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Early psychosis and early intervention: Clinical, functional, and cognitive outcomes

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Early psychosis and early intervention: Clinical, functional, and cognitive outcomes

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Editorial: Early psychosis and early intervention: clinical, functional, and cognitive outcomes

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Editorial on the Research Topic
Early psychosis and early intervention: clinical, functional, and cognitive outcomes

Psychotic disorders are a group of severe mental disorders that affect 2%–3% of the population and constitute one of the leading causes of disability worldwide. Early intervention (EI) represents a major paradigm shift in psychiatric service and has been demonstrated to be effective in outcome improvement for first-episode psychosis (FEP) (1) and clinical high risk for psychosis [CHR-P, or termed at-risk mental state (ARMS)]. Nonetheless, substantial evidence has shown that a significant proportion of people with early psychosis still experience suboptimal clinical outcome, functional impairment, and cognitive dysfunction. This Research Topic, which comprises a series of articles specifically focusing on early psychosis, aims to explore and clarify the complex inter-relationships among symptomatology, psychosocial functioning, and cognitive deficits in the early course of psychotic disorders, so as to address potential research gaps and facilitate the development of more targeted interventions to further enhance treatment outcomes of this vulnerable population.

It is well-recognized that psychotic disorders are associated with cognitive impairment across multiple cognitive domains (2). Importantly, cognitive impairment is a major determinant of functional outcome. Several articles of this Research Topic specifically investigated cognitive functioning in FEP and CHR-P, and its relationship with clinical features and psychosocial functioning. Kim et al. evaluated the association between cognitive functioning and suicidal ideation in a cohort of recent-onset schizophrenia-spectrum disorders (SSDs). The study categorized patients with SSD into those with versus without suicidal ideation and compared these two groups with traditional risk factors, such

as hopelessness, depressive symptoms, resilience levels, and perceived stress, and a comprehensive battery of cognitive functions. The results showed that patients with SSD who exhibited better cognitive abilities (especially executive functions, verbal and visual learning, and social cognition) were more prone to experiencing suicidal ideation, thereby highlighting the need to take into consideration cognitive functions in suicide risk evaluation, particularly those patients who have traditional risk factors and good cognitive functions. Alternatively, Mackinley et al. adopted a novel automated speech analysis coupled with Bayes network analysis in an antipsychotic-naïve FEP sample to explore the potential clinical utility of speech and communication deficits as targets for EI and functional outcome enhancement. Their results demonstrated that baseline speech production, but not other linguistic variables, significantly predicted NEET status (i.e., non-engaged in employment, education, or training) after 6–12 months of treatment commencement. This speech production measure was also indirectly related to global functional level. The findings suggest that impoverished speech, even at the subclinical level, may constitute important prognostic value for functional outcomes in early psychosis. Kam et al. aimed to disentangle cognitive heterogeneity in a group of adult patients with FEP by using data-driven cluster-analytic approach and identified three distinct cognitive clusters, namely, globally impaired (34.9%), intermediately impaired (38.8%), and relatively intact (26.3%) cognition subgroups, compared to demographically matched healthy controls' performance. Importantly, these cognitive subgroups were differentially associated with demographic and illness-related variables. In particular, the globally impaired subgroup was older and displayed greater symptom severity, poorer insight, and worse subjective quality of life than the other two cognitive subgroups. Given the cross-sectional nature, future longitudinal research delineating patients into different cognitive trajectories and their relationships with clinical and functional outcomes would be particularly informative in treatment outcome prediction and development of tailor-made interventions to alleviate cognitive impairment in those at high risk for poorer cognitive functions in the early stage of illness. There is a paucity of research directly contrasting cognitive functions across established psychotic disorder and clinical and genetic high-risk (GHR) samples. Dong et al. presented a cross-sectional study comparing cognitive functions between first-episode schizophrenia (FES), CHR-P, and individuals at GHR for schizophrenia, relative to healthy controls. They found that FES, CHR-P, and GHR samples had significantly worse cognitive performance than controls in most of the cognitive domains. Notably, CHR-P and GHR showed no significant between-group difference across all cognitive domains, but demonstrated intermediate level of cognitive function in processing speed and attention/vigilance domains, relative to FES and controls, indicating that these two specific cognitive domains may represent cognitive markers indicating the risk for psychosis development. Of note, several issues in relation to cognitive impairment in FEP and CHR-P merit further discussion. First, a recent meta-analysis has indicated greater variability in cognitive functioning in individuals with FEP than in healthy participants, and suggested that subgroups of patients experience more severe disease-related cognitive dysfunction (3), which is in line with Kam et al. Second, although no differences in longitudinal cognitive changes between FEP and control groups were found, which suggests no evidence of continued cognitive decline (i.e., more akin to neurodevelopmental hypothesis rather than neuro-progressive hypothesis), this meta-analysis also revealed association between longer follow-up periods and greater cognitive decline in FEP samples. Given that the vast majority of the published data were based on studies with short follow-up durations, further research is required to clarify whether there is a subgroup of patients having a progressively deteriorating trend in cognitive functions along the course of illness, and if so, what are the potential risk factors or biomarkers for predicting declining cognitive trajectory, thereby facilitating early tailor-made cognitive remediation. Third, caution should be exercised in interpreting the findings of cross-sectional research on cognitive functions in CHR-P, which comprises a small proportion of at-risk individuals who will convert to full-blown psychosis as well as a majority of individuals who are non-converters. Hence, the profile and magnitude of cognitive impairment in CHR-P is indicative of both psychosis-specific vulnerability (based on converters) and transdiagnostic deficits (based on non-converters, comprising individuals with non-psychotic psychopathologies or even common mental disorders, and remitters from CHR-P) (4).

Identification of robust biomarkers in the early course of psychotic disorders will significantly enhance outcome prediction and disorder-subtype characterization. Ding et al. have examined a prepulse inhibition (PPI), a sensorimotor gating deficit, in the FEP sample by using a modified PPI paradigm, incorporating subjective attention component, and demonstrated enhanced discriminant validity for FEP relative to controls. The results also showed that perceived spatial separation PPI (termed PSS-PPI) was associated with symptoms and cognitive performance in patients with FEP, suggesting that PSS-PPI may be a useful biomarker for evaluating psychopathological symptoms in early psychosis. Arai et al. investigated exploratory eye movements (EEMs) and their relationships with white matter integrity, as measured by fractional anisotropy (FA) of superior thalamic radiation (STR; which connects frontal eye fields and thalamus) by diffusion tensor imaging (DTI) in individuals with attenuated psychosis syndrome (APS, a subgroup of CHR-P). Individuals with APS exhibited aberration EEMs relative to healthy controls, and EEM parameters including mean and total eye scanning length were related to STR alterations, thereby underscoring the idea that impairment of STR may contribute to the neurobiological mechanisms underlying manifestations of CHR-P and its related oculomotor disturbances. Further research with a larger sample size and using a prospective design will clarify the potential value of EEM in predicting psychosis and functional outcome. Aeberli et al. examined deficits in mismatch negativity (MMN) across various at-risk subgroups encompassing individuals with CHR-P, individuals with basic symptoms (BS) only, and individuals fulfilling both CHR-P and BS criteria. This study revealed that all three risk groups showed significantly lower MMN activity at frontal source compared with healthy controls. Further analysis suggested that this specific deficit was significantly associated with psychosis

transition at the 3-year follow-up (albeit based on a small sample of 15 participants who converted to psychosis). In sum, the results indicate that MMN deficit occurs already early in the course of the disease, as indicated by its presence in the BS risk group, and frontal MMN changes may be particularly relevant for predicting psychosis transition in at-risk groups. Although these studies indicate the potential utility of neurophysiological deficits as disease biomarkers for psychotic disorders, including psychosis prediction, it should be noted that few candidate predictors reached a level of evidence sufficient to inform clinical practice regarding prediction of CHR-P to full-blown psychotic disorders (5). Different neurophysiological measures may also be differentially associated with the nature (e.g., clinical versus genetic risk marker) and the degree of psychosis risk (6), and a combination of neurophysiological measures would likely yield an enhanced prediction model. Moreover, progression from at-risk status to psychosis is a dynamic developmental process, involving complex longitudinal interplays between multiple variables and risk factors. In this regard, earlier static models with candidate predictors derived on the basis of a single time point (baseline assessment) will unlikely generate a clinically applicable and accurate prediction algorithm. Application of dynamical prediction modeling, taking into consideration longitudinal, multiple time-point measurements, would improve psychosis and outcome prediction (7).

Substantial evidence has shown that psychotic disorders are associated with markedly elevated risk of premature mortality, physical comorbidity, and shortened life expectancy, compared with the general population (8, 9) Chua et al. measured weight trajectory patterns among patients who received FEP service over the first 2 years of treatment and demonstrated that a majority of patients belonged to the high-risk groups for clinically significant weight gain (38.6% as super high risk; 34% as high risk mitigated). The results highlight the importance of adopting early, preemptive strategies in the initial phase of treatment commencement for FEP to promote physical health and ensure adherence to guideline-concordant monitoring of cardiometabolic parameters on a regular basis to facilitate early detection and prompt interventions for those at high risk for obesity and metabolic syndrome. Maechling et al. conducted a systematic review on mobile health strategies for the management of FEP. The review is timely as mobile or digital health intervention has increasingly been applied in mental disorders, including early psychosis (10), and has the potential to further enhance the quality of and engagement with EI service for young people with FEP. Overall, the review affirmed the preliminary efficacy of various types of mobile health applications, including symptom monitoring, enhanced service engagement, and promoting the self-management of the illness and the recovery phase of FEP. However, major limitations are noted including the lack of randomized controlled trials and a small sample size. Moreover, ethical issues regarding data protection and patient privacy, as well as lack of consensus or regulations regarding mobile health applications, warranted further exploration and discussion.

Author contributions

WCC: Conceptualization, Project administration, Writing – original draft, Writing – review & editing. TN: Conceptualization, Project administration, Writing – review & editing. SC: Conceptualization, Project administration, Writing – review & editing. CT: Conceptualization, Project administration, Writing – review & editing. YCC: Conceptualization, Project administration, Writing – review & editing.

Conflict of interest

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

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More than words: Speech production in first-episode psychosis predicts later social and vocational functioning

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Background: Several disturbances in speech are present in psychosis; however, the relationship between these disturbances during the first-episode of psychosis (FEP) and later vocational functioning is unclear. Demonstrating this relationship is critical if we expect speech and communication deficits to emerge as targets for early intervention.

Method: We analyzed three 1-min speech samples using automated speech analysis and Bayes networks in an antipsychotic-naive sample of 39 FEP patients and followed them longitudinally to determine their vocational status (engaged or not engaged in employment education or training—EET vs. NEET) after 6–12months of treatment. Five baseline linguistic variables with prior evidence of clinical relevance (total and acausal connectives use, pronoun use, analytic thinking, and total words uttered in a limited period) were included in a Bayes network along with follow-up NEET status and Social and Occupational Functioning Assessment Scale (SOFAS) scores to determine dependencies among these variables. We also included clinical (Positive and Negative Syndrome Scale 8-item version (PANSS-8)), social (parental socioeconomic status), and cognitive features (processing speed) at the time of presentation as covariates.

Results: The Bayes network revealed that only total words spoken at the baseline assessment were directly associated with later NEET status and had an indirect association with SOFAS, with a second set of dependencies emerging among the remaining linguistic variables. The primary (speech-only) model outperformed models including parental socioeconomic status, processing speed or both as latent variables.

Conclusion: Impoverished speech, even at subclinical levels, may hold prognostic value for functional outcomes and warrant consideration when providing measurement based care for first-episode psychosis.

KEYWORDS

language, thought disorder, First Episode Psychosis, schizophrenia, NEET (neither education employment or training)

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1. Introduction

Schizophrenia is an illness of disordered thought, with symptoms often reflected in disturbances in language and communication (1). An impairment of verbal communication is one of several diagnostic features of schizophrenia, with a strong posited genetic component (2), but not all patients with schizophrenia exhibit clinically identifiable disordered speech. Speech disturbances, referred to as formal thought disorders (FTD), can be classified into positive or negative FTD. Positive FTD includes phenomena such as derailment, tangentiality, or in more severe cases, neologisms or even complete incoherence (schizophasia). Alternatively, negative FTD captures the characteristic poverty of speech that many patients experience (1). While several scales have been developed with the goal of identifying these elements of speech, such as the scale for Thought, Language, and Communication (TLC) (3) or the Thought Language Index (TLI) (4), many of the speech disturbances in psychosis are too subtle to be captured by clinicians during a cross-sectional clinical interaction (5).

Recent work has focused on identifying subtler forms of speech variation in naturalistic speech among schizophrenia samples, a goal that has been aided by the proliferation of automated linguistic analysis tools (6, 7). The utilization of these automated speech analysis software programs allows complex analysis of speech without the burdens (and expense) of manual scoring. Automated linguistic analyses have allowed researchers to identify disturbances in multiple levels of speech in schizophrenia, from phonological, morphological, syntactic, and pragmatic levels (8), and have been utilized in predicting psychosis onset in at risk populations (9).

While it is intuitive that social and vocational outcomes may relate to one's verbal abilities, the body of research demonstrating this link in schizophrenia have several limitations that preclude the use of linguistic features in functional prognostication. First, much of this work has been based on language impairments in experimental, rather than naturalistic, paradigms where the semantic space is defined by the researcher (10) [e.g., using verbal fluency tests (11, 12)]. Secondly, even in studies assessing unconstrained speech, objective aspects of conversations are not considered; instead, the clinically judged construct of thought disorder is employed. While studies have observed associations between functional outcomes and negative FTD (specifically poverty of speech and content) (13, 14), other studies have reported that positive, but not negative, elements of FTD are related to functional outcome (15). These inconsistencies in the extant literature may be related to the difficulties surrounding the clinical assessment of formal thought disorder. Thirdly, most studies to date make cross-sectional correlations between functioning and verbal assessments; there is a notable lack of longitudinal data to clarify whether the verbal deficits temporally precede (and thus lie on the causal pathway of) poor functioning seen in schizophrenia. Furthermore, functional outcomes in many prior studies have been conflated with severity of psychopathology when using tools such as Global Assessment of Functioning (15), and a lack of satisfactory definition of social dysfunction (16, 17). In addition, exposure to antipsychotics over a long period of time alters the nature of speech and our ability to assess FTD (18), thus necessitating the study of minimally treated or drug-naive subjects. Demonstrating this relationship will be of critical value in improving clinical decisions during early intervention based on long-term prognostic outlook, which at present is challenging to assess. To address this crucial gap, we sought to identify linguistic features of speech in an untreated FEP sample using a computational linguistic approach called parts-of-speech tagging implemented through Cohmetrix (19), and the Linguistic Inquiry Word Count (LIWC) (20).

While the feature space for selecting linguistic variables in relation to functional outcomes is relatively large, we focus exclusively on the variables that we have previously studied in an overlapping sample and demonstrated to have clinical relevance. In a prior cross-sectional analysis on this sample of untreated subjects, Mackinley et al. (21) used Coh-Metrix automated speech analysis software (19) to compare FEP patients and healthy controls on a number of variables at the word, sentence, and higher-order level. In this study, patients showed reduced speech production (number of words) and higher pronoun use compared to their healthy control counterparts but did not differ in a variety of other higher-order linguistic metrics (narrativity, formality, referential cohesion, or deep cohesion). Five types of connectives were analyzed in this earlier study including: causal connectives (words used to connect a cause to an effect), logical connectives (words linking two logically connected elements), temporal connectives (words to put ideas in order of time), contrastive connectives (words to compare and contrast ideas), and additive connectives (words used to add information, e.g., "additionally," "moreover"). The use was analyzed using data driven principal factor analysis, two factors, and one with a positive loading on "all connective types" and the second "acausal temporal connective factor" reflecting reduced use of causal and contrastive connectives, but higher use of temporal linkages and additive connections appeared. While patients and healthy controls employed these connective factors in a comparable manner during the picture description tasks, patients with higher connectives use had higher scores on clinically rated conceptual disorganization (21). This suggests that aberrant linguistic connective use may contribute to the clinician's detection of disorganized thought.

In an overlapping cross-sectional sample, we (22) analyzed the picture description speech samples using the Linguistic Inquiry Word Count (LIWC) software package (20) to determine the relative proportion of content words and function words. From this parts-of-speech tagging, we determined Pennenbaker's Analytic Thinking scores (higher scores suggesting a well-formed hierarchical thinking style suitable for academic expressions, and lower scores suggesting a narrative style which is more intuitive and episodic in nature) (23). A higher analytic score (more categorical thinking style) is linked with academic success due to this linguistic style's use in academic and professional settings (23). We observed that compared to HC, patients showed reduced analytic thinking in their speech. Further, among FEPs, reduced analytic thinking related to higher clinical metrics of disorganization (22). This suggests that less structured, less content-based speech may contribute to the clinician's detection of disorganized thought. Thus, it is possible that among FEP patients, analytic thinking styles are associated with later academic and occupational success; however, little evidence to assess this question has been gathered.

With longitudinal functional outcome data from this cohort, we aim to ascertain the role of connectives, analytic thinking index, total number of words, and frequency of pronouns on vocational status and social and occupational functioning ascertained after

6-to-12 months of treatment in an early intervention setting. The selected linguistic variables tap on distinct aspects of message generation and grammatical encoding in Bock and Levelt's language processing model (24). At the generation level, total number of words (verbosity) relates to the production plan (25); at the functional level, lexical selection influences the frequency of pronouns, while positional processing involving the assembly of constituent words influences the connective use and analytic thinking index. Given the prior observations that "negative FTD" relates more strongly to functional outcomes than "positive FTD," we expected a reduction in total number of words used during a picture description will be predictive of later functional outcomes. To this end, we used a Bayes network (a directed acyclic graph) to (1) identify dependencies among the baseline linguistic variables and vocational status or social functioning after six to 12 months of treatment in an early intervention program for psychoses and (2) parameterize these dependencies in terms of conditional probability distributions. In the network, the dependencies are represented as connections (edges) between nodes (variables) identified through a prototypical constraint-based algorithm (26, 27). Parameters (conditional probability distributions) are found *via* maximum likelihood estimation (28). We assessed the contribution of other explanatory variables such as parental socioeconomic status and speed of cognitive processing using probabilistic models of functional outcome. We quantified social functioning using the widely used Social and Occupational Functioning Assessment Scale (SOFAS) as a continuous measure, and a macroeconomic indicator of productivity in young adults reflecting participation in active Employment Education or Training (EET vs. not-EET or NEET) status as a categorical measure, as employed in our previous brain imaging study (29).

