS				
Positive symptoms (P1 to P7)	—	17.0 (4.3)		
Negative symptoms (N1 to N7)	—	14.1 (5.9)		
General psychopathology (G1 to G16)	—	35.3 (8.6)		
MMN Fz	−1.36 (0.81)	−1.05 (0.78)	0.047*	0.39
P50				
S1 amplitude	2.44 (1.06)	2.53 (1.4)	0.679	0.07
S2 amplitude	1.09 (0.64)	1.45 (0.84)	0.008**	0.48
P50 ratio	0.51 (0.34)	0.63 (0.38)	0.075	0.33
P50 difference	1.35 (1.07)	1.08 (1.39)	0.239	0.22
N100				
S1 amplitude	6.73 (3.27)	5.82 (2.95)	0.150	0.29
S2 amplitude	2 (1.31)	2.46 (1.3)	0.073	0.35
N100 ratio	0.36 (0.31)	0.51 (0.34)	0.017*	0.46
N100 difference	4.73 (3.35)	3.36 (2.62)	0.030*	0.46

UHR, ultra-high-risk group; FEP, first-episode psychosis group. ERP, event-related potential. MMN, mismatch negativity.

[a]*Some subjects failed to stay before the ERP session was terminated. The number of analyzable P50/N100 subjects was 20 UHR and 13 FEP. The number of analyzable MMN subjects was 18 UHR and 16 FEP.*

[b]*Chi-square tests.*

**p < 0.05.*

***p < 0.01.*

group's smaller amplitude of MMN was not so evident when pairwise comparisons were made between UHR and controls as well as between FEP and controls. Similarly, when UHR and FEP were compared to the control group separately, no significant difference could be found in P50 parameters. The only significant differences remained in N100-related parameters: the FEP had a significant lower amplitude in N100 S1 amplitude compared to the controls, and the UHR had a higher N100 S2 amplitude than the controls, while the larger N100 amplitude ratio became insignificant in both groups, but the N100 difference remained significantly smaller in the FEP group but not in the UHR group. Comparisons between control subjects and patients in P50 ratios, N100 differences and MMN values are shown in **Figure 1**. The average MMN waveforms are demonstrated in **Figure 2**.

TABLE 2 | Demographics and ERP results of three groups (SD in parentheses).[a]

	Control	UHR	FEP	Statistics	
				***Post hoc* Scheffe *p* values**	**Effect size (Cohen's *d*)**
	A (n = 120)	B (n = 23)	C (n = 19)		
Age	26.63 (5.09)	23.64 (5.08)	28.45 (8.33)	A vs. B: 0.064	
				A vs. C: 0.417	
				B vs. C: 0.022*	
Male gender (%)[b]	63 (52.5%)	14 (60.9%)	7 (36.8%)	$\chi^2 = 2.48$, $p = 0.29$	
Education (years)	15.62 (1.88)	13.74 (2.83)	14.32 (2.08)	A vs. B: 0.000**	
				A vs. C: 0.040*	
				B vs. C: 0.6655	
Smoking PPD	0.03 (0.1)	0.15 (0.4)	0.16 (0.4)	A vs. B: 0.044*	
				A vs. C: 0.057	
				B vs. C: 0.997	
PANSS					
Positive symptoms (P1 to P7)		15.0 (2.9)	19.4 (4.6)	B vs. C: 0.001**	1.14
Negative symptoms (N1 to N7)		14.2 (5.5)	14.0 (6.5)	B vs. C: 0.923	0.03
General symptoms (G1 to G16)		35.4 (8.4)	35.6 (9.1)	B vs. C: 0.923	0.02
MMN Fz	−1.36 (0.81)	−0.99 (0.88)	−1.11 (0.68)	A vs. B: 0.195	0.44
				A vs. C: 0.517	0.33
				B vs. C: 0.905	0.15
P50					
S1 amplitude	2.44 (1.06)	2.83 (1.59)	2.07 (0.89)	A vs. B: 0.366	0.07
				A vs. C: 0.550	0.38
				B vs. C: 0.180	0.59
S2 amplitude	1.09 (0.64)	1.48 (0.8)	1.41 (0.93)	A vs. B: 0.071	0.54
				A vs. C: 0.280	0.4
				B vs. C: 0.967	0.08
P50 ratio	0.51 (0.34)	0.58 (0.34)	0.71 (0.42)	A vs. B: 0.706	0.21
				A vs. C: 0.139	0.52
				B vs. C: 0.563	0.34
P50 difference	1.35 (1.07)	1.35 (1.53)	.66 (1.05)	A vs. B: 1	0
				A vs. C: 0.125	0.65
				B vs. C: 0.242	0.52
N100					
S1 amplitude	6.73 (3.27)	6.84 (2.92)	4.25 (2.3)	A vs. B: 0.991	0.04
				A vs. C: 0.030*	0.88
				B vs. C: 0.076	0.99
S2 amplitude	2 (1.31)	2.81 (1.1)	1.93 (1.43)	A vs. B: 0.037*	0.67
				A vs. C: 0.982	0.05
				B vs. C: 0.164	0.69
N100 ratio	0.36 (0.31)	0.48 (0.29)	0.55 (0.41)	A vs. B: 0.282	0.40
				A vs. C: 0.118	0.52
				B vs. C: 0.824	0.20
N100 difference	4.73 (3.35)	4.02 (2.48)	2.33 (2.58)	A vs. B: 0.657	0.24
				A vs. C: 0.038*	0.80
				B vs. C: 0.331	0.67

UHR, ultra-high-risk group; FEP, first-episode psychosis group.

[a]*Some subjects failed to stay before the ERP session was terminated. The number of analyzable P50/N100 subjects was 20 UHR and 13 FEP. The number of analyzable MMN subjects was 18 UHR and 16 FEP.*

[b]*Chi-square tests.*

**$p < 0.05$.*

***$p < 0.01$.*

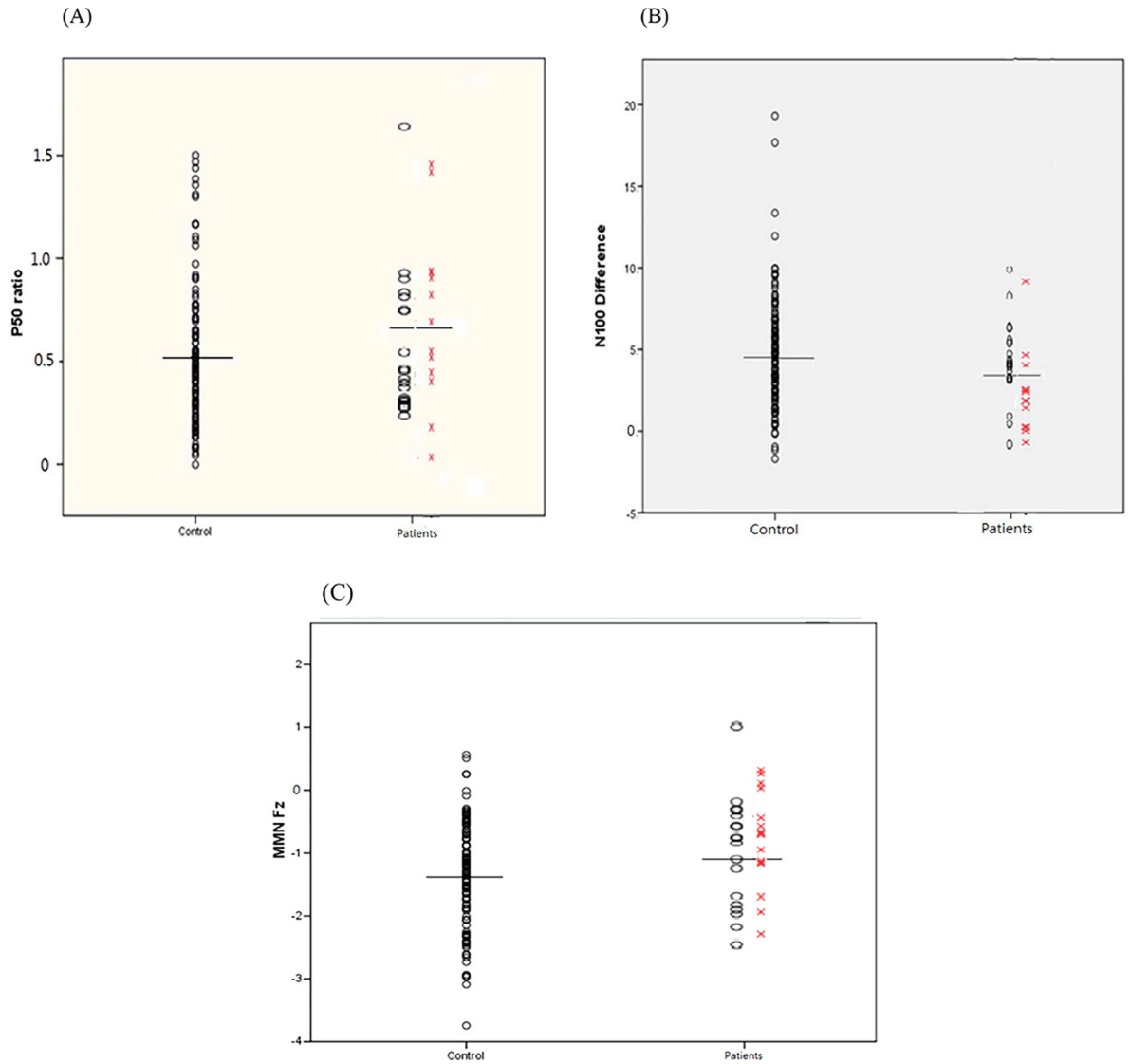

FIGURE 1 | P50 ratios (S2 amplitude/S1 amplitude) **(A)**, N100 differences (μV; S2 amplitude – S1 amplitude) **(B)**, and mismatch negativity (MMN) at electrode Fz **(C)** of individual participants between groups. The horizontal lines indicate the mean values within control vs. patient group, while the patient group consists of ultra-high-risk (UHR; oval) and first-episode psychosis (FEP; X) subjects. For P50 and N100, a larger ratio (S2/S1) and a smaller difference (S1 – S2) indicate poorer sensory gating. For MMN, a larger (less negative) value indicates poor deviance detection.

A head-to-head comparison of ERP results between the drug-naive subjects and the antipsychotic-short-exposure subjects is shown in **Table 3**. Apparently, there was no significant difference in any P50/N100 and MMN parameter between these two groups.

DISCUSSION

It is believed that clinical and cognitive deficits of psychosis may be due to dysfunction at the earlier stages of information processing (56). Bora and Murray's meta-analysis highlighted that cognitive deficits are already established before the prodromal phases of psychosis (57), compatible with our previous publication regarding neurocognitive performance in different stages of pre- and early-psychotic states (58). Such neurocognitive disturbance might represent different components of auditory modality in sensory processing dysfunctions in schizophrenia, and our neurophysiological paradigms measuring "pre-attentive, passive" auditory ERPs in UHR and first-episode psychosis subjects can add valuable information to this field (59).

Although many studies of MMN were conducted on subjects with UHR states, only few have also measured P50/N100 in the same study (60). Also, several studies have included patients with first-episode psychosis and examined them separately from chronic schizophrenia, and most publications reported

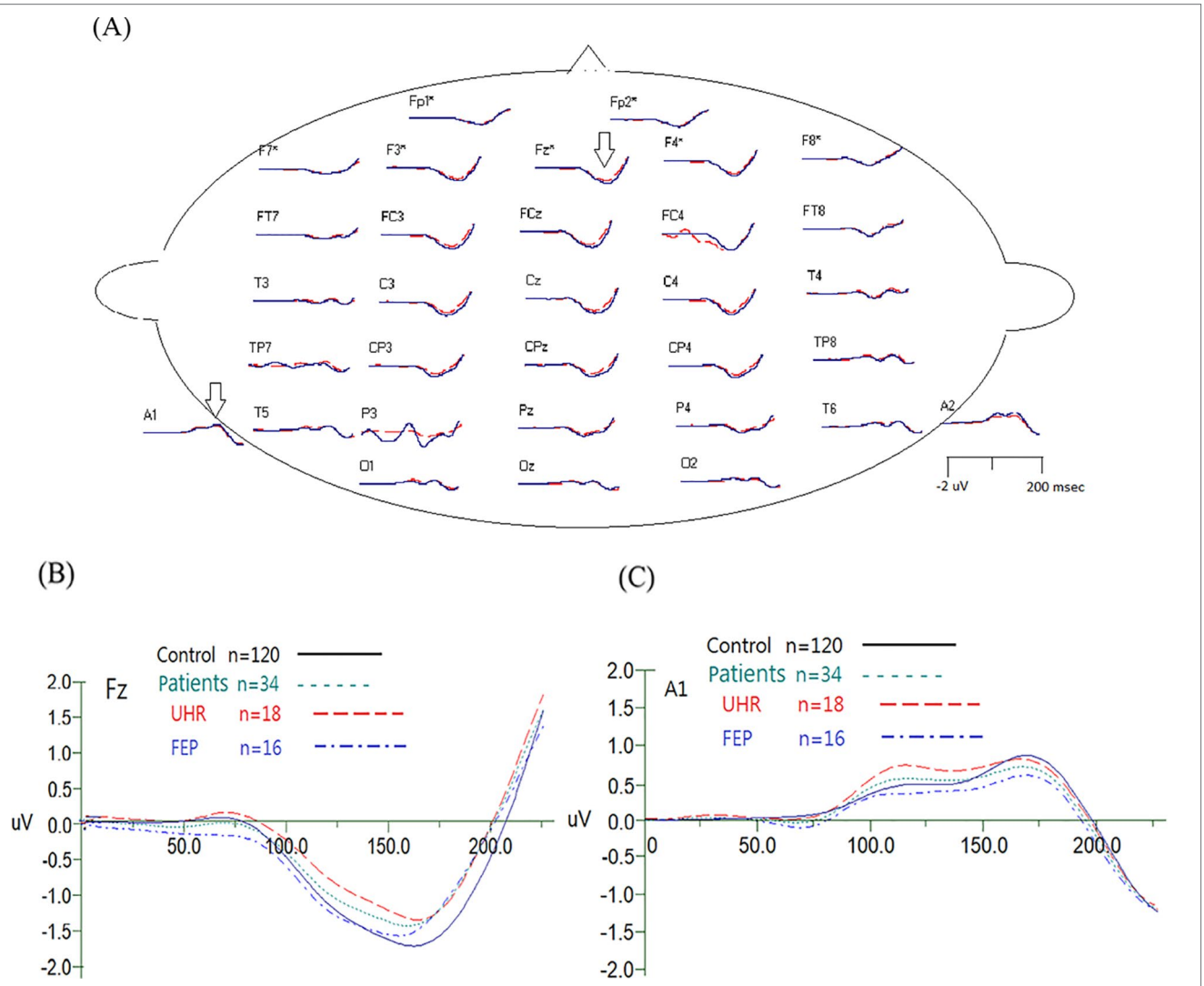

FIGURE 2 | (A) Demonstrated grand average MMN waveforms for healthy control subjects (in blue) and patients (in red). The arrows indicated the waveform reversed in polarity at the mastoid electrodes, which is typical for MMN. A close-up of grand average waveform at electrode Fz and A1 (mastoid) electrodes is shown in **(B)** and **(C)**.

auditory pre-attentive (passive) ERPs after the patients had been treated with antipsychotics. For example, Koshiyama et al. investigated duration vs. frequency MMN in 14 FEP patients, 16 UHR individuals, and 16 healthy controls. They concluded that duration MMN is superior to frequency MMN as a trait marker in the early stages of psychosis, and a smaller duration MMN amplitude in early stages of psychosis may reflect altered developmental process rather than progressive brain pathology (61). However, most of their patients with either FEP or UHR have been treated with antipsychotic medication prior to the experiment, leaving a possible confounder in their interpretation of results.

As Haigh et al.'s meta-analysis of MMN in first-episode schizophrenia patients highlighted a need to conduct study on medication-naive individuals (26), our report is one of the few studies focused on P50/N100/duration MMN in drug-naive or minimally treated FEP and UHR patients. Consistent with our previous report when drug naivety was not strictly defined in that study population, a linear trend of more deviance from controls across different levels of clinical severity was noticed in P50 ratios (S2/S1) and N100 differences, even though the differences in P50 and N100 between control and clinical groups were not statistically significant (39). Specific to study on sensory gating adopting P50/N100 paradigms, our findings are in line with Shaikh et al.'s 36 unmedicated patients who met attenuated psychosis syndrome (equivalent to our UHR) and have already exhibited P50 sensory gating deficits at this pre-psychotic state (62). Similarly, Brockhaus-Dumke et al. found impaired P50 suppression (S2/S1 ratio) in all clinical severities (at risk, true prodromal, first episode, and chronic

TABLE 3 | ERP results of control/drug-naive/antipsychotic-short-exposure groups (SD in parentheses).[a]

	Control (n = 120)	Drug-naive (n = 21)	Antipsychotic short exposure (n = 21)	Statistics	
				Post hoc Scheffe p values	Effect size (Cohen's d)
	A	B	C		
MMN Fz	−1.36 (0.81)	−1.08 (0.88)	−1.00 (0.67)	A vs. B: 0.396	0.34
				A vs. C: 0.267	0.45
				B vs. C: 0.967	0.10
P50					
S1 amplitude	2.44 (1.06)	2.77 (1.77)	2.33 (1.00)	A vs. B: 0.572	0.29
				A vs. C: 0.936	0.10
				B vs. C: 0.551	0.31
S2 amplitude[b]	1.09 (0.64)	1.32 (0.56)	1.56 (1.02)	A vs. B: 0.480	0.36
				A vs. C: 0.027[b]	0.67
				B vs. C: 0.600	0.28
P50 ratio	0.51 (0.34)	0.54 (0.24)	0.71 (0.45)	A vs. B: 0.942	0.09
				A vs. C: 0.083	0.56
				B vs. C: 0.402	0.46
P50 difference	1.35 (1.07)	1.45 (1.51)	0.77 (1.23)	A vs. B: 0.947	0.09
				A vs. C: 0.141	0.53
				B vs. C: 0.239	0.50
N100					
S1 amplitude	6.73 (3.27)	6.06 (3.01)	5.61 (2.96)	A vs. B: 0.751	0.21
				A vs. C: 0.391	0.35
				B vs. C: 0.923	0.15
S2 amplitude	2 (1.31)	2.64 (0.92)	2.32 (1.56)	A vs. B: 0.209	0.50
				A vs. C: 0.631	0.24
				B vs. C: 0.783	0.24
N100 ratio	0.36 (0.31)	0.50 (0.21)	0.52 (0.42)	A vs. B: 0.270	0.47
				A vs. C: 0.149	0.49
				B vs. C: 0.989	0.06
N100 difference	4.73 (3.35)	3.43 (2.40)	3.30 (2.86)	A vs. B: 0.336	0.40
				A vs. C: 0.214	0.43
				B vs. C: 0.993	0.05

[a]*Some subjects failed to stay before the ERP session was terminated. The number of analyzable P50/N100 subjects was 15 for drug-naive and 18 for antipsychotic short exposure. The number of analyzable MMN subjects was 18 for drug-naive and 16 for antipsychotic short exposure.*

[b]*Post hoc Scheffe test revealed significant differences between control and antipsychotic-short-exposure groups (p = 0.027).*

schizophrenia), while impaired N100 suppression (S1 − S2 difference) was also seen in all clinical groups except in the at-risk subjects (63); the latter is exactly the same with our finding. Specific to studies on MMN, our results are similar to Mondragon-Maya et al.'s (23) and During et al.'s (64) MMN and P3a studies, which revealed no impaired deviance detection ability among antipsychotic naive first-episode psychosis patients and individuals at clinical high risk for psychosis and control subjects.

In addition to verifying previous studies, we took a closer look into our findings. When UHR and FEP were compared to normal controls separately, the directions of changes of ERP parameters are of great interest. Based on the sensory gating failure theory, the patients are expected to reveal smaller S1 and larger S2 in P50 signals. This pattern could only be seen in our FEP subjects but not the UHR patients, while the latter exhibited larger, but not smaller, S1, together with larger S2. Although none of these findings reached statistical significance, our findings derived from subjects not confounded by antipsychotic medication might give a hint to understand the dynamic changes of sensory gating in patients with schizophrenia during the progress of their illness. Also, even though no difference in MMN could be detected when UHR and FEP were compared to normal controls separately, collectively as a patient group, their MMN deviance detection ability is lower than that of normal controls, also a finding not confounded by antipsychotics.

Two major limitations of the current study are worth noting. The relatively small sample size of the UHR (n = 23) and FEP (n = 19) groups limits our statistical power to detect smaller differences between groups, such as dividing the pure drug-naive UHR and FEP from those who had short exposure to antipsychotics in either group, but we believe that the majority of our participants had limited impact by antipsychotic treatment, comprising a very valuable sample. Future studies recruiting a larger sample would be necessary to verify our findings. Second, none of our UHR patients converted to full-blown psychosis during a period of 4 weeks. We did not know how many of them would eventually develop psychosis after 1 or 2 years, while previous studies suggested that ERP performance of the converters were likely worse than that of the nonconverters (11, 13, 65).

In summary, our ERP results of antipsychotic-free subjects with UHR state and first-episode psychosis are

not much different from those studies that did not control antipsychotic medication status. Our drug-naive subjects showed no significant difference from their antipsychotic-short-exposure counterparts as well. If this is true, it will be convenient to use this modality to measure patient's sensory gating performance regardless of the impact of antipsychotics, at least at the pre- and early-psychotic states. Nonetheless, we will examine if there are differences in ERP performance between baseline and by the end of a 4-week exposure to antipsychotic treatment. A longer follow-up of prospective longitudinal study will be helpful to provide more evidence to elucidate the role of antipsychotic medication on an individual's neurophysiological performance at different stages of psychosis.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the guidelines of National Taiwan University Hospital Research Ethics Committee with written informed consent from all subjects. All subjects gave written informed consent, including written assent given by minors with informed consent from their parents in accordance with the Declaration of Helsinki. The protocol was approved by the Research Ethics Committee of National Taiwan University Hospital.

AUTHOR CONTRIBUTIONS

MHH and C-ML reviewed literature and designed this study. MHH and Y-TL did the ERP study and data analysis. Y-LC performed the statistics. C-ML oversaw the clinical trial. C-CL, T-JH and H-GH handled the early psychosis studies. All authors have helped to recruit subjects and involved in clinical and diagnostic assessments. MHH wrote the first draft of the manuscript. C-CL finalized the writing and editing of the manuscript. All authors contributed to and have approved the final manuscript.

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Emerging Temporal Lobe Dysfunction in People at Clinical High Risk for Psychosis

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Clinical high-risk (CHR) individuals have been increasingly utilized to investigate the prodromal phases of psychosis and progression to illness. Research has identified medial and lateral temporal lobe abnormalities in CHR individuals. Dysfunction in the medial temporal lobe, particularly the hippocampus, is linked to dysregulation of glutamate and dopamine *via* a hippocampal–striatal–midbrain network that may lead to aberrant signaling of salience underpinning the *formation of delusions*. Similarly, lateral temporal dysfunction may be linked to the *disorganized speech and language impairments* observed in the CHR stage. Here, we summarize the significance of these neurobiological findings in terms of emergent psychotic symptoms and conversion to psychosis in CHR populations. We propose key questions for future work with the aim to identify the neural mechanisms that underlie the development of psychosis.

Keywords: schizophrenia, temporal lobe, clinical high risk, hippocampus, dopamine, glutamate

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INTRODUCTION

Over the last few decades, early clinical interventions for people with psychosis have become more widespread, with an increasing clinical and research interest in identifying people presenting with early signs and symptoms of psychosis (1). Globally, a number of clinical services have been established that are aimed at preventative interventions. Such services identify people, usually young help-seeking individuals, experiencing prodromal symptoms characterized by attenuated psychotic symptoms (APS), including perceptual disturbances (subthreshold hallucinations) and overvalued ideas (subthreshold delusions), a brief psychotic episode, or exhibit a decline in social and occupational function coupled with familial risk (2). Individuals meeting one or more of these criteria are considered to be at a clinical high risk (CHR) for psychosis (2, 3), and around 20% will develop an onset of first-episode psychosis (FEP) within 1 to 2 years (with transition rates varying from 18% at 6-month follow-up to 36% after 3 years) (1). In addition to putative clinical benefits associated with early identification and intervention, research into early and prodromal phases of the illness may provide important information about the pathology of psychosis that is not confounded by long-term medication and/or illness chronicity. One approach is to longitudinally track neural changes using neuroimaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET). In 2002, Philips and colleagues (4) published the first neuroimaging study in a CHR population, reporting changes in hippocampal

volume relative to age-matched healthy controls. This deficit neatly echoes the findings from meta-analyses in schizophrenia patients showing that the structure with greatest volume reduction compared to healthy individuals across the brain is the hippocampus (as well as amygdala and parahippocampus) (5, 6). Since then, several MRI studies [e.g., Refs. (7–10)] along with several PET studies [e.g., Refs. (11–14)] in CHR cohorts have been published, reporting a range of findings relating to brain function and connectivity, anatomy, and chemistry. While neuroimaging studies report neuroanatomical and neurofunctional changes across a range of cortical, subcortical, and cerebellar areas, neurobiological changes in two temporal lobe regions seem to feature prominently in the neurobiological basis of psychosis and the CHR state, namely, the medial temporal lobe (MTL) [e.g., Refs. (8, 15–20)] and the lateral temporal cortices [e.g., Refs. (21–24)]. Moreover, preclinical models [see Refs. (9, 25)] propose that neurobiological changes in temporal lobe regions may occur early in the developmental trajectory of psychosis and have a particular role in the development of attenuated psychotic symptoms (APS).

Furthermore, guided by work in animal models of schizophrenia (25–27) and findings from neuroimaging studies in patients with established schizophrenia, nascent neuroimaging research in CHR populations has identified the importance of an MTL and subcortical network involving the *hippocampus, midbrain, and striatum* (8, 9). Meanwhile, a separate body of neuroimaging work in CHR cohorts, again informed to a large extent by research in patients with established schizophrenia, has identified functional and anatomical alterations in the lateral temporal cortex and broader networks involving the frontal and parietal lobes (24, 28).

Given the role that progressive neurobiological changes in medial and lateral temporal lobe regions appear to play in the development of psychosis, we review evidence supporting dysfunction in temporal lobe-centered networks in people at CHR for psychosis and discuss how putative dysfunction in these regions and networks relates to the emergence of APS. We also consider how dysfunction and progressive changes in these regions track with conversion from the APS observed in CHR to first-episode psychosis (FEP).

CLINICAL HIGH-RISK SYMPTOMS AND THE ONSET OF PSYCHOSIS

Prodromal symptoms are operationalized into criteria for a CHR state and are assessed using instruments such as the Comprehensive Assessment of At Risk Mental State (CAARMS) (29, 30) and the Structured Interview for Prodromal Symptoms/Scale of Prodromal Symptoms (SIPS/SOPS) (31). The criteria apply to young help-seeking individuals and require one of the following presentations: i) attenuated psychotic symptoms (APS), i.e., subthreshold delusions, hallucinations, and thought and language disturbances for which insight is preserved, ii) threshold psychotic symptoms that are brief and self-limiting, and iii) a significant decrease in functioning in the context of schizotypal personality disorder (SPD) or genetic risk for schizophrenia (32). Additional prodromal criteria may include subjective disturbances of cognitive processing and the perception of the self and the world (33, 34) and nonpsychotic symptoms such as anxiety and depression (35). More than 90% of CHR individuals present with APS, in particular attenuated delusions of unusual thought content and suspiciousness (36). While APS are almost always present in CHR individuals at clinical presentation, factor analytical studies of the CAARMS assessment instrument report a "disorganized symptoms" dimension that includes disorganized speech and thought, which is the best predictor of later conversion to FEP (37, 38), a finding also identified using the SIPS/SOPS (39–42).

Taken together, these symptom studies in CHR cohorts might suggest a pattern in which attenuated delusional ideation characterizes nearly almost all CHR cases, while disturbance in thought and language is more characteristic of those CHR cases that later develop psychosis. Is there any neuroimaging evidence to support this view, and what are the implications of these symptom patterns for emerging brain network dysfunction in CHR cohorts?

MEDIAL TEMPORAL LOBE NETWORK

While a range of neurobiological changes are identified in people with schizophrenia, including enlarged ventricles and volumetric reductions in the frontal lobes, thalamus, amygdala, hippocampus, and lateral temporal cortex (5, 43, 44), two neurobiological findings appear to be particularly robust. First, there are neuroanatomical and physiological alterations in the hippocampus and medial temporal lobe (MTL) (45–48) and second, elevated dopamine function in the midbrain and striatum [see Ref. (49) for review].

Based on decades of neuroimaging work describing anatomical, functional, and physiological changes in the hippocampus and MTL [e.g., Refs. (8, 10, 15, 17, 50)], in recent years, a number of researchers have developed a pathophysiological model that characterizes the progression of schizophrenia from the premorbid through the prodromal stages to syndromal psychosis. This model posits dysregulation of glutamate neurotransmission occurring in the CA1 region of the hippocampus that elevates neuronal activity, reflected in metabolism and blood flow, and in doing so elicits the APS emerging in the prodromal stage of schizophrenia (8, 19). As glutamate-driven dysregulation of the CA1 region of the hippocampus persists, dysfunction expands to projection fields within and external to the hippocampus and frontal cortex, leading to onset of threshold psychosis. According to this heuristic, as the illness progresses, an atrophic process ensues in which the neuropil of hippocampal cells is reduced, compromising numbers of interneurons, and leading to the volumetric reduction in the MTL and other regions observed in patients with schizophrenia (8, 19).