2. Method

2.1. Participants

Data were collected from 39 treatment naïve FEP patients recruited from the Prevention and Early Intervention Program for Psychoses in London, Ontario, Canada, as reported in a previously published manuscript (21). All participants were in the acute phase of the illness, with fewer than 2 weeks of antipsychotic exposure lifetime. The mean lifetime defined daily dose was $M = 2.31$, SD = 3.68, with $n = 14$ being completely drug-naive (36%). Over the subsequent year, patients were longitudinally followed with assessments of social and occupational functioning completed when clinically stable between 6 and 12 months following the initial assessment. All participants used in the present analysis were native English speakers.

2.2. Clinical and linguistic assessment procedure

The local Research Ethics Board (Western University) approved all study procedures, and all patients provided informed consent before participating. All patients were enrolled in a first-episode psychosis program over the next 12 months, and we ascertained their social and vocational status between 6 to 12 months after entering treatment. Due to the need for multiple information sources, not all patient follow-ups were assessed at precisely the same time point after the onset of illness.

Licensed psychiatrists conducted all clinical interviews and rating scales to determine illness severity, and rule out exclusionary diagnoses (substance abuse, neurologic disorders). Graduate-level research assistants completed cognitive assessments and the Thought Language Index (TLI) interview and rating. During the TLI procedure, three 1-min speech samples were induced in response to photographs from the Thematic Apperception Task (30). Scorers of TLI interview were blinded to participant status consistent with the procedure described by Sommer et al. (31).

The Positive and Negative Syndrome Scale-8 Item (PANSS-8), which is highly correlated with the full 30-items PANSS (32), was utilized to measure the severity of clinical symptoms. Functional assessments were based on multiple sources of information (patient interviews, information from the psychiatrist providing care, case managers, and when required information from family members). Measures of social and occupational functioning were assessed using the Social and Occupational Functioning Assessment Scale (SOFAS) (33) at baseline and follow-up. The SOFAS is a single-item measure of functioning scored between 1 (indicating a persistent inability to maintain minimum even basic function) and 100 (superior functioning in a wide range of activities). In our study, SOFAS scores considered current functioning (rather than the highest level of functioning over the past year). Vocational assessments were conducted using a binary NEET status (not in employment education or training). Patients were deemed to be NEET (vocationally inactive) if they were unemployed and not in any form of schooling/education for more than half of the time since the onset of treatment for psychosis. Individuals classified as EET were engaged in work or school for more than half of the duration of treatment (vocationally active). This definition considers a longer period than the 1-week period used by the Organization for Economic Co-Operation and Development (OECD) (34), but is consistent with its use in early intervention services for psychosis (35, 36). When inconsistencies between patient and care provider accounts were noted, a consensus was reached among the members of the research team.

2.3. Instruments

2.3.1. Linguistic inquiry word count

Linguistic Inquiry Word Count Software (LIWC 2015 Edition) uses a computational-lexical approach, which provides summaries of psycholinguistic dimensions (i.e., analytic thinking score) and pre-defined content word themes (e.g., negative emotion words) derived from psychometric rates. In the two-step process, LIWC analyzes the current target word contained in texts comparing and matching every single word against master dictionaries using its own language corpora composed of "almost 6,400 words, word steams, and selected emoticons from a sample of ~181,000 text files." Secondly, a standard LIWC computes the percentage of co-occurrences. LIWC has recently gained attention in several research areas establishing the relationship between linguistic-thinking styles and both personality traits, and mental health conditions.

2.3.2. Coh-Metrix 3.0

Coh-Metrix (37) is a web-based automated speech analysis software that computes basic and higher-level linguistic variables from written and spoken speech samples. The software automatically computes several lower order (e.g., word counts, frequency of pronoun use, and use of connectives) and higher-order (e.g., narrativity, cohesion, and text formality) linguistic variables (19). While initially implemented for the analysis of larger text segments, the software has been applied in the analysis of brief language samples in clinical populations previously (38). Though there are no requirements for minimum number of words for applying Coh-Metrix to study texts, analyses of readability and cohesion have been generally reported for written materials with 100 words or above (39, 40). The incidence scores are based on frequency of occurrence of different parts of speech (e.g., pronouns, connectives etc.) in the units of numbers per 1,000 words. We based our project on the work in Willits et al. (41) with the focus of Coh-Metrix output on the frequency of connectives use as described in MacKinley et al. (21).

2.4. Statistical (Bayesian) analyses

For descriptive analyses, we used the JASP software (JASP version 0.16.3, 2022) to report Bayes factors against the null model (BF_{10}). Briefly, if $BF_{10} < 2$, we accepted the null hypothesis, whereas if $BF > 2$ provides support for the alternative hypothesis. To answer the research question, we used a prototypical constraint-based algorithm (PC) (26, 27) within the context of a Bayes network (a probabilistic graphical model) to identify dependencies in a set of variables. This set comprised NEET (6–12 months), SOFAS score (6–12 months), total words spoken, analytic thinking score, all connectives score, acausal connectives score, and pronoun use (all at baseline). We also included PANSS-8 total score as a nuisance variable to control disease severity at the time of linguistic data collection. The algorithm yielded a Bayes network upon which we applied an expectation maximization algorithm (42) to perform maximum likelihood estimation of parameters (parameters learning). Finally, we made a series of inferences (conditional probability queries in terms of causal and evidential reasoning) aiming to explain the relationships between our variables of interests (total words spoken, analytic thinking, connectives use, and pronoun use).

3. Results

3.1. Descriptive statistics

When baseline characteristics of patients who went on to be vocationally active (EET) were compared to patients that went on to be vocationally inactive (NEET), no evidence for group differences were seen for medication exposure, duration of untreated psychosis, age, sex, parental Socioeconomic status (SES), or the use of cannabis, alcohol, or tobacco, or symptom severity at baseline. As expected, given the overlapping nature of the SOFAS scale and vocational activity, very strong support was found that NEET patients differed from EET patients in measures of follow-up SOFAS score ($BF_{10} = 55.50$; EET mean = 65.00, SD = 10.54; NEET mean = 46.47, SD = 18.28). EET patients produced an average of 18% more speech in the three 1-min TLI interview trials than their NEET counterparts, providing support that patients who speak more words at baseline would go on to be vocationally active ($BF_{10} = 2.42$; EET mean = 123.22, SD = 38.50; NEET mean = 104.40, SD = 24.19). Finally, we report moderate evidence that those that perform better on the Digit Symbol Substitution Test (DSST), a measure of processing speed, would go on to be vocationally active ($BF_{10} = 3.32$; EET mean = 57.87, SD = 14.72; NEET mean = 46.92, SD = 12.14). We report no differences on other linguistic variables of interest (Table 1).

3.2. Bayesian network analyses

While a causal network (indicated by the directionality of the arrows in the graph, Figure 1) was observed among the linguistic variables of interest (the two connectives factors, pronoun use, and analytic thinking style), the graphical probabilistic model revealed that only the total number of words showed a direct association with NEET and an indirect association with SOFAS (Figure 1). The expectation maximization algorithm converged (Log likelihood = −712.39). We further investigated whether this model better explained the data than a null model. To this end, we applied the expectation maximization algorithm to a model without the direct and indirect causal relationships identified above and used the Bayesian information criterion (BIC) number two adjudicate between models. We confirmed that the converged null model (Log likelihood = −723.28, BIC = 1,512) underperformed the model estimated *via* the PC algorithm (BIC = 1,504).

However, the number of words one employs during a descriptive task may vary based on factors such as social environment during early development (specifically parental SES) (43) and cognitive capacity indexed by processing speed (44) both of which may also affect the later vocational outcomes. To address this, we undertook a specific model comparison approach with self-reported parental socioeconomic status and digit symbol substitution score (a proxy for processing speed) added into our model with four contingencies and compared using the BIC numbers. The first model (M1) comprised total words conditioned upon both the DSST and SES. In the second model (M2), total words were conditional on only DSST. In the third model, total words were conditional on SES. Finally, in model 4 (M4) neither DSST nor SES influence the total number of words. The model comparison procedure yielded M4 as the best model ($BIC_{M1} = 1777$, $BIC_{M2} = 1770$, $BIC_{M3} = 1774$, $BIC_{M4} = 1767$). This indicates that despite the putative role of processing speed and SES in vocational outcomes among patients, the role of reduced speech production is best considered as an independent predictor.

Directionalities (i.e., causality) in the graph (Figure 1) indicate that both the total number of words and the SOFAS score explain the NEET score. Interestingly, once the NEET score is known the number of words and SOFAS scores are independent of each other. In consequence, the directionalities in the graph allow us to estimate the probability distribution of NEET and SOFAS given an observed total number of words (conjointly). For example, for a patient that produces 48 words on average, the probability of NEET is 79.8%. On the other extreme, if the patient produced 211 words, they would have a probability of EET (i.e., NEET = 0) with 99% chance. Finally, at the midpoint of the observed distribution of word count, a patient in the 50th percentile (median = 113) would have 64.8% chance of

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TABLE 1 Demographic and linguistic characteristics of sample.

Variable	All patients *n*=39	Patients not in education employment or training (NEET) *n*=18	Patients engaged in employment education or training (EET) *n*=21	BF_{10}	95% highest density interval
Demographic and clinical variables					
Sex (Male/Female)	32/7	16/2	16/5	1.00	−1.72, 0.77
Age [M (sd)]	22.53 (4.76)	23.58 (6.02)	21.58 (3.15)	0.60	−0.955, 0.25
NS-SEC [M (sd)]	3.76 (1.20)	4.28 (1.07)	3.25 (1.02)	1.11	−1.14, 0.12
DUP in months [M (sd)]	8.82 (11.86)	7.57 (8.21)	10.00 (14.67)	0.32	−0.58, 0.54
Defined daily doses [M (sd)]	2.31 (3.68)	2.39 (3.65)	2.27 (3.80)	0.36	−0.53, 0.59
Non-antipsychotic meds (Y/N)	9/30	3/15	6/15	1.16	−1.59, 0.77
Tobacco smoker (Yes/No)	11/25	7/11	5/16	1.00	−1.61, 0.80
CAST score [M (sd)]	13.5 (6.59)	15.13 (6.65)	11.87 (6.34)	0.35	−1.07, 0.25
AUDIT-C [M (sd)]	2.64 (3.12)	2.07 (2.22)	3.31 (3.90)	0.53	−0.34, 0.99
PANSS-8 total [M (sd)]	26.46 (7.21)	27.44 (6.65)	25.62 (7.71)	0.40	−0.79, 0.36
PANSS-8 positive [M (sd)]	13.08 (2.98)	13.44 (2.72)	12.74 (3.24)	0.39	−0.77, 0.38
PANSS-8 negative [M (sd)]	7.76 (4.46)	8.33(4.52)	7.21 (4.44)	0.40	−0.79,0.37
CGI-severity [M (sd)]	5.34 (1.09)	5.44 (0.86)	5.26 (1.28)	0.35	−0.71, 0.44
SOFAS [M (sd)]	38.31 (12.50)	34.40 (8.35)	41.10 (14.32)	1.27	−0.10, 1.16
SOFAS 6–12 month [M (sd)]	55.74 (17.46)	46.47 (18.28)	65.00 (10.54)	55.50	0.39, 1.81
DSST [M (sd)]	52.40 (14.42)	46.92 (12.14)	57.87 (14.72)	3.32	0.06, 1.34
Months to NEET assessment [M (sd)]	7.95 (2.89)	8.17 (3.38)	7.75 (2.41)	0.34	−0.69, 0.45
Linguistic variables of interest					
Total words spoken	115.08 (34.03)	104.40 (24.19)	123.22 (38.5)	2.42	0.01, 1.29
Analytic thinking score	55.27 (21.65)	57.94 (22.24)	53.25 (21.52)	0.35	−0.69, 0.45
All connectives	0.095 (1.16)	−0.08 (1.61)	0.22 (1.17)	0.33	−0.50, 0.64
Acausal connectives	0.128 (0.99)	0.08 (0.79)	0.17 (1.14)	0.38	−0.39, 0.76
Pronoun use/thousand words	107.17 (24.11)	105.86 (19.93)	108.17 (27.83)	0.33	−0.50, 0.64

M, Mean; SD, standard deviation; NS-SEC, National Statistics -socioeconomic classification; DUP, Duration of Untreated Psychosis; CAST, cannabis abuse screening test; AUDIT-C, Alcohol use disorders identification test; PANSS, Positive and Negative Syndrome Scale – 8 Item Scale; CGI-Severity, Clinical Global Impression – Severity; SOFAS, Social and Occupational Functioning Assessment Score; DSST, Digit Symbol Substitution Test; BF, Bayes Factor.

being in the NEET category. Similarly, with 48 words spoken we could estimate the follow-up SOFAS with a distribution of (m = 55, sd = 10.9). With a median number of words spoken (113 words), we would expect a similar score (m = 56, SD =11). However, improvements in follow-up SOFAS scores can be seen in individuals with high speech production (211 words spoken) could expect an elevated SOFAS score (m = 65, SD =10) a 10-point difference from their peers.

Finally, to test if a constrained word production exercise (semantic fluency task) carries the same predictive value for vocational success as word production during our conversational task with a referent (picture description), we undertook further analysis. In a subgroup of patients (n = 22), we gathered data from the Category Fluency test (animals), but noted that baseline category fluency (number of correct items) did not differ notably between EET and NEET patients (BF_{10} = 1.163; EET mean = 19.69, SD = 4.36; NEET mean = 16.33, SD = 4.27). This suggests that word generation during naturalistic speech has a specific prognostic value in predicting social and vocational outcomes in first-episode psychosis.

4. Discussion

This study sheds light on how the way we speak when experiencing acute psychosis may provide insight into our

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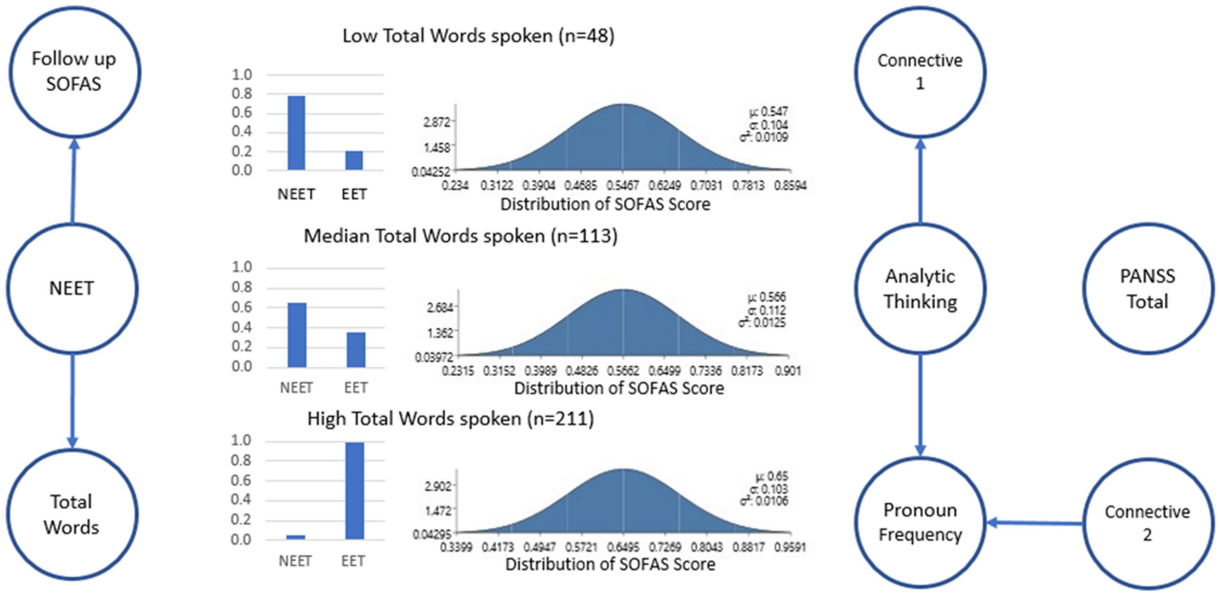

FIGURE 1
Bayes network that resulted from the application of the PC algorithm. Only the total number of words directly relates to NEET and indirectly relates to SOFAS. Furthermore, whereas the PANSS score was independent of all the other variables, the remaining predictors (Analytic thinking, Total connectives, acausal connectives, and pronoun use) show conditional dependencies among themselves. Binarized NEET/EET Probability and distribution of predicted SOFAS scores are shown based on Low, Median, and High number of words spoken. We have modified the figure to better explain the structure of the Bayes network by indicating that "circles represent variables of interest." Arrows (i.e., directed edges) connecting circles indicate a causal influence from the ancestor to the descendent—parameterized in a conditional probability distribution. For example, a line showing follow-up SOFAS score is dependent upon NEET status. Note that there are no edges between "total PANSS" and the other variables, indicating independence. *SOFAS, Social and Occupational Functioning Assessment Scale; Connectives 1, All connectives use; Connectives 2, Acausal Connectives use; PANSS, Positive and Negative Syndrome Scale 8-Item Version; NEET, Not in Employment, Education or Training; EET, Engaged in employment education, or training.

occupational/functional outcomes in the first year of early intervention. We report three major findings: (1) Speech production (total number of words spoken) during a three-minute descriptive task at the time of first presentation with psychosis, explained significant variance in NEET status after 6–12 months of treatment; (2) measures of parental socioeconomic status and processing speed did not explain this relationship; and (3) the linguistic features included in our analysis (connectives, pronoun use, and analytic thinking scores) formed their own causal network (i.e., inter-related) but were not related to vocational or social outcomes. Thus, the ability to find a productive vocational status following the experience of psychosis relates to the number of words an individual manages to deploy during a discursive task of describing a picture to another person, irrespective of parental social background, one's personal speed of processing information and linguistic style of expression, and the severity of core symptoms (PANSS-8 total). These findings supply an objectively detectable and intuitive speech metric that requires no clinical judgment as a prognostic marker of functional outcome. This takes rater-related factors out of consideration when considering prognosis, potentially complementing clinical decisions that may require an assessment of longer-term outcomes (e.g., duration of case management, employment, and placement support).

Individuals with robust speech production had a "protective" effect with respect to functional deterioration. While those with median speech production (113 words) still had an above chance level of poor vocational outcomes (65% NEET), the effects of high speech production on vocational outcomes were far more positive; our modeling would predict that patients with speech production on the upper tail of the distribution (211 words) to have a 99% chance of being vocationally active. There are several hypotheses that could explain this association between the abundance of speech production with good vocational outcome. First, patients with high speech production are far less likely to have broader dysfunction in other negative domains. Poverty of speech has been consistently associated with affective flattening (45) and reduced symptom remission in negative domains (46), as well as likely a marker for underlying cognitive deficits (47). While this contributes a strong case for why lower speech production is likely to impair vocational prospects, it fails to make an affirmative case for good outcomes among those producing higher speech. It is likely that the benefit of speech production to good vocational prospects related to patients with more speech production being rated as more socially adept and desirable by peers and employers. In both healthy control and patient samples, social skills are highly correlated with gaining and retaining competitive employment (48). Among the patient population, the social threshold for employment may in fact be more pronounced as patients are more likely to be involved in the service sector and routine/non-technical occupations where customer or client relations are of primary importance. This speculation warrants further investigation. While "verbosity" may not be readily modifiable among clinical samples, social skills training as part of

employment support in first-episode psychosis clinics may yield more robust results among patients who are on the cusp of functioning.

What does this finding mean for the study of speech, language, and communication in psychosis? As noted earlier, clinicians' rating of disorganization tracks the deviations in grammatical encoding (connectives, pronoun use and analytic thinking index), but the social outcomes relate more with the aspects of message generation or production plan (number of words). Interestingly, a causal network exists among the variables relevant to functional/positional processing, distinct from the word count. We expect future studies to parse the large feature space of computational linguistic metrics to provide further clarity on the message production vs. grammatical encoding components in psychosis.

Our study has several strengths including the assessment of minimally treated FEP subjects, the use of objective linguistic analysis and careful control of known confounders. Nevertheless, several limitations warrant consideration. The use of a binarized NEET status has a few limitations that warrant consideration, including failing to capture "underemployment," and its inability to capture the complexity of biological, psychological, and social factors underlying vocational outcome, and the potential instability of this metric for patients who experience a relapse of psychotic illness. Despite these limitations, the consistency between NEET status and SOFAS score (which includes a broader definition of functioning) suggests that this construct is indeed a valid measure of functioning, and simple vocational status remains a relevant goal for patients undergoing mental health treatment.

Further limitations include the lack of sufficient longitudinal speech data to assess the stability of 'verbosity' over time in this sample, and the lack of information on many mediators of educational/vocational success, e.g., parental support, workplace mentorship, motivational factors, or ratings of social desirability. As a result, our findings pertaining to the value of word counts in forecasting later functioning should be considered complementary information rather than being the best of all baseline predictors of functioning. Such a conservative interpretation also fits with effect-size noted in the primary Bayesian analysis (BF > 2 relating number of words to NEET status). Nevertheless, the use of acyclic graph models on longitudinal data allows us to draw causal inferences (49) from observational design. Finally, two limitations in clinical follow-up are present: the lack of longitudinal antipsychotic medication and the degree of clinical severity at the time of our follow-up vocational assessment. Antipsychotic medications may reduce articulation speed and reduce sentence length in patients with psychosis; thus patients with superior verbal output at baseline may be well positioned to offset any adverse treatment effects from antipsychotic medication, achieving superior vocational outcomes. However, in our sample, we were not able to assess the effect of long-term antipsychotic exposure on speech or clinical severity. Despite this gap, our data revealed that patients with high speech production at baseline tended to do better over time, despite no evidence of systematic differences in antipsychotic exposure or clinical severity at baseline. In future analyses, assessment of the association between baseline speech production, as well as longitudinal antipsychotic exposure and clinical response with vocational outcomes may allow researchers to parse the relationships between these variables which may provide more clarity on the mechanism underlying our observed relationship.

To conclude, we call for including the rate of word production during routine clinical assessments of first-episode psychosis. Our results suggest that this approach, while inexpensive and not requiring exhaustive training, may carry prognostic value above what is currently captured in general clinical practice.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by Western University Research Ethics Board, London, Ontario, Canada. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MM prepared the first draft, recruitment, data collection, and data analysis. RL and AS designed the analysis and implemented statistical procedures and critical review of the paper. HG, JR, and PS: contributed to recruitment and collecting the data, and critical review of the paper. LP conceived the study, designed the analysis, collected the data, and performed critical review of the paper. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Core of sensory gating deficits in first-episode schizophrenia: attention dysfunction

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Background: Sensory gating deficits are a common feature of schizophrenia and may be indicative of higher-order psychopathological impairments. It has been proposed that incorporating subjective attention components into prepulse inhibition (PPI) measures may improve the accuracy of assessing these deficits. This study aimed to investigate the relationship between modified PPI and cognitive function, with a specific focus on subjective attention, to gain a better understanding of the underlying mechanisms of sensory processing deficits in schizophrenia.

Methods: Fifty-four unmedicated first-episode schizophrenia (UMFE) patients and 53 healthy controls participated in this study. The modified Prepulse Inhibition paradigm, including Perceived Spatial Separation PPI (PSSPPI) and Perceived Spatial Colocation PPI (PSCPPI), was used to evaluate sensorimotor gating deficits. Cognitive function was assessed in all participants using the Chinese version of the MATRICS Consensus Cognitive Suite Test (MCCB).

Results: UMFE patients had lower MCCB scores and deficient PSSPPI scores than healthy controls. PSSPPI was negatively correlated with total PANSS scores and positively correlated with the speed of processing, attention/ vigilance, and social cognition. Multiple linear regression analysis showed that the PSSPPI at 60ms had a significant effect on attentional/ vigilance and social cognition, even after controlling for gender, age, years of education, and smoking.

Conclusion: The study revealed notable impairments in sensory gating and cognitive function in UMFE patients, best reflected by the PSSPPI measure. Specifically, PSSPPI at 60ms was significantly associated with both clinical symptoms and cognitive performance, suggesting that PSSPPI at 60ms may capture psychopathological symptoms related to psychosis.

KEYWORDS

schizophrenia, attention, cognitive function, MCCB, modified prepulse inhibition

1. Introduction

Schizophrenia is a severe mental disease characterized by positive symptoms, negative symptoms, and cognitive impairment (1), with a global prevalence of 1% (2). Individuals with

schizophrenia commonly display abnormal information processing, whereby they have difficulty inhibiting irrelevant stimuli. This can result in an overload of irrelevant information in their consciousness, leading to thought disorders and other core symptoms associated with schizophrenia (3). Some authors have proposed that changes in PPI (prepulse inhibition) in patients with schizophrenia may be a cause of the characteristic sensory information overload of this disease. This hypothesis is based on the idea that PPI can reflect the ability to regulate the amount of sensory information processed continuously and plays a crucial role in filtering relevant and irrelevant sensory information (3, 4). Over the past few decades, numerous studies have demonstrated the presence of defects in PPI among patients with schizophrenia (5, 6), which has established PPI as a potential phenotype of the disorder (7, 8).

PPI is a classical gating index that involves presenting a low-intensity pre-stimulus (known as the "prepulse") 10–500 ms before the startle stimulus ("pulse"), resulting in a reduction of the startle response (9, 10). PPI is an automatic processing process, and the corresponding neural circuits are primarily located in the brainstem, including the auditory mesencephalic inferior colliculus, the deep layer of the superior colliculus, and the tegmental nucleus of the pontine foot. These circuits have extensive neural connections with the sensory cortex, joint cortex, motor system, and limbic system, providing a biological basis for the top-down regulation of developed cognitive processes such as PPI attention (11). The modified PPI paradigm utilizes the condition of perceptual space separation to isolate the subjective sensory sound direction when the background noise is distinct from the perceived direction of the prepulse stimulus, has been successfully constructed for inducing spatial selective attention(i.e., the perceived spatial separation PPI paradigm) (12). There is substantial evidence indicating that introducing attention to the prepulse significantly increases PPI (13–15).

The relationship between PPI and cognitive function remains inconclusive in existing research. Mixed findings have been reported regarding the relationship between PPI and continuous performance task (CPT). While two studies found no correlation between PPI and behavioral measures of CPT in healthy controls and patients with schizophrenia (16, 17), another study found that higher PPI was associated with better CPT performance in healthy controls (18). Kirsty et al. (19) used novel methods for the measurement of PPI, introducing instructed PPI tasks, and found a correlation between PPI and attention and memory tasks under different conditions. The authors also showed that these relationships seem to be mediated by common attentional processes active within both PPI and cognitive tasks. Previous studies have found that this circuit overlaps with related areas of psychopathological manifestations in patients with schizophrenia, such as thought disorders (20), social cognition (21), and emotional perception deficits (22). Therefore, modified PPI can indirectly indicate high-order psychopathological impairments.

Attentional impairment may be at the core of all cognitive function impairments, with meta-analyses shuowing a medium to large effect size (23–25). Recent studies have also found attentional deficits in first-episode schizophrenia patients, and although these deficits improve over time, but still do not reach the level of healthy controls (26, 27). There is also evidence suggesting that schizophrenia patients have deficits in selective attention (28, 29). Considering these factors, we hypothesized that the modified PPI paradigm would be a more robust measure of impairment and could potentially provide a more sensitive measure of specific cognitive variables that are important in first-episode schizophrenia.

The cognitive evaluation tools used in assessing cognitive function in schizophrenia are contradictory in existing studies, and the domains of cognitive function assessment are inadequate and influenced by factors such as drug treatment and the course of the disease. For instance, patients with schizophrenia who received medication, particularly those who received second-generation antipsychotic drugs, had higher PPI compared to patients who did not receive medication (30). Although there is coherent research outcomes on the PPI deficits, there are few analyses on modified PPI, particularly on the association between it and cognitive function (31). To address this gap, this study utilized a standardized cognitive evaluation tool to assess the cognitive function of unmedicated first-episode schizophrenia patients and evaluate the relationship between prepulse inhibition and cognitive function. The aim of this study is to provide a better understanding of the correlation between PPI and cognition.

2. Materials and methods

2.1. Participants

The unmedicated first-episode schizophrenia group (UMFE) was recruited from both the outpatient and inpatient departments of Beijing Anding Hospital. Inclusion criteria were as follows: age between 15 and 45 years; normal hearing without any prior auditory system diseases; at least 9 years of education, and a Simple Wechsler intelligence test score of 80 or greater. The Chinese version of the MINI International Neuropsychiatric Interview (MINI) (6.0) was used to diagnose patients with schizophrenia according to the diagnostic criteria outlined in the Fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Additionally, patients with a duration of illness less than 5 years, who had not received medication or continuous application of antipsychotics since the onset of symptoms for fewer than 2 weeks, were included.

Exclusion criteria were as follows: serious abnormalities found in physical evaluation, laboratory biochemical indicators, or electroencephalogram (EEG), electrocardiogram (ECG); pregnant or lactating women; patients in a state of extreme excitement and impulsivity as determined by their treating physician; patients who were deemed likely to commit suicide or violence during the study; patients who had received electroconvulsive or magnetic stimulation treatment within 6 months prior to recruitment.

The healthy control group was matched for age, gender, and years of education with the patient group and had no personal or family history of mental diseases.

2.2. Sample size estimate

Sample size calculations were performed using online software and by consulting relevant literature and prior similar studies. Based on previous research demonstrating a medium effect size (Cohen's $d = 0.6$) in distinguishing between the two groups, a desired power of $1\text{-}\beta = 0.85$, and a significance level of $\alpha = 0.05$, a minimum sample size of 50 participants per group was determined.

2.3. Clinical and cognition assessments

A self-signed evaluation was used to collect general and disease-related information from the subjects. The Positive and Negative Syndrome Scale (PANSS) is a widely used clinical rating scale that measure the severity of symptoms in patients with schizophrenia (32). It consists of 30 items, 7 of which measure positive symptoms (e.g., hallucinations, delusions), 7 of which measure negative symptoms (e.g., blunted affect, social withdrawal), and 16 of which measure general psychopathology (e.g., anxiety, depression). Each item is rated on a scale of 1 (absent) to 7 (extreme), and the total score ranges from 30 to 210, with higher scores indicating more severe symptoms. We utilized the MATRICS Consensus Cognitive Battery (MCCB) tool to determine individual neuropsychological states (33). The Chinese version of the MCCB consists of 7 cognitive domains, and 9 tests were chosen to represent seven cognitive domains in the MCCB. Information processing speed, including Trail Making Test, Part A, symbol coding subtest, and animal naming; Attention/vigilance, including the Continuous Performance Test; Working memory, including the spatial span subtest; Verbal learning, including the Hopkins Verbal Learning Test; Visual learning, including the Brief Visuospatial Memory Test; Reasoning and problem-solving, including the mazes subtest; Social cognition, including the Mayer-Salovey-Caruso Emotional Intelligence Test. The PANSS assessment was administered by experienced psychiatrists who underwent consistent training to ensure the accuracy and reliability of the results. In addition, trained psychologists administered the MCCB evaluation.

2.4. PPI measures

The modified PPI test was conducted in a shielded room using the Xeye Human Startle Reflex system. Two Ag/AgCl electrodes were attached to the pupil and lateral canthus of the right eye to record the electrical activity of the orbicularis oculi muscle, and the electrodes were grounded using the right mastoid. The PPI paradigm was tested under the conditions of perceptual spatial separation and colocation.

The stimulus parameters were as follows: the startle stimulus was a 40 ms 100 dB SPL(Sound Pressure Level, SPL) white noise, the prepulse stimulus was an 800 Hz narrowband noise, 150 ms 64 dB SPL, and the background noise was 60 dB SPL white noise. The interval of stimulation (ISI) between the prepulse and startle stimulus was 120 ms/ 60 ms, and the interaural delay of background noise between the left and right ear was 3 ms.

The stimulus sequence involved playing the startle stimulus 5 times. If the subjects captured the startle reflex normally, the experiment continued. Two 800 Hz narrowband noises were played with an ISI of 120 ms/60 ms. If the subject heard both sounds, the test continued later. The background noise and the prepulse stimulus were played, and the subjects were asked to identify the sound from the left or the right. After a few practice sessions, the correct rate was set to >90%, and the experiment proceeded with two blocks.

In the first block, the background noise always came from the left with a total of 27 trials. In the second block, the background noise always came from the right with a total of 27 trials. Depending on the subjective feeling formed between the background noise and the prepulse stimulus, it was classified into perceptual space separation/colocation (PSSPPI/PSCPPI), resulting in a total of 4 types of prepulse stimulation (see Figure 1).

The PPI test was administered by experienced researchers who received consistent training to ensure accuracy and reliability.

2.5. Data processing

Each trial was evaluated to remove the electromyography (EMG) response caused by automatic blinking. The mean and maximum peak values of each trial's sampling period were identified. A trial was considered valid if the maximum peak was greater than or equal to the sampling period mean multiplied by 4 and the sampling period mean was greater than or equal to the response period mean; otherwise, the trial was considered invalid., the trial was considered invalid. The maximum peak latency range was 350–850 ms. PPI was calculated using the formula: PPI = (1-pp/p) *100%, where 'p' indicates the amplitude induced only under the condition of startle stimulation, and 'pp' represents the amplitude induced by prepulse stimulation plus startle stimulation.

2.6. Statistical analysis

Statistical analyses were performed using R4.1.1 software (Comprehensive R Archive Network, http://cran.rproject.org/). Continuous variables are presented as the mean (standard deviation), while categorical variables are presented as the frequency and percentage. Differences in demographic data, cognitive function, and modified PPI index between groups were assessed using the Chi-square test or independent sample t test. The relationship between the modified PPI index and PANSS score, as well as cognitive function, was assessed using Spearman correlation analysis, followed by multiple linear regression to further evaluate the correlation. Statistical significance was considered at the $\alpha = 0.05$ level, and multiple comparisons were adjusted using the Bonferroni correction.

3. Results

3.1. Demographics and clinical characteristics

A total of 107 participants were included in the study, consisting of 54 unmedicated first-episode schizophrenia patients and 53 healthy controls. The two groups were matched in terms of age, gender, and years of education, and there was no significant difference in the number of smokers between them. Table 1 shows the PANSS score of the UMFE group.

3.2. Cognitive function

After correcting for gender and age differences in MCCB cognitive assessments, the study found that the total cognitive scores and neurocognitive scores of the UMFE group were significantly lower than those of the healthy control group (all $p < 0.01$). However, there was no significant difference in social cognitive outcomes between the two groups ($p = 0.18$), as shown in Table 2.