In line with this model, there is evidence from a number of neuroimaging studies of reduced hippocampal gray matter in CHR cohorts. Cross-sectional studies comparing CHR subjects to healthy controls have reported reduced gray matter volume in the hippocampal and surrounding MTL (4, 21, 51, 52),

altered hippocampal function during word recognition (16), and elevated resting hippocampal perfusion (18, 53). Furthermore, prospective and longitudinal studies that include CHR subgroups who develop psychosis subsequent to scanning show that hippocampal volume, function, and perfusion changes can predict conversion to psychosis in CHR cohorts (8, 10, 15, 50, 54). However, it must be noted that there are negative studies too; see meta-analysis by Ref. (55). Within the MTL, reductions in volume and altered function have been localized to the anterior part of the hippocampus/parahippocampal gyrus (15, 50). A study by Schobel and colleagues (8) found that resting regional cerebral blood volume (CBV), a measure of metabolism and neuronal activity, was increased in the CA1 region of the hippocampus at baseline in CHR subjects who later developed psychosis. Moreover, longitudinal follow-up in this CHR cohort showed that the onset of psychosis was associated with a progressive increase in resting CBV in the anterior hippocampal subiculum that tracked with gray matter volume reduction in the same MTL region (8, 56).

That CA1 CBV is elevated in CHR *prior* to psychosis onset, and hippocampal subiculum CBV is elevated *after* onset, points to the progressive nature of hippocampal deficits in CHR that are associated with psychosis—and also offers a locus of enquiry as to how these two separate hippocampal regions may additively or differentially contribute to psychosis development in CHR. It is noteworthy that the subiculum is the primary output structure of the hippocampus (57), and also that the nucleus accumbens/ventral striatum receives its strongest excitatory input from the ventral subiculum—consistent with the central role of the ventral hippocampus in driving dopaminergic changes in the rodent model discussed below (25). The model proposed in the study by Schobel and colleagues (8) also posits that changes in hippocampal CBV during this pathophysiological process are driven by glutamate dysregulation. There is substantial evidence that glutamate is altered in schizophrenia and psychosis risk states (58–61). More recently, a prospective study by Bossong and colleagues (20) reports increased hippocampal glutamate levels in CHR subjects who later developed psychosis relative to CHR subjects who did not become psychotic. Additionally, ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist used as a model of schizophrenia, specifically raises CBV and glutamate levels in both CA1 and subiculum subregions of mouse hippocampus (8). By contrast, glutamate levels are generally *reduced* in medicated schizophrenia patients (62), together, suggesting that increased glutamate levels in the hippocampus may be more closely tied to the development and/or presence of symptoms rather than of a diagnosis of schizophrenia per se.

Given these findings, how might glutamate-driven dysregulation of hippocampal or MTL physiology relate to elevated striatal and midbrain dopamine? Experimental work in rodents illustrates how changes in these two neurotransmitter systems might be linked and contribute to the development of psychosis. Studies in rats show that lesions or local glutamate receptor modulation activation of the ventral hippocampus leads to changes in the activity of midbrain Dopamine (DA) neurons and striatal DA release [e.g., Refs. (63, 64)]. Subsequently, several rodent disease models developed with the aim of recapitulating schizophrenia-relevant developmental neuropathology have supported strong links between hippocampal pathology, altered basal hippocampal activity, and dysregulation of midbrain dopamine neurons. One of the earliest of these models showed that bilateral excitotoxic lesions of the ventral hippocampus on postnatal day 7 in the rat altered excitatory activity in the hippocampus and produced changes to striatal dopamine markers (65, 66). In another well-characterized model, the MAM E17 rat, perturbation of neurodevelopment by administration of methylazoxymethanol acetate (MAM) to pregnant rats on embryonic day (E) 17 was associated with a number of histological, neurophysiological, and cognitive/behavioral deficits in the offspring that are analogous to those observed in some schizophrenia patients (25, 26). The most prominent histological abnormalities in the MAM E17 model appear in the hippocampus, including a reduction in the thickness and deficit in parvalbumin-expressing (PV+) gamma-Aminobutyric acid (GABA) ergic inhibitory interneurons. The MAM E17 model has highlighted the potential role of a *hippocampal–midbrain–striatal circuit* in the development of striatal dopamine dysregulation that, in turn, could drive the emergence of APS and psychosis. In this model, midbrain dopamine neuron activity and striatal dopamine levels are elevated (25, 26, 67), possibly as a consequence of aberrant hippocampal drive of ventral striatal projections (25, 26, 67) (see **Figure 1**). Indeed, inactivation of ventral hippocampus in MAM mice completely reversed the elevated dopamine activity (68). Of note, the elevation of ventral hippocampal activity raises not only tonic dopamine, but further, aberrant responsivity of the dopamine system *phasically* (68).

Complementary work in a genetic mouse model of a selective PV+ interneuron deficit in the hippocampus further supports a role for hippocampal dysregulation of striatal DA inputs (69). Deletion of the *cyclin D2* gene during embryonic development leads to a reduction in PV+ interneurons destined for the hippocampus. As adults, these mice show a selective, partial (40–50%) reduction in hippocampal PV+ interneuron density and decreased hippocampal thickness. Application of gadodiamide-enhanced contrast MRI to this model showed increased resting CBV in the hippocampus, similar to the imaging phenotype observed in CHR cases that convert to psychosis within 2 years (8). Neurophysiological studies show that, in adulthood, *cyclin D2* null mice show a deficit in inhibitory synaptic inputs onto hippocampal projection neurons, which is concurrent with excessive activity in midbrain/ventral tegmental area (VTA) dopamine neurons. Moving beyond descriptive and correlational studies, a seminal stem-cell transplant study in the *cyclin D2* null mouse and MAM E18 rat established a causal link between hippocampal disinhibition and excess activity of midbrain dopamine neurons. Specifically, restoring/supplementing GABAergic interneuron numbers in the hippocampus in adulthood through transplantation of PV+ interneuron precursor cells from the embryonic medial ganglionic eminence in these models, reduces metabolic activity in the hippocampus (69) and normalizes both the spike activity of the midbrain DA neurons and behaviors mediated by striatal DA transmission (70).

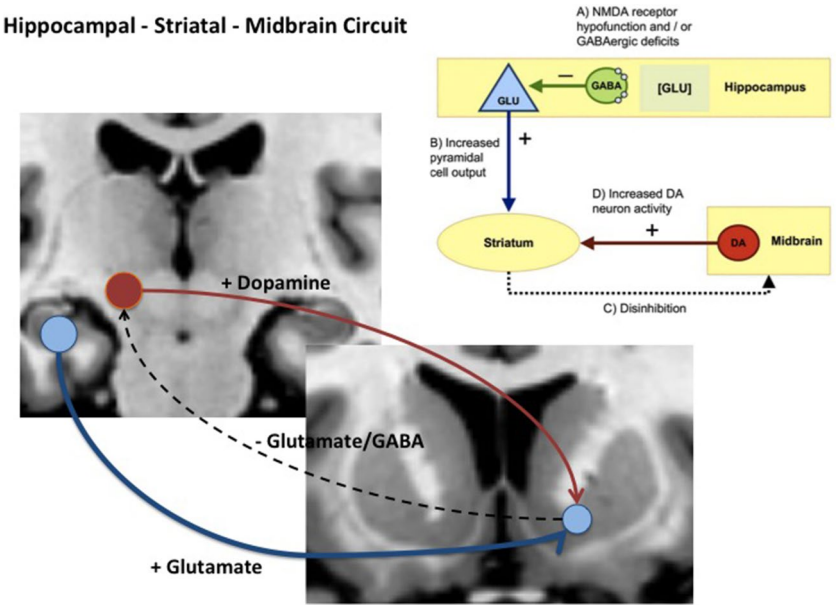

FIGURE 1 | Diagram showing hippocampal midbrain striatal circuit involved in the regulation of striatal dopamine *via* glutamatergic, GABAergic projections (+) = excitatory pathway and (–) = inhibitory pathway. In schizophrenia and clinical high-risk (CHR) states, it is hypothesized that increased glutamatergic output from the hippocampal subiculum to the ventral striatum (blue pathway) reduces inhibition *via* glutamatergic and GABAergic pathways that ultimately drives ventral tegmental area (VTA) dopamine cells and dopamine release back to the striatum (red pathway).

Consistent with the above animal models of schizophrenia highlighting abnormal hippocampal disinhibition, Allen and colleagues (18) reported increased resting cerebral blood flow (rCBF) across hippocampal, striatal, and midbrain regions in a CHR cohort relative to healthy controls [using an magnetic resonance (MR) perfusion measure known as arterial spin labeling] (71), a finding largely replicated in a second independent CHR cohort (53). Further, longitudinal analysis showed that normalization of hippocampal rCBF tracked with clinical improvement of symptoms in the CHR cohort, while elevated hippocampal rCBF persisted in those who remained symptomatic or developed psychosis (18).

To summarize, guided by work in experimental animals, the available evidence in humans, although limited, points toward emerging network dysfunction in a hippocampal–striatal–midbrain network that is driven by glutamate dysregulation resulting in disrupted hippocampal physiology, function, and eventually reduced volume. Furthermore, increased hippocampal neural activity leads to dysregulation of striatal–midbrain dopamine signaling. How dysfunction in this network relates to APS and conversion to FEP is discussed in more detail later (section Discussion: Emerging Temporal Lobe Dysfunction in Clinical High-Risk Populations, Attenuated Symptoms, and Transition to Psychosis). Currently however, most clinical studies investigate only one neurobiological component of the preclinical models discussed above. Clearly, to test preclinical models more rigorously, there is a need for more multimodal neuroimaging work that can better integrate information about neurochemical, physiological, functional, and anatomical factors.

LATERAL TEMPORAL LOBE NETWORK

Disordered brain connectivity is thought to be a central pathophysiological feature of schizophrenia (72–75). The disconnection hypothesis of schizophrenia was initially motivated by neuroimaging studies showing abnormal patterns of functional connectivity between lateral temporal and frontal lobe regions (76–80). Lateral temporal and frontal lobe networks are important for a range of cognitive functions, particularly speech, thought, and language [see Ref. (81)]. The language network usually refers to the superior temporal gyrus (STG), middle temporal gyrus (MTG), the superior temporal sulcus (STS), the inferior frontal gyrus (IFG), frontal operculum, and adjacent regions in the inferior parietal lobe of both hemispheres, but with lateralization to the left hemisphere (82, 83) (see **Figure 2**).

Dysfunction in lateral temporal-centered networks in patients with schizophrenia is thought to underlie positive symptoms relating to language, thought, and speech such as auditory verbal hallucinations (10, 84–86) and thought disorder (87). To date, there are a limited number of studies suggesting altered function and connectivity in this network during prodromal stages of illness (22–24, 28). In a cross-sectional study, Crossley et al. (22) studied participants with CHR for psychosis, FEP patients, and healthy controls using a working memory task. Effective connectivity between frontal and temporal lobe regions was explicitly examined. There were differences in effective connectivity between the STG and prefrontal regions across the three groups, with a negative coupling between these areas in controls, a positive coupling

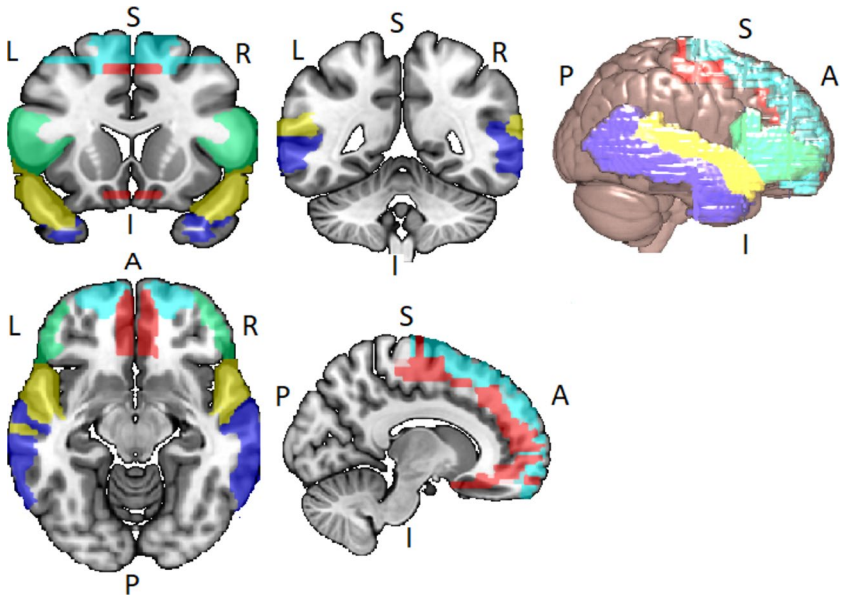

FIGURE 2 | Lateral temporal and frontal network encompassing the inferior frontal gyrus (IFG) (green), the superior frontal gyrus (SFG) (light blue), the Middle Frontal Gyrus (MFG) (red), the superior temporal gyrus (STG) (yellow), and the middle temporal gyrus (MTG) (blue). Networks identified *via* WFU_PickAtlas toolbox for SPM12 in Montreal Neurological Insitute (MNI) space.

in the FEP group, and intermediate effective connectivity parameters seen in the CHR group. In both the FEP and CHR groups, altered effective connectivity was accompanied by increased task-related STG activity. The authors concluded that a failure to deactivate the STG during tasks that engage the prefrontal cortex is already evident at psychosis onset and may reflect a disruption of frontal and lateral temporal connectivity in psychosis. These connectivity changes, albeit to a lesser extent, were also seen in the CHR stage (22). Also using a cross-sectional study design, Allen and colleagues (75) used the Hayling Sentence Completion Task (HSCT) to examine frontal and lateral temporal lobe connectivity in a CHR group. During the HSCT, the CHR group did not differ from healthy controls in terms of frontal or temporal activation. However, there was greater anterior cingulate cortex (ACC) activity in the CHR participants during incongruent HSCT trials. Effective connectivity analysis revealed intact task-dependent modulation of frontal to temporal effective connectivity in the CHR group, although endogenous connection strength between the ACC and the MTG was increased relative to healthy controls. The authors concluded that frontal and temporal functional integration in CHR states is intact, but may depend on increased engagement of the ACC, an effect not observed in healthy controls.

Using a prospective design, Sabb and colleagues (23) investigated language processing and underlying neural networks associated with discourse processing in a CHR group. CHR participants and healthy controls underwent Functional magnetic Resonance Imaging (fMRI) while performing a naturalistic discourse-processing paradigm. CHR participants were followed for 24 months post fMRI scanning to assess symptom severity and social outcome. Relative to controls, CHR participants showed increased neural activity in a network of language-associated brain regions, including the medial prefrontal cortex bilaterally, left IFG and MTG, as well as the anterior cingulate cortex (ACC). Further, increased activity in the left IFG, STG, and caudate predicted subsequent transition to psychosis in CHR subjects. Within the CHR sample, severity of thought disorder at follow-up was positively correlated with signal change in the left IFG, superior frontal gyrus, and left MTG.

Colibazzi and colleagues (24) also use a prospective design with data-driven approaches to resting-state fMRI data to examine resting functional connectivity in a CHR group. Multivariate analyses revealed between-group differences in whole-brain connectivity patterns in bilateral temporal areas, mostly affecting functional connections to the thalamus. The study shows that the established functional connectivity abnormalities in temporal lobe areas, observed in schizophrenia patients, are also present in the CHR period, with aberrant connectivity of the temporal cortex predictive of transition to psychosis in this CHR cohort.

A more recent prospective study investigating broader network organizations in a CHR cohort identified abnormal connectivity (88) in a cerebello-thalamo-cortical circuit and abnormal modular connectome organization (28) in CHR cases that later converted to psychosis. While these studies did not specifically set out to examine lateral temporal lobe connectivity, Collin et al. (28) reported that the brain regions implicated in early-course schizophrenia, including the STG, were most abnormal in terms of connectivity. Together, these functional imaging studies provide evidence of altered lateral temporal lobe

activity and connectivity in the prodromal phase of psychosis and that altered connectivity in temporal lobe areas predicts the later onset of FEP.

In addition to the functional studies discussed above, volumetric and diffusion tensor imaging (DTI) studies in CHR cohorts also report changes in frontal and temporal regions. In their cross-sectional analysis, Borgwardt and colleagues (21) report significant volumetric differences between CHR and healthy control groups in the left STG, as well as in the insula and cingulate gyrus. A prospective comparison of CHR participants based on their clinical outcomes at follow-up (approximately 2 years) revealed that those who later developed psychosis had less gray matter in the STG and frontal regions in the right insula and IFG than those who did not develop psychosis. These findings are in line with an earlier prospective volumetric study (50) that also reported that conversion to FEP in a CHR cohort was associated with reduced gray matter volume in lateral temporal and inferior frontal regions.

However, a later longitudinal volumetric study in a larger CHR cohort (89) reported that CHR subjects who developed psychosis demonstrated a greater rate of gray matter loss only in prefrontal cortex regions relative to CHR nonconverters and healthy subjects with no volumetric differences in temporal lobe regions. Diffusion tensor imaging (DTI) studies in CHR cohorts have also produced mixed results. A systematic review by Vijayakumar and colleagues (90) included 12 studies examining white matter connectivity changes in the CHR stage. The review reports that although the exact location of white matter abnormalities remains uncertain, altered white matter connections in frontal–lateral temporal and fronto-limbic pathways, including the superior longitudinal and uncinate fasciculus, cingulum and corpus callosum, appear to be implicated in the CHR stage.

In summary, there is evidence for altered lateral temporal activity and/or connectivity and reduced volume in people with a CHR for psychosis. Despite the mixed and negative findings regarding lateral temporal (STG) connectivity [i.e., Refs. (22, 75)], a recent large CHR study has implicated altered connectivity in lateral temporal region, particularly in the CHR cases that later convert to psychosis (28). Volumetric studies in CHR cohorts, while robustly reporting reduced gray matter volume in frontal regions, suggest that reduced volume in lateral temporal lobe may also predict those CHR cases that convert to psychosis. Studies of structural white matter connectivity using DTI do report altered white matter in pathways connecting lateral temporal and frontal regions in the CHR stage. Taken together, the limited evidence to date suggests that changes in lateral temporal volume, function, and connectivity are present in the CHR stage and may also predict conversion to psychosis (see section Discussion: Emerging Temporal Lobe Dysfunction in Clinical High-Risk Populations, Attenuated Symptoms, and Transition to Psychosis). However, much more work is needed to confirm these findings and to understand how changes in lateral temporal lobe-centered networks relate to APS in CHR cohorts, particularly disorganized speech and language symptoms.

DISCUSSION: EMERGING TEMPORAL LOBE DYSFUNCTION IN CHR POPULATIONS, ATTENUATED SYMPTOMS, AND TRANSITION TO PSYCHOSIS

Taken together, neuroimaging studies in CHR cohorts suggest that structural and functional changes are seen in both medial and lateral temporal lobe regions *and* related cortical and subcortical networks. We will now consider how these neurobiological changes relate to APS and how dysfunction in these networks is associated with conversion to psychosis.

Are Different Attenuated Psychotic Symptoms Related to Dysfunction in Different Temporal Lobe Networks?

The studies discussed above point to emerging structural and functional alterations in medial and lateral temporal lobe networks in people at CHR for psychosis. So, are different (attenuated) psychotic symptoms in the CHR stage associated with dysfunction in different brain networks? One of the most influential neurobiological models of psychosis proposes that the inappropriate attribution of salience, to what would normally be irrelevant or neutral stimuli or experiences, underlies the formation of delusions (91). In support of this model, increased hippocampal activity is reported in CHR groups in response to neutral relative to emotional stimuli, suggesting impaired salience processing (92). Further, dopamine has a central role in mediating salience, and hyperdopaminergic states can lead to the aberrant assessment of salience (91, 93). To better understand the bio-behavioral significance of altered hippocampal neuronal activity in CHR cohorts, Modinos and colleagues (Modinos et al., 2019) used a novelty salience task in CHR participants and healthy controls. In CHR individuals, the hippocampal response to novel stimuli was significantly attenuated compared to that in the control group, possibly due to increased hippocampal activity at rest or in the control condition, consistent with previous findings of increased hippocampal rCBF (18, 45, 46). Modinos and colleagues also performed an effective connectivity analysis on these functional data and revealed that stimulus novelty (salience) modulated connections from the hippocampus to the ventral striatum significantly more in CHR participants than in controls, a finding seemingly consistent with the notion of increased hippocampal signaling/output to the striatum in psychosis (25). Conversely, stimulus novelty modulated connectivity from the midbrain (VTA) to the ventral striatum was significantly less in CHR participants than in HC, particularly in those CHR participants who subsequently developed psychosis at clinical follow-up. This pattern of activity and disconnectivity would be in line with the maximal tonic activation of dopamine neuron firing that is hypothesized to occur in psychosis, thought to obscure salience-driven increases in population activity of meso-striatal dopamine neurons (94) (see **Figure 3A**). A consequence of this might be the aberrant assignment of stimulus salience.

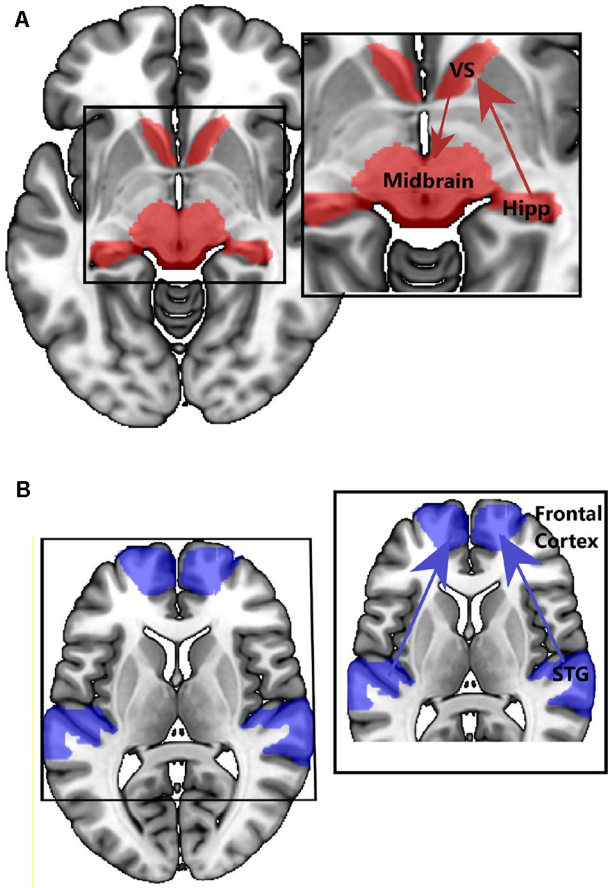

FIGURE 3 | Example of connectivity findings in CHR samples. (**A**) Increased connectivity between hippocampus and striatum, and midbrain and striatum (Modinos, et al., 2019, 96). (**B**) Decreased connectivity between STG and prefrontal regions (89).

Previous neuroimaging studies of motivational and reward salience processing also suggest salience dysregulation and altered activation within a hippocampal–striatal–midbrain network in people at CHR for psychosis (95–97). Using a salience attribution task, Roiser and colleagues (97) found that CHR individuals were more likely to attribute motivational salience to irrelevant stimulus features and this bias was related to the severity of their delusion-like symptoms. Moreover, ventral striatal responses to irrelevant stimulus features were also correlated with delusion-like symptoms in CHR participants. Winton-Brown and colleagues (95) report that reward-induced modulation of connectivity from the ventral striatum/pallidum to the midbrain was greater in CHR participants than controls, and that in CHR participants, the strength of connectivity in this pathway is correlated with the severity of their abnormal beliefs. Collectively, these studies suggest that the behavioral consequence of emerging hippocampal–striatal–midbrain network dysregulation is aberrant salience processing that underlies delusional formation in the psychosis prodrome. Furthermore, these functional and connectivity findings in human CHR cohorts provide support for preclinical work positing that hippocampal hyperactivity (19, 26) results in perturbed striatal function (9, 25). This is important because taken together, these preclinical and human studies identify mechanisms and processes that lead to the development of psychotic symptoms, potentially identifying targets for intervention. Indeed, understanding the sequence of these pathological events, i.e., glutamatergic/GABAergic dysregulation, hippocampal hyperactivity, striatal dopamine dysregulation, that lead to aberrant salience and delusional formation, is crucial in the development and refinement of new treatments.

Disorganization in thought and language (37–42) is also observed in CHR individuals, and form part of the APS operational criterion for the assignment of a CHR state. Decades of neuroimaging research in people with schizophrenia have largely linked these symptoms to dysfunction, not in a hippocampal–striatal–midbrain network, but instead to altered function in lateral temporal regions and connectivity in lateral temporal, frontal, and parietal networks (**Figure 3B**). While there has been less research in CHR cohorts aimed at studying lateral temporal networks (23–28), their dysfunction, and relationship to symptoms, there are a large number of neuroimaging studies in established schizophrenia patients reporting that lateral temporal dysfunction and disconnectivity are associated with disorganized speech and language [see Ref. (87) for review] and auditory verbal hallucinations (10, 84, 85). It is tempting to speculate that these symptoms, ostensibly based around language and sensory dysfunction, have a different neurobiological basis than those relating to aberrant salience. Given that disorganized symptoms appear to predict conversion to FEP in CHR cohorts [e.g., Ref. (37)], from a biomarker perspective, it could be argued that dysfunction in lateral temporal lobe regions (and their associated networks) is a better predictor of conversion to FEP than hippocampal dysfunction. We will examine the evidence of this in the next section.

Is Conversion to Psychosis Associated With Dysfunction in Just One or Both Temporal Networks?

At presentation, neuroimaging studies have identified a number of neurofunctional, neuroanatomical, and neurochemical changes in CHR cohorts relative to age-matched healthy controls. Furthermore, there is emerging evidence that neurobiological changes in temporal lobe regions at the CHR stage are directly related to APS. A small number of prospective and longitudinal neuroimaging studies have attempted to identify neural or biomarkers that predict conversion to psychosis in CHR cohorts. Multisite studies in CHR cohorts investigating volumetric changes associated with conversion to psychosis have reported different findings; one study reports that conversion to psychosis in CHR cohorts is associated with reduced left anterior hippocampal volume at presentation (15), while a second study reports that conversion is associated with reduced gray matter volume in prefrontal rather than temporal regions (89).

Functional MRI studies in CHR cohorts have reported that conversion to psychosis is associated with increased activation in the brainstem (midbrain/basilar pons) and the left hippocampus

(10), the left STG, IFG, and caudate (23), and altered VTA–striatal effective connectivity (Modinos et al., 2019). PET studies using 18 Fluorodopa (18F-DOPA) also report increased striatal (12–14) and midbrain (10) presynaptic dopamine synthesis in CHR cases at presentation that later convert to psychosis. Two magnetic resonance spectroscopy (MRS) studies report increased striatal (98) and hippocampal (20) glutamate levels in CHR conversion cases, although another study reports that CHR individuals have significantly *lower* hippocampal Glx (combined glutamate and glutamine) levels relative to both healthy volunteers and FEP patients (99).

While these findings are broadly consistent with models that posit altered neurobiology in lateral/medial lobe regions and associated networks, not all prospective/longitudinal studies in CHR cohorts implicate the temporal lobes. For example, a recent study by Cao et al. (88) reports that CHR individuals show an intrinsic abnormality in *cerebellar–thalamic–frontal cortical* circuitry associated with disorganization symptoms that is significantly more pronounced among converters than nonconverters. Moreover, multivariate approaches to CHR outcome classification implicate a much wider range of cortical, cerebellar, and subcortical regions [e.g., Ref. (100)] making it difficult to attribute emergent APS to any specific network.

Together, these neuroimaging findings suggest that conversion to psychosis in CHR cohorts is associated with a wide range of structural, functional, and neurochemical alterations, i.e., altered structure and function in hippocampal, prefrontal, lateral temporal, midbrain, striatal, thalamic, and cerebellar regions as well as increased mesolimbic dopamine function and altered hippocampal and striatal glutamate/glutamine function. On the basis of these diverse neurobiological findings, it is difficult to attribute conversion to psychosis in CHR groups to a discrete region, network, or circuit. Moreover, there is some evidence from rodent models that disrupted hippocampal development can lead to neurophysiological abnormalities across several cortical regions, most prominently observed in prefrontal cortex circuits (66). We speculate, therefore, that hippocampal/MTL pathophysiology is seen early in development, but as the brain matures with this abnormality, other circuits, perhaps involving the lateral temporal and prefrontal cortex, become dysregulated. Currently, there are no studies that directly test this chronological prediction in humans although a cross-sectional study by Benetti and colleagues does link altered hippocampal and prefrontal function in CHR subject (101). Alternatively, in schizophrenia, there may be a pathological process playing out across multiple cortical and subcortical circuits, and the hippocampal–striatal–midbrain circuit may be where it is most evident (and possibly most severe) in the CHR/prodromal stage.