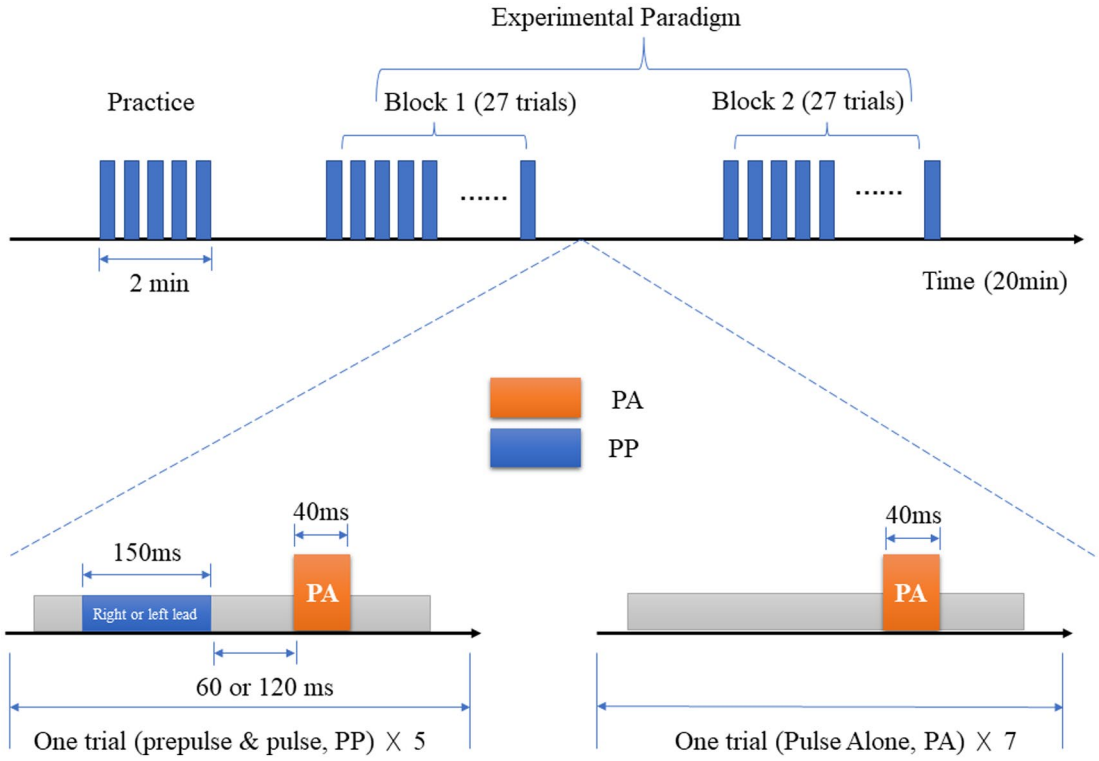

FIGURE 1
Modified experimental paradigm of prepulse inhibition.

3.3. Prepulse inhibition

There were no significant differences between the two groups in terms of the amplitude of startle stimulation and the latency of maximum amplitude. The UMFE group had lower scores than the healthy control group in the PPI index of perceptual spatial separation (PSSPPI) at both time intervals, while there was no significant difference in perceptual space colocation (PSCPPI) between the two groups at both the 60 ms and 120 ms intervals. The effect size of PSSPPI were 0.73 (Cohen's d = 0.73, 95% CI [0.34–1.12]) at 60 ms and 0.70 (Cohen's d = 0.70, 95% CI [0.31–1.09]) at 120 ms, with a statistically significant difference between the two groups ($p < 0.01$ for both). These results suggest that the UMFE group had impaired sensorimotor gating compared to the healthy control group. Table 2 and Figure 2 provide more details on these findings.

3.4. Correlation between Prepulse inhibition and clinical symptoms, cognitive function

Spearman correlation analysis showed that in the UMFE group, the PSSPPI at the 60 ms interval had significant correlations with some clinical symptoms and cognitive function. Specifically, it was negatively correlated with the PANSS total score ($r = -0.27$, $p = 0.049$), and positively correlated with speed of processing ($r = 0.27$, $p = 0.044$), attention/vigilance ($r = 0.27$, p = 0.049), and social cognition ($r = 0.27$, $p = 0.048$). However, no significant correlations were found between PSSPPI at the 120 ms interval and clinical symptoms or cognitive function. In the healthy control group, there were no significant correlations were found between PSSPPI and cognitive function. Table 3 shows correlation coefficients (r) between PSSPPI and clinical symptoms and cognitive function in the UMFE group, as well as between PSSPPI and cognitive function in the healthy control group. After Bonferroni correction, none of these results remained significant.

Furthermore, to verify the association between cognitive function and PSSPPI in UMFE group, a regression analysis was performed with the PSSPPI as the dependent variable and cognitive function as the independent variable. The potential confounding factors, such as gender, age, years of education, and smoking, were included in the regression model. Additionally, the variance inflation factor (VIF) method was employed to detect collinearity issues. If the VIF is less than 10, it is considered that there is no multicollinearity issue among all independent variables. Multiple linear regression analysis revealed that PSSPPI at 60 ms intervals had a significant impact on attention/vigilance ($\beta = 0.23$, $p = 0.02$) and social cognition ($\beta = 0.23$, $p = 0.04$), but had no effect on other cognitive domains. Additionally, PSSPPI at 120 ms intervals did not significantly affect the overall cognitive score or any of the specific cognitive domains.

4. Discussion

4.1. Cognitive deficits in UMFE

This study provides further evidence of prevalent neurocognitive impairment among unmedicated patients with first-episode schizophrenia, which is consistent with previous research (34, 35).

TABLE 1 Social-demographical and clinical characteristics of all the study subjects.

	UMFE (*n*=54)	HC (*n*=53)	t/ χ2	*p* value
Age (year, mean (SD))	25.65 (8.41)	24.68 (6.37)	0.78	0.44
Gender, male (%)	23 (42.59%)	31 (58.49%)	2.70	0.10
Education level (year, mean (SD))	13.52 (3.70)	14.11 (3.21)	0.89	0.38
IQ	103.05(11.43)	113.12(11.99)	−4.40	<0.001
Family history, *n* (%)	12 (22%)	0 (0%)	13.27	<0.001
Employment rate, *n* (%)				
Unemployed	11 (20.37%)	0 (0%)	14.02	<0.001
Employed	24 (44.44%)	37 (69.81%)		
Student	19 (35.19%)	24 (30.19%)		
Smoking, *n* (%)	4 (7.41%)	9 (16.98%)	2.30	0.13
Age at onset (year, mean (SD))	23.96(8.42)	NA		
DUP (month, mean (SD))	10.94(16.17)	NA		
PANSS (mean (SD))				
Total score	76.52 (14.45)	NA		
Positive symptoms	21.33 (5.55)	NA		
Negative symptoms	16.98 (7.09)	NA		
General symptoms	38.20 (7.53)	NA		

UMFE, unmedicated first-episode schizophrenia. HC, healthy controls. IQ, Intelligence Quotient. DUP, duration of untreated psychosis. PANSS, the Positive and negative symptoms scale.

Specifically, our study found a large effect size for impaired working memory and attentional vigilance in UMFE patients compared to healthy controls. Interestingly, no deficits in social cognition were observed in this group, which contradicts the findings of most earlier studies (34, 36, 37). For example, Pablo et al. (38) reported that both first-episode and chronic schizophrenia were associated with social cognition deficits. A recent meta-analysis of cross-sectional studies on cognitive function in schizophrenia also found a large effect size for social cognition (SMD = 0.88) (25). In contrast, a large sample study of schizophrenia in China reported a smaller effect size (Cohen's d = 0.42) for the social cognition domain (39). Additionally, in another study, patients with first-episode schizophrenia scored slightly lower on the MSCEIT test than the controls (SMD = −0.38) (40). Social cognition is widely recognized as a mediator between neurocognitive deficits and functional outcomes (41). However, this study did not find significant results in social cognition. We analyzed that the small sample size and the short duration of illness in our study, as well as the relatively better functioning of our participants, may explain the lack of significant social cognition impairment in UMFE patients compared to healthy controls. Our study suggests that working memory and attention may be potential candidate biomarkers of schizophrenia. Overall, our findings highlight the importance of assessing cognitive functioning in UMFE patients and developing targeted interventions to improve cognitive outcomes in this population.

4.2. PPI deficiency In UMFE and Its correlation with clinical symptoms

This study also found significant deficits in PSSPPI with 60 ms and 120 ms intervals in patients with schizophrenia, with effect sizes significantly larger than those reported in a recent meta-analysis on PPI deficits in chronic schizophrenia (PPI 60 ms (SMD = −0.50) and PPI 120 ms (SMD = −0.44)) (42). Given the abundant evidence showing continuous and selective attention deficits in schizophrenia (43, 44), the PPI experimental paradigm used in this study assessed the subjective attention component, increasing the discriminant validity for the disease with medium to large effect sizes. Scholes et al. (45) reported that attention to auditory stimuli did not decrease the sensitivity of patients to startle stimuli, and the PPI deficits observed in schizophrenia patients resulted from selective attention deficits, which is consistent with our findings. Previous research has shown PPI deficits not only in patients with first-episode schizophrenia (46) but also in those at high clinical risk of psychosis (47) and unaffected first-degree relatives (48).It is noteworthy that modified PPI can be considered a potential biomarker for the disease.

Moreover, there is a correlation between the PSSPPI and PANSS total score, indicating its association with symptom severity of the disease. Dawson et al. (49) also proposed that the impaired attentional modulation of PPI reflects fundamental neurocognitive processes related to thought disorder in schizophrenia. In addition, studies have confirmed that PPI deficits occurring when the prepulse is attended are more strongly associated with symptom severity in the schizophrenia spectrum (50), and that no correlation between symptoms and PPI deficits can be detected in passive attention PPI paradigms in schizophrenia patients (51). Hamm et al. (52) reported that there is a specific relationship between PPI and curative effect. Therefore, modified PPI may serve as an objective predictor of clinical symptom relief. Antipsychotic drug treatment can partially enhance PPI deficits, with atypical drugs, such as quetiapine (53), being more effective. PPI is a useful endophenotype predictor of the disease (54), with close ties to the disease state and potential applications as a predictive indicator for clinical remission. Future research should examine potential influencing factors, such as single nucleotide polymorphisms (SNPs) (55), DNA methylation, childhood trauma, nicotine use, and medication treatment (51), to investigate mechanisms underlying the improvement of PPI defects and better understand the relationship between improved PPI and disease symptoms.

4.3. Correlation between the PSSPPI and cognitive function

In this study, a significant correlation was found between PSSPPI and attention/vigilance and social cognition, even after controlling for gender, age, smoking, and years of education. The research team had

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TABLE 2 Cognitive function and PPI index results of participants.

	UMFE (*n*=54)	HC (*n*=53)	*t*	*p* value	*Cohen's d* (95%CI)
MCCB					
Speed of processing	38.30 ± 10.89	45.81 ± 8.00	−4.07	<0.01	0.78(0.392–1.178)
Attention/vigilance	37.21 ± 12.48	46.09 ± 8.47	−4.31	<0.01	0.83(0.436–1.226)
Working memory	39.41 ± 10.26	47.53 ± 7.18	−4.75	<0.01	0.92(0.517–1.314)
Verbal learning	42.75 ± 10.43	48.68 ± 8.77	−3.19	<0.01	0.62(0.227–1.003)
Visual learning	42.92 ± 13.56	48.30 ± 9.19	−2.40	0.02	0.45(0.069–0.836)
Reasoning and problem-solving	39.95 ± 12.26	44.66 ± 11.15	−2.08	0.04	0.40(0.019–0.785)
Social cognition	38.61 ± 12.47	41.51 ± 9.84	−1.34	0.18	0.26(−0.123–0.638)
Overall composite	39.22 ± 9.00	46.37 ± 6.93	−4.61	<0.01	0.89(0.492–1.286)
PPI					
PA	58.56 ± 36.33	71.11 ± 31.98	−1.90	0.06	0.37(−0.016–0.749)
Latency	451.5 ± 71.21	465.51 ± 71.19	−1.03	0.31	0.20(−0.183–0.577)
PSCPPI 60	27.78 ± 21.18	33.37 ± 15.92	−1.55	0.13	0.30(−0.083–0.679)
PSSPPI 60	27.94 ± 21.99	42.35 ± 17.34	−3.77	<0.01	0.73(0.336–1.118)
PSCPPI 120	24.17 ± 23.81	32.07 ± 11.77	−1.95	0.05	0.42(0.036–0.803)
PSSPPI 120	25.72 ± 23.73	39.67 ± 15.42	−3.61	<0.01	0.70(0.305–1.086)

PSCPPI, Perceived spatial colocation PPI. PSSPPI, Perceived spatial separation PPI. UMFE, unmedicated first-episode schizophrenia. HC, healthy control.

previously discovered a positive correlation between attention and PSSPPI in patients with chronic schizophrenia, suggesting that attention deficit may be the core problem of PPI deficiency (31). Previous studies using traditional PPI did not find a significant link between PPI at 60 ms and 120 ms and the composite score of MCCB and each domain (56). This may be due to disparities in the inclusion of the disease population and the PPI paradigm. Numerous studies have demonstrated that patients with schizophrenia have deficits in PPI, which may be due to the involvement of several brain regions in the PPI regulation circuit and the pathophysiology of schizophrenia (57). The sensorimotor gating mechanism is controlled by a complex circuit that includes the downlink forebrain pathway (58). Animal studies first associated PPI with the ventral striatum and dopamine (59), which was later presumed to be controlled by the cortico-striato-pallido-pontine circuit (8). This circuit overlaps significantly with the areas linked to the pathological manifestations of schizophrenia, suggesting a behavioral association. Therefore, PPI may be an indicator of higher-order psychopathological injuries.

This study did not find any significant association between PSSPPI and cognitive function in healthy individuals. However, in the UMFE group, a significant correlation was observed between PSSPPI and deficits in attention and working memory, which may be attributed to a core deficit in attention among individuals with schizophrenia. The attention component highlighted by the modified PPI in this study enhanced the effect size of this deficit, indicating a specific relationship between the two. This finding may help explain why a correlation was observed in the patient group but not in the healthy control group.

The study found that PPI deficits were more pronounced at 60 ms intervals than at 120 ms intervals in patients with UMFE. It was also observed that there was a significant association between PPI at 60 ms intervals and higher cognitive functions, such as attention, working memory, and social cognition. However, no such link was found at 120-ms intervals. This suggests that PPI deficiency at 60 ms intervals is more sensitive to the disease and impairment of higher cognitive functions, which aligns with the fact that PPI deficits are most commonly reported at this interval in schizophrenia. (9, 60, 61).

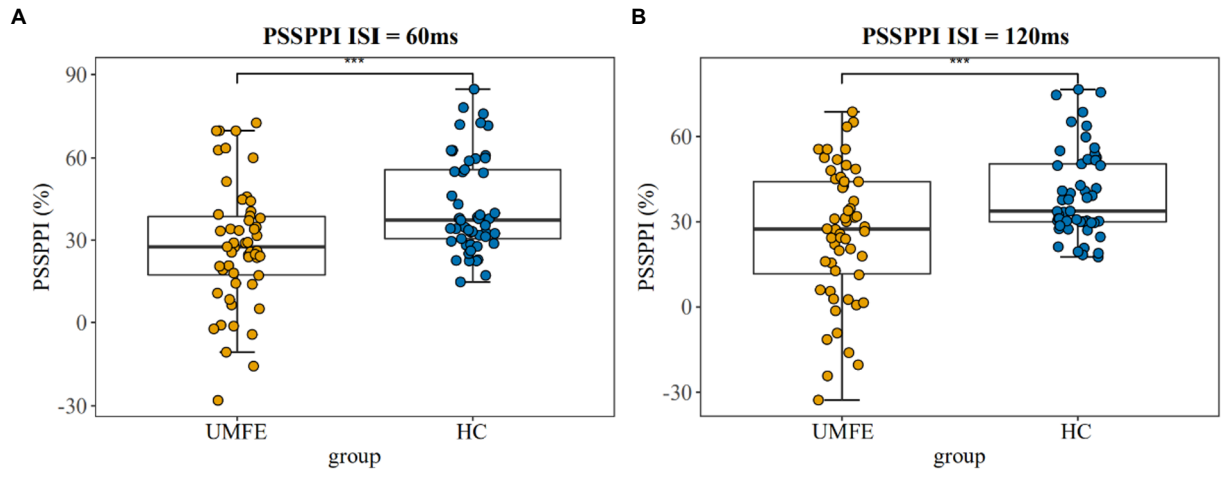

FIGURE 2
Prepulse Inhibition of perceptual space separation at 60ms intervals (Left); Prepulse Inhibition of perceptual space separation at 120ms intervals (Right). UMFE: unmedicated first-episode schizophrenia, HC: healthy control. ***p value <0.001.

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TABLE 3 Correlations between PSSPPI and clinical symptoms/cognitive function in UMFE group, and with cognitive function in HC groups.

	UMFE (n=54)		HC (n=53)	
	PSSPPI 60	PSSPPI 120	PSSPPI 60	PSSPPI 120
PANSS				
Total score	−0.27*	−0.15	NA	NA
Positive symptoms	−0.1	−0.06	NA	NA
Negative symptoms	−0.22	−0.14	NA	NA
General symptoms	−0.24	−0.15	NA	NA
MCCB				
Speed of processing	0.27*	0.20	0.07	0.04
Attention/vigilance	0.27*	0.08	0.06	0.08
Working memory	0.14	0.17	−0.17	0.01
Verbal learning	0.16	−0.01	0.07	0.02
Visual learning	0.10	0.08	−0.08	−0.12
Reasoning and problem-solving	0.23	0.12	−0.17	0.06
Social cognition	0.27*	0.06	−0.04	0.07
Overall composite	0.23	0.13	−0.02	0.10

UMFE, unmedicated first-episode schizophrenia. HC, healthy controls. PANSS, the Positive and negative symptoms scale. PSCPPI: Perceived spatial colocation PPI. PSSPPI: Perceived spatial separation PPI. *p*-value for spearman rank correlation analysis. NA: not application, *$p<0.05$

Research has discovered that reflection inhibition 60 ms after prepulse appears to be controlled by the process between automatic inhibition and attention-sensitive inhibition (62). In other words, the time domain of this inhibition is at the transition point between the information that is automatically modified and the information that can be influenced at will. Theoretical models have suggested that the transition zone between conscious accessibility and unconscious processing is specifically critical for regulating the content of consciousness, and it may also be a specifically fragile period of psychopathological state (63, 64). This fact implies that gating at 60-ms intervals may be especially critical for the biology of schizophrenia.

5. Limitation

This research has several potential limitations. First, the limited sample size of this study may restrict the generalizability of the findings. This may also be one of the reasons why the social cognition domain did not yield any significant results. Second, this study is the first to explore the relationship between modified PPI and cognitive functions in UMFE patients. As these findings are preliminary, none of the results were significant after multiple comparisons. However, this study can serve as a foundation for future research in this area. Another study suggested that there may be differences in the underlying structure of the MSCEIT between individuals with schizophrenia and healthy controls (65). Additionally, it is important to note that the internal consistency of the MSCEIT scale is low in China (66). Moreover, social cognition may mediate information processing speed, attention, and function, suggesting that analyzing the association between a single cognitive dimension and PSSPPI may be insufficient to elucidate the high pathological impairment reflected by PSSPPI (64). Finally, the direct analysis of the relationship between PPI and cognitive function did not consider the potential mediating role of other factors, such as childhood trauma. Future research could use genetic imaging and other technologies to evaluate the specific mechanisms of PPI defects and predict drug efficacy and disease outcomes in prospective cohort studies.

6. Conclusion

This study represents the first investigation of the relationship between cognitive functions and modified PPI in Chinese patients with first-episode unmedicated schizophrenia. Modified PPI is considered an index for evaluating attention, cognition, and sensory integration. The study found that the modified PPI includes a subjective attention component, which enhances its discriminant validity for the disease. Moreover, the modified PPI was significantly associated with attention/vigilance, indicating that advanced cognitive function deficits in patients with schizophrenia may be reflected by the modified PPI. Specifically, PSSPPI at 60 ms intervals in UMFE patients was significantly related to clinical symptoms and cognitive function, suggesting that PSSPPI may be a useful tool for evaluating psychopathological symptoms associated with psychosis.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by Beijing Anding Hospital, Capital Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YD: data acquisition, data curation, formal analysis, investigation, methodology, and writing—original draft. QT: data analysis. WH: data acquisition and formal analysis. ZC: data acquisition. ZM: data

acquisition. QB: writing—review. FD: funding acquisition, and writing—review and editing. CW: funding acquisition, supervision, and writing—review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Are attention-deficit/hyperactivity disorder symptoms associated with negative health outcomes in individuals with psychotic experiences? Findings from a cross-sectional study in Japan

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Objective: Although research has indicated that the prevalence of attention-deficit/hyperactivity disorder (ADHD) may be elevated in individuals with psychotic disorders, as yet, there has been comparatively little research on this association and its effects among adults at the subclinical level. To address this deficit, the current study examined the association between psychotic experiences (PE) and ADHD symptoms in Japanese individuals and whether the presence of ADHD symptoms increases the risk for negative health outcomes in people with PE.

Method: Data were analyzed from an online sample of 1,452 individuals (age 18–89; 51.5% female) collected in 2021. Information on PE was obtained with the PRIME Screen-Revised (PS-R), while the Adult ADHD Self-Report Scale (ASRS) Screener was used to measure ADHD symptoms. Information was also obtained on a number of health outcomes including anxiety and depressive symptoms and suicidal ideation. Logistic regression was used to assess associations.

Results: In a fully adjusted analysis PE were associated with almost three times higher odds for ADHD symptoms (OR: 2.92, 95%CI: 1.19–7.17). In an analysis that was restricted to individuals with PE, ADHD symptoms were associated with significantly increased odds for depressive symptoms, lifetime suicidal ideation, perceived stress and severe sleep problems.

Conclusion: ADHD symptoms are present in some individuals with PE and increase the odds for several detrimental health outcomes in this population. Identifying co-occurring PE and ADHD/ADHD symptoms may facilitate treatment options and help prevent negative health outcomes in individuals with these conditions.

KEYWORDS

ADHD, comorbidity, depression, psychosis, suicidal ideation

Introduction

Psychotic experiences (PE) consist of subclinical hallucinations and delusions that occur among individuals in the general population (1). An earlier review study that used data from 61 cohorts found that the median estimated prevalence of PE was 7.2% in the general population (2), while more recent research has indicated that the self-reported lifetime prevalence of at least one PE may

be substantially higher (16.5%) in some instances (3). PE have been linked to a variety of detrimental outcomes in adults including worse physical (4) and mental health (5). Regarding the latter, a study that used data from 18 countries that were collected in the World Mental Health Survey found that PE were linked to mood and anxiety disorders, eating disorders and substance use disorders in adults (5). More recent research has further shown that the co-occurrence of PE and common mental disorders increases the odds for negative outcomes such as poor physical functioning and suicidal behavior (6).

PE have also been linked to impulse control disorders (5). In particular, there is a growing body of evidence that PE are associated with attention-deficit/hyperactivity disorder (ADHD), which is a condition characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity that negatively affects functioning in different settings (7). A recent study that used data from US individuals aged 8–21 found that ADHD was elevated in psychosis spectrum (PS) symptom youth vs. non-PS youth (45% > 20%) (8). In addition, cross-sectional research from South Korea and longitudinal research from England has also, respectively, linked psychotic-like experiences in adolescents with deficits in attention (9), and the ADHD combined subtype at age 7 to PE at age 12 (10). The association has also been observed in adults. A study that used data from the Adult Psychiatric Morbidity Survey 2007 found that a higher level of ADHD symptoms was associated with PE (11). Further, in the above-mentioned World Mental Health Survey study ADHD was found to predict the subsequent onset of PE (but not vice versa) (5). Several mechanisms might underlie the association between PE and ADHD. For instance, there may be a biological component; recent research has reported a shared genetic liability between PE and ADHD (12), while other authors have highlighted that altered dopamine (DA) levels may play a role in the development of both PE and ADHD symptoms (13). Alternatively, it is possible that other factors such as substance use disorder might also link ADHD and PE as recently hypothesized for the ADHD-psychotic disorder association (14).

This study will examine the association between PE and higher ADHD symptoms (i.e., possible ADHD cases that are deemed subclinical in the absence of a diagnosis) in Japanese individuals aged 18 and above and whether ADHD symptoms increase the risk for negative health outcomes in persons with PE. This research is warranted for several reasons. First, until now, there has been comparatively little research on PE in Japanese adults. This is an important omission as a recent study found that PE were linked to severe social withdrawal (*hikikomori*) in the Japanese general population (15) raising the possibility that they are associated with other detrimental outcomes in this setting and thus requiring further research. Second, it is important to study the relationship between PE and ADHD in a non-western setting to further elucidate the association – especially as not all studies from the West have found that ADHD increases the risk for PE (16). Third, given that an earlier study from Japan found that ADHD symptoms were associated with an increased risk for suicide attempts in outpatients with psychosis (17), it can be speculated that ADHD symptoms might also be important for negative outcomes in individuals with PE. However, to the best of our knowledge this issue has not been examined.

A focus on the association between PE and ADHD symptoms in Japan may be particularly instructive. Previous research has suggested that the stigma surrounding mental illness may lead to delays in seeking treatment for mild mental disorders in Japan, as well as a longer duration of untreated psychosis (18, 19). This might also explain why some research has indicated that there may be a large number of adults with undiagnosed and untreated ADHD in Japan (20). Although an earlier study found that attenuated psychotic symptoms were not associated with help-seeking behavior in Japan (21), other research has suggested that PE may serve as a general marker for a variety of adverse outcomes including more severe psychopathology (22), while ADHD symptoms have been associated with worse physical and mental health outcomes in undiagnosed Japanese adults (20). Given this, the current study had two main aims: (i) to examine if PE are associated with ADHD symptoms in Japanese individuals; (ii) to explore whether ADHD symptoms are important for negative health outcomes in people with PE. As previous research has indicated that both ADHD and ADHD symptoms may be more common in those with PE and that ADHD symptoms are themselves linked to worse physical and mental health, it was hypothesized that PE would be significantly associated with ADHD symptoms and that ADHD symptoms would be linked to worse health outcomes in individuals with PE.

Methods

Study sample

Data came from an online survey of the Japanese general population undertaken in late February 2021. The survey was administered by a commercial survey company, Macromill. A questionnaire was initially sent to 8,628 respondents that were drawn from the company's online commercial web panel. An additional 1728 respondents were subsequently surveyed to increase the size of the final sample. After both phases of surveying were completed the final sample comprised 1,452 respondents who were selected based on three main demographic criteria – age (aged 18 and above), sex (representative of the total Japanese population) and residency area (respondents should be drawn from each of Japan's 47 prefectures). Permission for the survey was provided by the Ethics Committee at the National Center of Neurology and Psychiatry, Tokyo, Japan (approval number: A2020-088). Informed consent was provided by all participants.

Measures

Psychotic experiences

PE were assessed with the PRIME Screen-Revised (PS-R). This 12-item self-report scale measures (positive) psychosis symptoms: hallucinations, delusional ideas, persecutory ideas, unusual thought content, perceptual abnormalities, suspiciousness, and grandiose ideas (23). Items are rated on a seven-point scale from 0 (definitely disagree) to 6 (definitely agree). We used the scoring method suggested by the scale's developers to categorize positive cases using three main criteria – (i) the strength of item agreement (a rating of 5 or 6) in conjunction with, (ii) the duration of the symptom, or (iii) having a total PS-R score of 39 or above. The PS-R has been previously validated in Japan (23).

ADHD symptoms

The Adult ADHD Self-Report Scale (ASRS) Screener was used to assess ADHD symptoms (24, 25). This 6-item screening scale enquires

about inattention and hyperactivity symptoms in the previous six months using a 5-point response option that runs from never (scored 0) to very often (scored 4). The total score ranges from 0 to 24 with higher scores signifying increased ADHD symptoms. The Screener has been validated in numerous studies as being able to discriminate potential ADHD cases from non-cases (26) as well as for use in community epidemiological surveys (25). Following the suggestion of the scale's developers, in this study a score of 14 and above was used to categorize higher ADHD symptoms (25). Cronbach's alpha for the scale was 0.87.

Covariates/health outcomes

Information was also obtained on several sociodemographic and other health variables. Besides sex (male, female), information was also obtained on age which was subsequently categorized into three groups: 18–34, 35–59 and ≥ 60, representing young, middle-aged and older adults, respectively. For education level, individuals were categorized into those with a higher education (two-year college, university, graduate school) and those who had received less than a higher education (junior high school/below, high school, vocational high school). For marital status respondents were categorized as married or not married. The economic situation of respondents was assessed with a question that inquired about household financial income. This was measured in millions of yen and divided into three categories, (i) < 4 million, (ii) 4 < 10 million, and (iii) ≥ 10 million (106.55 JPY = U.S. $1 at the time of the survey). Given the large portion of respondents that failed to answer this question (22.7%) and our desire to keep as many individuals in the analysis as possible, a fourth (iv) 'missing' category was also created.

Self-rated health was categorized as either good/very good, fair, or poor/very poor. In the health analysis poor self-rated health (comprising both poor and very poor self-rated health) was used as the outcome. The occurrence of depressive symptoms in the past two weeks was assessed with the self-report Patient Health Questionnaire (PHQ-9) (27). This scale has nine items that produce a total score between 0 and 27 with higher scores indicating greater depressive symptomatology. A cut-off score of 10 and above was used to categorize at least moderate depressive symptoms. The self-report Generalized Anxiety Disorder-7 (GAD-7) scale was used to assess anxiety symptoms in the past two weeks (28). This 7-item scale produces a total score that can range between 0 and 21 with higher scores indicating increased anxiety symptoms. Following the suggestion of the scale's developers a score of 10 and above was used in the current study to categorize at least a moderate level of anxiety (28). Perceived stress was assessed with the Perceived Stress Scale (PSS-14) (29). This self-report scale consists of 14 items that when summed produce a score that ranges from 0 to 56 with higher scores indicating greater stress. The scale has been validated in Japan previously (30). In the current study, the scale was used as a continuous score when employed as a covariate, while in order to focus on those individuals experiencing the highest levels of stress, the top decile of scores was chosen as a cut-off point (a score of 37 and above) when examining stress as a health outcome. Lifetime suicidal ideation was assessed with a question enquiring about suicidal thoughts that has been used in previous research (31). Severe sleep problems were assessed with a question which asked, "Overall in the last 30 days, how much of a problem did you have with sleeping, such as falling asleep, waking up frequently during the night, or waking up too early in the morning?" with five response options ranging from 'none' to 'extreme'. Those who responded that they had either severe or extreme sleep problems (options 4 and 5) were categorized as having severe sleep problems. Loneliness was assessed with the Three-Item Loneliness Scale (32). Scores from the summed items create a total score that ranges from 3–9 with higher scores indicating greater loneliness. In this study, the top 15% of scores (a score ≥ 7) were used to categorize loneliness. Cronbach's alpha for the scale was 0.70. Finally, those who agreed with the statement, "I feel that what happens in my life is often determined by factors beyond my control" were categorized as having a low locus of control. This item has been used previously by researchers when assessing perceived control (33).

Statistical analyses

Descriptive statistics were first calculated for the study sample. Next, we examined whether the detrimental health outcomes were elevated in individuals with PE and those with ADHD symptoms compared to their counterparts without these symptoms with Chi-square tests used to assess differences. Logistic regression was then used to assess the association between PE and ADHD symptoms. Five models were used in the analysis: Model 1 examined the association between PE and ADHD symptoms. Model 2 included sociodemographic variables – sex, age, education, marital status and household income. Model 3 included the same variables as in Model 2 and also self-rated health. Model 4 included the same variables as in Model 3 and additionally included anxiety and depressive symptoms. The fully adjusted Model 5 included the same variables as in Model 4 and also included stress as a continuous score. Finally, restricting the analysis to those individuals who were categorized as having PE, we ran a series of separate logistic regression analyses to examine if ADHD symptoms were linked to seven detrimental health outcomes – depressive symptoms, lifetime suicidal ideation, perceived stress, severe sleep problems, poor self-rated health, loneliness and low locus of control. Given the low number of cases included in these analyses they were only adjusted for sex and age.

The analyses were performed with SPSS version 24. Results are presented as odds ratios (OR) with 95% confidence intervals (CI). The level of statistical significance was $p < 0.05$ (two-tailed).

Results

The study sample consisted of 1,452 individuals aged between 18 and 89 (mean age: 51.6 years, SD: 18.1 years) with 51.5% of the sample being female. Details of the main, sociodemographic and health variables are presented in Table 1. More individuals were, respectively, categorized as having PE than ADHD symptoms (4.2% [$N = 61$] vs. 3.5% [$N = 51$]) while 23.0% (14/61) of those individuals with PE also had ADHD symptoms. The prevalence of all of the detrimental health outcomes was significantly higher in individuals with PE and ADHD symptoms (Table 2).

In Model 1 PE were associated with over nine times higher odds for ADHD symptoms (Table 3). Adjusting the analysis for sociodemographic variables and self-rated health reduced the OR and there was an especially large reduction in the OR (over 40%) when the mental health variables were included in the analysis. The OR was further reduced when

TABLE 1 Characteristics of the study sample.

Main/ sociodemographic variables	*N* (%)	Negative health outcomes	*N* (%)
Psychotic experiences		Anxiety	
No	1,391 (95.8)	No	1,295 (89.2)
Yes	61 (4.2)	Yes	157 (10.8)
ADHD symptoms		Depression	
No	1,401 (96.5)	No	1,205 (83.0)
Yes	51 (3.5)	Yes	247 (17.0)
Sex		Lifetime suicidal ideation	
Male	704 (48.5)	No	948 (72.4)
Female	748 (51.5)	Yes	361 (27.6)
Age		Stress (Mean (SD))	27.1 (8.0)
18–34	322 (22.2)		
35–59	572 (39.4)	Severe sleep problems	
≥ 60	558 (38.4)	No	1,350 (93.0)
		Yes	102 (7.0)
Education			
Higher education	937 (64.5)	Self-rated health	
<Higher education	515 (35.5)	Good/very good	698 (48.5)
		Fair	586 (40.7)
Marital status		Poor/very poor	155 (10.8)
Married	890 (61.3)		
Not married	562 (38.7)	Loneliness	
		No	1,234 (85.0)
Household income (yen)		Yes	218 (15.0)
< 4 million	415 (28.6)		
4 million to <10 million	599 (41.3)	Low locus of control	
≥ 10 million	109 (7.5)	No	1,089 (84.5)
Missing data	329 (22.7)	Yes	200 (15.5)

ADHD, Attention-deficit/hyperactivity disorder; SD, Standard deviation.

self-perceived stress was included. Nonetheless, in the fully adjusted Model 5, PE continued to be associated with almost three times higher odds for ADHD symptoms (OR: 2.92, 95%CI: 1.19–7.17). Other variables that were positively associated with ADHD symptoms were depressive and anxiety symptoms and stress symptoms, while adults aged 35–59 had significantly reduced odds for ADHD symptoms compared with those in the youngest age group.

When the analysis was restricted to individuals with PE, ADHD symptoms were associated with significantly higher ORs for four of the seven health outcomes examined – depressive symptoms (OR: 5.36), lifetime suicidal ideation (OR: 11.54), self-perceived stress (OR: 17.52), and severe sleep problems (OR: 7.34), while the association was of borderline statistical significance for low locus of control (OR: 4.36, $p = 0.054$) (Table 4).

Finally, several sensitivity analyses were undertaken for the seven health outcomes. First, all of the regression analyses were also adjusted for location. Second, they were then adjusted for all of the sociodemographic variables, i.e., age, sex, education, marital status and household income. Third, they were subsequently adjusted for all of the sociodemographic variables and mental health (anxiety symptoms when depressive symptoms was the outcome and depressive symptoms in all other analyses). There were no changes in the results when controlling for location. When adjusting for all of the sociodemographic variables there was just one change – ADHD symptoms were now significantly associated with a low locus of control (OR: 6.67, 95%CI: 1.20–36.99). When adjusting for all sociodemographic variables and mental health variables ADHD symptoms continued to be significantly associated with perceived stress and severe sleep problems, while low locus of control was of borderline statistical significance ($p = 0.064$). In addition, the health analyses were also undertaken using the ADHD variable as a continuous score. This produced similar results to those obtained previously. Specifically, when adjusting for sex and age ADHD symptoms were significantly associated with depressive symptoms, stress, severe sleep problems and low locus of control, while the association with suicidal ideation was of borderline significance ($p = 0.05$) (data not tabulated).