In summary, while there is evidence for emerging dysfunction in a range of cortical and subcortical regions in CHR cohorts, altered structure and function in medial and lateral temporal lobe regions, along with prefrontal regions, appear to be seen to a greater extent in CHR cases that convert to psychosis. While the evidence remains equivocal, several imaging studies adopting whole brain analytical approaches support this view [e.g., Refs. (10, 15, 21, 23, 24, 89)] and recent connectivity studies in large CHR data sets show that lateral temporal (28) and prefrontal cortex (88) disconnectivity are particularly associated with conversion to psychosis. Intriguingly, analysis of speech in CHR cohorts (a function strongly related to lateral temporal, frontal, and parietal lobe function) (81) shows that reduced semantic coherence and syntactic complexity predicted later psychosis development with 100% accuracy, outperforming classification from clinical interviews (102). These findings were cross-validated in a second larger cohort using a speech automated machine-learning speech classifier—comprising decreased semantic coherence, greater variance in that coherence, and reduced usage of possessive pronouns. This classifier had 83% accuracy in predicting psychosis onset (103). These findings are broadly in line with earlier factor analytical studies for CHR symptom dimensions that report disorganized thought and speech as predictor of subsequent conversion to psychosis (37). More generally, the neuropsychological data in CHR cohorts suggests that later conversion to psychosis is associated with marked deficits in verbal fluency, processing speed and memory domains (1), cognitive functions likely to rely on frontal, lateral temporal, and hippocampal activity and connectivity.

Based on the studies discussed here, several questions remain about emerging brain network dysfunction in CHR cohorts. Firstly, is dysfunction in both lateral and medial temporal networks necessary for the emergence of a CHR for psychosis or is dysfunction in one or the other network sufficient? Secondly, what is the pathological relationship between dysfunction in these temporal lobe networks? Third, do alterations in volume, function, and connectivity in these regions/networks occur at the same time, or is there a chronological progression related to illness stage, symptom severity, and risk (conversion) for psychosis? Fourth, is dysfunction in these networks related to different pathological or etiological processes?

Studies investigating schizotypal personality disorder (SPD) might provide preliminary insight regarding the first question, as SPD is conceded to represent an intermediate schizophrenia-spectrum phenotype (104). Evidence for temporal and frontal lobe alterations appears to be fairly robust in SPD samples. Similar to findings in CHR samples [e.g., Ref. (90)], investigations utilizing DTI in SPD populations report reduced fractional anisotropy in the uncinated fasciculus (but not in the cingulum) (105), reduced frontal and temporal lobe gray matter (106–109), and reduced temporal lobe gray matter thickness (106). Probabilistic tractography approaches also indicate that healthy individuals higher on psychometric schizotypy traits present with lower fractional anisotropy in the inferior fronto-occipital fasciculus overall (106). A recent fMRI study in an SPD population, investigating symptom clusters, reported that higher resting-state functional connectivity between the frontal and lateral temporal cortex was linked to positive and disorganized dimensions, respectively (110).

However, in SPD populations, there appears to be less evidence in line with rodent models of psychosis and findings in CHR cohorts. One recent study has shown that participants that score highly on measures of schizotypal personality traits (healthy participants with psychotic-like experiences) show higher rCBF in the right hippocampus compared to low-scoring individuals (111), although no differences were observed in midbrain or striatum. However, results from one early single-photon emission computed tomography (SPECT) study suggested relatively greater presynaptic dopamine release in the striatum of SPD individuals relative to healthy controls, similar to levels observed in patients with remitted schizophrenia (112).

Taken together, studies in SPD cohorts seem to provide more evidence for lateral temporal and frontal lobe dysfunction than they do for dysfunction in a hippocampal–striatal–midbrain circuit, although this may be because far less research has been conducted that explicitly examines the hippocampal–striatal–midbrain circuit in psychometric schizotypy/SPD populations (110–113).

Regarding the final question about etiology, there are some interesting clues from previous research. Although increased striatal dopamine function has been reported in CHR cohorts (12–14, 114), no increase in striatal dopamine synthesis was seen in a cohort of nonclinical voice hearers (114). However, increased lateral temporal activity while experiencing voices has been reported in nonclinical voice hearers (115). This finding suggests that dysfunction in the STG and wider frontal and temporal networks, which underlies the experience of auditory verbal hallucinations (10), is not necessarily related to elevated striatal dopamine function, suggesting the possibility of a different etiological pathway. However, it should be noted that a recent PET study by Cassidy et al. (116) reported a relationship between striatal dopamine release and auditory perceptual disturbances and outlined a novel dopamine-dependent mechanism for perceptual modulation that may confer vulnerability to hallucinations in hyperdopaminergic states underlying psychosis.

CONCLUSIONS AND FUTURE WORK

The literature discussed here strongly suggests that altered structure, function, and connectivity in both the medial and lateral temporal lobe play a key role in the development of CHR states and psychosis. Critically, increased rCBF and neural activity in the hippocampus seems to be a well-established factor in CHR populations, suggesting that abnormalities are present at the earliest stages of the condition. Further, studies have linked increased hippocampal glutamate and rCBF with conversion to psychosis, in line with rodent models suggesting that abnormalities in the hippocampus lead to dopamine dysfunctions and abnormal salience processing. While the etiology behind these hippocampal changes is not clear at this stage, immune/inflammatory responses appear to be a factor (117, 118).

Studies also report functional and volumetric abnormalities in the lateral temporal lobe and associated frontal–temporal and parietal language networks, possibly linked to the disorganized language and speech symptoms during the CHR stage. However, while disorganized speech and language symptoms appear to be a strong predictor of conversion to FEP in CHR cohorts, supported by recent findings using speech algorithms, findings from neuroimaging studies are far less equivocal, i.e., there is no clear evidence that lateral temporal lobe-centered networks are the best predictor of conversion to FEP.

While the findings discussed here strongly implicate hippocampal, lateral temporal lobe, and broader network dysfunction in CHR samples, the specific mechanisms or chronology of emerging brain network dysfunction in CHR cohorts remains unclear. Hippocampal abnormalities (leading to dopamine dysregulation) could lead to widespread abnormalities in other regions, particularly other (local) temporal lobe regions, which then lead to psychosis conversion. Alternatively, psychosis progression might be linked to widespread neural circuit abnormalities (with hippocampal dysfunction being most prominent). More sophisticated multimodal longitudinal studies are needed to test these alternative possibilities.

In addition to more sophisticated mechanistic studies, those utilizing novel pharmacological agents could provide valuable insights into whether potentially blocking increases in extracellular glutamate in MTL regions can ameliorate hypermetabolism and atrophy in CHR cohorts. A recent rodent study reported that glutamate dysregulation in the CA1 region of the hippocampus initiated the transition to syndromal psychosis (19). Investigating whether the administration of glutamate regulating drugs in CHR samples would normalize hippocampal hypermetabolism and prevent symptomatic and pathological progression may help to elucidate the mechanistic chronology during emerging psychosis.

Finally, it needs to be noted that schizophrenia is symptomatically heterogeneous and that symptoms and clinical outcomes in prodromal cases are even more heterogeneous. This may be because dysfunction in different neural circuits and neurotransmitter systems may predominate in different subtypes and stages of the disease, which, as defined, represents only a final common syndrome.

AUTHOR CONTRIBUTIONS

All authors listed have made substantial, direct, and intellectual contribution to the work and approved it for publication.

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SYSTEMATIC REVIEW
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Social Cognition Deficits as a Target of Early Intervention for Psychoses: A Systematic Review

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Backgrounds: Social cognition deficits are a core feature of schizophrenia and deteriorate functionality of patients. However, evidence is sparse for the treatment effect on social cognition impairments in the early stage of psychosis. Here, we provide a systematic review of the literature on social cognitive impairment in early psychosis in relation to its intervention.

Methods: A literature search was conducted on English articles identified by Web of Science and PubMed databases, according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.

Results: Five papers met the inclusion criteria. Results from two studies of cognitive training and one study of modafinil indicate positive results regarding social cognition outcomes in patients with early psychosis. On the other hand, two studies with oxytocin and modafinil did not suggest such effects.

Conclusions: Further research is warranted to explore the benefit of early intervention into disturbances of social cognition in psychoses.

Keywords: first-episode psychosis, schizophrenia, ultra-high risk, at risk mental state, theory of mind, emotion recognition, randomized controlled trial

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INTRODUCTION

Schizophrenia affects approximately 0.7% of the world's population (1) and is characterized by positive (hallucinations, delusions), negative (apathy, anhedonia, social withdrawal, etc.), and cognitive symptoms. The first signs and symptoms usually appear between the end of adolescence and beginning of early adulthood. The disease has a chronic course with continual psychotic episodes that generally lead to deterioration in cognitive and social functioning (2, 3), as well as unemployment in more than 70% of patients at the chronic stage (4, 5).

Cognitive impairment is a core feature of schizophrenia and is present over the course of the illness (6). Research has shown that neurocognitive domains, such as memory, attention, executive functions, language, and intelligence, are most severely affected (7). Similar impairments are also found in social cognition (8), i.e., mental operations underlying social behavior. Social cognition is understood as a multidimensional construct that comprises emotional processing, social perspective and knowledge, attributional bias, and theory of mind (ToM). Some studies report that social cognition explains the variance of functional outcome more effectively than does

neurocognition. Thus, social cognition has been considered an important treatment target for functional improvement in people with psychoses (9–12).

Impairment of social cognition, including emotional recognition (13, 14), ToM (15), and attributional biases (16), is evident before the onset of psychosis, continues throughout the early phase of illness, and may even worsen during the first episode (17–19). There have been attempts to determine the relationship between social cognition and social functioning in early psychosis (20). Available research suggests that deficits in social functioning due to social cognition deficits are present early in the course of psychotic disorders (21–23) and also in first-degree relatives of patients (24, 25).

Individuals in the early phase of psychosis exhibit a greater brain plasticity and milder structural and functional brain changes than those in patients with chronic illnesses, providing the rationale for early treatment (26, 27). So far, most published trials of cognitive remediation have used middle-aged, chronically ill patients (28), and its efficacy for those in the prodromal phase or first episode of psychotic illness is largely unknown. As data from current pharmacological interventions suggest limited effects on social cognition impairments of schizophrenia (29, 30), there is a clear need to develop effective therapeutics to target them.

Here, we provide a systematic review of the literature regarding intervention for social cognition deficits in individuals with early psychosis or high risk for developing psychosis.

MATERIALS AND METHODS

Data Sources and Search Terms

This systematic review was performed based on the PRISMA guidelines (31). From inception to March 15, 2019, YY and TI independently examined the Web of Science and PubMed databases. The following search terms were used as keywords: ("early psychosis" OR "first-episode psychosis" OR "FEP" OR "first-episode schizophrenia" OR "ultra-high risk" OR "UHR" OR "psychosis prodrome" OR "at risk mental state" OR "ARMS" OR "clinical high risk") AND ("social cognition" OR "theory of mind" OR "emotion recognition" OR "attributional style" OR "social knowledge" OR "social perception") AND ("training" OR "rehabilitation" OR "remediation" OR "cognitive behavioral therapy" OR "CBT" OR "intervention" OR "pharma*" OR "drug" OR "antipsychotics" OR "antidepressant") AND ("randomized controlled trial" OR "RCT"). Only studies with human participants and written in English were included. The senior reviewer (TS) approved the final list of the studies included.

Eligibility Criteria

Prespecified inclusion criteria were as follows: 1) randomized controlled trials (RCTs) comparing a social cognition intervention with treatment as usual, a minimal educational intervention, sham training, or placebo therapy; 2) participants were adults or adolescents between 10 and 40 years old diagnosed with early psychosis (i.e., schizophreniform disorder, schizophrenia, or schizoaffective disorder) (<5 years illness duration) without a) current substance dependence on alcohol or drugs, b) intellectual disability (intelligence quotient <70), c) a history of a significant neurological disorder, and d) florid psychotic or related symptoms likely to require immediate intervention (e.g., suicidality); 3) interventions were training or pharmacotherapy targeted to one or more social cognition domains; 4) comparisons were treatment as usual, a minimal educational intervention, sham training, or placebo therapy; and 5) outcomes were objective scales defined as ToM, emotion recognition, attributional style, social perception, and social knowledge.

Outcome Measures

Outcome measures identified by this search were discussed in relation to three domains of social cognition, i.e., emotion recognition, theory of mind (ToM), and attributional bias (see **Table 1**).

Emotion Recognition

Mayer–Salovey–Caruso Emotional Intelligence Test (MSCEIT) (37) measures the participant's ability to perceive, use, understand, and regulate emotions, while Facial Expressions of Emotions Task (FEEST) (38) requires subjects to identify six basic emotions (happiness, sadness, anger, fear, surprise, and disgust) from facial expressions, although Cacciotti-Saija et al. (34) gave no information about whether they used morphing images of different emotional valences or varying degree of emotional intensities. Movie Stills Task (39) requires identification of emotions (happy, surprised, afraid, angry, disgusted, sad, or neutral) from a complex movie scene. On the other hand, Pictures of Facial Affect (POFA) (40) uses facial photos providing the morphing faces of different emotions, or emotional face of different emotional intensities (0% fearful,

TABLE 1 | Cognitive scales used.

Study (year)	Emotion recognition	Theory of mind	Attributional bias
Scoriels et al. (2011) (32)	ERT	–	–
Lees et al. (2017) (33)	MCCB-social cognition	–	–
Cacciotti-Saija et al. (2015) (34)	FEEST Movie Stills Task	FBPST, Faux Pas Task, Empathy Quotient, RMET	Ambiguous Intentions Hostility Question
Fernandez-Gonzalo et al. (2015) (35)	POFA	ToM 1st order, ToM 2nd order, Hinting Task, RMET	IPSAQ
Mendella et al. (2015) (36)	MSCEIT	–	–

ERT, Emotion Recognition Task; MCCB,Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery; FEEST, Facial Expressions of Emotions Task; POFA, Pictures of Facial Affect; MSCEIT, Mayer–Salovey–Caruso Emotional Intelligence Test; FBPST, False Belief Picture Sequencing Task; RMET, Reading the Mind in the Eyes Test; IPSAQ, Internal, Personal and Situational Attributions Questionnaire.

10% fearful, 20% fearful, 30% fearful, … and 100% fearful). In this task, subjects are instructed to recognize basic emotions (happiness, sadness, anger, disgust, and surprise) in 60 faces. Furthermore, Emotion Recognition Task (ERT) consists of a series of mixed ethnic background faces photographs depicting seven emotions: happiness, surprise, neutral, fear, disgust, anger, and sadness (41). Finally, a subdomain of social cognition of the MATRICS Consensus Cognitive Battery (MCCB) (42, 43) was developed for use in schizophrenia.

Theory of Mind

False Belief Picture Sequencing Task (44) consists of arrangement of picture-cards into a logical sequence of events to test the ability to go beyond objective information to reason that a story protagonist is acting on the basis of a false belief. Reading the Mind in the Eyes Test (RMET) (45) assesses the ability to infer mental states from images of eye regions, and provides a sensitive measure of social cognition impairments in early psychosis (46). The modified Faux Pas Task (47) requires participants to respond when faux pas are present. The Empathy Quotient (48) is a self-report measure of cognitive and affective aspects of empathy.

ToM task consists of four classic false belief/deception stories; the "Sally & Anne" (49) and "Box of Chocolate" stories (50) are used to assess first-order ToM abilities, while "Burglar" (50) and "Ice-Cream Van" (50) are used to assess second-order ToM skills. These stories are read aloud by the examiner, and subjects are asked to listen and subsequently answer a ToM question and a control question. In order to avoid a possible learning effect, two homologous false belief/deception first-order ToM stories ["Cigarettes" (51) and "Piggy bank" (51)] and second-order ToM stories ["Train station" (52) and "Coke" (52)] are administered at baseline and posttreatment. Hinting Task (53) is also used, in which patients have to understand indirect speech and infer the mental state of one of the characters.

Attributional Bias

Ambiguous Intentions Hostility Questionnaire (54) contains five short vignettes describing negative interpersonal events with ambiguous causality. Internal, Personal, and Situational Attributions Questionnaire (IPSAQ) (55) is designed to assess the extent to which individuals attribute negative and positive events to different attributional loci. The task consists of 32 social items describing 16 positive and 16 negative events. Patients are asked to generate the most likely cause of each event and state whether the cause is due to self, other people, or circumstances. Six subscale scores are generated (number of positive events attributed to self, other people, and circumstances, and corresponding scores for negative events), which are used to calculate two composite scores: externalizing bias (EB) and personalizing bias (PB).

Procedures and Data Extraction

Initially, titles and abstracts were screened to identify eligible studies. Full-text articles were obtained for all the studies considered compatible based on the abstract screening and were further reviewed for eligibility.

Risk of Bias in Individual Studies

We selected the Cochrane Collaboration's risk of bias tool to evaluate risk of bias in each trial. Two independent reviewers (YY and TI) determined 1) if patients were correctly randomized, 2) if the randomization method was properly concealed, and 3) if subjects and/or investigators and/or raters were blinded. We assessed whether the authors collected and reported all results for all pre-specified outcomes. A senior reviewer (TS) approved the final decision of the assessment of risk of bias.

RESULTS

The initial search provided a total of 39 records. After removing duplicates, 32 articles were screened, of which 11 English full texts were available. Five articles found eligible for the systematic review. Articles describing studies that involved only secondary analysis of baseline data from RCT ($n = 3$), and no social cognition outcome measures ($n = 3$) were excluded. The PRISMA study selection flowchart is shown in **Figure 1**. The summary of risk of bias is presented in **Figure 2**.

Characteristics of Studies

The five studies included in the current review encompassed 212 subjects (151 men and 61 women). Characteristics of the selected studies are shown in **Table 2**. There were considerable differences between the studies in terms of demographics, intervention type, and outcome measures. Two studies (32, 36) targeted first-episode psychosis (FEP) subjects, while three (33–35) included early psychosis patients with less than 5-year illness duration. Two studies used cognition training or rehabilitation as their intervention (35, 36), while one concerned intervention with oxytocin (34), and two with modafinil (32, 33). For these studies, treatment as usual (35, 36) or placebo therapy (32–34) was used as a comparison group.

Systematic Review

Social Cognitive Deficits at Baseline

Social cognitive impairment, including emotional recognition, ToM, and attributional biases, was evident during the early phase of psychosis, as shown in **Table 3**.

Effect Sizes of Interventions for Social Cognitive Deficits

Social Cognitive Training

Social cognitive training exhibited significant effects in limited domains. The three studies included in the systematic review used social cognitive training, two of which found significant effects, as shown in **Table 2**. Effect sizes by means of Cohen's *d* (56, 57) indicated large effects on emotional recognition domains in two studies (35, 36), while other domains were not affected (see **Table 3**).

Pharmacological Treatment

There were no significant effects of oxytocin on any outcomes of social cognition (34). One study found that modafinil significantly improved the recognition of sad facial expressions (32), although there was no significant effect on social cognition

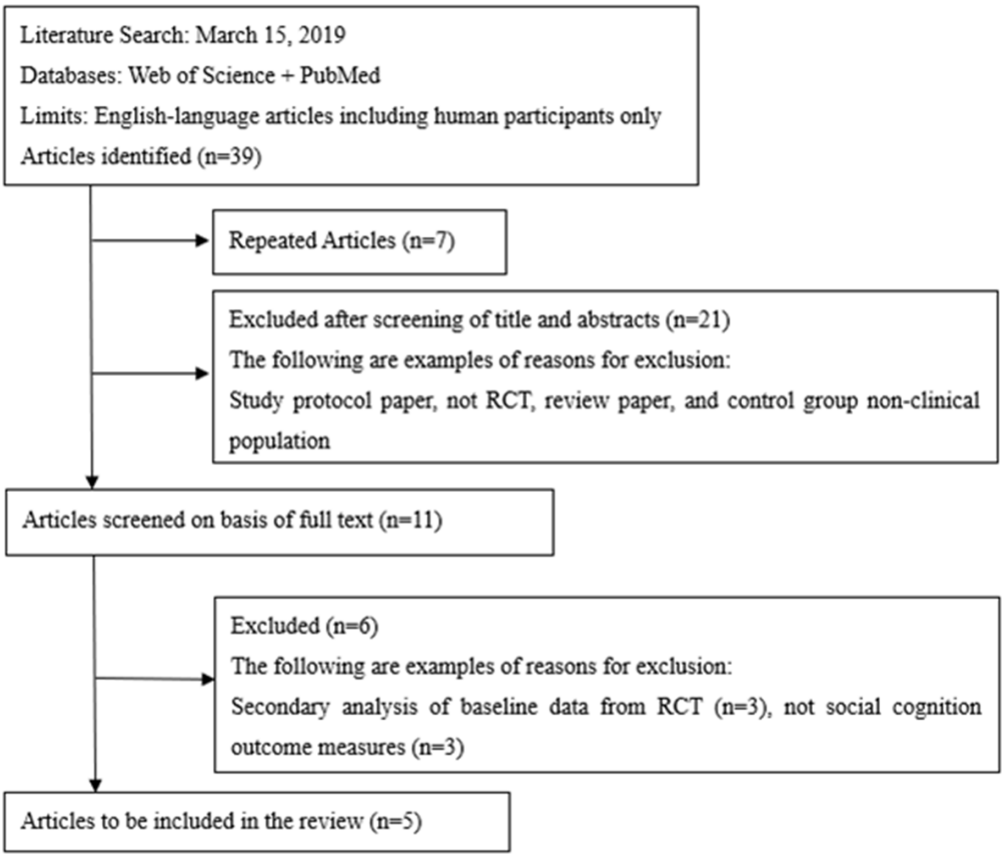

FIGURE 1 | Study selection flowchart, following the guidelines of the PRISMA statement. Initially, titles and abstracts were screened to identify eligible studies. Full-text articles were obtained for all the studies considered compatible, based on the abstract screening, and were further reviewed for eligibility.

performance, as measured by the MCCB, in another study of modafinil (33) (**Table 3**).

DISCUSSION

Five papers met the inclusion criteria for the current review. Two studies of cognitive training showed positive results in terms of social cognition. One study (32) of modafinil also reports improvement of recognition of sad facial expressions. On the other hand, two pharmacological studies (33, 34) on oxytocin or modafinil did not exhibit such effects.

Social cognition training was shown to improve emotional processing in early psychosis (35). Patients with first-episode schizophrenia present difficulties in identifying facial emotions, specifically negative ones (58), which have been related with functionality (9). Current reviews suggest that emotional processing may be improved by cognitive training even at early stages of the illness. On the other hand, efficacy of cognitive remediation was not evident in other domains of social cognition, which requires further investigations.

Social cognitive training programs aim to improve specific domains of social cognitive impairments that are related to social functioning and readily transferable to real-world situations (59). These cognitive models of early psychosis rest on aberrant salience and biased appraisal processes (60). These biological processes consist of increased striatal dopamine release, which is associated with aberrant salience. Aberrant salience opens the gates to consciousness for trivial stimuli to enter the center of attention, and the salient stimulus cries out for an appraisal (60, 61). The appraisal process elicited by aberrant salience is a key mechanism of developing delusions. A characteristic of individuals with early psychosis is that they are still open for multiple explanations for extraordinary experiences. Cognitive therapy targets appraisal processes that accompany perceptual aberrations and suspiciousness to normalize extraordinary experiences with education (61).

Although Cacciotti-Saija et al. (34) and Fernandez-Gonzalo et al. (35) used the same Ekman's photos as dependent measure, their studies reported different intervention effects. This suggests that social cognitive training and oxytocin treatment may change different neurobiological substrates.

Although existing evidence indicates that oxytocin impacts favorably on domains of social cognition (62), its treatment effects, in comparison with placebo, were absent in young people with early psychosis. Oxytocin is a neuropeptide that interacts with a variety of neuromodulators, including serotonin and dopamine,

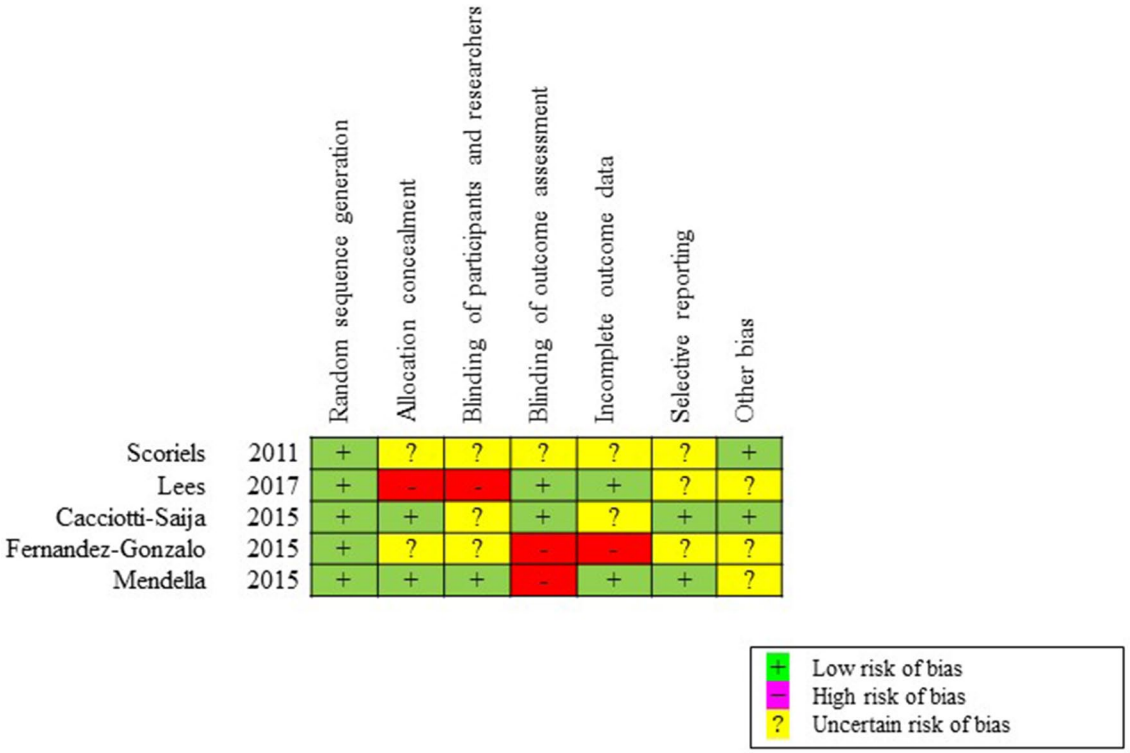

FIGURE 2 | Assessment of risk of bias for included studies, based on the Cochrane Collaboration's risk of bias tool. We determined whether each trial had a low, high, or uncertain risk of bias in terms of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases.

TABLE 2 | Summary of studies comparing the performance on social cognition tasks in individuals with early psychosis.

Study (year)	Participants (number)	Age (years) Mean (SD)	Gender Male, %	Intervention (number)	Control (number)	Outcome domains	Results
Scoriels et al. (2011) (32)	FEP (40)	Crossover design 25 (2)	77.5	Modafinil (40)	Placebo (40)	Emotion recognition	Significant effects
Lees et al. (2017) (33)	Early psychosis (40)	Crossover design 25.7 (4.9)	73.8	Modafinil (40)	Placebo (40)	Emotion recognition	No significant effects
Cacciotti-Saija et al. (2015) (34)	Early psychosis (52)	Intervention 21.5 (4.2) Control 22.3 (4.4)	69.2	SCT + Oxytocin (27)	SCT + Placebo (25)	Emotion recognition Theory of mind Attributional bias	No significant effects in any domains
Fernandez-Gonzalo et al. (2015) (35)	Early psychosis (53)	Intervention 30.9 (5.9) Control 30.0 (7.4)	64.2	NPT-MH (28)	Nonspecific computer training (25)	Emotion recognition Theory of mind Attributional bias	Significant effects only in emotion recognition
Mendella et al. (2015) (36)	FEP (27)	Intervention 25.0 (3.9) Control 24.8 (2.6)	74.1	CCT (16)	TAU (11)	Emotion recognition	Significant effects

FEP, first-episode psychosis; SD, standard deviation; SCT, social cognition training. Participants underwent a 6-week group-based program. The program involved a combination of group learning activities (70% of total session time) and computer-based training tasks (30% of session time) completed in pairs. NPT-MH, Neuro Personal Trainer–Mental Health; a new cognitive exercise based on multimedia content; CCT, compensatory cognitive training; TAU, treatment as usual.

in the nucleus accumbens and amygdala (63). Results from a previous study (64) suggest that genetic variants of oxytocin receptors may be responsible for social cognitive impairments of schizophrenia. The reliability of benefits of oxytocin and other neuropeptides, e.g., vasopressin, across population and contexts remains an ongoing issue.

Modafinil is a wake-promoting agent for the treatment of excessive daytime sleepiness. It activates monoamines and glutamate, and inhibits γ-aminobutyric acid neurotransmitters in several brain regions, including the prefrontal cortex, hippocampus, hypothalamus, thalamus, and basal ganglia. Modafinil also induces changes of neurotransmissions in the

TABLE 3 | Effect of intervention on social cognition performance.