Discussion

This study used data from 1,452 individuals aged 18 and above collected from an online sample to examine the association between PE and ADHD symptoms in the Japanese general population. Results showed that there was a strong association between PE and ADHD symptoms. Specifically, in a fully adjusted logistic regression analysis individuals with PE had almost three times higher odds for ADHD symptoms. There was also evidence that ADHD symptoms may increase the risk for negative health outcomes in people with PE as when the analysis was restricted to those with PE, ADHD symptoms were linked to depressive symptoms, suicidal ideation, high levels of stress and severe sleep problems.

Previous research has shown that there is a high level of comorbidity between PE and mental health disorders (5, 34, 35) although until now, there has been comparatively little research that has focused specifically on the association between PE and ADHD and prevalence estimates have varied between the studies that have been undertaken. For example, in a study of 172 adolescents aged 11–12 years old with a lifetime history of PE 4.7% had ADHD (36), while among 262 children with an average age of 12.4 years, 22 had PE and 14% ($N = 3$) of these also had ADHD (37). In contrast, in a sample of over 6,800 individuals aged 8–21, among the 1,320 people with PS the prevalence of ADHD was 45% (8). Further, among 2,385 adults with lifetime PE collected during the World Mental Health Survey 5.1% had ADHD (5). Similarly, in a sample of 509 adults with ADHD with a mean age of 25.12 years 5.1% had screened positive for psychotic symptoms during a 10-year follow-up period (16). In the current study 23.0% of individuals with PE had ADHD symptoms. Comparing this figure with those from previous studies among adults is complicated by the fact that those studies examined PE in adults meeting DSM-IV criteria for ADHD. Nonetheless, it can

TABLE 2 Negative health outcomes in Japanese individuals with PE and ADHD symptoms.

	No-PE	PE	*p*-value	No-ADHD	ADHD	*p*-value
	N (%)	*N* (%)		*N* (%)	*N* (%)	
Anxiety symptoms			< 0.001			< 0.001
No	1,261 (90.7)	34 (55.7)		1,278 (91.2)	17 (33.3)	
Yes	130 (9.3)	27 (44.3)		123 (8.8)	34 (66.7)	
Depressive symptoms			< 0.001			< 0.001
No	1,174 (84.4)	31 (50.8)		1,196 (85.4)	9 (17.6)	
Yes	217 (15.6)	30 (49.2)		205 (14.6)	42 (82.4)	
Lifetime suicidal ideation			< 0.001			< 0.001
No	928 (74.0)	20 (36.4)		937 (74.3)	11 (22.9)	
Yes	326 (26.0)	35 (63.6)		324 (25.7)	37 (77.1)	
Stress			< 0.001			< 0.001
No	1,270 (91.3)	37 (60.7)		1,287 (91.9)	20 (39.2)	
Yes	121 (8.7)	24 (39.3)		114 (8.1)	31 (60.8)	
Severe sleep problems			0.001			< 0.001
No	1,300 (93.5)	50 (82.0)		1,310 (93.5)	40 (78.4)	
Yes	91 (6.5)	11 (18.0)		91 (6.5)	11 (21.6)	
Poor self-rated health			< 0.001			< 0.001
No	1,240 (89.9)	44 (76.6)		1,249 (89.8)	35 (72.9)	
Yes	140 (10.1)	15 (25.4)		142 (10.2)	13 (27.1)	
Low locus of control			< 0.001			0.001
No	1,062 (86.1)	27 (48.2)		1,057 (85.2)	32 (66.7)	
Yes	171 (13.9)	29 (51.8)		184 (14.8)	16 (33.3)	

PE: Psychotic experiences; ADHD: Attention-deficit/hyperactivity disorder.

be speculated that the prevalence of ADHD may be comparatively high in the current study because a screening instrument was used to collect information on this condition.

In a fully adjusted logistic regression analysis PE were associated with almost three times higher odds for ADHD symptoms. Previous studies among adults have produced mixed findings on the association between PE and ADHD showing that there was either no association (16), that ADHD predicted the subsequent onset of PE but PE did not predict later ADHD (5), and that delusion-proneness was correlated with ADHD symptoms in a sample of 925 men in Sweden aged 18 to 35 (38). Interestingly, in an earlier longitudinal study Hennig and coauthors found that ADHD at age 7 was associated with PE at age 12 in statistical analyses that were unadjusted and then adjusted for demographic and maternal factors. However, when the analysis was further adjusted for other mental health diagnoses the association became non-significant indicating that certain psychiatric disorders may be important for the association (10). There is some indication that mental health might also play a role in the current study as when anxiety and depressive symptoms were included in the analysis the OR for the association between PE and ADHD symptoms reduced sharply, although it remained statistically significant.

In an analysis that was restricted to individuals with PE, ADHD symptoms were associated with significantly increased odds for several negative health outcomes. Earlier research has shown that adults with PE may be at increased risk for outcomes such as depression (5, 34), suicidal ideation (39), stress sensitivity (40) and sleep problems (41). However, until now, there has been little attempt to focus on the mechanisms linking PE and worse health outcomes even though a previous study showed that co-occurring depressive symptoms and PEs increased the risk for negative outcomes (35). This study focused on ADHD symptoms not only because PE and ADHD/ADHD symptoms can co-occur (5, 11) but also because ADHD symptoms have themselves been associated with the same negative health outcomes that PE have been linked to (42–45) as was further confirmed in the analysis in Table 2 in this study. Hence, this study was designed to determine if the presence of ADHD symptoms further increased the risk for these outcomes in individuals with PE.

Given the observed associations it is possible that various mechanisms might link ADHD symptoms with negative health outcomes in individuals with PE. For example, a recent study found that ADHD symptoms were associated with the presence of more (severe) psychotic symptoms in PS youth (8). This may be important as there is some evidence that a higher number of psychotic symptoms may greatly increase the odds for negative outcomes such as suicidal ideation (39). Alternatively, factors that are inherent in ADHD may have also played a role. In particular, a recent study has suggested that sleep problems might represent an intrinsic feature of adult ADHD (46), while impulsivity has been found to positively correlate with depression and stress

TABLE 3 Association between PE and ADHD symptoms in individuals in the Japanese general population (*N*=1,439).

	Model 1	Model 2	Model 3	Model 4	Model 5
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Psychotic experiences	9.53 (4.66–19.49)***	7.69 (3.54–16.69)***	7.20 (3.25–15.96)***	3.72 (1.56–8.88)**	2.92 (1.19–7.17)*
Sex					
Female		1.19 (0.64–2.19)	1.23 (0.66–2.29)	1.31 (0.67–2.55)	1.16 (0.59–2.30)
Age					
18–34		Ref.	Ref.	Ref.	Ref.
35–59		0.26 (0.12–0.54)***	0.22 (0.10–0.47)***	0.34 (0.15–0.77)*	0.30 (0.13–0.69)**
≥ 60		0.18 (0.07–0.45)***	0.16 (0.06–0.40)***	0.40 (0.14–1.14)	0.44 (0.15–1.26)
Education					
Less than higher education		0.87 (0.44–1.72)	0.77 (0.39–1.55)	0.83 (0.40–1.72)	0.81 (0.38–1.73)
Marital status					
Not married		1.45 (0.71–2.96)	1.22 (0.59–2.52)	1.11 (0.51–2.41)	1.07 (0.48–2.37)
Household income (Yen)					
≥ 10 million		Ref.	Ref.	Ref.	Ref.
< 4 million		0.67 (0.19–2.29)	0.59 (0.17–2.04)	0.56 (0.15–2.09)	0.48 (0.12–1.84)
4 < 10 million		0.50 (0.15–1.64)	0.48 (0.15–1.56)	0.63 (0.18–2.23)	0.52 (0.14–1.91)
Missing data		0.72 (0.21–2.45)	0.67 (0.20–2.26)	0.79 (0.21–2.93)	0.65 (0.17–2.49)
Self-rated health					
Good/very good			Ref.	Ref.	Ref.
Fair			1.88 (0.92–3.86)	1.66 (0.77–3.60)	1.36 (0.61–3.02)
Poor/very poor			4.11 (1.77–9.51)**	1.78 (0.72–4.42)	1.37 (0.53–3.52)
Depressive symptoms				7.46 (3.02–18.43)***	4.86 (1.91–12.37)**
Anxiety symptoms				4.06 (1.86–8.88)***	2.78 (1.23–6.26)*
Stress symptoms					1.09 (1.04–1.14)***

PE, Psychotic experiences; ADHD, Attention-deficit/hyperactivity disorder.
OR, Odds ratio; CI, Confidence interval; Ref, Reference category.
***$p < 0.001$, **$p < 0.01$, *$p < 0.05$.

across different age groups (47). Common underlying factors may also underpin the observed associations. Specifically, the altered transmission of DA may play a role in the emergence of both PE and ADHD symptoms (13), while other research has proposed that changes in DA neurotransmission might also be important in the pathophysiology of depression (48).

Limitations

This study has several limitations that should be discussed. First, the data analyzed in this study came from individuals in the Japanese general population who were not randomly sampled but rather participated in an online survey. This may have increased the risk for selection bias (49) linked for example, to issues such as internet access. Second, given the potential sensitivity associated with issues such as mental health it is possible that non-responding may have been an issue, although a recent study from Australia found that participants may be more likely to respond to questions on sensitive topics in online surveys (50). Third, due to the relatively small number of individuals with PE we were limited in the number of variables we could safely adjust for in the analyses when examining the association between ADHD symptoms and health outcomes in individuals with PE, given the commonly applied rule that a minimum number of 10 events is needed per variable in logistic regression (51). Being able to control for a larger number of variables would have affected the observed results (as indicated in the sensitivity analyses when fewer associations were significant when adjusting for all demographic variables and mental health). In addition, it is possible that some of these analyses were underpowered to detect associations, while the confidence intervals were wide indicating imprecision in the estimates obtained. Fourth, we lacked information on whether respondents had diagnosed mental health conditions such as psychotic disorder or ADHD. This might have been important as there is some evidence, for example, that ADHD medication may be linked to the occurrence of reduced suicidal behavior (attempts) (52). Fifth, due to an absence of data we were not able to determine the effects of potentially important factors in the association between PE and ADHD symptoms such as illicit drug use. For example, cannabis use has been associated with the

TABLE 4 Association between ADHD symptoms and negative health outcomes in individuals with PE ($N=61$).

	Depressive symptoms	Lifetime suicidal ideation	Stress symptoms	Severe sleep problems	Poor self-rated health	Loneliness	Low locus of control
Variable	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
ADHD symptoms	5.36 (1.27–22.66)*	11.54 (1.23–107.94)*	17.52 (3.25–94.50)**	7.34 (1.60–33.59)*	1.73 (0.39–7.65)	1.93 (0.53–6.97)	4.36 (0.98–19.44)
Sex							
Female	1.79 (0.59–5.42)	3.75 (0.97–14.53)	2.17 (0.60–7.87)	2.67 (0.57–12.58)	4.48 (1.08–18.50)*	0.41 (0.13–1.27)	0.89 (0.29–2.75)
Age							
18–34	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
35–59	0.57 (0.16–1.99)	0.28 (0.06–1.29)	0.58 (0.15–2.36)	1.69 (0.31–9.16)	1.55 (0.36–6.72)	0.74 (0.22–2.47)	1.76 (0.48–6.44)
≥ 60	0.67 (0.15–3.08)	1.08 (0.17–6.78)	0.50 (0.08–3.02)	2.02 (0.22–18.61)	1.47 (0.24–9.17)	0.25 (0.04–1.52)	2.43 (0.52–11.23)

PE: Psychotic experiences; ADHD: Attention-deficit/hyperactivity disorder.
OR: Odds ratio; CI: Confidence interval; Ref: Reference category.
*$p<0.05$; ** $p<0.01$.

occurrence of both PE and ADHD symptoms (53, 54) and has also been linked to worse health outcomes such as depression and suicidal ideation (55, 56). Finally, as the data were cross-sectional we were not able to determine the directionality of the observed associations.

Conclusion

This exploratory study showed that PE are linked to ADHD symptoms in the Japanese general population and that in individuals with PE, ADHD symptoms are associated with negative health outcomes. Screening for PE in individuals with ADHD/ADHD symptoms and ADHD symptoms in people with PE and first-episode psychosis may help with developing treatment options and facilitating better outcomes in both populations.

Data availability statement

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

Ethics statement

Permission for the survey was provided by the Ethics Committee at the National Center of Neurology and Psychiatry, Tokyo, Japan (approval number: A2020-088). The participants provided their written informed consent to participate in this study.

Author contributions

ASt had the study idea, analyzed the data, and wrote the main text. ASh liaised with the data collection company, discussed the analysis, and commented on the main text for intellectual content. TS supervised the project and critically reviewed and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

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Mobile health in the specific management of first-episode psychosis: a systematic literature review

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Purpose: The purpose of this systematic literature review is to assess the therapeutic efficacy of mobile health methods in the management of patients with first-episode psychosis (FEP).

Method: The participants are patients with FEP. The interventions are smartphone applications. The studies assess the preliminary efficacy of various types of application.

Results: One study found that monitoring symptoms minimized relapses, visits to A&E and hospital admissions, while one study showed a decrease in positive psychotic symptoms. One study found an improvement in anxiety symptoms and two studies noted an improvement in psychotic symptoms. One study demonstrated its efficacy in helping participants return to studying and employment and one study reported improved motivation.

Conclusion: The studies suggest that mobile applications have potential value in the management of young patients with FEP through the use of various assessment and intervention tools. This systematic review has several limitations due to the lack of randomized controlled studies available in the literature.

KEYWORDS

early psychosis, first-episode psychosis, early intervention, mobile health, mobile applications, digital intervention, smartphone

1. Introduction

1.1. Early intervention in psychosis

The central issues in emerging psychosis are accessing and maintaining effective care. One factor that justifies early intervention is the stage of life at which FEP occurs: late adolescence and early adulthood. This period coincides with a critical phase of development, in which life plans can be disrupted. The aim of early intervention in psychosis (EIP) is to provide recovery-oriented care for young patients with FEP (1).

The first goal of early intervention is to reduce the duration of untreated psychosis (DUP). Long DUP may have a significant social impact, accentuating social withdrawal and stigmatization (1). The other goals concern the prevention of relapse and of unfavorable long-term evolution. The aim is to prevent allowing functional disability and social exclusion to set in (1).

The two main components of EIP are an adapted form of case management and the initiation of treatment as soon as possible after FEP (2).

The deployment of EIP programmes has been an important development in recent decades. Current scientific evidence suggests that these programmes are associated with better outcomes than standard treatment in the early stages of psychosis. A recent meta-analysis including 10 randomized controlled trials on three continents (Europe, North America and Asia) demonstrates the superiority of EIP programmes in terms of treatment discontinuation rates, proportion of patients requiring hospitalization, occupational and educational progression, global functioning and severity of positive and negative symptoms (3).

1.2. Patient engagement

Patient engagement in care is fragile for psychotic disorders, and FEP in particular. A Swiss study estimated that 50% of patients were lost to follow-up or disengaged after their first hospitalization in a standard psychiatric department (4). The greater the patient's engagement, the lower the risk of relapse. Early intervention programmes aim to involve patients in their care by fostering a therapeutic alliance. AS a result, they limit the traumatic nature of early psychotic experiences (1).

Nevertheless, a significant proportion of patients (20.5%−40%) still drop out of specialized follow-up within the first 2 years (5). Factors associated with disengagement from early intervention programmes are lack of family support, poor adherence to treatment, substance misuse, coming from an ethnic minority and having a criminal record (5, 6). To reduce the risk of disengagement, particular attention should be paid to these factors by offering targeted intervention. These factors at patient level may thus influence engagement, but the level of care provided may also be at the root of patient disengagement. The most common reason given by patients is that the care does not meet their needs (7).

1.3. mHealth

Recovery is now one of main objective in the field of schizophrenia-related disorder (mainly FEP) (8). Recovery includes, amongst others, perceived social integration and empowerment (9). However, individuals with psychosis report experiences of loneliness and social withdrawal (10, 11). The Survey of High Impact Psychosis indicates that loneliness and social withdrawal rank second on the list of challenges to recovery (12–14). Moreover, the face-to-face relationship could be reduced for individuals with psychosis due to a diminution of pleasure (anhedonia) and a sense of threat (15). Schlosser et al. (16) highlighted that internet-based interventions focusing on social connection could decrease social withdrawal in this population. Moreover, young patients going through FEP fear being stigmatized, that clinicians do not acknowledge their experiences and are unable to respond appropriately to their needs (17). Technology can offer the possibility of accessing resources or coping strategies without the fear of the stigma associated with mental health. It can provide platforms for young people to share their experiences and feel supported, provide new ways of working with their careers, allow more accurate assessment of their symptoms and promote positive changes in their daily lives. In addition, mobile health could help patient to increase their own empowerment (18).

Studies in Canada show that most young people admitted for FEP have access to a smartphone (19). A study conducted in an EIP programme in Montreal shows that over 90% of young people diagnosed with FEP have access to a smartphone (20) and many are receptive to using this technology for their mental health care (21). People with FEP report that the use of mobile technologies could be an acceptable way to access mental health information and support, decrease the stigma associated with care and could provide a sense of control over their recovery (referred to internationally as "empowerment") (22). Most of these young people are open to using technology to receive therapy (21), to get in touch with their peers with similar problems, and they particularly appreciate it when the sites are professionally moderated (23).

The restrictions resulting from the COVID-19 pandemic have heightened the demand for mental health care and imposed a reorganization of our care system by stepping up the use of digital technologies, notably telemedicine (24–26). A 17-country study reports increased use of digital health in mental health care settings, as well as support to facilitate its adoption during the pandemic (27).

Mobile health uses mobile devices such as smartphones to deliver health care. These devices are compact, wireless and universally available at an affordable cost. They provide connectivity, Internet access and multimedia resources at any time and almost anywhere.