Study	Scales	Intervention		Control		p-value	Effect size
		Baseline mean (SD) score	Posttreatment mean (SD) score	Baseline mean (SD) score	Posttreatment mean (SD) score		Partial η^2
Scoriels et al. (32)	ERT-sadness	83.6 (3.18)	91.8 (2.09)	83.6 (3.18)	91.8 (2.09)	0.003	0.330 (Hedges' *g*)
Lees et al. (33)	MCCB-social cognition	38.8 (9.4)	40.2 (11.5)	38.8 (9.4)	40.2 (11.5)	0.22	0.139 (Hedges' *g*)
Cacciotti-Saija et al. (34)	FEEST	45.0 (7.3)	49.4 (6.5)	44.9 (7.5)	48.8 (8.3)	0.93	0.001
	Movie Stills—no face	9.8 (1.8)	10.3 (2.2)	9.7 (1.8)	10.3 (2.1)	0.88	0.002
	Movie Stills—face	11.9 (3.0)	11.7 (2.0)	11.3 (1.6)	11.7 (1.7)	0.44	0.015
	FBPST	18.7 (4.7)	21.1 (4.8)	20.1 (4.8)	20.7 (5.2)	0.12	0.042
	Faux Pas—Hit Rate	0.9 (0.1)	0.9 (0.2)	0.8 (0.2)	0.9 (0.2)	0.09	0.047
	Faux Pas—False Alarm	0.2 (0.3)	0.1 (0.2)	0.1 (0.3)	0.1 (0.2)	0.73	0.006
	Empathy Quotient	11.8 (6.2)	10.9 (4.8)	12.6 (4.7)	13.0 (4.8)	0.21	0.032
	RMET	66.1 (17.0)	66.6 (17.8)	69.7 (14.2)	71.7 (14.4)	0.53	0.013
	AIHQ—Hostility Bias	26.2 (10.3)	23.2 (8.4)	21.3 (3.6)	19.1 (3.3)	0.67	0.007
	AIHQ—Blame	42.4 (14.9)	41.8 (14.3)	41.1 (12.4)	38.8 (11.3)	0.36	0.020
	AIHQ—Aggression	22.8 (7.3)	22.6 (9.3)	22.3 (4.4)	21.0 (4.0)	0.79	0.004
Fernandez-Gonzalo et al. (35)	POFA	45.6 (6.0)	50.2 (5.0)	45.2 (5.0)	46.8 (4.2)	0.009	0.167
	ToM 1st order	3.9 (0.5)	3.9 (0.3)	3.8 (0.6)	3.9 (0.3)	0.76	0.003
	ToM 2nd order	3.1 (0.8)	3.1 (1.1)	3.1 (1.0)	2.6 (0.8)	0.25	0.035
	Hinting Task	4.6 (1.3)	5.6 (0.8)	4.2 (1.4)	5.5 (0.9)	0.53	0.011
	RMET	23.1 (4.5)	24.1 (5.2)	22.4 (4.7)	22.0 (4.9)	0.25	0.035
	IPSAQ—Externalizing	0.2 (3.0)	3.6 (14.5)	0.0 (3.4)	−0.1 (2.8)	0.32	0.027
	IPSAQ—Personalizing	1.1 (0.6)	1.0 (0.8)	1.2 (0.5)	1.1 (0.4)	0.98	<0.001
Mendella et al. (36)	MSCEIT	42.8 (12.2)	47.3 (9.5)	46.3 (10.8)	42.3 (10.7)	0.04	0.17

SD, standard deviation, Effect sizes (partial η^2) indicate small > 0.01, medium > 0.06, and large > 0.14 effects. ERT, Emotion Recognition Task; MCCB, MATRICS Consensus Cognitive Battery; FEEST, Facial Expressions of Emotions Task; FBPST, False Belief Picture Sequencing Task; RMET, Reading the Mind in the Eyes Test; AIHQ, Ambiguous Intentions Hostility Question; POFA, Pictures of Facial Affect; IPSAQ, Internal, Personal and Situational Attributions Questionnaire; MSCEIT, Mayer–Salovey–Caruso Emotional Intelligence Test.

hippocampus and limbic regions, an action related to memory- and mood-enhancing properties (32).

Scoriels et al. (32) reported the efficacy of modafinil on emotional recognition using the Emotion Recognition Task (ERT). Critical nodes in the emotional face recognition circuitry include the amygdala, which is activated during performance on the ERT (65). Modafinil activates amygdala (66) and increases serotonin levels in it (67). These observations suggest that modafinil improves emotional face recognition in patients with FEP through serotonergic effects on the amygdala. On the other hand, Lees et al. (33) did not find the ability of modafinil to improve social cognition in early psychosis, as measured by the MCCB. These results indicate that the prosocial cognition effects of modafinil or other compounds depend on the type of cognitive tests used.

The neural network of social cognition consists of orbitofrontal cortex, medial prefrontal cortex, superior temporal sulcus, and amygdala, whose functional connectivity is decreased in psychotic patients (68, 69). Previous studies showed that the amygdala plays a key role in perception of facial emotional expression (39), while the prefrontal cortices are strongly associated with ToM (70). On the other hand, the superior temporal sulcus is related to both domains of social cognition (71). These lines of evidence may provide a clue to the development of novel therapeutics, including those of neuromodulation methods.

The differential effects of treatment on emotion recognition, ToM, and attribution styles deserve discussions. Emotion processing shows a consistent relationship with community functioning, which includes a wide range of activities and behaviors related to work functioning and independent living (72, 73). ToM relates to the capacity to interpret beliefs and feelings of others, i.e., predicting general psychotic symptoms, especially negative ones (74). Moreover, ToM is strongly associated with multiple dimensions of social functioning, including interpersonal communication, recreational activities, independence, and performance (73). On the other hand, attributional bias describes how individuals make sense the causes of the positive and negative social events and interactions encountered in life, providing a significant impact on behaviors (75). These findings support the roles for individual domains of social cognition in mediating neurocognition and functional outcomes, which may be relevant to early psychosis.

To conquer social cognition impairments in established schizophrenia, psychosocial approaches, e.g., social cognition and interaction training (SCIT), metacognitive training, training of affect recognition (TAR), emotion and ToM imitation training, emotion processing, and ToM video-based training, as well as pharmacological approaches, e.g., aripiprazole and risperidone, have been attempted. However, there is no such attempt targeting early psychosis, indicating a need for further efforts in this area.

Since no definite strategy has been established to treat social cognition deficits in early psychoses, some types of neuromodulation have been drawing attention. For example, repetitive transcranial magnetic stimulation (rTMS) has been shown to ameliorate facial affect recognition, assessed by "Picture of Facial Affect," in patients with chronic schizophrenia (76).

This result may indicate that noninvasive brain stimulations may improve social cognition in patients with psychosis. Transcranial direct current stimulation (tDCS) is another type of transcranial electrical stimulation procedures. So far, tDCS has been shown to improve neurocognition, as well as daily-living skills and depressive symptoms, in patients with schizophrenia (77). Of note, the effect on psychotic symptoms was associated with oxy-hemoglobin concentrations in cortical regions, as measured by near-infrared spectroscopy (78). Based on these considerations, efforts to evaluate the benefit of neuromodulation on social cognition in psychosis are warranted.

In the present review, we did not find any study exploring the influence of antipsychotic treatments on social cognitions, such as ToM, emotion recognition, and attributional style, in patients with early psychosis. This area also deserves further investigations.

LIMITATIONS

The limitations of the present review should be noted here. Although 2006 workshop sponsored by the National Institute of Mental Health (NIMH) (11) recommended five domains (attributional style, emotion recognition, social knowledge, social perception, and ToM) for the evaluation of social cognition in psychotic disorders, no study to date has comprehensively examined these domains in the same sample; heterogeneity in terms of social cognitive domains across studies may have obscured findings on the efficacy of treatments. Further investigations circumventing these methodological issues deserve considerations.

CONCLUSIONS

As interventions into disturbances of social cognition in early psychosis provide an important issue, further studies, including those with novel paradigms, are warranted.

AUTHOR CONTRIBUTIONS

YY and TS planned the study. YY designed it and drafted the first manuscript. YY and TI independently searched and assessed the literature. TS approved the final list of included studies. TI, MM, KS, NS, NU, YO, NH, and TS critically reviewed the draft and revised it. All authors made substantial contributions and approved the final manuscript.

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Negative Life Events and Problematic Internet Use as Factors Associated With Psychotic-Like Experiences in Adolescents

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Objectives: Psychotic-like experiences (PLEs) and problematic internet use (PIU) are common in adolescents. However, little is known about the association between PLEs and PIU among adolescents. The present study examined the associations between PLEs and PIU and negative life events among adolescents.

Methods: In total, 1,678 adolescents attending high school were recruited for a cross-sectional survey. They completed self-reported assessments of PLEs using the Prodromal Questionnaire-16 (PQ-16) and measures of depression, anxiety, self-esteem, internet use, and negative life events using the Center for Epidemiological Studies Depression Scale (CES-D), the State-Trait Anxiety Inventory (STAI), the Rosenberg Self-Esteem Scale (RSES), the Korean Scale for Internet Addiction (K-scale), and the Lifetime Incidence of Traumatic Events for Children (LITE-C), including cybersexual harassment and school violence.

Results: A total of 1,239 subjects (73.8%) scored at least 1 on the PQ-16. The mean total and distress PQ-16 scores were significantly higher in students who used mental health services. The total and distress prodromal questionnaire-16 (PQ-16) scores were positively correlated with the CES-D, STAI-S, STAI-T, LITE-C, and K-scale scores but negatively correlated with the RSES score. Hierarchical linear regression analysis revealed that PLEs were significantly associated with a high K-scale score and the incidence of negative life events, such as LITE-C, cybersexual harassment, and bully–victims.

Conclusion: Our results demonstrate that PIU and negative life experiences were significantly associated with PLEs in adolescents. Assessment and therapeutic intervention with regard to internet use as a coping strategy for stress are needed to prevent the development of clinical psychotic symptoms.

Keywords: psychotic-like experience, internet use, stress, coping, anxiety, depression

INTRODUCTION

Psychotic-like experiences (PLEs) are subclinical hallucinations and delusions that are common among adolescents (1) and are a manifestation of at-risk mental states (ARMS) for psychosis (2, 3). The presence of PLEs does not necessarily predict future conversion to psychosis (4), but it is important to address such experiences as they cause distress and functional impairment similar to individuals who transition to psychosis (5). Several psychosocial factors, such as depression, anxiety, poor self-esteem, and negative life experiences, have been reported to be risks for PLEs (6–9). In the context of negative life experiences, PLEs are associated with childhood trauma and recent life events (10, 11). Because adolescence is a distinct life stage with specific developmental tasks, adolescents must cope with various psychological events and bodily changes (12). In particular, school bullying creates substantial stress, especially during adolescence, when peer relationships become important. Cyberbullying (including sexual harassment) has become common, especially among teenagers who use the internet extensively (13). Research has revealed several serious mental health problems caused by the cyberbullying of adolescents (14).

The literature indicates that coping with the stress associated with PLEs may be important in terms of determining psychiatric outcomes (15, 16). Maladaptive coping is associated with the strong relationship between psychopathology and poor functioning in those with psychotic disorders (17, 18). Recent studies in adolescents have indicated that individuals who report subclinical psychotic experiences also commonly use poor coping styles (19). Addictive behaviors, including internet addiction, are known to be negative coping strategies with stressful events and deteriorate the individual functioning (20–22). Problematic internet use (PIU), conceptualized as "internet addiction," is characterized by persistent compulsive use of the internet that interferes with daily life, leading to significant clinical impairment (23).

PIU is a serious public mental health problem worldwide, especially in adolescents (24). In addition, adolescents who consult for PIU have comorbid mental health problems (25). From a clinical perspective, it is important to explore mental health problems in adolescents with PIU and vice versa. A recent study showed that nonclinical PLE is positively associated with PIU in young adults (26). In our previous study, PIU in patients with a schizophrenia spectrum disorder was significantly associated with dysfunctional coping with stressful events. However, few studies have investigated the association between PLEs and PIU among adolescents. In particular, as South Korea has high-speed internet and a high rate of excessive smartphone use among teenagers (95.9%) (27), PIU is becoming a serious social problem, particularly among adolescents.

This study investigated the associations among PLEs, negative life events, and PIU in Korean community high school students. In particular, we assessed negative life events among adolescents due to not only childhood trauma but also recent stressful events including cybersexual harassment and bullying at school. This study will further facilitate our understanding of these issues in the community setting, including intervention and prevention for adolescents with PLE symptoms.

METHODS

Study Design and Participants

This study was a community-based cross-sectional survey undertaken between July and September 2016 in Gwangju, Korea. In total, 2,013 first- and second-grade students from five high schools participated in the survey. Of the 2,013 students, 1,678 (83.4%) were included in the analyses after excluding incomplete or inappropriate responses on the scales. This survey was approved by the principal of each school, and the sample comprised students who voluntarily agreed to complete the questionnaires with informed consent. All measures, including data on sociodemographic characteristics, were self-administered. The Institutional Review Board of Chonnam National University Hospital approved the study. All participants gave written informed consent prior to participation in the study.

Measures

Sociodemographic characteristics. Gender, age, religion, and academic achievement information were obtained from the students. The students were asked about their experience using mental health services offered by a psychiatric clinic, a community center, a counseling center, and a Wee Center (the name given by the Education Office of Korea); the Wee Center offers programs and counseling to city-based students with mental health problems.

Psychotic-like experiences. The Prodromal Questionnaire-16 (PQ-16) is a brief self-report screening questionnaire that assesses the presence of positive and negative symptoms on a two-point scale (true/false) (28). The total score on the PQ-16 was calculated by adding up the agreed items. For each endorsed item, distress was rated on a four-point scale (ranging from no distress to high distress). The distress scale ranged from 0 to 96. The validity of the Korean version of the PQ-16 has been well established (29).

Depression and anxiety. Depression was measured using the Center for Epidemiological Studies Depression Scale (CES-D) (30). The CES-D contains 20 items regarding depressive symptoms experienced in the past week that are rated on a Likert-type scale ["less than 1 day" to "most or all (5–7) days"]. Possible total scores range from 0 to 60, and a higher score reflects greater depression. The reliability and validity of the Korean version of the CES-D have been well established (31). Anxiety was measured using the State-Trait Anxiety Inventory for Children (STAIC) (32). The STAIC consists of two independent domains with 20 items that measure state (STAI-S) and trait (STAI-T) anxiety levels on a three-point Likert scale. Total scores range from 20 to 60 on each domain, with higher scores indicating a higher level of anxiety. The reliability and validity of the Korean version of the STAIC have been well established (33).

Self-esteem. To measure self-esteem, we used the Rosenberg's Self-Esteem Scale (RSES), which contains 10 items on a four-point Likert scale. A higher score indicates more positive self-esteem (34).

Internet use. PIU was assessed by the short-form Korean Scale for Internet Addiction (K-scale) for adolescents, which was developed by the Korea National Information Society Agency and has been validated in a Korean population (35). The scale

consists of 15 items measuring daily life disturbances, virtual interpersonal relationships, deviant behaviors, withdrawal, and tolerance; items are rated on a four-point Likert-type scale.

Negative life events. Lifetime Incidence of Traumatic Events–Child (LITE-C) is a self-checklist that assesses loss and traumatic experiences in children and adolescents (36). The score is calculated by adding the number of "yes (presence)" responses to 16 types of trauma in the LITE-C. In addition to the LITE-C, we added some negative life events, such as cyber harassment and bullying; we included victims, witnesses, and bully–victims.

Statistical Analyses

We calculated PQ-16 numbers and percentages. The mean score differences between various categorical sociodemographic factors were analyzed using the *t*-test and analysis of variance (ANOVA). Descriptive statistics were employed to estimate the means and standard deviations of continuous variables. Pearson's correlation coefficient analysis was performed to evaluate the relationships between clinical variables and PQ-16 scores. We used hierarchical linear regression to examine the effects of clinical status, negative life events, and PIU, which were related to PQ-16 score in univariate analyses on PQ-16 score. In step 1, participants' clinical information (depression, anxiety, and self-esteem), which were significantly correlated with dependents, were entered. In step 2, negative life experiences including LITE-C, which were significantly differences in PQ-16 score tested by *t*-test or Pearson's correlation, were entered. Final step, K-scale indicating PIU that was significantly correlated with dependents, was entered. Output results including R^2, R^2-changes, F value, and standardization regression coefficient (β) were provided in the regression models. Statistical Package for the Social Sciences (SPSS) for Windows software (ver. 21.0; SPSS Inc., Chicago, IL, USA) was used to perform the statistical tests. All statistical tests were two-tailed, and *p*-values <0.05 were considered significant.

RESULTS

Of the 1,678 students, 1,078 were boys (64.2%) and 600 were girls. The mean age was 18.6 ± 0.5 years. The mean total and distress scores on the PQ-16 were 2.3 ± 2.6 and 38.0 ± 3.0, respectively. The distribution of PQ-16 total scores is shown in **Figure 1**. A total of 1,239 subjects (73.8%) scored at least 1 on the PQ-16; 11.9% scored 6 or more, indicating the clinical significance of ARMS. **Table 1** shows the mean differences in PQ-16 scores by demographic factors. We found no significant difference in PQ-16 scores by gender, religion, or academic achievement. The mean total and distress PQ-16 scores were significantly higher in students who used mental health services. The Wee Center was the most frequently visited institution ($n = 87$), followed by the community center ($n = 46$), the counseling center ($n = 34$), and the psychiatric clinic ($n = 29$). In terms of negative life events, students who experienced cybersexual harassment scored significantly higher in total and distress PQ-16 scores. Both mean scores were significantly higher for students who experienced school violence as victims, witnesses, and bully–victims.

Correlational analyses revealed that both the total and distress PG-16 scores were positively correlated with the CES-D, STAI-S, STAI-T, LITE-C, and K-scale scores and negatively with the RSES score (**Table 2**). The results of the hierarchical multiple regression analyses for PQ-16 score are shown in **Table 3**. The hierarchical multiple regression for PQ-16 total score revealed that at step 1, clinical information (depression, anxiety, and self-esteem) contributed significantly to the regression model, $F(4,15) = 147.72$, $p < 0.001$, and accounted for 28.1% of the variation in PQ-16 total score. Adding negative life events to the regression model explained an additional 8.5% of the variation in PQ-16 total score, and this change in R^2 was significant, $F(5,15) = 40.58$, $p < 0.001$. Finally, the addition of K-scale to the regression model explained an additional 1.0% of the variation in PQ-16 total score, and this change in R^2 was also significant, $F(1,15) = 25.07$, $p < 0.001$. The independent variables accounted for 37.7% of variance in PQ-16 total score. The hierarchical multiple regression for PQ-16 distress score revealed that at

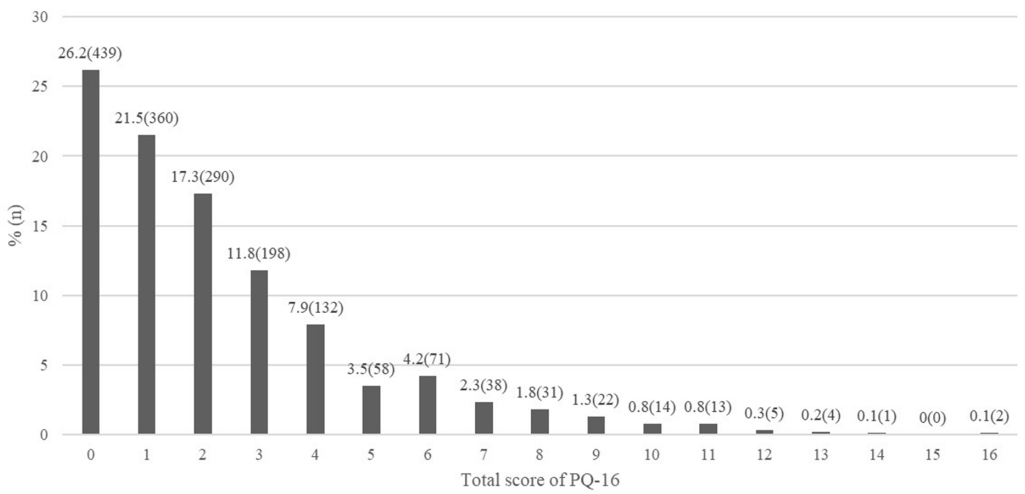

FIGURE1 | Percentage of number on the total score of PQ-16 ($n = 1,678$).

TABLE 1 | Sociodemographic factors that influence PQ-16 score.

		PQ-16 total score			PQ-16 distress score		
		Mean (SD)	Statistics	p	Mean (SD)	Statistics	p
Gender	N (%)						
Male	1,078 (64.2)	2.3 (2.5)	–0.367	0.714	3.0 (3.8)	–0.581	0.561
Female	600 (35.8)	2.4 (2.6)			3.1 (4.0)		
Religion							
Yes	655 (39.0)	2.5 (2.7)	1.640	0.101	3.2 (4.1)	1.571	0.116
No	1,023 (61.0)	2.3 (2.4)			2.9 (3.7)		
Academic achievement							
Good	590 (35.4)	2.5 (2.6)	4.518	0.104	3.2 (3.8)	5.445	0.066
Average	527 (31.4)	2.2 (2.5)			2.8 (3.8)		
Poor	550 (32.8)	2.3 (2.6)			2.9 (4.0)		
Use for mental health service							
(–)	1,523 (90.8)	2.2 (2.4)	–5.768	<0.001	2.8 (3.5)	–5.876	<0.001
(+)	155 (9.2)	3.5 (3.4)			4.7 (6.3)		
Negative life events							
Cybersexual harassment							
(–)	1,505 (89.7)	2.2 (2.4)	–7.201	<0.001	2.8 (3.7)	–6.044	<0.001
(+)	172 (10.3)	3.7 (3.0)			4.7 (4.7)		
Bullying, victims							
(–)	1,503 (89.6)	2.1 (2.3)	–10.327	<0.001	2.7 (3.4)	–11.114	<0.001
(+)	174 (10.4)	4.2 (3.4)			6.0 (5.9)		
Bullying, witness							
(–)	1,327 (79.2)	2.0 (2.2)	–12.129	<0.001	2.4 (3.1)	–12.117	<0.001
(+)	349 (20.8)	3.8 (3.1)			5.2 (5.4)		
Bullying, bully–victims							
(–)	1,577 (94.0)	2.2 (2.4)	–11.867	<0.001	2.7 (3.4)	–12.893	<0.001
(+)	101 (6.0)	5.1 (3.5)			7.6 (6.4)		

PQ-16, Prodromal Questionnaire-16.

TABLE 2 | Clinical measures and their Pearson's correlation coefficients with PQ-16 score.

Scales (mean ± SD)	PQ-16 total score	PQ-16 distress score
CES-D (12.2 ± 9.3)	0.435**	0.449**
STAI-S (39.1 ± 8.9)	0.184**	0.184**
STAI-T (31.2 ± 7.8)	0.514**	0.515**
RSES (26.9 ± 5.5)	–0.185**	–0.190**
LITE-C (2.6 ± 2.1)	0.404**	0.388**
K-scale (25.3 ± 7.1)	0.314**	0.309**

CES-D, Center for Epidemiological Studies Depression Scale; STAI, State-Trait Anxiety Inventory; RSES, Rosenberg Self-Esteem Scale; LITE-C, Lifetime Incidence of Traumatic Events-Child; K-scale, Korean Scale for Internet Addiction.
***p < 0.001.*

step 1, clinical information contributed significantly to the regression model, F (4,15) = 147.68, $p < 0.001$, and accounted for 28.0% of the variation in PQ-16 distress score. Adding negative life events to the regression model explained an additional 7.8% of the variation in PQ-16 distress score, and this change in R^2 was significant, F (5,15) = 37.10, $p < 0.001$. Finally, the addition of K-scale to the regression model explained an additional 0.9% of the variation in PQ-16 distress score, and this change in R^2 was also significant, F (1,15) = 22.68, $p < 0.001$. The independent variables accounted for 36.8% of variance in PQ-16 distress score. Ultimately, high scores on the CES-D, STAI-T, K-scale, and LITE-C scale; low scores on the RSES scale; and status as a bully–victim were strongly associated with both the total and distress PQ-16 scores. Cybersexual harassment predicted the total PQ-16 score but not the distress score.

DISCUSSION

The fact that a high percentage of participants scored at least 1 on a PQ-16 item (73.8%) is consistent with previous research in young community samples (37). Also, the percentage of students who scored at least 6 on positive PQ-16 items (indicative of clinical significance) was 11.9%, thus higher than the prevalence rate of 5–8% in the general population (38, 39). This result is in line with the prevalence of PLEs in adolescents (about 10%; thus generally higher than in adults) (40, 41).

In this study, students who used a mental health service had higher mean PQ-16 total and distress scores. It is possible that students with a variety of mental health problems, such as emotional and behavioral difficulties, use mental health services. PLEs are more frequent in help-seeking subjects (42, 43). In particular, PLE-associated distress may encourage help-seeking behavior (44). Our findings suggest that students with mental health problems and PLEs tend to have help-seeking behavior. Furthermore, individuals seeking help to deal with their PLEs could be viewed as being in the prodromal phase of various disorders. However, our results show that approximately half of students who used mental health services were referred to the Wee Center, which offers counseling services

TABLE 3 | Hierarchical linear regression analyses predicting PQ-16 score.

	PQ-16 total score			PQ-16 distress score		
	Step 1(β)	**Step 2(β)**	**Step 3(β)**	**Step 1(β)**	**Step 2(β)**	**Step 3(β)**
Independent variables						
CES-D	0.173***	0.144***	0.140***	0.189***	0.159***	0.156***
STAI-S	0.011	0.021	0.019	–0.003	0.007	0.004
STAI-T	0.425***	0.355***	0.325***	0.413***	0.346***	0.317***
RSES	0.090**	0.073*	0.073*	0.083*	0.067*	0.068*
LITE-C		0.256***	0.245***		0.237***	0.227***
Cybersexual harassment		0.057*	0.053*		0.036	0.032
Bullying, victims		–0.041	–0.045		–0.056	–0.060
Bullying, witness		0.001	–0.006		–0.004	–0.010
Bullying, bully–victims		0.083*	0.091**		0.128***	0.136***
K-scale			0.110***			0.105***
R^2	0.281	0.366	0.377	0.280	0.358	0.368
ΔR^2	0.281	0.085	0.010	0.280	0.078	0.009

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

to students. Our recent study showed that school counselors are unfamiliar with the concept of high risk for psychosis and lack of confidence in treating those who have had PLEs (45). Early detection and timely delivery of psychiatric services for those who have PLEs is important to prevent a delay in the implementation of an early intervention. In this regard, teachers and school counselors should be provided with proper education regarding students with PLEs.

The severity levels of PLEs and distress as measured by the PQ-16 were associated with psychological difficulties, such as depression, anxiety, and low self-esteem. These results are in line with those of previous studies showing that PLEs were associated with various psychopathologies (46–49). Depression increased the risk of transition to a full-blown psychotic disorder in the ARMS study (50). One previous work suggested that the association between PLEs and poor functioning might be explained by the extent of depression (42). We found that low self-esteem was significantly associated with both total and distress PQ-16 scores. One cognitive model of psychosis suggests that a low self-concept is related to the development and maintenance of PLEs (51). A recent study indicated that those experiencing more hallucinatory-like events exhibited lower levels of self-esteem (52). In our study, trait anxiety was significantly associated with PLEs according to the regression analysis. Trait anxiety serves as a proxy for proneness in those who experience maladaptive anxiety (53); those who score high in "trait anxiety" exhibit differential processing of threatening information. This tendency is termed "attentional threat bias"; one previous study reported that trait anxiety significantly influenced the relationship between cognitive bias and PLEs (54). Our results suggest that biased cognitive processes in adolescents exhibiting high levels of trait anxiety may independently affect PLEs.

Although most PLEs experienced during adolescence are transitional in nature, 20% of subjects experience persistent PLEs, and 7% develop psychotic disorders in adulthood (55). Psychopathologies, such as depression, anxiety, and poor self-esteem, should be routinely assessed and considered for treatment given that they may contribute to later psychosis.

In this study, students who had negative life events, including losses or trauma and recent stressful events, such as cybersexual harassment and school violence, exhibited higher total and distress PQ-16 scores. A strong body of literature has addressed the role of childhood trauma as one of the risk factors for developing a psychotic illness in adolescence (46, 56). Furthermore, although many researchers investigating the relationship between trauma and psychosis have focused on the role of childhood adversity, there is growing evidence for a role of recent stressful life events in the development of psychosis (10, 57). Accordingly, in our study, cybersexual harassment and bullying were significantly associated with PLEs in adolescents. Cybersexual harassment is a type of internet abuse, which can take various forms, such as unsolicited posts and comments on social media sites. There is evidence that individuals with unwanted sexual experiences are at higher risk for developing PLEs (58). Public attention has focused on adolescent internet-mediated victimization, including unwanted exposure to online pornography and sexual messaging, which increase their vulnerability to sexual victimization (59). Our research suggests that cybersexual harassment may be a negative and threatening event that is predictive of PLEs in adolescents.

In particular, the regression analysis showed that the bully–victim status after school violence was a predictor of PLEs. Our findings support previous studies indicating that the prevalence of PLEs is greater in adolescents who have been exposed to school violence, including both victims and perpetrators of bullying (46). This finding suggests that traumatic experiences related to school violence seem to have a salient impact on PLEs, particularly during adolescence when peer relationships become critical to consolidate personal identity (60, 61).

In our study, the PLE was significantly associated with PIU measured by the K-scale in the regression analysis. PIU can be recognized as a maladaptive way of coping with life's stressors (20, 21). Several studies have found that ARMS individuals tend to engage in more maladaptive coping than nonpsychiatric controls (62, 63). Furthermore, there is some evidence that individuals with schizophrenia experience a disruption in the biological system that responds to stress (64, 65). In a population of stabilized patients with schizophrenia, PIU was significantly associated with ineffective coping strategies to alleviate stress (66). Our findings suggest that

the development of PLEs is associated with maladaptive coping strategies during the process of responding to stressful events. This is the first study to determine the relationship between PLEs and PIU among adolescents. Specialized interventions, including problem solving and coping skills training, are needed to help adolescents who have more access to the internet to exploit the internet as a positive coping strategy.

Our study had several limitations. First, this study was cross-sectional; therefore, longitudinal studies are required to confirm the directionality of the relationships in the present analysis, particularly between PIU and PLEs. Additionally, as it is probable that PLEs could make adolescents more likely to be victimized, we may have underestimated the associations between PLEs and negative life events. Second, the generalizability of the results is limited given the targeting of recruited students from one community. Third, we relied on self-reported measures and did not conduct clinical interviews, limiting the clinical validity of the data.

In conclusion, PLEs among adolescents were likely to co-occur with emotional problems, particularly depression, trait anxiety, and low self-esteem. In addition, this study highlights the associations among PLEs, negative life events, and PIU in community adolescents. Our results suggest that a number of traumatic events, including cybersexual harassment and bullying, may increase the risk of PLEs among adolescents. PIU, a maladaptive strategy used to cope with negative life events, was associated with PLEs in adolescents. These have potentially important clinical implications to manage and help adolescents with traumatic events and PIU to prevent the development of more serious clinical psychosis.

ETHICS STATEMENT

This survey was approved by the principal of each school, and the sample comprised students who voluntarily agreed to complete the questionnaires with informed consent. All measures, including data on sociodemographic characteristics, were selfadministered.

The Institutional Review Board of Chonnam National University Hospital approved the study. All participants gave written informed consent prior to participation in the study.

AUTHOR CONTRIBUTIONS

SWK and JYL were involved in the conception and design of the study. DB conducted the data collection. SWK and JYL were involved in the analysis and drafted the manuscript. JMK, SYK, ILS, and JSY revised the manuscript critically for important intellectual content. All authors contributed to and have approved the final manuscript.

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City Avoidance in the Early Phase of Psychosis: A Neglected Domain of Assessment and a Potential Target for Recovery Strategies

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Background: A considerable amount of research has explored the link between living in an urban environment during childhood and the increased risk to develop psychosis. However, the urban milieu is more than a risk factor as it is also a place for socialization and enrichment. The aims of the current study were to explore, in a large sample of early psychosis (EP) patients, their pattern of use of the city, their perception when exposed to various critical stressors, and their sensitivity to diverse forms of stimuli.

Methods: We sent a questionnaire (based on previous work conducted in a group of patients, including video-recorded walk-along in the city and a literature review) to 305 EP patients and to 220 medical students.

Results: Response rate in patients was low (38%). City avoidance and negative perceptions towards the urban environment increased in patients after onset of psychosis. Patients' tendency to avoid city center correlates with both problematic social interactions and stimuli perceived as unpleasant. Patients seemed less likely to enjoy urban spaces considered as relaxing, suggesting a lower capacity to benefit from positive aspects of this environment.

Conclusions: The development of psychosis influences the way EP patients perceive the city and their capacity to feel at ease in the urban environment, leading to a high rate of city avoidance. Considering the possible influence of city avoidance on social relations and the recovery process, the development of strategies to help patients in this regard may have a significant effect on their recovery process.

Keywords: psychosis, urbanicity, city, stress, recovery, treatment

INTRODUCTION

An important body of literature suggests that growing up in an urban environment during childhood is a risk factor for the later development of psychosis (1–4). Although various authors have proposed hypotheses to explain this correlation, the mechanisms involved in this phenomenon are still unknown. This is a matter of concern, considering the very high

proportion of the world population living and growing in an urban environment, and this domain evidently deserves more research effort.

The urban environment is however more than a risk factor: it is also a place of enrichment, through interpersonal interactions, access to cultural events, and globally through socialization. Within the city and psychosis nexus, researchers in psychiatry have so far neglected to study the way patients experience the urban environment, how they use it, and to what degree they manage to gain access to it. This failure to address this aspect of the problem and the absence of studies doing so through the eyes of patients are limitations that need to be overcome. Indeed, the exploration of patients' experience of the city environment may contribute not only to generate hypotheses to explain why growing up in an environment is a risk factor for later development of psychosis; it could also increase our understanding of the phenomenon of social withdrawal often described in psychosis patients.

In recent publications (5, 6), we have reported on a study that we are currently conducting in the context of a collaboration between psychiatrists, psychologists, geographers, and linguists. Through a combination of approaches, mixing exploratory focus groups with case managers, psychiatrists, and psychologists, interviews with patients, video-recorded go-along with a sample of 10 early psychosis (EP) patients, and a semi-structured interview with 20 EP patients, we managed to proceed to a first exploration of this domain.

In a first paper (5), we studied the way EP patients experience being in the city, with the aim to identify places of stress. This "unpacking of the city" revealed three ways to relate to the city among patients. While a first group tended to avoid the city center altogether, a second group used the city exclusively at certain times of the day and a third group reported having no problem in relation to the urban environment. When exploring sources of stress, patients mentioned four elements: a) crowd density; b) excess of stimuli, mainly auditory (sensory overload); c) situations of unavoidable social interactions; and d) hindrance to mobility (either by physical obstacles or by traffic).

In a second paper (6), we identified some of the strategies EP patients adopt in order to face these stressful elements, such as establishing sensory bubbles (through headphones or being accompanied by a friend), creating niches and breaks in the city (developing trajectories including parks or churches for example), or carefully programming trajectories in the city.

Based on these elements and on data stemming from the literature, we developed a questionnaire exploring the way EP patients use the city and the nature of their experience while being in an urban milieu. The aims of the study were to explore, in a large sample of EP patients, their pattern of use of the city, their perception of the various critical stressors that we identified through the previous abovementioned studies, and their sensitivity to various forms of stimuli. In addition, we wanted to assess the impact of the emergence of psychosis on these elements and to compare patients with a control group regarding these issues.

METHODS

Patients and Control Groups

Patients included in this study stem from a clinical EP cohort receiving treatment in a specialized EP program (TIPP: Treatment and early Intervention in Psychosis Program) implemented in Lausanne, Switzerland, in 2004 (7). Based on a case management model, this program provides 3 years of treatment to patients aged 18 to 35 who have developed a psychotic disorder and have not had more than 6 months of treatment, with routine outcome assessments every 6 months. Since its implementation in our catchment area of 350,000 inhabitants, the program had provided treatment to more than 400 patients at the time of the study. Clinical case managers recruited the patients who were still involved in the program at the time of the study, and the research team contacted the rest of the cohort first by mail, followed by a phone call 2 weeks later. We recruited controls among students completing their third year of medical studies at Lausanne University, Switzerland. The local ethics committee approved the research protocol and all subjects provided informed consent to participate to the study.

Development of the Questionnaire

The development of the self-administered questionnaire followed a succession of stages. First, we conducted video-recorded go-along through the city of Lausanne, with a sample of 10 EP patients. Second, in order to explore their reactions to the immersion in the urban milieu, we visualized and analyzed the video of the go-along in their presence in a process of video elicitation during which we took note of elements of the urban milieu generating either a sense of stress or a sense of protection. After spontaneous evocation of relevant elements by the patient, we completed the exploration through a fine-grained analysis of the go-along video in their presence and through questions proposed by the researchers (at least one geographer and one psychiatrist). These video elicitation sessions were video-recorded and subsequently analyzed by the research team. Third, we constructed a list of items based on the main factors of stress or protection that stemmed from the abovementioned procedure. Fourth, we used this list to conduct semi-structured audio-recorded interviews with 20 EP patients, exploring the same issue of factors of stress and protection in the city, but without conducting walk-alongs. Fifth, the verbatim of the interviews underwent thematic analysis, and the extraction of the main themes as well as a comprehensive literature review (Abrahamyan Empson et al., in revision) guided the design of the questionnaire. Finally, we refined the content of the questionnaire in the interdisciplinary research team and benefited from critical comments from clinical case managers through the organization of focus groups.

The questionnaire (available in French upon request to the corresponding author) consists of three main parts. The first section gathers information on the sociodemographic characteristics (for example, place of birth, migrant status, residential mobility, level of education, and marital status)

that seemed relevant, based on a systematic literature review conducted in the frame of the project (Abrahamyan Empson et al., in revision). The second section evaluates the rate of city attendance (frequency and duration) and their perception of various specific places of the city (rated from very unpleasant to very pleasant). The third part explores the sensory and interactional dimensions of city living (ranging from sensitivity to sensory stimulations, to reactions towards interactions with other persons through gaze for example). All items are rated according to five-point Likert scales, where a score of 1 would mean "very pleasant" while 5 would represent "very unpleasant." The questionnaire given to patients included additional questions regarding the impact of the development of psychosis on each particular dimension, rated from "much worse" to "no change" after the onset of psychosis.

Data Analysis

Comparisons between groups were performed with independent *t* tests for continuous variables and Mann–Whitney *U* tests for ordinal or highly skewed variables. For nominal variables, analyses were performed with Pearson's chi-square tests or Fisher exact tests when appropriate. Differences between perceptions before and after illness onset were tested with a one-sample sign test using the neutral value (no change) as the null hypothesis. Predictors of city avoidance were evaluated with two linear stepwise regression models fitted separately in each group. Items related to relation with others, gaze, and unpleasant stimulus were entered as independent variables with city avoidance as the dependent variable. All statistical analyses were performed with IBM-SPSS 23. All statistical tests were two-tailed and significance was determined at the .05 level.

RESULTS

Although 400 patients were eligible at the time of the study, the questionnaire was sent to 305 of them. Ninety-five questionnaires were not sent because of the following reasons: patient moved out of Switzerland, diagnosis of organic psychosis, substance abuse as first-line diagnosis, patients whose address could not be found, and patients who had died. While 124 questionnaires were returned, 117 (38%) were usable and 7 were incomplete. Among the 220 students who attended third year of medical school at the time of the study, 205 (93%) returned their questionnaire. The characteristics of both groups are shown in **Table 1**. Comparison of both groups revealed significant differences, with patients being significantly older than controls, and more likely to be male, to be a migrant, and to live independently. In addition, patients had moved houses more frequently and were less likely to have a regular activity at the time of the study.

TABLE 1 | Patients and controls' profile.

	Patients, *N* = 117	Controls, *N* = 205	Statistic	*p* value
Age, M (SD)	29.67 (5.85)	24.51 (6.65)	$t(320) = 6.979$	<.001
Gender, % male (*n*)	69.2 (81)	59.0 (121)	$\chi^2(1) = 3.319$	.068
Migrant status, %, (*n*)	40.5 (47)	20.0 (41)	$\chi^2(1) = 15.672$	<.001
Activity, % (*n*)				<.001
Full or part time or studies	25.3 (21)	100.0 (205)	$\chi^2(2) = 195.142$	
Medical leave	31.3 (26)	0.0 (0)		
Unemployed, disability pension	43.4 (36)	0.0 (0)		
Living status, % (*n*)			f	<.001
Independent household	29.9 (35)	13.7 (28)		
In couple	11.1 (13)	7.8 (16)		
In couple with children	8.5 (10)	3.9 (8)		
With family	21.4 (25)	49.3 (101)		
Shared flat	6.8 (8)	22.4 (46)		
Pension/care home	12.8 (15)	0.0 (0)		
Unsettled	1.7 (2)	0.5 (1)		
Other	7.7 (9)	2.4 (5)		
Number of moves, M (SD)	3.54 (2.22)	2.36 (2.20)	$t(315) = 4.544$	<.001
Time spent out of home, % (*n*)				
Almost never	7.9 (9)	1.0 (2)	$U = 5534.0$	<.001
Less than 1 h	20.2 (23)	2.0 (4)		
Between 1 and 4 h	31.6 (36)	4.9 (10)		
More than 4 h	40.4 (46)	92.1 (187)		
Diagnostic, % (*n*)		–	–	–
Schizophrenia	66.3 (55)			
Schizophreniform/brief	10.8 (9)			
Schizo-affective	8.4 (7)			
Major depression[a]	3.6 (3)			
Bipolar disorder	2.4 (2)			
Other	8.4 (7)			

f, Fisher exact test.
[a]*with psychotic features.*

City Attendance and Perception of the Urban Milieu

Patients go significantly less to the city center than controls (U = 8702.500, p < .001) and report a significant decrease in their city attendance since the occurrence of the first psychotic episode (Z = −5.715, p < .001). In addition, patients perceive city center as significantly more unpleasant than controls (U = 9219.000, p < .001). Here, again, their perception of the city became significantly less favorable since illness onset (Z = −6.013, p < .001).

Sensory and Interactional Dimensions of City Attendance

Perception of the crowd is negative for the majority of patients, but this rate of negative perception does not differ from the perception by controls (U = 11,149.000, p = .320). Perception of the crowd is reported as worse in patients after illness onset than before (Z = −4.596, p < .001).

A smaller proportion of patients feel indifferent to (meaning undisturbed by) others than controls [$\chi^2(1) = 5.179$, p = .023] and a higher proportion of patients feel ill at ease with eye contact in the city than controls [$\chi^2(1) = 20.128$, p < .001] (see **Table 2**). In addition, openness to contact decreases significantly in patients after illness onset (Z = −3.283, p < .001).

Perception of various urban spaces: Patients dislike crowded places to a similar extent as controls, but enjoy relaxing places with less intensity than controls (cf. **Table 3**).

Sensitivity to external stimulations in the urban space: 26.8% of patients reported feeling "flooded" by stimuli (sensory overload) compared to only 10.2% for the controls [$\chi^2(1) = 14.681$, p < .001]. This phenomenon worsened significantly in patients after illness onset (Z = −4.571, p < .001).

Patients were more likely than controls to consider visual elements (their complexity and the excess of visual stimulation) as unpleasant [$\chi^2(1) = 9.549$, p = .002]. However, controls were more likely than patients to consider noise [$\chi^2(1) = 4.303$, p = .038] and smell [$\chi^2(1) = 40.697$, p < .001] as unpleasant. There was no difference in the perception of physical contact with others between patients and controls [$\chi^2(1) = 1.036$, p = .309].

Correlates of City Avoidance

The perception of certain distinct stimuli as unpleasant was significantly more likely to occur in patients who avoided specific places in the city. Sensitivity to physical contact was more likely to occur in patients who avoid going to the city center and to go in metro stations. Sensitivity to noise was more likely to occur in patients who avoid metro stations, downtown center, malls, and the old part of the city. In contrast, patients who do not report any stimuli as unpleasant are more likely to enjoy the city (see **Table 4**).

A higher degree of city avoidance was found in patients with absence of openness to contact (U = 1047.0, p = .002), who felt disturbance by proximity with others (U = 762.5, p = .025), and who reported uneasiness with eye contact (U = 825.0, p = .001).

Taken together, city avoidance within patients was predicted by uneasiness with physical contact (β = .255, p = .005) and absence of openness to contact (β = .217, p = .017). Overall, this model was able to explain 13.4% of the variance of city avoidance. Within controls, city avoidance was only predicted by uneasiness with physical contact (β = .158, p = .025), which explained only 2.5% of the variance.

TABLE 2 | Perception of the gaze of others.

	Patients, *N* = 117	Controls, *N* = 205	Statistic	*p* value
Eye contact is stressful, % (*n*)	17.1 (20)	3.4 (7)	$\chi^2(1) = 18.017$	<.001
The gaze of others is bothering, % (*n*)	18.8 (22)	11.3 (23)	$\chi^2(1) = 3.497$	.061
I feel judged by others, % (*n*)	21.4 (25)	11.3 (23)	$\chi^2(1) = 5.956$	.015
I feel observed by others, % (*n*)	17.1 (20)	12.7 (26)	$\chi^2(1) = 1.145$	.284
I feel that the others analyze me, % (*n*)	18.8 (22)	9.8 (20)	$\chi^2(1) = 5.295$	.021
I feel threatened, % (*n*)	6.0 (7)	0.5 (1)	$\chi^2(1) = 9.231$	.002
I feel inferior, % (*n*)	14.5 (17)	2.0 (4)	$\chi^2(1) = 19.213$	<.001
I feel vulnerable, % (*n*)	14.5 (17)	4.4 (9)	$\chi^2(1) = 10.227$	.001
I am indifferent to the gaze of others, % (*n*)	28.2 (33)	36.8 (75)	$\chi^2(1) = 2.440$	.118

TABLE 3 | Negative perception of various urban spaces.

	Patients, *N* = 117	Controls, *N* = 205	Statistic	*p* value
Downtown center, Mdn (IQR)	3.0 (1.0)	2.0 (1)	U = 10608.0	.156
Mall, Mdn (IQR)	3.0 (2.0)	3.0 (1.0)	U = 10903.5	.368
Metro station, Mdn (IQR)	3.0 (1.0)	3.0 (1.0)	U = 10761.5	.238
Ouchy (lake shore), Mdn (IQR)	2.0 (2.0)	1.0 (1.0)	U = 7278.5	<.001
Parks, Mdn (IQR)	2.0 (2.0)	1.0 (1.0)	U = 7429.0	<.001
Old city, Mdn (IQR)	2.0 (1.0)	2.0 (1.0)	U = 7513.5	<.001[a]

[a]*Patients > Controls.*

TABLE 4 | Correlation between stimuli perceived as unpleasant and likelihood to avoid certain urban places.

	Stimuli perceived as unpleasant (*p* value of difference <.05)				
	Noise	**Contact**	**Smell**	**Visual**	**No stimuli perceived as unpleasant**
Avoid city center		.001			
Enjoy city center					.009
Avoid metro	.007	.020		<.001	
Avoid downtown center	.030				
Avoid old town	.032				
Avoid mall	.046				
Avoid lake			.033		
Enjoy all places					.001

DISCUSSION

There are three main findings in our study. First, the development of psychosis seems to influence city perception and the rate of avoidance of the city among patients. Second, patients' tendency to avoid city center correlates with both problematic social interactions and stimuli perceived as unpleasant. Third, comparison between patients and controls reveals similarities regarding the type of urban space characterized as unpleasant, but patients seemed less likely to enjoy urban spaces considered as relaxing, suggesting a lower capacity to benefit from positive aspects of this environment.

Patients globally report that the onset of the illness induces an increase in city avoidance, a greater feeling of uneasiness with the crowd and towards eye contact, as well as a global higher sensitivity to stimuli. In addition, onset of psychosis correlates with a marked decrease in time spent outside of home and regarding openness to others. The fact that patients report a similar degree of negative perception of the crowd to controls as well as the feeling that this perception has become much worse since illness onset suggests that they may overestimate their status before the first episode. Nevertheless, our data strongly suggest that living in a city has become much more difficult for patients after psychosis onset. This globally suggests that emergence of psychosis restricts capacities to use urban space and to access the options it offers, due to various changes in the perception of the urban milieu. In turn, this may partly explain the withdrawal observed in patients, and it could therefore be useful to focus on this aspect through specific interventions, considering the potential self-perpetuating nature of city avoidance.

City avoidance is associated with two domains of difficulties. First, it is apparently linked to problematic social interactions, such as a decrease in openness to contact with others occurring after illness onset, and uneasiness with eye contact and proximity. Globally, these elements are probably linked to a mechanism of self-stigma, which may also constitute a target for psychological treatments through psychoeducation and work on self-esteem. Second, city avoidance is also linked to stimuli perceived as unpleasant, principally noise and physical contact. This may be explained by the phenomenon of aberrant salience (8), where all stimuli gain similar importance and contribute to the feeling of flooding, which is reported by a third of patients. There, again, some strategies might be developed to help patients cope with stimuli in order to regain some freedom.

Finally, we were not astonished that the comparison between patients and controls revealed that the former are more avoidant of the city and more disturbed by eye contact than the latter. It was more revealing to observe that while patients and controls are similar in their dislike of crowded places, patients were less likely to enjoy relaxing places such as the lakeshore or parks. This suggests that patients strongly experience the negative aspects of the city, but that they fail to benefit from the positive aspects of relaxing environment, a phenomenon that may stem from anhedonia and/or self-stigmatization. It is important to explore this issue in more depth, considering that recent studies have shown that exposure to natural features within the built environment may have a positive impact on mental well-being in a normal population (9). Conducting similar smartphone-based studies in patient samples would clarify if such a beneficial effect is also present after illness onset. In addition, while controls were more likely to report some aspects of the city as unpleasant (for example, they were more likely to perceive noise and smell as unpleasant), city avoidance was much less prevalent among them than among patients, which illustrates their greater capacity to cope with these perceptions and to access the city.

There are obvious limitations to this paper. First, it stems from a relatively small sample of patients and a low percentage of responses. Indeed, only 38% of patients responded to the questionnaire, which induces an important risk of non-response bias. Although this response rate is in keeping with surveys in metal health research (10), our results need replication in larger groups of patients with a similar profile. Second, the assessment of the impact of illness onset on city perception and city avoidance in patients is retrospective, and as mentioned above, this could bias the results through an overestimation of the way they felt before illness onset. A prospective study conducted among At Risk Mental State (ARMS) (11) subjects may overcome this issue, although we know that ARMS subjects can already display important functional impairment (12). Third, the control group is composed of medical students exclusively, a group that may not be representative of the general population. However, although medical students may, at first sight, look like a "super-healthy group," various studies and review papers have recently shown that the prevalence of mental health issues among them is high and may even exceed

the rate of the general population (13, 14), therefore limiting the impact of this potential bias. Fourth, while some patients who filled in the questionnaire were still in treatment and therefore would have been accessible for clinical assessment, a large number of subjects were not available for symptoms evaluation. Considering the potential impact of depressive, anxiety, as well as positive or negative symptoms on city avoidance, the absence of such assessment is a limitation of the study. However, in this paper, we explore city avoidance per se in a descriptive manner and the reasons subjects put forth to explain it but do not attempt to identify which illness dimensions may explain it, which may be the focus of later studies.

Despite these limitations, our study suggests that the development of psychosis has a great influence on the way EP patients perceive the city and on their capacity to feel at ease in the urban environment, leading to a high rate of city avoidance and decreased opportunity to interact with others. This aspect of the impact of the illness has not received the attention it deserves, although city avoidance can have a major influence on social relations and the recovery process. The development of strategies to help patients in this regard may have a significant effect on their recovery and therefore should be explored in more depth.

ETHICS STATEMENT

The local ethics committee (Commission cantonale (VD) d'éthique de la recherche sur l'être humain) approved the research protocol and all subjects provided informed consent to participate to the study.

AUTHOR CONTRIBUTIONS

PC, LA, ZC, PB, OS, DS, and PG have contributed to the design of the study, the grant application, the realization of the various stages of the research project, and the design of the questionnaire used in this part of the study. LA, ZC, and PB conducted the invoice of the questionnaire and the gathering of data. PG conducted the data analysis. PC and LA drafted the first version of the paper and all other co-authors contributed to the finalization of the paper.

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Relationship Between Polyunsaturated Fatty Acids and Psychopathology in the NEURAPRO Clinical Trial

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Background: Deficiencies in membrane polyunsaturated fatty acids (PUFA) such as omega-3 (n-3) fatty acids are thought to contribute to the pathophysiological processes underlying psychotic disorders. Emerging evidence suggests that the levels of PUFA are related to clinical symptoms but significant heterogeneity exists between studies. Here, we investigated associations of membrane PUFA with clinical symptoms and functioning in a large sample of individuals at ultra-high risk (UHR) for psychosis.

Methods: A total of 285 participants of the NEURAPRO clinical trial were investigated for erythrocyte PUFA levels, including the n-3 index, n-6/n-3 PUFA ratio, docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA). Severity of general psychopathology [Brief Psychiatric Rating Scale (BPRS)], psychotic symptoms (BPRS psychosis subscale), negative symptoms [Scale for the Assessment of Negative Symptoms (SANS)], manic symptoms [Young Mania Rating Scale (YMRS)], depressive symptoms [Montgomery Asberg Depression Rating Scale (MADRS)], and functioning [Social and Occupational Functioning Scale (SOFAS), Global Functioning Social (GF-S) and Role (GF-R) scales] were assessed concurrently. Partial correlation taking into account the effects of gender, age, and smoking was used to examine the relationship between PUFAs and symptoms severity.

Results: The n-3 index negatively correlated with the severity of general psychopathology, psychotic symptoms, depressive symptoms, and manic symptoms. The n-6/n-3 PUFA ratio positively correlated with severity of psychotic and depressive symptoms. The n-3

PUFA DHA negatively correlated with the severity of general psychopathology, positive, manic, and depressive symptoms. EPA negatively correlated with manic symptoms. Nervonic acid, an n-9 monounsaturated fatty acid, positively correlated with general psychopathology, positive and negative symptoms, depressive symptoms, and manic symptoms. The long-chain saturated fatty acid tetracosanoic acid positively correlated with general psychopathology, positive, manic, and depressive symptoms.

Conclusions: Partially consistent with a previous study, psychotic symptoms, depressive symptoms, and symptoms of mania were associated with several classes of FAs in the present study. These findings support the relevance of membrane fatty acids for the onset of psychotic symptoms and indicate that FAs should be further evaluated as biomarkers in the UHR for psychosis group.

Clinical Trial Registration: ANZCTR, identifier: 12608000475347

Keywords: ultra-high risk, omega-3 fatty acids, psychosis, psychopathology, outcomes

INTRODUCTION

Young people at ultra-high risk (UHR) for psychosis have an elevated risk of developing psychosis of about 20% within 2 years and a significant risk for non-psychotic disorders (1, 2). The biological correlates underlying this risk state remain poorly understood but emerging evidence suggests the involvement of brain structural and functional alterations as well as peripheral pathology including immune activation, oxidative stress, endocrine abnormalities and deregulation of membrane lipid metabolism (3, 4). Given that it is currently unclear how to determine the biological risk for psychosis transition and other clinically relevant outcomes and how to develop treatments that target specific pathophysiological processes, it is important to elucidate the biological processes accompanying the UHR state. Moreover, declining transition rates in individuals who are clinically identified as being at UHR for psychosis (5) as well as uncertainty about the efficacy of specific interventions (6, 7) further add to the need to refine and improve risk prediction and consequently the identification of predictive biomarkers.

Deficits in long-chain omega-3 (n-3) polyunsaturated fatty acids (PUFAs) are one mechanism thought to contribute to psychosis risk (8, 9). In fact, n-3 PUFAs are integral components of the lipid bilayer forming the cell membrane and are found in high abundance in the human brain (10). There, they modulate the rigid formation of tightly packed saturated fatty acids through their structural characteristics, thereby also contributing to the biophysical properties of the neuronal membrane (11, 12). These in turn affect the function of ion channels and neurotransmitter receptors. Importantly, n-3 PUFA are essential fatty acids, meaning that their abundance in cell membranes is determined by intake from food and metabolic conversion. The lipid derivates of n-3 PUFA include anti-inflammatory eicosanoids such as resins and resolvins, which mediate the effects of n-3 PUFA on immune function (13, 14). Molecules derived from n-6 PUFA in contrast are known to have pro-inflammatory properties. First postulated by Horrobin et al. (15), the phospholipid structure of the cell membrane may be altered in schizophrenia and such alterations may contribute to various aspects of the pathophysiology observed in psychotic disorders, including neurotransmission, immune activation, and antioxidative defense. This is supported by studies showing n-3 PUFA deficiency in patients with schizophrenia compared to controls (16). Much less is known about the UHR for psychosis state, but evidence suggests lower levels of several n-3 and n-6 PUFA (17). Additionally, the balance between n-3 and n-6 PUFA, which is often seen as an indicator of immune activation, seems to be associated with depression in young people at UHR for psychosis (18).

More recently, clinical trials have tested the efficacy of n-3 PUFA for the prevention of psychosis transition in UHR individuals (19–21). While the first single-center trial showed significant benefits of n-3 PUFA over placebo in terms of the transition to psychosis risk (19), a multicenter replication study failed to show significant effects of n-3 PUFA supplementation on the transition rate (21). Possible reasons for the failure to replicate a reduction of transitions include true inefficacy of n-3 PUFA in this particular outcome measure, the background intervention of high-quality psychosocial care in both groups that may have created a ceiling effect, the use of antidepressants, or the high rate of non-adherence (57%) (22). Importantly, investigating the relationship between pre-treatment PUFA levels and symptom measures can provide further insight into potential mechanisms underlying lipid biology in regard to psychosis risk. A secondary analysis of the original single-center trial revealed associations of several classes of fatty acids with clinical symptoms and psychosocial functioning (23). In light of these observations, it seems important to replicate the findings of the original trial in the larger sample of the NEURAPRO clinical trial.

The aim of the present analysis was to examine associations of the cell membrane levels of fatty acids with clinical symptoms and functioning at baseline (i.e., prior to the intervention) in the NEURAPRO RCT. Specifically, we hypothesized that the n-3 index would be associated with less severe symptoms and better functioning. Given the limited evidence for fatty acid variations in the UHR stage, we did not formulate specific hypotheses for other fatty acid classes.

METHODS

Participants

The study cohort consisted of 285 of 304 (94%) participants in the NEURAPRO study who provided consent for additional biomarker analysis. NEURAPRO was a double-blind placebo-controlled randomized clinical trial of fish oil (1.4 g fish oil/day) in people at UHR for psychosis (21) (ANZCTR identifier: 12608000475347) with 10 study sites (Amsterdam, Basel, Copenhagen, Jena, Hong Kong, Melbourne, Singapore, Sydney, Vienna, and Zurich). The intervention was administered in addition to cognitive behavioral case management (CBCM) for 6 months followed by a 6-month follow-up period. Help-seeking individuals attending UHR services in the trial centers were eligible if they were aged 13–40 years and met UHR criteria (24, 25). Exclusion criteria were a previous psychotic episode, acute intoxication, organic brain disease, serious developmental disorder, abnormal coagulation profile or thyroid function, physical illness with a psychotropic effect, current treatment with mood stabilizers, past neuroleptic exposure to a total lifetime haloperidol equivalent dose of more than 50 mg, IQ of less than 70, dangerous behavior, aggression or suicidality, pregnancy, or current supplementation with n-3 PUFA (25). All participants provided written informed consent (parent/guardian consent for participants aged <17 years). The NEURAPRO study was approved by the local human research ethics committees of the study centers.

Data Collection

Psychiatric symptoms at baseline were assessed with the Brief Psychiatric Rating Scale (BPRS), the Scale for the Assessment of Negative Symptoms (SANS), the Montgomery Asberg Depression Rating Scale (MADRS) for depressive symptoms, the Young Mania Rating Scale (YMRS) for manic symptoms, the Social and Occupational Functioning Scale (SOFAS), and the Global Functioning Social (GF-S) and Role (GF-R) scales.