The most common mHealth strategies take the form of applications. It is now quite easy to create new applications, find them on online platforms, download them and share them. Mental health applications can be used for Ecological Momentary Assessment (EMA) or Ecological Momentary Intervention (EMI).

EMA is an assessment system that collects data from participants, in their environment and at different times. It includes active data, which generally refers to symptom monitoring questionnaires to be filled in by the individual on their smartphone. It also includes passive data, obtained automatically through sensors on the smartphone or on a wearable device (bracelet or connected watch).

EMI has a similar structure, but the content includes reminders, feedback messages or instructions to adopt specific behaviors or those important for psychotherapy (28). This type of intervention aims to provide support in daily life by sending electronic notifications that encourage therapeutic behaviors at the time they are needed (8). These mobile application-based interventions provide on-demand access to specific therapeutic or psycho-educational tools. Heron and Smyth (29) define these interventions as treatments that are provided to people during their everyday lives (i.e., in real time) and in natural settings (i.e., in the real world). This tool also provides access to a social network. Promising pilot data has been reported for the Moderated Online Social Therapy (MOST) model, an online intervention platform that offers personalized therapy combined with social links and other features. This system combines therapeutic tools, psycho-educational content and a secured, moderated social network. It

was developed in Australia by eOrygen, the digital arm of Orygen, The National Center of Excellence in Youth Mental Health, and is led by Professor Mario Alvarez-Jimenez, Chief of Orygen Digital. It is a moderated online social therapy platform that targets 15 to 25-year-olds to improve the social functioning of young people at risk of psychosis (30). The platform can be accessed on mobile phones, tablets and computers. MOST was piloted in Victoria and expanded rapidly in Australia during the COVID-19 pandemic. It consists of a network of peers and expert mental health clinicians. The young patients can also use the platform to interact with other patients.

These tools are used in various ways, ranging from symptom monitoring, medication compliance and promotion of self-management strategies through to access to psycho-education and social relationships.

1.4. Current literature and purpose of the review

The evidence to date suggests that smartphone applications could provide an accessible, flexible and inexpensive means of delivering effective self-management interventions for depression and anxiety symptoms (31, 32). A meta-analysis of 18 randomized controlled trials covering 22 mobile applications has shown that using applications for symptom relief significantly reduces patients' depressive symptoms compared with the control group, mainly for people with mild to moderate depression (31). A second meta-analysis of 66 randomized controlled trials found results in favor of intervention groups for depressive symptoms, generalized anxiety and social anxiety (33).

The current published literature on the use of applications in psychosis is more limited. Reviews have highlighted the growing potential of technologies for the treatment of psychosis (26, 34–36) and studies of smartphone applications have shown that they are acceptable and feasible for this population. One review reports the feasibility of using smartphones to improve care for people with schizophrenia, with high rates of engagement and satisfaction over a wide range of applications (34). The FOCUS smartphone intervention study (37) trialed in 2014 on a population of schizophrenic patients shows that the intervention significantly reduces psychotic symptoms.

There are two recent literature reviews on early psychosis: Mar Rus-Calafell and her team summarize the main results of studies between 2009 and 2019 on the use of digital technologies (virtual reality, smartphones and online interventions) to improve the treatment of early psychosis. Most of the studies included are only at the protocol stage and the participants are in an at-risk mental state for psychosis or have FEP (38). The systematic review by Erica Camacho and her team also includes participants in the prodromal and FEP phases. It includes 21 studies: seven papers on protocols, six on feasibility studies, five on validity studies and three on interventions (39). The published literature demonstrates the acceptability and feasibility of interventions. The results show that it is possible to use digital technologies to deliver psychological interventions in the early stages of psychosis, with participants expressing high levels of acceptability and willingness to use them to support their progress and recovery.

To our knowledge, assessment of the therapeutic efficacy of mobile health methods in the management of patients with FEP has not previously been summarized in a systematic review. We have therefore conducted a systematic review of the literature on the preliminary clinical outcomes of digital applications for the support or delivery of treatment for new-onset psychotic disorders. In this literature review, we focus only on patients with FEP and only on one type of technology, mobile smartphone applications that have been developed and validated for acceptability and feasibility. We have focused on studies that assess the preliminary efficacy of this type of tool. In addition, several studies published between 2019 and 2022 have been added. Most of these studies assess the value of adding mobile digital interventions alongside early intervention care or to extend its benefit.

2. Method

2.1. Eligibility criteria

Following the PICO model, the inclusion criteria were: (i) population representing young patients with first-episode psychosis, no more than 5 years after diagnosis; (ii) intervention using a mobile smartphone application; (iii) in comparison with usual care; (iv) paper written in English or French; (v) describing the effects of mobile health interventions in the management of young patients with FEP and (vi) studies assessing clinical outcomes that could be related to intervention objectives.

The exclusion criteria were: (i) any intervention using technology not provided by a smartphone; (ii) papers not published in English or French and literature reviews; (iii) papers describing experimental protocols with no current results or exploratory studies. Papers including patients in an at-risk mental state for psychosis were excluded, to make the patient sample as comparable and homogeneous as possible.

We have studied smartphone applications rather than other digital platforms because of their mobility and accessibility. We have included studies without a control group due to the fact that this literature is in its infancy.

2.2. Literature search strategy

A systematic search of the international literature was carried out using the Pubmed and Embase search engines. The search covered papers published between the creation of the database and 13 May 2022 using a search equation including the following Medical Subject Headings (MESH): (Psychosis OR Schizophrenia) AND (Early Medical intervention) AND (Digital Technology OR smartphone OR mobile applications OR social media OR internet). The references cited in the selected papers were reviewed to identify any additional relevant studies.

2.3. Study selection process

Two authors (CM and AC) screened the titles of the publications identified in the databases using the search strategy

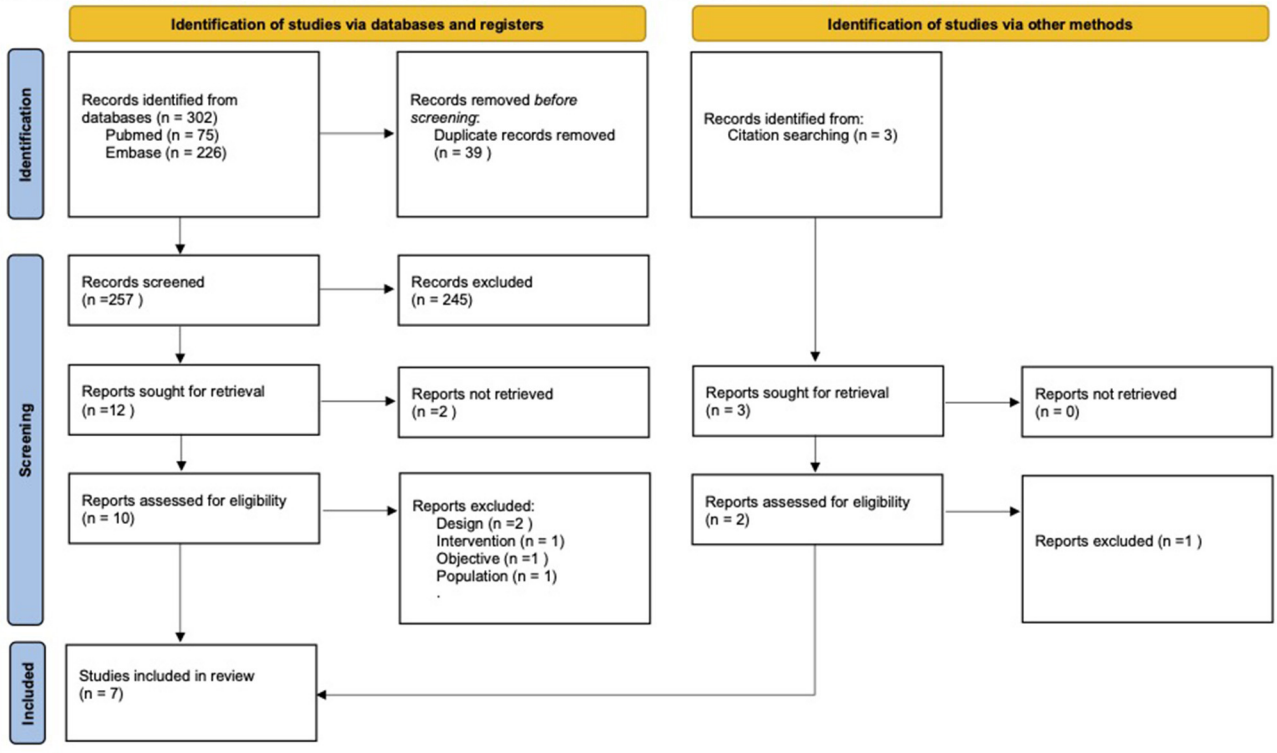

FIGURE 1
Flow chart of study selection according to PRISMA 2020 guidelines.

defined above to identify potentially eligible studies. Both authors, first independently and then jointly, screened the studies based on their abstracts. All online abstracts were reviewed and full-text papers were retrieved where relevant. In case of disagreement, a third author (AY) was called on to arbitrate. This search procedure followed PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (40) (Figure 1).

2.4. Bias assessment

To our knowledge, no rigorously validated method of assessing the quality of studies in this field exists. We applied the method using the Jaddad scale (41) that includes: randomization, masking/double blind and a description of losses during follow-up. The variable of the existence or not of a "control group" was added as done by Bonet et al. in the 2017 review to conduct a reproducible analysis of the study quality (18).

The assessment is based on the presence or absence of the following criteria:

1. Randomized.
2. Double blind.
3. Losses.
4. Sufficiently randomized (studies that indicate the randomization technique used (computer-generated table of random numbers, throwing a coin, properly shuffled envelopes, etc.).
5. Sufficiently double blind.
6. Control group.
7. Total.

We considered studies to be of poor quality when they scored <3 points, and they were considered to be of maximum quality at 5 and 6 points.

3. Results

3.1. Selection of studies

The flow chart (Figure 1) describes the study selection process and shows the initial selection of 302 papers and then the selection of 257 papers for in-depth assessment after eliminating duplicates. Two hundred forty-five further papers were excluded after review of their titles and abstracts. Full-text versions were retrieved for 12 papers, of which five were eligible for inclusion. Two further papers were added from the references cited in the papers studied. Hence, a total of seven studies have been included in this review.

3.2. Characteristics of the selected studies

The full details of each study are shown in Table 1 (and Supplementary Data S1). Results were available for four randomized controlled trials, one pragmatic clinical trial and two open trials. The average age of the sample was 24.4 years.

TABLE 1 Characteristics of seven studies on mobile health (mHealth) in the treatment of first-episode psychosis.

References	Application	*N*	Mean age	Population origin	Design	Objective	Intervention	Results
Lewis et al. (42)	ClinTouch	44	26.1	"Early psychosis" sub-group: patients receiving care in an EIP programme In the first three years following FEP London (United Kingdom)	Two-center open-label randomized controlled trial Active monitoring of symptoms under ClinTouch plus treatment as usual compared with treatment as usual alone Length of intervention: 12 weeks	Assess the acceptability and safety of continuous monitoring for 3 months, the impact on positive psychotic symptoms at 6 and 12 weeks, and the feasibility of detecting early signs of relapse by the care team through the application	EMA Active symptom monitoring Alerts sent to the care coordinator when personalized warning-sign thresholds were exceeded	Significant reduction in positive PANSS in the "early intervention center" sub-group (adjusted mean difference −3.04; CI −5.49, −0.59; $p = 0.016$) The performance of the prototype early warning signs algorithm was "sub-optimal" with a sensitivity of 75%, a specificity of 8%, giving a positive predictive value of 29%
Bonet et al. (43)	ReMind Care	90	32.8	17–65 years old Patients receiving care in an EIP programme since 2018 Within 5 years after FEP Valencia (Spain)	Pragmatic clinical trial comparing ReMindCare with TAU over 19 months Length of intervention: 50 weeks	Assess the efficacy and clinical results of application use in terms of adherence to ReMindCare, prevention of relapse, hospital admissions and A&E visits	EMA ReMindCare offers active symptom monitoring and alerts to doctors in case of low engagement or sudden changes to questionnaire replies	Significantly fewer relapses ($\chi^2 = 13.7$, $p = 0.001$), hospitalizations ($\chi^2 = 4.6$, $p = 0.03$) and A&E consultations ($\chi^2 = 7.4$, $p = 0.006$) in the ReMindCare group
Alvarez-Jimenez et al. (44)	Horyzons	170	20.9	16–27 years old. After 18–24 months' care in an Early Psychosis Prevention and Intervention Center (EPPIC) Melbourne (Australia)	Phase 4 randomized controlled trial, parallel groups, single blind Compare Horyzons plus TAU with TAU alone Length of intervention: 18 months (72 weeks)	Assess whether digital intervention is an effective strategy to extend the benefits of EIP treatment and promote social and vocational recovery beyond discharge from these specialized EIP programmes and prevent relapse after FEP	EMI Horyzons is based on the MOST model	No significant change in social functioning (PSP score; mean difference = −0.29, 95% CI: −4.20 to 3.63, effect size = −0.01, $p = 0.77$) or in secondary endpoints (CDSS, UCLA, MOS-SSS, SERS-SF, MHCS, SWLS, AQoL, PANSS). 5.5 times more likely to find a job and/or enroll in education (OR = 5.55, 95% CI: 1.09–28.23, $p = 0.04$). Significantly less likely to visit A&E (p = 0.03) twice as many hospitalizations for psychosis in the TAU group, without significant difference
Ludwig et al. (12)	Horyzons	26	24.9	18 to 35 years old, cared for by three EIP departments in North Carolina (United States)	Uncontrolled open trial Length of intervention: 12 weeks	Assess acceptability and feasibility, assess whether participation in this platform correlates with a reduction in the feeling of loneliness, and an improvement in social integration and the feeling of wellbeing	EMI Horyzons is based on the MOST model	Improvement in PANSS psychosis-related symptoms ($d = 0.81$). Moderate reduction in UCLA experience of loneliness ($d = 0.27$), BDI depressive symptoms ($d = 0.30$), and mDES NEG negative emotions ($d = 0.27$). Login frequency was significantly associated with improved psychological wellbeing in actively engaged participants

(Continued)

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TABLE 1 (Continued)

References	Application	*N*	Mean age	Population origin	Design	Objective	Intervention	Results
McEnery et al. (45)	Embrace	10	23	Participants in the Horyzons study after 2 years' EIP care and 18 months' online social support (Horyzons)	Single-arm open-label trial Length of intervention: 8 weeks.	Assess the feasibility, acceptability and safety of online intervention using Embrace, designed to treat social anxiety as the primary target in young people with FEP	EMI Embrace is based on the MOST model The clinical content targets a specific CBT therapeutic goal related to management of social phobia	Statistically significant decreases for social anxiety symptoms with SIAS ($d = -1.70$, $p = 0.0005$) and LSAS ($d = -1.35$, $p = 0.002$). Non-statistically significant decreases for depression ($d = -0.22$, $p = 0.50$) and loneliness ($d = -0.23$, $p = 0.48$; DASS and UCLA)
Schlosser et al. (16)	Prime	43	24	16–36 years old with new-onset schizophrenia spectrum disorder, first 5 years of illness (United States)	Randomized controlled trial comparing the Prime group with the TAU control group Length of intervention: 12 weeks	Assess the ability of the application to improve motivational disorders during first-episode psychosis	EMI Designed to target motivation by setting goals to be achieved, with individualized CBT-based follow-up and coaching The application's interventions consisted of automated reminders of goals and challenges and real-time messaging with a clinician	Significant improvements in favor of the intervention group were found for two motivational components (anticipated pleasure and effort expenditure). Respectively: $F_{(1, 56)} = 4.75$, $p = 0.03$ and $F_{(1, 56)} = 4.66$, $p = 0.04$ A trend toward significant improvement in reward learning was found $F_{(1, 56)} = 3.53$, $p = 0.07$ Significant differences for defeatist beliefs, $F_{(1, 57)} = 5.58$, $p = 0.02$, for depressive symptoms, $F_{(1, 56)} = 7.06$, $p = 0.01$, and for feelings of self-efficacy, $F_{(1, 55)} = 5.76$, $p = 0.02$ No differences in changes in positive or negative symptoms (PANSS), quality of life (QOL-A) or functioning (RFS)
Bucci et al. (22)	Actissist	36	19.3	>16 years old Within the first 3 years after FEP Cared for in an EIP programme North-west England	Pilot single-blind randomized controlled trial comparing Actissist plus TAU with ClinTouch plus TAU Length of intervention: 12 weeks	Assess the safety, feasibility and acceptability of Actissist intervention Provide preliminary evidence of the effects of the intervention on clinical and functional outcomes	EMI compared with EMA (Active control) Intervention based on CBT tools	Greater improvement in negative symptoms (negative PANSS), general psychotic symptoms (general and total PANSS) and mood (Calgary score) in the Actissist + TAU group compared with the ClinTouch + TAU group with numerically higher regression coefficients (adjusted mean differences) and standardized effect sizes (Cohen's *d*) for the post-treatment assessment with Actissist

EIP, Early Intervention in Psychosis; FEP, first-episode psychosis; EMA, Ecological Momentary Assessment; EMI, Ecological Momentary Intervention; MOST, Moderated Online Social Therapy; TAU, treatment as usual; PSP, Personal and Social Performance Scale; BDI, Beck Depression Inventory; mDES Neg, modified Differential Emotions Scale - Negative Sub-scales; AQoL, Assessment of Quality of Life; CDSS, Calgary Depression Scale for Schizophrenia; UCLA, UCLA Loneliness Scale; MOS-SSS, Medical Outcomes Study Social Support Survey; SERS-SF, Self-Esteem Rating Scale - Short Form; MHCS, Mental Health Confidence Scale; SWLS, Satisfaction with Life Scale; AQoL-8D, Assessment of Quality of Life - 8D; PANSS, Positive and Negative Syndrome Scale; RFS, Role Functioning Scale; SIAS, Social Interaction Anxiety Scale; LSAS, Liebowitz Social Anxiety Scale.