Fatty Acid Analysis

Total fatty acid levels were quantified from erythrocyte samples collected at baseline. Erythrocytes were separated from plasma and extracted using an automated extraction method described previously by (26). Fatty acid levels were measured using mass spectrometry utilizing a hybrid triple quadrupole linear ion trap mass spectrometer (QTRAP 5500 AB Sciex, MA, USA) with an automated chip-based nanoelectrospray source (Triversa NanoMate, Advion Biosciences, New York, USA). Ionized lipids identified with a minimum signal-to-noise ratio of 10 were included in the analysis. Identification and quantification was accomplished using LipidView (v1.2, Sciex, MA, USA). Quantification was performed using LipidView software by comparing the spectral peak area of individual lipids to their class specific internal standards following isotope correction. Mass spectrometry is unable to identify fatty acid double bond isomers which limited our ability to distinguish between 18:1n-7/9, 20:3n-3/6/9 and 22:5n-3/6, respectively.

Statistical Analysis

The n-3 index was calculated as the proportion of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) expressed as percent of total fatty acids. The n-6/n-3 PUFA ratio was calculated as arachidonic acid (AA) divided by the sum of EPA and DHA. To examine the relationship between PUFA and psychopathology, partial correlation coefficients (adj. R) were calculated adjusting for age, gender, and smoking, as these covariates have been found to influence both fatty acid levels and psychopathology. Given the explorative nature of the study and the fact that variations in PUFA concentrations in the UHR stage is still in a hypothesis-generating phase, we did not to correct for multiple testing. The significance for all tests was set at $\alpha < 0.05$. Stata 13.1 (StataCorp, College Station, TX, USA) for Mac OS was used for all analyses.

RESULTS

Relevant demographic and psychological variables are presented **Table 1**. The sample comprised 285 participants (mean age 19.0 years ± 4.5; 45.26% male).

Partial correlations between fatty acids and related indices and psychological variables, adjusted for age, gender and smoking, are reported in **Table 2**. BPRS scores were positively correlated with 24:0 ($p < 0.001$), 24:1n-9 ($p < 0.001$) and the n-6/3 PUFA ratio ($p=0.01$), and negatively correlated with the n-3 index ($p=0.003$), **20:3** ($p=0.010$), 22:6n-3 ($p < 0.001$), 20:4n-6 ($p=0.037$) and 18:2n-6 ($p < 0.001$). The BPRS psychotic symptoms sub-scale was positively correlated with 24:1n-9 ($p=0.009$) and with the n-6/3 PUFA ratio ($p=0.01$), and negatively correlated with 18:2n-6 ($p=0.04$) and the n-3 index ($p=0.008$). Negative symptoms (SANS) were positively correlated with 24:0 ($p < 0.001$) and 24:1n-9 ($p < 0.001$) and negatively correlated with 16:0 ($p < 0.001$), 20:3 ($p < 0.001$), 18:2n-6 ($p < 0.001$) and 18:1 ($p=0.004$).

YMRS scores were positively correlated with 24:0 ($p < 0.0001$) and 24:1n-9 ($p < 0.0001$) and negatively correlated with 20:3 ($p=0.002$),20:5n-3 ($p=0.03$), 22:6n-3 ($p < 0.0001$), 18:2n-6 ($p < 0.0011$), 20:4n-6 ($p < 0.0001$) and the n-3-index ($p < 0.0001$). MADRS scores were positively correlated with 24:0 ($p < 0.0001$),

TABLE 1 | Demographic and clinical characteristics and inflammatory markers of 285 NEURAPRO study participants.

Age, mean (SD)	18.97 (4.49)
Sex	
Female, n (%)	156 (54.74)
Male, n (%)	129 (45.26)
Smoking, n (%)	110 (38.6)
BPRS, mean (SD)	41.02 (9.72)
SANS, mean (SD)	17.79 (12.81)
MADRS, mean (SD)	19.27 (8.97)
SOFAS, mean (SD)	53.30 (12.44)
GF-S, mean (SD)	6.51 (1.22)
GF-R, mean (SD)	5.95 (1.54)

BPRS, Brief Psychiatric Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; SANS, Scale for the Assessment of Negative Symptoms; SOFAS, Social and Occupational Functioning Scale.

TABLE 2 | Partial correlations of fatty acids with symptom and functioning scores in 285 participants of the Neurapro-E study.

	BPRS		BPRS psy		SANS		MADRS		YMRS		SOFAS		GF-S		GF-R	
	adj. R	*p*-value	adj. R	*p*-value	adj. R	*p*-value	adj. R	*p*-value	adj. R	*p*-value	adj. R	*p*-value	adj. R	*p*-value	adj. R	*p*-value
16:0	−0.111	0.06	−0.011	0.86	**−0.210**	**<0.001**	−0.082	0.16	0.009	0.86	0.104	0.08	0.105	0.08	0.072	0.23
17:0	−0.015	0.79	0.029	0.63	−0.084	0.16	−0.011	0.85	−0.006	0.91	0.034	0.57	0.085	0.16	**0.136**	**0.02**
18:0	−0.029	0.62	−0.019	0.76	0.053	0.37	0.039	0.50	−0.055	0.35	**−0.129**	**0.03**	−0.113	0.06	−0.112	0.06
18:1*	**−0.119**	**0.04**	−0.008	0.90	**−0.191**	**0.001**	**−0.123**	**0.03**	**−0.140**	**0.02**	0.109	0.06	0.065	0.28	**0.121**	**0.04**
18:2n-6	**−0.344**	**<0.0001**	**−0.119**	**0.04**	**−0.328**	**<0.0001**	**−0.264**	**<0.0001**	**−0.324**	**<0.0001**	0.033	0.57	**0.146**	**0.01**	0.047	0.44
20:3#	**−0.175**	**0.003**	−0.105	0.08	**−0.202**	**<0.001**	**−0.192**	**0.001**	**−0.184**	**0.002**	0.102	0.08	**0.153**	**0.01**	**0.150**	**0.01**
20:4n-6	**−0.162**	**0.006**	−0.075	0.21	0.016	0.78	**−0.122**	**0.03**	**−0.280**	**<0.0001**	−0.016	0.78	0.016	0.79	−0.044	0.47
20:5n-3	0.005	0.92	−0.069	0.25	0.099	0.09	−0.039	0.50	**−0.128**	0.03	0.048	0.42	0.027	0.65	0.022	0.72
22:4n-6	−0.017	0.77	−0.065	0.28	0.109	0.07	−0.053	0.36	−0.080	0.18	−0.047	0.43	−0.071	0.24	**−0.129**	**0.03**
22:5^	0.015	0.80	0.040	0.50	0.113	0.06	0.082	0.16	**0.144**	**0.02**	−0.002	0.97	−0.067	0.27	−0.116	0.05
22:6n-3	**−0.198**	**<0.001**	**−0.166**	**0.006**	−0.081	0.17	**−0.191**	**0.001**	**−0.234**	**<0.0001**	0.026	0.65	−0.007	0.90	−0.053	0.38
24:0	**0.389**	**<0.001**	0.099	0.09	**0.289**	**<0.0001**	**0.307**	**<0.0001**	**0.375**	**<0.0001**	−0.074	0.21	−0.098	0.10	−0.005	0.93
24:1n-9	**0.365**	**<0.001**	**0.157**	**0.009**	**0.293**	**<0.0001**	**0.307**	**<0.0001**	**0.377**	**<0.0001**	−0.074	0.21	−0.115	0.05	−0.047	0.44
n-3 index†	**−0.176**	**0.003**	**−0.160**	**0.008**	−0.057	0.34	**−0.177**	**0.002**	**−0.230**	**<0.0001**	0.031	0.59	−0.002	0.97	−0.044	0.47
n-6/3 ratio§	**0.153**	**0.01**	**0.147**	**0.01**	0.093	0.12	**0.169**	**0.005**	0.118	0.05	−0.083	0.16	−0.021	0.73	0.035	0.56

** 18:1 could be 18:1n-7 or 18:1n-9, or a combination of both.*

 # 20:3 could be 20:3n-3, 20:3n-6 or 20:3n-9, or a combination of all 3 isomers.

^ 22:5 could be 22:5n-3 or 22:5n-6, or a combination of both.

†The n-3 index is calculated as the amount of EPA and DHA expressed as the percent of total fatty acids.

§The n-6/3 ratio is calculated as AA/(EPA + DHA).

Bold numbers indicate statistical significance.

24:1n-9 ($p < 0.0001$) and the n-6/3 PUFA ratio (p=0.005), and negatively correlated with the n-3-index (p=0.002), 20:3 (p=0.001), 22:6n-3 (p=0.001), 18:2n-6 ($p < 0.0001$), 20:4n-6 (p=0.03) and 18:1 (p=0.03). SOFAS scores were negatively correlated with 18:0 (p=0.031). GF-S scores were positively correlated with 18:2n-6 (p 0.01) and 20:3 (p=0.01). Finally, GF-R scores were positively correlated with 17:0 (p=0.02), 18:1 (p=0.04), 22:4n-6 (p=0.03) and 20:3 (p=0.01).

DISCUSSION

The aim of this study was to investigate associations of cell membrane fatty acids with clinical characteristics in a large multi-centre RCT of fish oil supplementation in individuals at UHR for psychosis. After taking into account the effects of age, gender and smoking, we found several PUFAs related to psychopathology, including general psychopathology (BPRS), psychotic symptoms (BPRS), negative symptoms (SANS), manic symptoms (YMRS) and depressive symptoms (MADRS). The n-3 index, DHA, AA, 20:3, and 18:2n6 were negatively correlated with BPRS, MADRS and YMRS scores, while the n-6/3 PUFA ratio was positively correlated with general psychopathology (BPRS), psychotic symptoms (BPRS) and depressive symptoms (MADRS). 24:0 and 24:1n-9 in turn were significantly positively correlated with BPRS, SANS, MADRS and YMRS scores. Collectively, these findings support the notion that several classes of fatty acids are associated with symptom severity in this group.

Our analysis contributes important insights into the relationship between PUFA and psychopathology by replicating findings of our previous smaller study in UHR (23) in a large (n=285) and well-characterised sample. Overall, our results confirm that higher levels of n-3 PUFA (n-3 index) correspond to fewer symptoms in this population. The n-3 index, calculated as the sum of EPA and DHA as percent of total fatty acids, was significantly associated with lower general psychopathology (BPRS) scores, which is broadly consistent with a previous study (27), as well as with lower manic (YMRS) and depressive (MADRS) symptoms. The n-6/n-3 PUFA ratio, reflective of the balance between n-3 and n-6 PUFA, was positively correlated with psychotic symptoms (BPRS) and MADRS scores, suggesting that a higher relative proportion of n-6 PUFA compared to n-3 PUFA correlates with more severe symptoms. Consistent with the present findings, Kim et al. (23) found that the n-6/n-3 PUFA ratio was associated with psychotic symptoms, and the sum of n-3 PUFA negatively with negative symptoms. This suggests that the n-3 index is relevant to a range of symptoms in the UHR state. Consistent with this, DHA was also associated with lower BPRS scores in our study. DHA is the most abundant n-3 PUFA in the human brain and integral to the neuronal membrane. Importantly, erythrocyte DHA correlates with grey matter DHA (28) and may be particularly relevant during adolescence, where increases in the level of DHA may be critical for the development of the prefrontal cortex and cortical maturation more generally (29–31). Given that the UHR state and the onset of psychotic disorders fall within this developmental period in many cases,

n-3 PUFA including DHA may play a particularly important role in this phase.

Our results also support an association of the n-3 index and the n-6/n-3 PUFA ratio with depressive symptoms in this UHR cohort. Considering that young people at UHR for psychosis have a high risk for depression of up to 42% (1), these findings are highly relevant to the UHR group. There is ample evidence to support n-3 PUFA deficiency in patients with major depressive disorders (32) and for the efficacy of n-3 PUFA as a potential treatment of depressive symptoms [see meta-analyses in Refs. (33–35)]. Moreover, we recently reported that in individuals at UHR for psychosis, a high n-6/n-3 PUFA ratio is predictive of depression within a 7-year follow-up (18). Our present findings support an association of the n-3 index as well as of DHA levels with depressive symptoms, thereby confirming previous results. However, EPA, the n-3 PUFA found to be most effective for the treatment of depression (34), was not related to depressive symptoms in this study.

In addition to n-3 PUFA, linoleic acid (18:2), an n-6 PUFA and precursor to arachidonic acid, EPA and DHA, was inversely associated with symptoms severity and positively associated with functioning. Previous studies examining the relationship between linoleic acid and psychopathology have yielded mixed results. For example, in a recent study of 154 patients with major depressive disorder, linoleic acid was found to be reduced compared to controls and inversely correlated with depressive symptoms severity (36). Similarly, in a population-based study of otherwise healthy adults, low levels of linoleic acid were associated with depressive symptoms (37). However, other studies found no association of linoleic acid with depression (38, 39). While our results suggest that linoleic acid is associated with fewer symptoms and better functioning, these observations warrant further confirmation.

An interesting observation in our study was that tetracosanoic acid (lignoceric acid; 24:0), a very long chain saturated fatty acid mainly found in peanut and canola oil (40), was strongly positively correlated with all symptom scores. Few studies to date have investigated saturated fatty acids in the UHR group. Of note, Hamazaki et al. (41) found elevated levels of these fatty acids in post-mortem brain tissue of patients with schizophrenia compared to controls.

The mechanisms linking deficits in n-3 PUFA with psychopathology in the UHR group are only partially understood but likely include effects on serotonergic and dopaminergic neurotransmission through the modulation of membrane fluidity and ion channel function (42), PUFA effects on HPA axis regulation and the regulation of antioxidative defense (43), as well as the production of pro- and anti-inflammatory derivatives of PUFA (14, 44, 45). EPA rapidly beta-oxidized once in the brain (46, 47), and oxidation products are not specific for EPA. Therefore, EPA effects in depression cannot be explained by effects in the brain; rather, peripheral anti-inflammatory effects may be relevant. EPA's oxidation products are anti-inflammatory eicosanoids, and oxidative stress as seen in psychiatric disorders would only increase these. This is supported by Rapaport et al. (48), who showed that high inflammation is a predictor of response to n-3 PUFA supplementation.

Other fatty acids related to psychopathology in our study include NA. NA, an n-9 monounsaturated fatty acid, is abundant in the white matter of the central nervous system and important for the biosynthesis and maintenance of the myelin sheath. For example, the levels of NA (but also AA and DHA) were found to be related to decreased white matter integrity in the corpus callosum, parietal, occipital, temporal, and frontal lobes (49). Impaired myelin pathways and impairments in white matter integrity in the medial frontal lobe and other brain areas relevant to psychosis have been observed in individuals who later transitioned to psychosis (50). Decreased levels of NA have previously been observed in association with more severe psychotic symptoms and with higher transition risk (23, 51). The present findings seem difficult to reconcile as they suggest the opposite relationship. However, differences in the methodology between the present study and previous studies may explain these discrepancies (52). While Amminger et al. (51) measured NA from the phosphatidylethanolamine fraction of erythrocytes using gas chromatographic analysis, NA was quantified in this study from whole erythrocyte membranes using mass spectrometry. In patients with major depressive disorder, where white matter dysfunction is similarly hypothesized, both increases and decreases in NA have been observed (52, 53).

An important question not answered by our study is whether young individuals at UHR for psychosis show deficits in those n-3 PUFAs associated with more severe symptoms compared to healthy (non-UHR) individuals. To date, only one study of our group addressed this question and reported deficits in two n-3 PUFAs and several n-6 PUFAs (17). We are currently investigating this question in the NEURAPRO trial and a matched control group. Studies in patients with chronic schizophrenia provided heterogeneous findings and showed decreases in AA, DPA, and DHA (54). However, several studies in schizophrenia patients including a more recent study showed increases in these fatty acids in patients compared to controls as well as in unaffected siblings compared to controls (55–57). Findings in youth at UHR for bipolar disorder showed deficits in the n-3-index compared to healthy controls (58, 59). It therefore seems important to clarify if low n-3 PUFA levels precede the onset of psychosis.

A strength of our study is the sample size, making this the largest examination of membrane PUFA in UHR to date. A second strength is the well-characterized sample and the availability of a variety of clinical measures. Limitations include the cross-sectional nature of this analysis, which precludes causal inferences. The effects sizes of several correlations reported here—while statistically significant—are small (adj. $R < 0.2$). Also, the selection of fatty acids measured is not fully consistent with a previous study (23) due to the choice of methods used for the analysis. The present study used mass spectrometry, a novel method recently published (26), while previous studies used mostly gas chromatography. While dietary habits were not considered here, we argue that membrane PUFA status is a valid biological measure of lipid biology irrespective of source. Finally, we did not correct for multiple comparisons in the present study due to its exploratory nature.

Future studies should further confirm if the UHR for psychosis group has deficits in PUFA compared to healthy individuals

as well as other high-risk groups; clarify causality by testing whether the relationship with clinical symptoms persists at follow-up and is predictive of treatment response and long-term remission; if supplementation with fish oil can reverse potential deficits and associations with psychopathology; and whether the relationship between lipid biology and symptoms is attributable to inflammation or other biological mechanisms that may serve as potential treatment targets.

In conclusion, our study confirms that membrane PUFAs are associated with the severity of clinical symptoms in individuals at UHR for psychosis. In particular, we found that the n-3 index was negatively correlated with multiple measures, including total BPRS scores, MADRS, and YMRS scores. These results suggest that n-3 PUFA are important in the pathophysiology of the UHR state and may indicate risk for poor mental health outcomes. Given that recent RCTs of n-3 PUFA in the UHR were unable to demonstrate superiority of n-3 PUFA over placebo for transition to psychosis, biomarker studies are warranted to clarify if low n-3 PUFA levels predispose for adverse outcomes and are indicative of treatment response with n-3 PUFA.

ETHICS STATEMENT

This study was approved by the local human ethics review board of each site (Melbourne, Australia: Melbourne Health Research Ethics Committee; Sydney, Australia: Sydney South West Area Health Service Ethics Review Committee; Basel, Switzerland: Ethics Commission for Basel; Zurich, Switzerland: Cantonal Ethics Commission Zurich; Jena, Germany: University Clinic Jena Ethics Commission; Copenhagen, Denmark: Capital Region Research Ethics Committee; Hong Kong: Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster; Vienna, Austria: Medical University of Vienna Ethics Commission; Singapore: National Healthcare Group Domain Specific Review Board; and Amsterdam, the Netherlands: Academic Medical Centre Medical Ethics Committee). This study was carried out in accordance with the Declaration of Helsinki and The National Health and Medical Research Council of Australia National Statement on Human Research with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

MB and GA designed the study. MB analyzed the data and wrote the manuscript. BN, CM, HY, MRS, NM, MS, SS, IH, GB, EC, LH, DN, MN, AR-R, SV, AY, PM, and GA contributed to the primary study that provided data for this analysis, including acquisition of funding, recruitment of participants, and/or collection of data. TM and BM analyzed erythrocyte fatty acids. All authors contributed to the interpretation of results and to the manuscript.

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Factors Associated With Psychosocial Functioning and Outcome of Individuals With Recent-Onset Schizophrenia and at Ultra-High Risk for Psychosis

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Background: Patients with schizophrenia have impairments in social functioning and are readmitted to healthcare institutions frequently. Individuals at ultra-high risk (UHR) for psychosis already present poor social functioning; among those individuals, the conversion rate from the putative prodromal phase to overt psychosis is 20%–30% within 1–2 years. Here, we analyzed the factor structure of self-related variables and neuro- and socio-cognitive function, and investigated whether these factors were associated with psychosocial function and prognostic outcome in individuals with recent-onset schizophrenia (ROSPR) or at UHR for psychosis.

Methods: We evaluated 60 individuals at UHR for psychosis, 47 individuals with ROSPR, and 71 healthy controls using a comprehensive neurocognitive test battery and self-reported attribution scales, self-esteem, resilience, aberrant subjective experiences of schizotypy (physical anhedonia, social anhedonia, magical ideation, and perceptual aberration), and basic symptoms. We assessed psychosocial function with the Quality of Life Scale (QLS).

Results: Factor analysis of all subjects revealed a four-factor structure comprising social-cognitive bias, reflective self, neurocognition, and pre-reflective self factors. Multiple regression analysis at baseline revealed that the factor structure predicted QLS. In the UHR group, social-cognitive bias, reflective self, neurocognition, and negative symptoms were significant determinants, explaining 38.0% of total QLS score variance. In the ROSPR group, reflective self and negative symptoms were significant determinants, explaining 54.4% of total QLS score variance. During follow-up, 13 individuals at UHR for psychosis developed psychosis (cumulative prevalence: 31.2% ± 7.6% at 6 years), with neurocognition score at baseline remaining a significant predictor of conversion [$\chi^2(1) = 4.009$, $p = 0.045$;

hazard ratio 0.56, 95% confidence interval 0.31–0.99, p = 0.048]. Five patients with schizophrenia were (re)admitted during follow-up (cumulative prevalence: 16.1% ± 7.1% at 6 years); no factor was found to predict (re)admission.

Conclusion: Factor analysis revealed an intrinsic four-factor structure of social-cognitive bias, reflective self, neurocognition, and pre-reflective self. The four factors were associated with social functioning at baseline and prodrome-to-psychosis conversion during follow-up, indicating the clinical significance of the four-factor structure. These findings provide a framework for understanding schizophrenia.

Keywords: conversion, readmission, psychosocial function, schizophrenia, ultra-high risk for psychosis

INTRODUCTION

Patients with schizophrenia have impairments in social functioning and are readmitted to healthcare institutions frequently. Declining social functioning, a hallmark of schizophrenia, occurs throughout the course of the disorder and may begin even prior to overt psychotic symptoms (1). Frequent readmission to healthcare institutions affects not only social functioning but also the quality of life of patients with schizophrenia. Understanding the factors associated with impaired social functioning and readmission to a healthcare institution may be crucial to help patients with schizophrenia achieve better quality of life.

Vulnerability factors of patients with schizophrenia include impaired neurocognition and social cognition. Neurocognitive impairment is related to a decline in social functioning, and verbal memory (2), spatial organization (3), visual memory, and intelligence quotient (4) have been suggested to correlate with social and vocational outcome in patients with schizophrenia (5). Poor performance on the Wisconsin card sorting test has been suggested as a predictor of rehospitalization in patients with schizophrenia, even after controlling for adherence to medication (5, 6). Social cognition impairment has also been suggested to be associated with social functioning. Impaired facial affect recognition is correlated with social functioning in patients with first- or multi-episode schizophrenia (7). There is also a correlation between impaired social perception and role functioning in patients with schizophrenia (8), and attribution bias has been found to have an effect on social functioning impairment in patients with bipolar disorder and schizophrenia (9). A recent meta-analysis showed that while overall impairments in social cognition are more strongly correlated with community functioning than impaired neurocognition is, cognitive functioning only explains 25% of outcome variance in patients with schizophrenia (10). Besides the abovementioned objective cognitive deficits, patients with schizophrenia experience subjective symptoms, including basic symptoms (11) and schizotypy (12), both of which are suggested to result from deficits in information processing (13). Previous longitudinal studies suggested that basic symptoms have a negative relationship with social functioning and quality of life in patients with schizophrenia (14) and that schizotypy predicts social functional impairment (15). One review article suggested that basic symptoms are associated not only with disease itself but also with relapse of schizophrenic episodes; since basic symptoms occur prior to relapse, they are considered an early sign of relapse (16). Schizotypy is associated with dopamine changes (17). It occurs in patients genetically prone to psychotic episodes (18). Therefore, schizotypy may affect schizophrenia relapses (19) and be associated with rehospitalization.

Regarding the protective factors, resilience has been associated with social functioning in patients with schizophrenia (20, 21). Self-esteem has also been reported to correlate with social functioning in psychiatric outpatients, including those with schizophrenia (22). Patients with schizophrenia who are less resilient have more frequent and more severe episodes, including rehospitalization (23). Low self-esteem of patients with schizophrenia is associated with stigma (24) and higher rehospitalization rates (25).

Ultra-high risk (UHR) for psychosis is a putative prodromal phase when poor social functioning is already present. The conversion rate to overt psychosis is around 30% during the follow-up period (26). It is important to find the factors associated with social functioning and conversion to overt psychosis in individuals at UHR for psychosis. Declining neurocognitive function has been reported to be associated with social functioning impairment (27, 28) and psychotic conversion (29–33) in individuals at UHR for psychosis. Neurocognitive functions, such as verbal learning, memory, processing speed, attention, and verbal fluency, predict social functioning outcome in UHR for psychosis (34). Spatial memory is one of the factors that significantly predict conversion (29, 30). Working memory and verbal ability deficits are possible predictors of psychotic conversion in initial prodromal states (32). In line with these observations, working memory, visual memory, and executive function have been included in the psychotic conversion model of individuals at UHR for psychosis (31). Social cognition, including the theory of mind, is impaired in individuals at UHR for psychosis (35, 36); it plays an important role in social functioning impairment (37) and predicts psychotic conversion (31). Resilience is also an important influencing factor of social functioning in individuals at UHR for psychosis. Individuals with higher resilience present better psychosocial functioning (38). Conversely, the conversion rate is higher in low-resilience patients (38). Basic symptoms and schizotypy of physical anhedonia are other predicting factors of conversion in individuals at UHR for psychosis (39).

As mentioned above, psychosocial functioning and readmission of patients with schizophrenia or psychotic conversion in individuals at UHR for psychosis are associated with loss of the ability to form complex and integrated ideas and experiences of the self and others. This ability may include verbal memory, spatial memory, facial affect recognition, theory of mind, attribution style, resilience, basic symptoms, and schizotypy as mentioned previously. In our previous study, we concluded these factors can be categorized as cognitive and self-related factors (40). Cognitive factors include neurocognitive factors (spatial memory, verbal memory, intelligence quotient, etc). and social cognitive functions (facial affect recognition, theory of mind, attribution style, etc). Self-related factors include resilience, self-esteem, basic symptoms, and schizotypy; they can be subcategorized as two levels of self: pre-reflective and reflective levels (40). These two levels of concept of self were firstly introduced as phenomenological theory for understanding self-experience. Furthermore, the underlying neural underpinnings of these two levels of self were found to be dissociated from each other. For example, Esslen et al. (41) revealed biological evidence that ventral parts of medial prefrontal cortex were related to pre-reflective self and dorsal parts of medial prefrontal cortex were related to reflective self. The pre-reflective self is a first-person perspective and minimal level of self; it is also called basic self, minimal self, or ipseity (41). This aspect is a result of direct and non-reflective experiencing of self. Basic symptoms and schizotypy, such as perceptual aberrations and magical ideation, are measures of the pre-reflective level of self. In contrast, the reflective level of the self is a result of self-introspection and explicit awareness of the self; it is also regarded as the narrative self (42). Since the reflective self includes all aspects of an individual's personality (42), self-esteem and resilience can reflect this level of self. Previous studies provided disseminated information of relationships among these aspects with social functioning/readmission of patients with schizophrenia and social functioning/conversion of individuals at UHR for psychosis, but there was no study that integrates and categorizes the cognitive and self-related factors associated with functioning and prognostic outcome. Thus, we wanted to find and construct a proper factor structure of cognitive and self-related factors that is associated with social functioning/readmission of patients with schizophrenia and social functioning/conversion of individuals at UHR for psychosis. This factor structure provides an integrated perspective to understand social functioning/readmission of patients with schizophrenia and social functioning/conversion of individuals at UHR for psychosis.

The aims of this study were to analyze the factor structure of self-related psychosocial variables and cognitive function and investigate whether these factors were associated with social function and prognostic outcome in individuals with recent-onset schizophrenia (ROSPR) or at UHR for psychosis. We hypothesized that i) cognitive function and self-related variables can be categorized into representable factors in all subjects, and these factors contain the characteristics of neurocognitive function, social-cognitive bias, reflective self, and pre-reflective self; ii) these factors are significantly different among the UHR, ROSPR, and control groups; and iii) these factors are associated with psychosocial function at baseline in the UHR and ROSPR groups, with the psychotic conversion rate, and with the (re)admission rate during follow-up in the UHR and ROSPR group, respectively.

MATERIALS AND METHODS

Subjects

We included 60 individuals at UHR for psychosis, 47 individuals with ROSPR, and 71 healthy controls (HCs) in this study. The HC group was recruited through online advertising between July 2007 and September 2016; subjects with any past or current psychiatric or neurological illness were excluded. The UHR and ROSPR groups comprised help-seeking individuals recruited at the early psychosis clinic (Clinic FORYOU) at Severance Hospital of Yonsei University Health System in the Seoul metropolitan area during the same period. In all subjects, axis I psychiatric disorders were assessed by a trained psychiatrist (K.K.R.) using the Structured Clinical Interview for DSM-IV (SCID-IV) (43, 44). Individuals at UHR for psychosis were diagnosed according to the criteria of the Structured Interview for Prodromal Syndromes (SIPS) (45). To be diagnosed with UHR for psychosis, individuals had to satisfy one or more of the following prodromal syndromes outlined in the SIPS: 1) brief intermittent psychotic syndrome (BIPS), which has emerging psychotic symptoms with spontaneous remission in less than 1 week; 2) attenuated positive prodromal syndrome (APS), which has attenuated subthreshold positive psychotic symptoms; and/or 3) genetic risk and deterioration syndrome (GRDS), which is a combination of genetic risk for schizophrenia and recent functional decline. After inclusion in the study, individuals in the UHR group were re-assessed every month for 24 months and at regular outpatient follow-up intervals after 24 months by the psychiatrist-in-chief (A.S.K.) to determine whether the conversion to overt psychosis had occurred. Conversion to overt psychosis was defined when the patient met the DSM-IV criteria for psychotic disorders, including schizophrenia, schizoaffective disorder, psychotic disorder not otherwise specified, and mood disorders with psychotic features. ROSPR was diagnosed according to the criteria of the DSM-IV using the SCID-IV. At baseline, patients with ROSPR were limited to those who had experienced their first (n = 42) or second (n = 5) psychotic episode within less than 36 months from the first frank psychotic episode. Of the 47 patients with ROSPR, 17 were inpatients, 9 were outpatients with a history of one psychiatric hospitalization, and 21 were outpatients without a history of hospitalization. After inclusion in the study, individuals in the ROSPR group were re-assessed every month for 24 months and at regular outpatient follow-up intervals after 24 months by the psychiatrist-in-chief (A.S.K.) to determine whether psychiatric (re)admission had occurred due to relapse of psychotic episodes.

This study was carried out in accordance with the Declaration of Helsinki. The Institutional Review boards at Severance Hospital reviewed and approved this study. All subjects, or the parents of subjects who were under 18 years old, gave written informed consent to participate in the study.

Measures

Cognitive Variables

We assessed the neurocognitive function of the subjects using a comprehensive neurocognitive test battery, as described in our previous study (28). The battery comprises the Rey Complex Figure Test (46), California Verbal Learning Test (47), 3–7 Continuous Performance Test (48), Controlled Oral Word Association Test (49), Figure Fluency Test (50), Trail Making Test Part A and B (51), Verbal and Spatial 2-back Test (52), Stroop Test (53), and Wisconsin Card Sorting Test (54). The *z* scores were converted from each neurocognitive test score based on the performance of the HC group (n = 94) (29). These scores were categorized into five dimensions representing the factor structure determined previously (28): verbal memory, spatial memory, psychomotor speed, attention/working memory, and executive function. Summary scores for each dimension were calculated as the mean of the test scores in that same category. The internal consistencies of these five dimensions of neurocognitive function were good (for verbal memory, Cronbach's alpha = 0.891; for spatial memory, Cronbach's alpha = 0.975; for attention/working memory, Cronbach's alpha = 0.807) in the entire groups of subjects, except psychomotor speed (Cronbach's alpha = 0.635) and executive function (Cronbach's alpha = 0.594).

We assessed social-cognitive bias using the Ambiguous Intentions Hostility Questionnaire (AIHQ) (55, 56). The AIHQ is a self-report checklist of 15 hypothetical negative situations. The situations vary in intentionality: five are accidental, five are ambiguous, and five are intentional situations. The AIHQ yields scores of hostility, aggression bias, and composite blame bias. The hostility and aggression biases are rated by the rater based on the participant's written response according to the sample scores for each item, provided in the AIHQ scoring form. The composite blame score is the mean of intent, anger, and blame scores. In this study, we only used the hostility and composite blame scores for each hypothetical situation. The validity of each score was good in blame intentional (Cronbach's alpha = 0.840) and blame accidental (Cronbach's alpha = 0.820). Acceptable internal consistencies were found in blame ambiguous (Cronbach's alpha = 0.770), hostility ambiguous (Cronbach's alpha = 0.745), and hostility accidental (Cronbach's alpha = 0.777), except for hostility intentional (Cronbach's alpha = 0.641).

Self-Related Variables

Self-related measures comprised self-esteem [Rosenberg's Self-esteem Scale (57)], resilience [Connor–Davidson Resilience Scale (58)], features of schizotypy [Chapman's true-false self-report questionnaires for social anhedonia (59), physical anhedonia (60), perceptual aberration (61), and magical ideation (62)], and basic symptoms [Frankfurt Complaint Questionnaire (63)]. The internal consistencies of these self-related variables were good (for self-esteem, Cronbach's alpha = 0.898; for resilience, Cronbach's alpha = 0.937; for social anhedonia, Cronbach's alpha = 0.926; for physical anhedonia, Cronbach's alpha = 0.926; for perceptual aberration, Cronbach's alpha = 0.896; for magical ideation, Cronbach's alpha = 0.835; for basic symptom, Cronbach's alpha = 0.976).

Psychopathology

We assessed symptom severity using the Scale for the Assessment of Positive Symptoms (SAPS) (64) and the Scale for the Assessment of Negative Symptoms (SANS) (65).

Psychosocial Function

We assessed psychosocial function using the Heinrichs–Carpenter Quality of Life Scale (QLS) (66). The QLS is a rater-administered scale with 21 items, each scoring 0–6 points. The result of the QLS reveals the total score and the scores of its four subscales: interpersonal relations, instrumental role, intrapsychic foundation, and common objects and activities (38). The Korean version of the scale has been widely used in studies of social functioning in schizophrenia (67).

Statistical Analysis

We used univariate analysis of variance (ANOVA) and χ^2 tests to compare the differences in demographic and clinical characteristics among the three groups. In addition, we performed exploratory factor analysis to categorize the measures to establish the factor structure. We applied exploratory factor analysis, not confirmative analysis, due to the absence of factor structure information from previous studies. A scree plot and factors with eigenvalues >1 were used to determine the number of factors. After varimax rotation, items with factor loading ≥0.4 were considered to be significant. Factor scores were derived by weighted sum of each variable score with factor loadings for use in multiple regression analysis. Items with two significant factor loadings were assigned to the factor with higher loading. We compared the factor scores among the three groups using ANOVA and analysis of covariance (ANCOVA) with age and education years as covariates, followed by *post hoc* analysis with Bonferroni correction. Statistical significance was set at $p < 0.05$.

We used Kaplan–Meier survival analysis to determine the cumulative rate of conversion from UHR for psychosis to overt psychosis and the (re)admission rate of patients with ROSPR. We used Cox regression analysis to estimate possible predictors for conversion in the UHR group and (re)admission in the ROSPR group.

RESULTS

Subject Characteristics

The demographic and clinical characteristics of each group are presented in **Table 1**. The average duration of illness in the ROSPR group was 11.4 months.

Factor Analysis of Cognitive and Self-Related Variables

Table 2 presents the results of exploratory factor analysis with varimax rotation. Eighteen variables were reduced to four factors with eigenvalues of 5.89, 2.55, 1.70, and 1.42, respectively. A Kaiser–Meyer–Olkin (KMO) value of 0.79 confirmed sampling adequacy, and Bartlett's test of sphericity was statistically

TABLE 1 | Baseline demographic and clinical characteristics of the study groups.

	HC (*n* = 71)	UHR (*n* = 60)	ROSPR (*n* = 47)	Statistical analysis			
				Value	*p*	Post hoc	*p**
Age (years)							
Mean (SD)	22.0 (3.4)	20.3 (3.5)	23.0 (4.1)	$F = 6.6$	0.002	H vs. U	0.038
						H vs. S	0.59
						U vs. S	0.002
Range†	15–28	16–28	15–35				
Gender (male/female)	34/37	34/26	21/26	$\chi^2 = 1.725$	0.422		
Education							
Years (SD)	13.9 (1.8)	13.0 (1.9)	13.6 (2.0)	$F = 3.85$	0.023	H vs. U	0.02
						H vs. S	1.0
						U vs. S	0.26
SAPS (summary score)	0.014 (0.12)	3.62 (2.39)	6.17 (2.90)	$F = 135.93$	<0.001	H vs. U	<0.001
						H vs. S	<0.001
						U vs. S	<0.001
SANS (summary score)	0.54 (1.26)	8.32 (4.11)	8.89 (5.27)	$F = 99.96$	<0.001	H vs. U	<0.001
						H vs. S	<0.001
						U vs. S	<0.001
Number of episodes							
1st episode			42				
2nd episode			5				
Types of UHR							
APSS only		43					
BIPS only		1					
GRDS only		0					
APSS + BIPS		5					
APSS + GRDS		11					
Duration of illness (months)			11.4 (11.4)				
Antipsychotic medication status							
Medicated/unmedicated		18/42	45/2	$\chi^2 = 47.05$	<0.001		
Chlorpromazine equivalent (mg/day)‡		114.0 (95.2)	433.42 (323.09)		<0.001		

HC, healthy control; UHR, ultra-high risk for psychosis; ROSPR, recent-onset schizophrenia; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms; APSS, attenuated positive symptoms syndrome; BIPS, brief intermittent psychotic syndrome; GRDS, genetic risk and deterioration syndrome.
**Corrected p values are derived from post hoc comparisons with Bonferroni correction.*
†Ranges presented in this table were 5–95 percentile age of each group.
‡All medicated ROSCR and UHR participants were taking atypical antipsychotic medications (68).

TABLE 2 | Loadings on factors derived by exploratory factor analysis with varimax rotation.

	Factor 1: Social-cognitive bias	Factor 2: Reflective self	Factor 3: Neurocognition	Factor 4: Pre-reflective self
Blame ambiguous	**0.766***	0.284	0.027	0.231
Hostility accidental	**0.765***	0.1	–0.199	–0.009
Blame accidental	**0.763***	0.027	–0.133	0.237
Blame intentional	**0.709***	0.1	0.178	0.020
Hostility intentional	**0.689***	0.237	0.062	–0.014
Hostility ambiguous	**0.588***	**0.433***	–0.033	0.171
Self-esteem	–0.232	**–0.819***	0.052	–0.192
Resilience	–0.250	**–0.809***	0.136	–0.100
Physical anhedonia	0.097	**0.790***	–0.060	0.145
Social anhedonia	0.272	**0.772***	–0.084	0.260
Magical ideation	0.151	0.140	–0.080	**0.871***
Perceptual aberration	0.078	0.170	–0.109	**0.837***
Basic symptoms	0.164	**0.460***	–0.119	**0.759***
Verbal memory	–0.074	–0.024	**0.774***	–0.111
Attention/working memory	0.017	–0.179	**0.738***	–0.131
Psychomotor speed	0.035	–0.361	**0.674***	0.035
Executive function	–0.062	0.063	**0.629***	–0.145
Spatial memory	0.037	0.015	**0.603***	0.052

*All loadings are represented such that positive scores indicate higher scores on the item. *Loadings > 0.40.*

significant ($p < 0.001$). High loadings on factor 1 were mainly from AIHQ scores. High loadings on factor 2 were mainly from high physical/social anhedonia and less self-esteem and resilience. High loadings on factor 3 were from all the neurocognitive tests. High loadings on factor 4 were from high magical ideation, perceptual aberration, and basic symptom scores. Considering the high loadings on each of the factors 1–4, they were named social-cognitive bias, reflective self, neurocognition, and pre-reflective self, respectively.

Comparison of Baseline Social Cognitive Bias, Reflective Self, Neurocognition, and Pre-Reflective Self Factors among the UHR, ROSPR, and HC Groups

There were significant differences among the three groups in reflective self, neurocognition, and pre-reflective self factors, but not in the social cognitive bias factor (**Table 3**). Post hoc analysis with Bonferroni correction revealed that the UHR group had the highest reflective self factor score, followed by the ROSPR and HC groups. The neurocognition factor score of the ROSPR group was significantly poorer than that of the UHR ($p < 0.001$) and HC ($p < 0.001$) groups, and there was no significant difference between the UHR and HC groups ($p = 0.096$). The pre-reflective self factor score of the HC group was significantly lower than that of the UHR ($p = 0.004$) and ROSPR ($p = 0.03$) groups, and there was no significant difference between the UHR and ROSPR groups ($p > 0.999$). Results from ANCOVA with age and education year as covariates revealed a significant interaction between education year and the neurocognition factor ($p = 0.014$); no other significant interactions were found.

Associations Between Baseline Factor Structure and Qls in the Uhr Group

In the UHR group, SANS score and social-cognitive bias, reflective self, and neurocognition factors were significant determinants explaining 38.0% of the total QLS score variance (**Table 4**). SANS score and reflective self and neurocognition factors accounted for 27.2% of variance in the regression model of interpersonal relations, with statistical significance. Social-cognitive bias and neurocognition factors were significant determinants in the regression model of instrumental role, with an explanatory power of 22.6%. For the intrapsychic foundation, SANS score and social-cognitive bias, reflective self, and neurocognition factors were significant determinants accounting for 46.0% of variance. Common objects and activities of QLS had no significant predictors in the regression analysis. When initial antipsychotics dose was treated as a covariate, the results did not change.

Associations Between Baseline Factor Structure and QLS in the ROSPR Group

In the ROSPR group, SANS score and the reflective self factor were significant determinants explaining 54.4% of the total QLS score, 46.3% of the interpersonal relations score, and 49.9% of the intrapsychic foundations score (**Table 4**). Regression analysis revealed no significant predictors of common objects, activities and instrumental role in the ROSPR group. Treating initial antipsychotics dose as a covariate did not change the results.

Conversion From UHR for Psychosis to Overt Psychosis During Follow-Up and Its Predictive Factors

During follow-up, 13 cases of UHR for psychosis converted to overt psychosis. The cumulative prevalence rate and standard error from Kaplan–Meier estimates was 9.4% ± 4% at 1 year, 18.3% ± 5.6% at 2 years, and 31.2% ± 7.6% at 6 years. The Kaplan–Meier curve is shown in **Figure 1**. Cox regression analysis to evaluate the hazard ratio of each of the four factors revealed that only neurocognition factor score remained significant as a predictor for conversion [$\chi^2(1) = 4.009$, $p = 0.045$; hazard ratio, 0.56; 95% confidence interval, 0.31–0.99; $p = 0.048$].

TABLE 3 | Factor scores of each group.

	HC (n = 71)	UHR (n = 60)	ROSPR (n = 47)	Statistical analysis			
				Value	p	Post hoc	Corrected p values*
Factor 1: Social-cognitive bias	−0.096 (0.59)	0.16 (1.17)	−0.063 (1.24)	$F = 1.04$	0.378	H vs. U	0.588
						H vs. S	1.0
						U vs. S	1
Factor 2: Reflective self	−0.68 (0.66)	0.71 (0.95)	0.12 (0.80)	$F = 33.9$	<0.001	H vs. U	<0.001
						H vs. S	<0.001
						U vs. S	0.004
Factor 3: Neurocognition	0.47 (0.50)	0.11 (0.84)	−0.85 (1.20)	$F = 23.9$	<0.001	H vs. U	0.096
						H vs. S	<0.001
						U vs. S	<0.001
Factor 4: Pre-reflective self	−0.32 (0.71)	0.28 (1.10)	0.13 (1.13)	$F = 5.15$	0.002	H vs. U	0.004
						H vs. S	0.028
						U vs. S	1.0

HC, healthy control; UHR, ultra-high risk for psychosis; ROSPR, recent-onset schizophrenia.
**Corrected p values are derived from post hoc comparisons with Bonferroni correction.*

TABLE 4 | Multiple regression analysis to predict QLS from factor structure.

	Dependent variable	Independent variables	B	SE	β	*t*	*P*	Model's properties
UHR (*n* = 60)	Total score of QLS	(Constant)	70.100	5.355		13.091	<0.001	R^2 = 0.443, adj. R^2 = 0.380, F = 7.027, p < 0.001
		SANS	–1.585	0.560	–0.323	–2.830	0.007	
		Social-cognitive bias	–4.079	1.839	–0.236	–2.287	0.026	
		Reflective self	–5.852	2.559	–0.275	–2.287	0.026	
		Neurocognition	9.295	2.857	0.388	3.253	0.002	
	Interpersonal relations of QLS	(Constant)	23.973	2.657		9.024	<0.001	R^2 = 0.346, adj. R^2 = 0.272, F = 4.677, p = 0.001
		SANS	–0.728	0.278	–0.324	–2.619	0.011	
		Reflective self	–2.845	1.270	–0.292	–2.241	0.029	
		Neurocognition	3.851	1.417	0.351	2.717	0.009	
	Instrumental role of QLS	(Constant)	2.410	0.436		5.522	<0.001	R^2 = 0.303, adj. R^2 = 0.226, F = 3.867, p = 0.003
		Social-cognitive bias	–0.415	0.150	–0.329	–2.770	0.008	
		Neurocognition	0.706	0.233	0.405	3.032	0.004	
	Intrapsychic foundation of QLS	(Constant)	26.074	1.706		15.285	<0.001	R^2 = 0.515, adj. R^2 = 0.460, F = 9.389, p < 0.001
		SANS	–0.471	0.178	–0.281	–2.641	0.011	
		Social-cognitive bias	–1.651	0.586	–0.280	–2.818	0.007	
		Reflective self	–2.897	0.815	–0.398	–3.553	0.001	
		Neurocognition	3.447	0.910	0.422	3.787	<0.001	
	Common objects and activities of QLS	(Constant)	8.233	0.727		11.318	<0.001	R^2 = 0.146, adj. R^2 = 0.050, F = 1.514, p = 0.192
ROSPR (*n* = 47)	Total score of QLS	(Constant)	83.543	6.142		13.602	<0.001	R^2 = 0.603, adj. R^2 = 0.544, F = 10.135, p < 0.001
		SANS	–3.008	0.464	–0.718	–6.488	<0.001	
		Reflective self	–6.981	2.949	–0.254	–2.367	0.023	
	Interpersonal relations of QLS	(Constant)	31.487	3.033		10.383	<0.001	R^2 = 0.533, adj. R^2 = 0.463, F = 7.605, p < 0.001
		SANS	–1.252	0.229	–0.656	–5.467	<0.001	
		Reflective self	–3.355	1.456	–0.268	–2.304	0.027	
	Instrumental role of QLS	(Constant)	3.065	0.523		5.856	<0.001	R^2 = 0.203, adj. R^2 = 0.083, F = 1.696, p = 0.147
	Intrapsychic foundation of QLS	(Constant)	32.506	2.571		12.643	<0.001	R^2 = 0.564, adj. R^2 = 0.499, F = 8.624, p < 0.001
		SANS	–1.067	0.194	–0.637	–5.495	<0.001	
		Reflective self	–3.370	1.235	–0.307	–2.730	0.009	
	Common objects and activities of QLS	(Constant)	7.920	0.878		9.023	<0.001	R^2 = 0.180, adj. R^2 = 0.057, F = 1.459, p = 0.217

HC, healthy control; UHR, ultra-high risk for psychosis; ROSPR, recent-onset schizophrenia; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms.

(Re)admission of Patients With ROSPR During Follow-Up and Its Predictive Factors

During follow-up, five patients with ROSPR were (re)admitted to the hospital. The Kaplan–Meier curve is shown in **Figure 2**. The cumulative prevalence rate and standard error from Kaplan–Meier estimates were 2.5% ± 2.5% at 1 year, 10.5% ± 5.0% at 2 years, and 16.1% ± 7.1% at 6 years. Cox regression analysis revealed no significant factor affecting the (re)admission rate [$\chi^2(1) = 2.630$, $p = 0.105$].

DISCUSSION

In the present study, we identified a four-factor structure of social cognitive bias, reflective self, neurocognition, and pre-reflective self in UHR, ROSPR, and HC individuals. There were overall group differences in these four factors between the UHR, ROSPR, and HC groups. Importantly, these factors were found to be associated with baseline psychosocial function in the UHR and ROSPR groups as well as with conversion rate in the UHR group during follow-up.

The four-factor structure contained several self-related and cognitive variables. Scores from AIHQ subsets were categorized as one factor named social cognitive bias, which is one of the components of social cognition and a measure of social cognition in previous studies (69, 70). Among the self-related factors, two distinct factors were found: self-esteem, resilience, physical anhedonia, and social anhedonia contributed to one factor, which we named the reflective self; magical ideation, perceptual aberration, and basic symptoms comprised the pre-reflective self factor. These two distinct factors were compatible with the previous idea of two aspects of the self and the characteristics of each level (41). Although basic symptoms were categorized as pre-reflective self due to the high loading on the factor (0.759), it also had meaningful

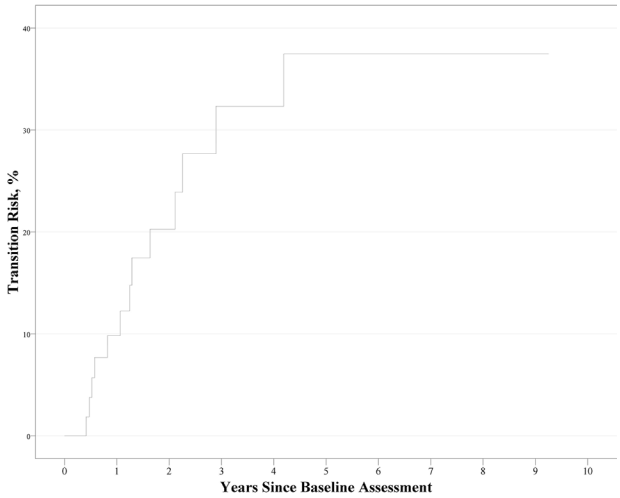

FIGURE 1 | Kaplan–Meier curve for the conversion to psychosis in ultra-high risk participants (*n* = 60).

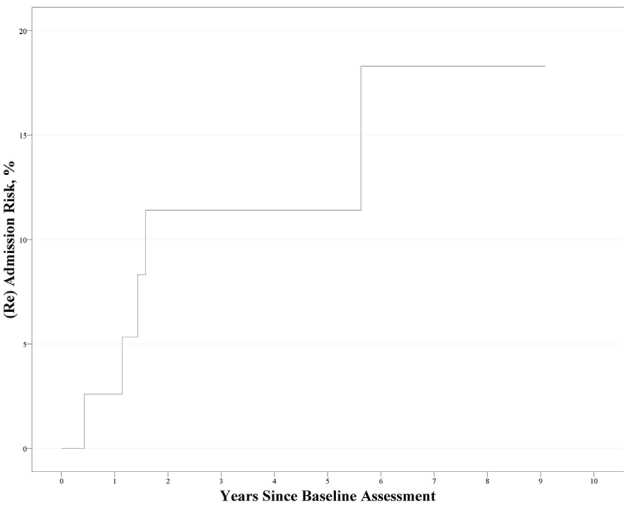

FIGURE 2 | Kaplan–Meier curve for the (re)admission of recent-onset schizophrenia patients (*n* = 47).

loading on reflective self (0.460). This result showed that pre-reflective sense of self is an important foundation for reflective self, as indicated in a previous study (71). Four components of schizotypy were split into two factors: physical and social anhedonia in the reflective self factor; and perceptual aberration and magical ideation in the pre-reflective self factor. This finding may be explained by the characteristics of the questionnaires for physical and social anhedonia. Since the questionnaires required the subjects to describe how they feel in the face of hypothetical situations, intrinsic reflective selfhood might be reflected in the result of social anhedonia and physical anhedonia self-reports (72). The last factor was neurocognition; it included verbal memory, attention/working memory, psychomotor speed, executive function, and spatial memory. These domains constituted five important factors of neurocognition, with differences between the UHR group and the normal control in a previous study (29).

Factor scores differed among the three groups in this study. The social-cognitive bias score was higher in the UHR group than in the other two groups, yet not significantly so. This finding is not compatible with previous findings of bias in UHR (40, 73) and first-episode groups (73). However, it may be derived from the differences of hostility perception and blaming bias scoring; the AIHQ scoring in the previous study was related to the ambiguous situations, and not to the intentional and accidental ones. On the contrary, in this study, the AIHQ scoring was related to all three types of situations. The reflective self factor score was significantly different among the three groups. Since higher reflective self factor score implies lower self-esteem and resilience and higher anhedonia, the score of the HC group was the lowest of the three groups, as expected. This finding was compatible with previous reports of lower resilience and self-esteem in patient groups (38, 73). The UHR group showed higher reflective self score than the ROSPR group. This might suggest that individuals at UHR for psychosis experience more negative self-representation, and incomplete compensation occurs after progression toward overt psychosis. The neurocognition factor score was also significantly different among the three groups: the HC group had the highest score, followed by the UHR group and the ROSPR group. This result is in agreement with previous studies showing that patients with schizophrenia present lower neurocognitive function (3, 74, 75) and that individuals at UHR for psychosis already have neurocognitive impairments (29). The pre-reflective self factor score was significantly lower in the HC group than in the other two groups. Considering the high loadings of magical ideation, perceptual aberration, and basic symptoms of the pre-reflective self factor, the higher scores in the clinical groups were reasonable and compatible with previous studies showing higher basic symptoms and schizotypy scores in individuals at UHR for psychosis (39). Higher factor scores in the UHR and ROSPR groups are consistent with the concept that the basic symptoms of schizophrenia allow the identification of the earliest-experienced subjective symptoms (76).

Regarding the psychosocial function at baseline, multiple regression analysis of the four factors and QLS scores revealed the associated and predictive factors of psychosocial functioning. In individuals at UHR for psychosis, the total QLS score was negatively associated with SANS, social-cognitive bias, reflective self, and neurocognition factors. This finding was compatible with previous studies showing that lower social cognition and higher resilience are associated with better psychosocial functioning (37, 38) and that better neurocognitive performance is associated with higher total QLS scores (34). SANS, but not SAPS, was identified as an important factor affecting psychosocial function in the regression model. Negative symptoms are known to be associated with social functioning of individuals at UHR for psychosis and patients with schizophrenia (77). QLS subscores revealed correlations between each factor and social functioning, which was compatible with the results of the total QLS score. In the

ROSPR group, the total QLS score was negatively associated with negative symptoms and the reflective self factor. This finding was compatible with a previous study showing that high resilience and self-esteem are correlated with better social functioning (20–22). Social cognitive bias, neurocognition, and pre-reflective factors were not predictive of psychosocial function in the ROSPR group. However, previous studies had suggested that social cognition (7–9) and neurocognition (2–4) were associated with social functioning. Neurocognition lost power for explaining QLS in the ROSPR group, probably due to its relationship with other highly affecting factors. Previous studies suggested that neurocognition in schizophrenia was related with the symptom domain, especially negative symptoms (78). Negative symptoms are a key factor affecting social functioning in schizophrenia (77, 79, 80). Considering previous studies and our results, negative symptoms could play a mediating role between social functioning and neurocognition in schizophrenia. SANS and the reflective self factor accounted for substantial variance of the QLS score; hence, other factors had probably lost their predictive power. Considering the results in the UHR and ROSPR groups, reflective self factor and SANS scores were associated with total, interpersonal relations, and intrapsychic foundation scores of QLS in the same pattern. These results may suggest that the reflective self factor is highly related with psychosocial function throughout the clinical course of schizophrenia. The finding that the pre-reflective factor was not associated with QLS probably indicates that the pre-reflective level of self was less associated with social functioning than the reflective level of self, yet there was not enough previous study about the association between social functioning and the pre-reflective aspect of self.

During follow-up, the neurocognition factor in the UHR group significantly predicted the conversion to overt psychosis in the Cox regression analysis. This finding was compatible with previous studies showing that low neurocognitive performance predicts higher conversion rate in the UHR group (29). In contrast to previous studies (31, 39), other factors failed to predict conversion. Among the social cognitive measures, we used AIHQ to measure social cognitive bias; however, previous studies suggested that the theory of mind, among social cognition, was related to conversion in the high-risk group (31). Including other domains in social cognition would increase the power of predicting the conversion of the UHR group. Therefore, further study is needed. Basic symptoms and schizotypy predicted conversion of UHR to overt psychosis in a previous study; however, in the present study, the pre-reflective and reflective self factors were not significant factors in the regression model. Considering the components of each factor, schizotypy was divided into two levels of self aspect, which can reduce the predicting power of each factor. One study suggested the predictive value of schizotypy; however, among the subscores, only physical anhedonia predicted conversion in the high-risk group (81). Another study failed to demonstrate basic symptoms and schizotypy as predicting factors for conversion when using combined variables (39). Further research is needed to determine the different effects of each component for predicting conversion. In the ROSPR group, meanwhile, the four factors failed to establish a statistically significant model to predict (re)admission. In a previous study on rehospitalization of patients with schizophrenia, 19 subjects were rehospitalized; this number was substantially higher than ours (n = 5) (5). Further studies with a larger sample could improve our knowledge about the predictive factors for (re)admission in patients with schizophrenia.

This study had several limitations. First, we could not establish any causal relationships of psychosocial function due to the cross-sectional design of the study and small sample size. A long-term study with a larger sample size could provide more information about this four-factor structure and its possible causal relationships with psychosocial function of individuals with ROSPR or at UHR for psychosis. Second, patients with ROSPR were mostly clinically stable and cooperated with the evaluation at baseline. Therefore, psychosocial functioning and other measures might have been underestimated at the moment of assessment. Subsequent regular follow-up could eliminate underestimation of the measures and increase the explanatory power of the results.

In conclusion, factor analysis revealed an intrinsic four-factor structure of social-cognitive bias, reflective self, neurocognition, and pre-reflective self. The four factors were associated with social functioning in the UHR and ROSPR groups at baseline and prodrome-to-psychosis conversion during follow-up in the UHR group. However, no factor was found to predict (re)admission in the ROSPR group. These findings indicate the clinical significance of the four-factor structure for patients with schizophrenia spectrum disorders, and provide a framework for understanding schizophrenia.

ETHICS STATEMENT

This study was carried out in accordance with the Declaration of Helsinki. The Institutional Review boards at Severance Hospital reviewed and approved this study. All subjects, or the parents of subjects who were under 18 years old, gave written informed consent to participate in the study.

AUTHOR CONTRIBUTIONS

SA designed the study. SA, EL, JK, JP, and KK recruited subjects. HK undertook the statistical analysis and wrote the first draft of the manuscript. HK, HP, ES, MB, YS, SL, and KK interviewed patients and collected data. All authors contributed to revising the manuscript.

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The Provision of Education and Employment Support At the Outreach and Support in South London (OASIS) Service for People at Clinical High Risk for Psychosis

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Clinical services for the early detection of individuals at clinical high risk of psychosis, such as Outreach and Support in South-London (OASIS), have been successful in providing psychological intervention and psychosocial support to young people experiencing emerging signs of serious mental disorders. Despite this, several studies have repeatedly shown that vocational and functional recovery in the clinical high risk for psychosis population is still low. This study aimed at evaluating the presence and nature of educational and employment focused interventions within the OASIS service, in order to inform research and clinical interventions aimed at supporting young people with early signs of psychosis on their path to vocational recovery. The specific objectives were to compare current practice i) to standards defined by the National Institute of Care Excellence guidelines; and ii) to principles defined by Individual Placement and Support (IPS). Nine standards of practice were derived. The OASIS caseload electronic records entered between January 2015 and January 2017 were manually screened. Data collected include sociodemographic, assessment of employment and educational status and support needs, interventions received, contacts with schools, employers and external vocational providers, employment, and educational status. Standards were considered as "met" if they were met for at least 90% of clients. Results suggest that, two out of nine standards were met while the remaining standards were only partially met. In particular, support provided was always focused on competitive employment and mainstream education and support was always based on people's interest. Implications for clinical and research practice are discussed.

Keywords: education, employment, vocational support, clinical high risk for psychosis, early detection in psychosis

INTRODUCTION

The first symptoms of psychosis typically emerge around late adolescence and early adulthood (1), a time during which a young person is devoting full-time to complete compulsory education or is about to enter the job market. At their first contact with early detection for psychosis services (EDP), many young people who meet criteria for being at ultra high risk of psychosis [UHR (2)], more broadly termed as clinical high risk for psychosis [CHR-P, hereafter (3)] are already falling out of education or are experiencing difficulties in finding or keeping an employment (4). In fact, they display functional impairments of a level that is comparable to that of other established mental disorders (5). Decline in social and occupational functioning often continues despite the regular contact with clinical services (4, 6, 7) and is a core predictive factors of poor clinical outcomes (8). As a result of this, CHR-P individuals often either do not complete their studies or they do so without reaching their full potential (9) with consequent future difficulties in securing competitive employment (4).

The rates of unemployment in CHR-P individuals at the time in which they first access EDP services are high. About one third of CHR-P individuals are unemployed or are not in education, and this figure is similar across different clinical services (4, 6–8). When looking at the short to medium-term outcome, despite some differences across countries, rates of unemployment—excluding students—range between 25 and 40% (4, 6, 7, 10). This indicates that despite specialized treatment being offered early, the type of interventions currently available might not be effective in preventing or improving social and occupational functioning decline and it is in line with persistent symptoms and disability in a substantial proportion of these clients (11).

To date, the evidence base for psychosocial interventions for CHR-P individuals mainly involves cognitive behavioral approaches or family intervention that aim at targeting symptoms reduction as opposed to overall social and occupational functioning (12). In line with this, several studies have repeatedly shown that vocational and functional recovery in CHR-P samples is still dramatically low (6, 8, 13, 14) and when low functioning is present at intake this is often predictive of worse long-term outcome (8, 10, 13, 15). Thus, there is an urgent need for improving social and occupational functioning recovery in this population.

For young people with emerging psychosis employment and education are highly desired outcomes and are often prioritized over relationship, housing, and symptom reduction (16). Despite this, young people with emerging psychosis are often at a disadvantage with regards to participating in education or employment which, amongst other factors, is also due to low expectations and fears of health care professionals (17, 18).

The recent National Audit for Schizophrenia (19) highlighted substantial variations in service delivery of vocational support with over half of service users not having their vocational needs met. The "Early Intervention in Psychosis Access and Waiting Time Standards" (20) state that mental health services should assist CHR-P individuals to engage with employment, education or training. However, to date, there is no indication about which intervention should routinely be employed. To add further complexity to the picture, young CHR-P individuals are a clinically heterogeneous group and are therefore more likely to require individualized treatment (21, 22).

IPS is the most successful evidence-based intervention developed to support individuals with severe mental illness gaining competitive employment (23–25). This intervention has been tested with people with a first episode psychosis (26–28) and has recently been expanded to also target educational outcomes in the same population (27, 29). However, to date, there are no randomized controlled trials investigating the benefits of vocational interventions within EDP services. Individualized interventions targeting education and/or employment, such as IPS, could significantly improve functioning, an area which has not been the primary focus of current CHR-P treatments (30). Young people accessing EDP services could be the ideal target group for this intervention for at least three reasons: i) CHR-P individuals are young and likely to be in education or to be in the process of securing their first paid job; ii) compared to patients who have experienced a first episode of psychosis, CHR-P individuals are experiencing less severe cognitive and clinical symptoms (31), iii) IPS can address key risk factors, such as unemployment and low educational level, that impact their clinical outcomes (15). In addition, some of the IPS principles, such as focusing on competitive as opposed to supported employment; attention to client preferences; benefit counseling (32) would likely already be in use in the EDP teams.

The aim of this study was therefore to evaluate the presence and quality of educational and employment focused interventions in Outreach and Support In South London (OASIS), a clinical service for CHR-P individuals within the South London and Maudsley (SLaM) NHS Foundation Trust (33) to inform clinical practice and future research in this area. The specific objectives were to compare current practice around the provision of education and employment support to i) standards defined by the National Institute of Care Excellence guidelines (34, 35); and ii) principles defined by IPS (24).

METHODS

OASIS services are part of SLAM and currently cover four boroughs: Lambeth, Southwark, Croydon, and Lewisham. OASIS was established in 2001 and receive on average about 300 referrals each year, one third of each will eventually meet criteria for a CHR for psychosis state (33). Data presented in this work were collected as part of a clinical audit which received approval from the Psychosis Clinical Academic Group in February 2018. Clinical electronic records for all clients who were accepted into the OASIS service between January 2015 and January 2017 were screened between March and November 2018. All clients meet criteria for an at risk mental state for psychosis as defined by the Comprehensive Assessment of an At Risk Mental State (2). As NICE standards partially overlap with IPS principles, nine standards based on the NICE guidelines for adults (33) and children and young people (34) with psychosis and schizophrenia and on IPS principles were developed (see **Table 1**

TABLE 1 | Standards.

Standard 1	Quality of vocational assessmenta. a. Assessment of current vocational engagement b. Assessment of vocational goals c. Assessment of vocational support needs d. Assessment of vocational history
Standard 2	Vocational activities feature in care plan Expected: all clients
Standard 3	Clients have access to a vocational support program Expected: all clients (when appropriate)
Standard 4	Early psychosis services liaise with educational and employment providers Expected: all clients (when appropriate)
Standard 5	Early psychosis services liaise with local stakeholders Expected: all clients (when appropriate)
Standard 6	Support is focused around competitive employment/mainstream education Expected: all clients (when appropriate)
Standard 7	Support is provided based on people's interest Expected: all clients (when support is provided)
Standard 8	Support is time unlimited[1] Expected: all clients (when support is provided)
Standard 9	Benefits counseling is provided Expected: all clients (when appropriate)

[1]Support is provided for as long as the client is under the care of the team and as long as support is wanted.

and below). NICE guidelines are widely recognized for their high standard and the wide body of evidence they draw upon and they form the basis for many clinical audits (36). Employment and education status at intake were collected by reviewing intake forms or/and care plans. At follow-up, these were collected by reviewing notes or/and discharge letters. In order to assess adherence to the nine standards, clinicians' notes, care plans, and outcome measurements were comprehensively screened by two experienced clinical researchers supervised by two senior clinicians. Clear evidence in clinical notes, correspondence, or care plan was necessary in order to code information, unclear evidence was conservatively considered as "not available information". Data were included if an individual had been under the care of OASIS for at least 6 months. Based on previous studies, a minimum of 6 months was deemed sufficient to allow vocational assessment and intervention (28, 29). Anonymized data was analyzed using IBM SPSS version 24. Demographic data was analyzed using means and standard deviations for continuous data and frequencies for categorical data. As OASIS teams in Croydon and Lewisham were set up in 2014–2015 while those in Southwark and Lambeth were established in 2001, we also compared how the standards were met across all four OASIS SLaM boroughs (Lewisham, Croydon, Lambeth and Southwark) using $\chi 2$.

Definition of Standards

Standard 1: Quality of Vocational Assessment

Standard 1 relates to quality of vocational assessment and is divided into (1.a) assessment of current vocational engagement; (1.b) assessment of vocational goals; (1.c) assessment of support needs; and (1.d) assessment of vocational history. Standard (1.a) is based on the NICE guidelines (35) for adults with psychosis and schizophrenia, section 1.3.3.1 and on the NICE (34) guidelines for children and young people with psychosis and schizophrenia, section 1.3.4. The guidelines do not specifically state to additionally assess vocational goals (1.b), support needs (1.c), and history (1.d) however NICE guidelines state that services should provide vocational interventions (34: section 1.5.8.1; 33: section 1.1.5 and section 1.3.9) and one of the foundational principles of supporting people with vocational engagement and goals is the detailed assessment of their previous experiences, their wishes, and their support needs (37).

Standard 2: Vocational Activities Feature in Care Plan

Standard 2 relates to the formal recording of vocational activities within the care plan and was based on a key recommendation within the NICE guidelines for adults (35) as stated in section 1.5.8.3 and within the NICE guidelines for children and adolescents (34) as stated in section 1.3.6. According to SLaM Care Programme Approach Policy, the care plan needs to be developed in collaboration with the service user. Therefore, the formal recording of vocational activities is a further indicator that these have been assessed and discussed with the client.

Standard 3: Clients Have Access to a Vocational Support Program

Standard 3 is based on the NICE guidelines (35), section 1.5.8.1, which recommend supported employment program, including support around educational activities. The NICE guidelines for children and adolescents (34) recommend support for young people to continue their education in section 1.3.4 or facilitate alternative input for people who are currently unable to attend mainstream schooling, as stated in section 1.3.9. As there was no vocational specialist within the OASIS teams during the period the audit took place, clients were not specifically referred to a vocational program within the team. Instead, support was often provided during discussions with psychologists and care coordinators or *via* referral to external program. For the purpose of the audit the definition of vocational support was kept broad and included any form of intervention aimed at supporting clients with their vocational goals and needs. Examples of support are writing supporting letters to educational institutions, longer-term psychological support aimed at managing, for example, anxiety in the work place.

Standard 4: Early Psychosis Services Liaise With Educational and Employment Providers

Standard 4 is based on the NICE guidelines (34) on psychosis and schizophrenia in children and young people, which recommend for early psychosis services to liaise with educational providers (section 1.1.5). It is also influenced by one of the IPS principles which requires the clinical team to liaise and build relationships with employers (32).

Standard 5: Early Psychosis Services Liaise With Local Stakeholders

Standard 5 is based on section 1.5.8.2 of the NICE guidelines (35) and section 1.8.14 of the NICE (34) which highlight the value of

including a local and diverse range of stakeholders in the process of supporting people with their vocational needs. Additionally, the NICE guidelines (34) recommend to jointly work with people's parents or careers (sections 1.3.6 and 1.8.12).

Standard 6: Support Is Focused Around Competitive Employment or Mainstream Education

Standard 6 is not specifically drawn from early psychosis guidelines although the NICE guidelines (34) on psychosis and schizophrenia in children and young people mention educational support aimed at mainstream education. This standard is a key principle of IPS (32) which recommends supporting people into mainstream employment and education as opposed to special program or voluntary work.

Standard 7: Support Is Provided Based on People's Interest

Standard 7 is not stated in the NICE guidelines (2014, 2013) but was included as it is a key principle within the IPS model (32) which recommends that services are based on clients' preferences and choices rather than providers' judgment.

Standard 8: Support Is Time Unlimited

Standard 8 is not stated in the NICE guidelines (34, 35) but was included as it is a key principle within the IPS model (32) which recommends that support is provided for as long as the client wants and needs the support.

Standard 9: Benefits Counseling Is Provided

Standard 9 was included as it is a key principle within IPS (32). In the UK, this would translate, for example, into giving advice on permitted work hours when in receipt of state benefits such as the Employment and Support Allowance, changes to housing benefits, if applicable, and accessing student loans and grants as well as grants for business start-ups.

Coding of Standards

Standards 1a, 1b, 1c, 1d, and 3 were coded as follows: "no," "at initial assessment" (standard 1 only); "within 3 months"; "within 6 months"; "within 12 months"; "after 12 months." Standard 2 was coded as follows: "yes"; "no"; "no care plan." Standard 4 was coded as follows: "yes"; "no"; "not employed/not in education"; "employer/school/university already aware"; "client liaised with employer/school/university." Standard 5 was coded as follows: "parents/relatives"; "external stakeholders"; "job centre"; "recovery college"; "other clinicians"; "multiple stakeholders"; "others"; "no stakeholders involved." Standards 6, 7, and 9 were coded as follows: "yes"; "no"; "not applicable." Standard 8 was coded as follows: "ongoing"; "none provided"; "termination of psychology sessions"; "discharge." In order to classify a standard as "met," this had to be met for at least 90% of the clients.

RESULTS

Socio-Demographic Characteristics of the Sample

Data on 109 CHR-P individuals were retrieved, 39 were excluded because discharge happened within the first 6 months. This resulted in a total of 70 individuals eligible to be included in this study. Sociodemographic characteristics are presented in **Table 2**. The mean age of the sample was 22.93 years (SD = 5.552, range 14–36), 30 individuals were females and 40 males. There were no significant differences in terms of age, gender, ethnicity across the four SLaM boroughs (see **Table 2**). Individuals were followed up for an average of 18.41 months (range 6–29). Employment and education status at baseline and at the last available follow-up are reported in **Tables 3** and **4**. Data on standards are reported below and summarized in **Table 5**.

Adherence to Standards

Standard 1: Quality of Vocational Assessment

Current vocational engagement (1.a.) was assessed at initial assessment for most clients (75%). All clients were assessed within the first 12 months. There were no significant differences across boroughs [$\chi2$ (6, N= 70) = 3.241 p = .778]. Vocational goals were assessed (1.b) at initial assessment for 34.8% of CHR-P clients, and within 6 months for another 44.9% of clients. According to the records, vocational goals do not appear to have been assessed in 10% of cases. There were no significant differences across boroughs [$\chi2$ (15, N = 69) = 20.849 p = .142]. With regards to assessment of support needs (1.c), these were assessed at initial assessment for 36.2% of clients, and within 6 months for another 34.8% of clients. According to the records, support needs do not appear to have been assessed for 18.8% of clients. There were no significant differences across boroughs ($\chi2$ [15, N = 69) = 13.449 p = .568]. According to the records, vocational history (1.d) was recorded for 50% of included clients. There were no significant differences across boroughs [$\chi2$ (3, N = 70) = 7.043 p = .071]. For standard 1, having at least 3/4 sub-standards met,

TABLE 2 | Socio-demographic characteristics of the sample.

	Total	SouthwarkN = 17	LambethN = 27	CroydonN = 12	LewishamN = 14	Statistics
Age	22.93SD 5.55	20.41SD 3.20	23.37SD 5.86	23.75SD 5.64	24.43SD 6.65	F = 1.70p = 0.17
Gender (F/M)	30/40	9/8	13/14	5/7	3/11	$\chi2$ (3, N = 70) = 3.64p = 0.30
Ethnicity						
White	31 (44.3%)	7	11	5	8	$\chi2$ (9, N = 70) = 15.93
Black	20 (28%)	3	11	2	4	p = 0.068
Asian	7 (10%)	0	3	2	2	
Other	12 (17.1%)	7	2	3	0	

TABLE 3 | Employment status baseline—follow-up.

Employment status baseline	Employment status follow-up	
		Change status = 27
Full-time	Unemployed	2
Full-time	Part-time	1
Part-time	Sick leave	1
Part-time	Internship/volunteer	1
Student	Unemployed	4
Sick leave	Unemployed	1
Unemployed	Full-time	1
Unemployed	Part-time	1
Unemployed	Internship/volunteer	2
Sick leave	Full-time	1
Sick leave	Part-time	2
Student	Full-time	5
Student	Part-time	1
Student	Internship/volunteer	3
Unknown	Part-time	1
		Same status = 40
Full-time		10
Part-time		3
Student		11
Unemployed		16
		Maternity = 2
Part-time	Maternity	1
Unemployed	Maternity	1
		Missing = 1

TABLE 4 | Education status baseline—follow-up.

Education status baseline	Education status follow-up	
		Progressed = 17
None	GCSE	5
GCSE	A levels	6
A levels	Started undergraduate degree	2
Started undergraduate degree	Completed undergraduate degree	4
		Same level = 45
None		5
GCSE		12
A levels		12
Started undergraduate degree		10
Completed undergraduate degree		5
Completed postgraduate degree		1
		Missing = 8

GCSE, General Certificate of Secondary Education.

was considered as overall "met". For 56/70 clients (80%) standard 1 was met, therefore standard 1 was considered overall "not met" at the service level.

Standard 2: Vocational Activities Feature in Care Plan

The care plan was not retrievable through the electronic recording system for 42.9% of the included CHR-P clients (= 30). Out of all retrievable care plans (= 40), 75% had vocational activities recorded. There were no significant differences across boroughs [$\chi 2$ (6, N = 70) = 9.564 p = .144]. Standard 2 was met for 42.9% of clients (= 30), therefore standard 2 was overall "not met" at the service level.

TABLE 5 | Number of standards met per client.

Standards met	Number of clients	%
0	**3**	**4,3**
1	**6**	**8,5**
2	**2**	**2,8**
4	**3**	**4,2**
5	**6**	**8,6**
6	**17**	**24,2**
7	**16**	**22,8**
8	**11**	**16**
9	**6**	**8,6**
	70	**100**

Standard 3: Clients Have Access to a Vocational Support Program

Retrievable data suggests that only 20% (= 14) of included CHR-P individuals did not receive a specific intervention aimed at supporting employment or educational needs. Of the remaining (= 56), 62.9% of clients received support within the first 3 months, 22.2% within the first 6 months, and 17.3 within 12 months or shortly after. There were no significant differences across boroughs [$\chi 2$ (12, N = 68) = 10.331 p = .587]. Standard 3 was considered as "met" if clients received support within the first 12 months. 51/70 clients (72%) received support within the first 12 months, therefore standard 3 was considered "not met" at the service level.

Standard 4: Early Psychosis Services Liaise With Educational and Employment Providers

In 36% (= 25) of cases OASIS services liaised with vocational providers while in 37% (= 26) they did not. The remaining percentages are explained by clients not being employed or in education (21.4%), the vocational provider already being aware of clients' difficulties (2.9%) or clients choosing to liaise with their employer/educational provider themselves (2.9%). There were no significant differences across boroughs [$\chi 2$ (12, N = 69) = 16.800 p = .157]. Standard 4 was considered as met if there was evidence that i) the service liaised with employer/education provider, ii) the employer/school/university was already aware," or iii) the "client liaised with employer/school/university". Standard 4 was met for 29/70 clients (42%), therefore this standard was overall "not met" at the service level.

Standard 5: Early Psychosis Services Liaise With Local Stakeholders

Stakeholders involved to support clients with their vocational needs varied greatly. They included parents or relatives, employment or support programs, educational institutions, and job centers. Borough-specific external support services were involved in 27.1% of cases, job centers were involved in 2.9% of

cases, recovery colleges in 2.9% of cases, multiple stakeholders—including parents and relatives—in 11.4% of cases. For 41.4% (= 29) of clients there was no involvement of local or external stakeholders. The remaining was either referred to other clinicians or, in one case, to a solicitor. There were no significant differences across boroughs [$\chi 2$ (18, N = 70) = 18.982 p = .393]. Standard 5 was met for 41/70 clients (41.4%); therefore, it was considered as "not met" at the service level.

Standard 6: Support Is Focused Around Competitive Employment or Mainstream Education

Standard 6 is not specifically drawn from early psychosis guidelines although the NICE guidelines (34) on psychosis and schizophrenia in children and young people mention educational support aimed at mainstream education. This standard is a key principle of IPS (32) which recommends supporting people into mainstream employment and education as opposed to special programs or voluntary work. Out of all clients who did receive vocational support (56/70; 80%), this was always aimed at mainstream education and competitive employment. Standard 6 was met for all clients who received vocational support (100%), therefore it was considered as "met" at the service level.

Standard 7: Support Is Provided Based on People's Interest

Out of all clients who did receive vocational support (56/70; 80%), this was always in line with their individual interests. Standard 7 was met for all clients who received vocational support (100%), therefore it was considered "met" at the service level.

Standard 8: Support Is Time Unlimited

Out of the clients who did receive vocational support (80%), in 62% of cases vocational support was terminated due to discharge, in 15% of cases vocational support was still ongoing at the time of data collection, and in 22.6% of cases vocational support ended with the termination of psychology sessions. There were no significant differences across borough [$\chi 2$ (9, N = 69) = 5.051 p = .830]. Standard 8 was considered as met if there was evidence that i) support was ongoing, or ii) support ended when the client was discharged from the service. Standard 8 was met for 42/70 clients (60%), therefore it was considered as "not met" at service level.

Standard 9: Benefits Counseling Is Provided

For 43% of included clients (= 30) this standard did not apply as clients were either financially supported by their parents, in full-time employment or not legally allowed to work and access benefits in the UK. Of the remaining, 50% (= 20) received benefits counseling and/or support in accessing financial means to support their return to education. There were no significant differences across borough [$\chi 2$ (9, N = 69) = 2.782 p = .972]. Standard 9 was considered as met if there was evidence that i) benefit counseling was provided or that ii) it was not applicable. Standard 9 was therefore met for 51/70 (72.8%) of clients, therefore it was considered as "not met" at the service level.

DISCUSSION

We sought to evaluate the provision of vocational interventions offered by OASIS, one of the oldest and largest EDP services in Europe and worldwide. We defined a set of nine standards based on the NICE guidelines and IPS principles and assessed whether current clinical practice in OASIS met these standards. Results showed that 80% of clients (56/70) met at least five out of nine standards (**Table 3**).

The results suggest that overall NICE standards of practice and the IPS principles were only partially met. In particular, standards 6 and 7 were met: results confirmed that the focus of the support provided is on helping clients to re-engage or remain in competitive employment or mainstream education and that this support is based on clients' interests rather than providers' judgment (32). This is particularly important as these standards were both based on IPS principles rather than on the NICE guidelines, suggesting that the OASIS team might already score highly on some of the IPS fidelity scale items (32).

Standards 1, 2, 3, 4, 5, 8, 9 were only partially met. OASIS appears to be doing particularly well with regards to assessing clients' current vocational engagement (standard 1.a), vocational goals (standard 1.b), and support needs (standard 1.c). On the contrary, vocational history (standard 1.d) was formally assessed in only 50% of cases. This could be at least in part explained by the fact that 23.3% of clients were in mainstream education and 28% were working part or full-time, therefore assessing vocational history might not have appeared relevant at the time.

The assessment of standard 2, "vocational activities feature in care plan", revealed that, among the retrievable care plans, vocational activities were recorded for the majority of clients (75%). Unfortunately, an electronic care plan was not retriable for 42% of cases, therefore it was difficult to assess adherence to this standard. It is possible that the care plans could have been saved in a paper format rather than electronically. In some cases, the care plan was identifiable within the clinical notes, it was however not included as part of this analysis as a formal care plan developed in collaboration with the client was not found.

Assessment of standard 3, revealed that clients had access to vocational support in 80% of cases. This is relatively high considering that OASIS does not yet have a dedicated vocational specialist. It is also encouraging that for the majority of clients (85%), when vocational support was offered, it was offered early on, within 6 months. On the other hand, the relatively high percentage of people who had access to vocational support could also be the result of the use of a broad definition which might not apply to specific vocational support program.

Standard 5 assessed whether OASIS was liaising with local or external stakeholders when providing vocational support. While there was variety in the type of stakeholders involved, for 41.4% of clients these were not involved at all. The external stakeholders included borough-specific external agencies (e.g. https://www.princes-trust.org.uk) or teams (such as recovery colleges, or vocational services) aimed at supporting young people or people with mental health issues in gaining employment. This is a valuable resource which however might not be equally present across all catchment areas within or outside the UK. However, it

is important to remember that south London is one of the most deprived regions in the UK (38). Therefore, mental health services in south London are likely to experience increased difficulties in identifying suitable employment opportunities and people living in this area might experience greater difficulties in finding or keeping a job.

Standard 8, "support is time unlimited", was also based on one of the IPS principles. When a client is taken on by the OASIS service, support and management is provided for up to 2 years, after which the person is discharged to a general practitioner or referred to another service, if appropriate. For 15% of the clients, support was still ongoing at the time of the audit. For 62% of clients, vocational support was terminated due to discharge suggesting that support was provided for as long as possible within the current structure of the team. For another 22.6% support ended with the termination of psychology sessions. Currently, OASIS offers up to 24 psychology sessions, which can be increased if needed. This is more than what is currently suggested as part of the manualized CBT treatment for those at risk of a first episode of psychosis (39) and indicates that although support ended with the psychology sessions, this has been provided over the course of several weeks. While the role of psychology is primarily to address psychological distress, within the current structure, psychology sessions also provided extensive vocational support. Vocational support provided might have not been delivered in a standardized way and might have been limited to discussion within the psychology sessions. A dedicated IPS worker would ensure the presence of dedicated time to work on vocational issues and engage in a more flexible way with external stakeholders (e.g. schools, employers).

Standard 9, "benefit counseling is provided" is one of the IPS principles (32). 43.5% of clients were employed, in education, supported by their parents or not legally allowed to access benefits in the UK, therefore this standard did not apply. Of the remaining, only 50% received advice on accessing benefits.

NICE guidelines recommend providing support with education and employment needs and goals; however, there is no specific recommendation as to which framework or theoretical model to use and how to integrate this within the current structure of the early detection and intervention teams (34, 35). In this context, IPS provides a clear framework in which different health care professionals can work conjunctly to help young individuals to complete their educational course successfully, to move toward employment and improve their mental wellbeing (23, 24, 27, 40, 41).

In the short-term, improving educational and employment support within the existing structure of the teams might require some adjustments. For example, the implementation of more standardized vocational assessments and recording of goals and needs. The fact that this was not done for all included clients might reflect the fact that in mental health services the main focus is on clinical symptoms, therefore, the support offered often takes the form of psychological intervention around clinical symptoms rather than vocational support. Nevertheless, this is an area that should be assessed routinely. In order to address this, we propose two changes. Firstly, the care coordinator could dedicate a specific session early in the care pathway to complete a more comprehensive and structured vocational assessment including vocational history. Secondly, automated prompts on the electronic care plan could be implemented to remind the care coordinator to include vocational goals and the support offered to work toward them.

In the long-term, EDP services like OASIS are likely to benefit from having an IPS worker whose task is solely to provide support with education and employment needs. This is particularly important given the current high rates of unemployment in this (i.e. 37% at the last available follow-up) and similar samples (4, 6, 8). The expectation is that having a dedicated IPS trained worker based in the team will improve performance on all standards and generally address the low social and occupational functioning (12). As the clients in EDP teams are relatively young (i.e. 14–35), they are likely to benefit from IPS with focus on both employment (26–28) and education (27, 29).

The results also showed that there are no significant differences in the nine standards across boroughs despite the fact that two of the four OASIS teams (i.e. Croydon and Lewisham) were set up only recently (i.e. 2014–2015). While this is reassuring samples were relatively small, therefore further analyses with larger samples are needed to confirm that there are no significant differences in the delivery of education and employment support across boroughs.

This study has a number of strengths. Firstly, OASIS is a well-established EDP service operating since 2001. The setting is therefore ideal to evaluate if NICE standards are met. Secondly, the case-load of the service made it possible to look at the different aspects of vocational interventions in a modest sample. This study has also a number of limitations. Firstly, results are limited to well-established and specialized team within SLaM NHS Foundation Trust. While this is one of the most deprived areas in the UK (38), we do not know to what extent these results can be generalizable to other areas in or outside the UK where employment, education, and training opportunities might differ. Thirdly, data was collected retrospectively, through the screening of electronic clinical records. This can be a limiting factor for at least two reasons. Data which is marked as missing, might have been present but not recorded electronically thus providing only a partial picture. Furthermore, data was initially recorded as part of routine clinical work, therefore, there was no formal quality check on how data was collected and entered. Despite this, we are confident the quality of the data is of satisfactory standard as periodic checks are carried out to ensure outcome measures are recorded consistently. Fourthly, data available did not allow to determine whether, to what degree and which element of vocational support influences health and vocational outcome. To address these limitations future studies should test feasibility, challenges, and benefits of implementing vocational interventions, such as IPS, in EDP teams in the UK. As prior studies indicated that difficulties during education or during employment contribute to increase distress (15, 42), future studies should also investigate the effect of implementing interventions that are specifically focused on improving coping strategies in this context (42, 43).

Much has been done to date to provide treatment as early as possible to young people who present with symptoms that suggest they might be at high risk of developing psychosis in the near future. However, this work suggests that there are

areas that have not been addressed sufficiently and one of these is vocational recovery. Therefore, the focus of the intervention provided by EDP teams should go beyond management of symptoms and be broadened to include interventions that selectively target vocational recovery. In this context, IPS offers an implementable framework which is expected to enhance the work of EDP teams and help young people with their vocational goals.

ETHICS STATEMENT

This study was carried out as part of a clinical audit in accordance with the recommendations of South London and Maudsley Psychosis Clinical Academic Group.

AUTHOR CONTRIBUTIONS

ST designed the evaluation, prepared the first draft of the manuscript, and assisted with data extraction and data analysis. LG assisted with the design of the evaluation, contributed to prepare the first draft of the manuscript, and performed the data extraction. SV performed the data extraction and data analysis. TS designed the evaluation and assisted with data extraction and data analysis. All co-authors contributed to the critical revision of the manuscript.

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