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Smartphone interventions lasted for an average of 25 weeks. Table 1 summarizes the papers included and their characteristics.

The seven studies assessed smartphone interventions focusing on symptoms monitoring, therapeutic intervention and/or social networks.

3.3. Quality

No study attained the highest score for methodology, as the lack of blind was their main limitation. In addition, four studies scored <3 and were considered to be of poor quality (Table 2). Only four of the studies were randomized controlled trials (16, 42, 44, 46), one out of four was from a sub-group (47). The samples included in this study are small and the follow-up periods short. One study used a sample from a previous intervention.

3.4. Symptom monitoring and improvement

The symptom monitoring studied here consists of daily assessment of patients' state of health through short questionnaires covering positive psychotic symptoms, anxiety and mood. The mobile applications can monitor symptoms and may include a secure portal where the clinician receives clinical information. The clinician is thus aware of changes in symptoms and can adjust interventions accordingly, in addition to conventional clinical follow-up (48). Lewis et al. did not show any significant difference between the groups in the total positive PANSS after 6 and 12 weeks, and no difference in secondary endpoints. However, after a separate intention-to-treat analysis for each site, the study shows a significant reduction in positive PANSS after 12 weeks of ClinTouch monitoring in the Early Intervention sub-group (adjusted mean difference −3.04; CI −5.49, −0.59; $p = 0.016$). The results regarding the performance of the prototype early warning signs algorithm are "sub-optimal" for the accuracy of ClinTouch alerts compared with the warning signs as documented in the electronic patient record, with a sensitivity of 75%, a specificity of 8%, giving a positive predictive value of 29% (42). Bonet et al. (43), showed that after 19 months of using ReMindCare, only 20% of patients in the ReMindCare group suffered a relapse, while 58% of TAU patients had one or more relapses ($\chi^2 = 13.7$, $p = 0.001$). In addition, ReMindCare patients had fewer urgent care unit visits ($\chi^2 = 7.4$, $p = 0.006$) and fewer hospitalizations than TAU patients ($\chi^2 = 4.6$, $p = 0.03$). Of the 59 ReMindCare patients, 31% requested an urgent consultation, 20% relapsed while using the application and 8% developed a delusion involving the application and the research group. After 19 months of intervention, 63% of patients continued using the application, while 12% stopped using the application because they were discharged from the EIP department and 25% opted to stop using ReMindCare. Reasons for discontinuation: 33% of patients felt suspicious about the technology (among these patients, 4 had a relapse while using the application); 40% (6/15) perceived the application as boring and did not perceive any benefit; and 27% (4/15) of patients left treatment and did not

TABLE 2 The methodological quality of studies analyzed.

References	Application	Randomized	Double blind	Losses	Sufficiently randomized	Sufficiently double blind	Control group	Total
Lewis et al. (42)	ClinTouch	1	0	0	1	0	1	3
Bonet et al. (43)	ReMind Care	0	0	0	0	0	1	1
Alvarez-Jimenez et al. (44)	Horyzons	1	0	1	1	0	1	4
Ludwig et al. (12)	Horyzons	0	0	1	0	0	0	1
McEnery et al. (45)	Embrace	0	0	0	0	0	0	0
Schlosser et al. (16)	Prime	1	0	0	0	0	1	0
Bucci et al. (22)	Actissist	1	0	1	1	0	1	4

0 = No; 1 = Yes.

continue in the programme. The 2018 Actissist (46) showed greater improvement in negative symptoms (negative PANSS), general psychotic symptoms (general and total PANSS) and mood (Calgary score) in the Actissist + TAU group compared with the ClinTouch + TAU group with numerically higher regression coefficients (adjusted mean differences) and standardized effect sizes (Cohen's *d*) for the post-treatment assessment with Actissist. The effects were not fully maintained at the 22-week follow-up, though there was no decline in any of the clinical outcomes measured. Focusing on Horyzons project, there was no significant difference in the hospitalization rate and no significant difference in psychotic symptoms. There were no significant changes in secondary endpoints (psychotic symptoms measured by PANSS, depressive symptoms measured by the Calgary Depression Scale for Schizophrenia CDSS, selfesteem measured by the Self-Esteem Rating Scale SERS-SF, selfefficacy measured by the Mental Health Confidence Scale MHCS). In addition, participants assigned to Horyzons were significantly less likely to visit A&E over the 18-month period ($p = 0.03$) compared with the TAU group. The TAU group had twice as many A&E visits as the Horyzons plus TAU group from baseline to 18 months, a statistically significant difference (39 vs. 19% respectively; OR=0.31, 95% CI: 0.11–0.86, $p = 0.03$, NNT = 5).The TAU participants had twice as many hospitalizations for psychosis as the Horyzons plus TAU group, without significant difference (27 vs. 13% respectively; OR = 0.36, 95% CI: 0.11–1.08, $p = 0.07$, NNT = 7). In Horyzons US (12), the results showed an improvement in psychosis-related symptoms (PANSS): large effect size from baseline to mid-treatment (Cohen's $d = 0.81$) and medium to large effect size from baseline to end of treatment (Cohen's $d = 0.65$). They also showed a moderate reduction in experiences of depressive symptoms and negative emotions after 6 weeks of using the platform. Self-reported experience of negative emotions (mDES NEG): small to medium effect size between baseline and end of treatment (Cohen's $d = 0.27$). Depressive symptoms (BDI): small to medium effect size between baseline and mid-treatment (Cohen's $d = 0.30$). McEnery et al. (47) using Embrace, showed a statistically significant reduction in social anxiety symptoms as measured by the Social Interaction Anxiety Scale [SIAS, (49)] between baseline and the end of the intervention ($d = -1.70$, $p = 0.0005$). This significant reduction is also confirmed using the Liebowitz Social Anxiety Scale (50), ($d = -1.35$, $p = 0.002$). Finally, non-statistically significant decreases were found for depression ($d = -0.22$, $p = 0.50$) the secondary endpoint. Participants reported that the application provides them with a sense of control over their social anxiety symptoms.

The 2018 Prime group (16) did not highlight differences between the groups in changes in positive or negative symptoms (PANSS). In addition, there was a trend toward significant improvement in reward learning, $F_{(1, 56)} = 3.53$, $p = 0.07$ and the results showed significant differences for defeatist beliefs, $F_{(1, 57)} = 5.58$, $p = 0.02$, for depressive symptoms, $F_{(1, 56)} = 7.06$, $p = 0.01$.

Three interventions can monitor symptoms (42, 43, 46). Except Horyzons that did not show any difference focusing on symptoms (44), the others interventions were associated with improvement of general (12, 46), positive (42, 46), negative symptoms (46), mood (12, 16, 46) and anxiety (47). One intervention was associated with a reduction of hospitalization (43) and A&E visits (43, 44).

3.5. Social network and interaction

Horyzons (44) incorporating a moderated social network aimed at recovery after FEP is, to date, the most advanced online psychosocial intervention programme for early psychosis. However, the results showed no difference in social functioning, the primary endpoint. There was no significant change in Personal and Social Performance Scale (PSP) scores at 18 months follow-up (mean difference = −0.29, 95% CI: −4.20 to 3.63, standardized effect size = −0.01, $p = 0.77$). The level of functioning remained stable for both groups between the start and 18-month follow-up. However, patients in the Horyzons intervention group were 5.5 times more likely to find a job and/or enroll in education compared with the TAU group (OR = 5.55, 95% CI: 1.09–28.23, $p = 0.04$).

According to a *post-hoc* analysis, participants in the top quartile of logins (i.e., logging in >77 times) show greater improvement in employment and education outcomes (OR = 59.71; 95% CI: 2.40–1484.37, $p = 0.01$) compared with those in the bottom quartile of logins (i.e., <9 logins; OR = 1.40; 95% CI: 0.03–72.40, $p = 0.87$).

In US version (12), focusing on loneliness (UCLA), they highlighted small to medium effect size between baseline and mid-treatment (Cohen's $d = 0.27$). Login frequency is significantly associated with improved psychological wellbeing in actively engaged participants. Minimum use of the platform is defined as an average of at least one login per week (12 logins in total) and at least 10 uses of the application (e.g., comments, talking points, etc.). The rate of active participants (patients who met or exceeded this threshold) is 79%, while the rate of inactive participants (patients who did not meet the minimum usage) is 21%. The *Embrace* programme (45) was associated with a non-statistically significant decreases of loneliness ($d = -0.23$, $p = 0.48$) scores.

None study showed an impact on functioning or loneliness scale. However, Horyzons program was associated with a return to working life.

3.6. Engagement

Most of the programs were associated with an engagement range from moderate to high. Six studies highlighted an engagement over 70% (16, 42–44, 46, 47). Moreover, Preliminary findings suggested active engagement in Horyzons was associated with enhanced social integration, improved psychological wellbeing, increased positive emotions, as well as decreased negative emotions and depressive symptoms (12). However, the methods for measuring engagement with the applications were different in each study, making comparisons difficult.

4. Discussion

The results of this systematic review provide preliminary evidence for the efficacy of digital mobile applications in the

treatment of young patients with FEP. Our review highlighted that mobile health can be used to monitor symptoms (42, 43, 46). Most of programs were associated with an improvement of symptoms (12, 16, 42, 43, 46, 47) and an acceptable engagement (16, 42–44, 46, 47). MHealth seemed have an impact on hospitalization (43) and A&E visits (43, 44) on the one hand and on the return to working life, on the other hand (44). In addition, none program was associated with functioning or social scale.

Regarding interventions based solely on EMA (symptom monitoring) methods, one study found that remote monitoring of symptoms minimized relapses, A&E visits and hospitalizations. The second indicated a reduction in positive psychotic symptoms.

Concerning EMI interventions, one study found an improvement in anxiety symptoms and two studies noted an improvement in psychotic symptoms. One EMI demonstrated its efficacy in helping participants return to studying and employment. One EMI study reported improved motivation. Two out of four studies found no significant changes in psychotic symptoms.

The studies have demonstrated the promising potential of applications in the recovery phase after FEP. They could facilitate self-management of the illness through symptom monitoring by providing instructions for self-management of symptoms in daily life. The addition of therapy modules increases access to evidence-based tools, improves the quality of treatment, facilitates goal achievement and encourages autonomy.

Nevertheless, there are several limitations. Chief among them are internal validity and power.

Moreover, these results should be interpreted with caution as two trials were not controlled, one trial was not randomized (PCT) and we included a sub-group from one trial in an intention-to-treat analysis.

Four studies scored <3 and were considered to be of poor quality and the three others were considered as moderate quality. These methodological limitations reflect the fact that this field of research is in its infancy. A number of studies identified as relevant for this review were excluded as they did not present preliminary clinical outcome data. They highlight the feasibility and acceptability of a range of additional applications that use the EMA and EMI methods.

It should be noted that the methods for measuring engagement with the applications were different in each study, making comparisons difficult. In addition, engagement may have been encouraged (e.g., through a financial incentive) which may have increased the take-up rate.

Barriers to the implementation of digital technologies in mental health are highlighted (51–54), particularly in the care of new onset psychosis. A number of practical issues are described in relation to digital interventions in psychiatry, including the cost of installing and maintaining equipment and software (technical support, storage, data analysis and technology upgrades), the ability of healthcare IT infrastructures to adapt to new technologies and incorporate them into clinical practice. Cost-effectiveness data has not yet been reported. In addition, new technologies are not progressing at the same pace as clinical trials, which may affect the acceptability of digital interventions (52). A review of engagement with popular commercially available mental health applications found that only 4% of users who downloaded a mental health application reopened it after 15 days (55).

In a paper that reviews the challenges surrounding user engagement with smartphone mental health applications (56), the authors state that "low engagement," in other words poor adherence to the intervention, represents a major barrier to widespread use of these technologies. In addition, there is no uniformity in the measurement of engagement across the studies. There are no standard measurements to compare engagement with applications in the various papers published and often engagement data is not reported.

Moreover, digital technology tools also raise important ethical issues regarding informed consent, confidentiality, data protection and patient privacy. These factors are all the more important when vulnerable populations and private health information are involved. This is problematic when digital health tools involve the collection of massive amounts of personal data. In a study of the views of patients with psychotic disorders on mobile health, Their first concern was privacy (followed by the reliability of the application) (57). Another study suggests that people with mental health problems are less comfortable with automatically sharing personal data (58). This suggests the importance of a patient-centered approach, and of working closely with future users from the start of any project. A 2016 review examined the specific features of 208 mental health applications and found that only 9% provided data security or privacy protection and 89% made no mention of it. Fifty-nine percent of the applications provided no information on the efficacy of the application (59).

In addition, in 2017, more than 10,000 mental health-related applications were commercially available (60), yet despite the proliferation of health applications, few can be considered to be of good quality. There is currently limited evidence on the value and robustness of the theoretical foundations provided by the applications (61). Research in 2019 found that only 3% of commercially available mental health applications had an evidence base to support their claims of efficacy (61, 62). In addition, access to these interventions is still restricted for non-English speaking populations.

There is no regulation or consensus on health applications and few guidelines or standards on which to base application research and quality assessment. The disparity in the quality of mobile applications has stimulated the development of assessment tools. The American Psychiatric Association (APA) has developed a model to help clinicians improve informed decision-making about mental health applications: the "APA App Advisor" (63). It assesses the accessibility, confidentiality, safety, clinical basis, ease of use and data integration of the tool in terms of a therapeutic goal.

The *Mobile Application Rating Scale* (MARS) is another tool that aims to provide a standardized assessment of mental health applications for clinicians (64). The "uMARS" version has been developed for users. In 2019, the World Health Organization (WHO) published a guide to pilot and assess digital solutions and help harmonize practices, with summary tables of the different methodological approaches according to the clinical assessment goals of these applications.

Nevertheless, it remains difficult for users and clinicians to identify the quality and usefulness of the applications available.

In future, passive data and personalized interventions could improve the use of mHealth. The term "active data" refers to data generated through the active involvement of a patient, such as self-questionnaires, while "passive data" refers to data generated without the patient's involvement (GPS, accelerometer, voice calls and SMS) (65). The many sensors built into smartphones offer a wealth of data, such as GPS to monitor spatial location, an accelerometer to record movement and overall motor activity, call and messaging histories to document social activity, voice and sound recordings to estimate mood, a camera for facial expression. The sensors may be on the smartphone or on a wearable device (a connected watch or bracelet). Often referred to as "digital phenotyping," passive monitoring provides a means of understanding mental health experiences in context.

Qualitative data from studies on the ClinTouch application report that some patients find the self-questionnaires repetitive (66). This may lead to disengagement in the longer term. Researchers are currently investigating whether passive monitoring of psychotic relapse indicators using sensor technologies embedded in smartphones may be more acceptable to users and more responsive to change than active self-assessment. The Crosscheck system (67) is currently being developed and tested by Dr Ben-Zeev's team, to detect changes in speech properties, physical activity and location to generate personalized alert patterns. An early prototype of the system appears to be acceptable to participants with psychosis, although the research team notes that self-selection is likely: those who are concerned about such monitoring will choose not to participate in the tests. If successful, Crosscheck could be used to signal a potential relapse and trigger an early intervention response in the same way as ClinTouch (52). The Crosscheck application combines the use of active EMA data with passive data such as physical activity (accelerometer), geospatial activity (GPS), speech frequency and duration (microphone) and phone use (telecommunication, application use, screen unlocking) to predict relapse in people with psychosis. The results of the study reveal that the digital indicators of relapse are not the same for each person with psychosis.

In the study by Cella et al. (68), the investigators combine active and passive digital technology using a wrist-worn device (the Empatica E4) and the ClinTouch application. The study assessed whether there was a link between psychotic symptoms and a physiological response. The results showed increased electrodermal activity during hallucinations or delusions, but no association between symptoms and heart rate variability. This study suggests that it may be possible to identify a reliable biosignature indicating worsening symptoms and a risk of relapse.

Other research supports the feasibility of digital phenotyping in psychotic disorders, such as the study of the Beiwe application (69). This study suggests that 2 weeks before relapse, people with schizophrenia show significant changes in mobility indicators derived from GPS data, sociability indicators derived from text messages and call data, and symptom exacerbation indicators derived from self-assessment surveys within the application. This indicates that it may be possible to capture digital indicators of relapse. The rate of behavioral abnormalities detected in the 2 weeks prior to relapse is 71% higher than the rate of abnormalities in other periods.

As Torous points out (51), this could help to understand the heterogeneity of clinical presentation and offer a more personalized understanding of psychotic illness. Smartphones and other portable devices can now capture real-time environmental data on behavioral indicators. This data offers potential insights into how symptoms can lead to clinical presentations such as social withdrawal and anhedonia via changes in call/text reciprocity, or avolition and lethargy via changes in GPS-tracked movements (70). This wealth of readily available information offers a new perspective to better characterize the lived experience of people with FEP and to explore new subtypes and clusters of psychoses based on new data.

Digital technologies could also be used to predict illness trajectory: smartphones and related mobile devices offer a means of capturing daily fluctuations in the multitude of indicators needed to better understand, model and predict the trajectory of the illness. It remains to be seen whether this means of data capture is acceptable to users and whether it risks increasing the symptoms of paranoia in people with psychotic disorders.

This objective measure of digital phenotyping occurs in the context of patients' lived experience, reflecting how they function in their environment. The smartphone may be an opportunity to measure real-world functioning and potentially offer real-time interventions (71). In just-in-time adaptive intervention (JITAI), active and passive data is collected to help develop personalized, real-time intervention strategies. For example, the smartphone can deduce low mood in the context of social isolation and suggest a relevant intervention, while if it deduces low mood in the context of poor sleep, it can recommend an alternative intervention. While still in its infancy, the use of JITAI to deliver mental health interventions would be an interesting area for future research (72).

A major opportunity offered by digital technology is to improve engagement, especially among young people. Gamification is promising in this respect (73), e.g., by adapting the techniques of digital gaming, offering rewards and challenges to complete activities. The most commonly observed gamification features in mental health are: progress tracking; points; rewards; introduction of themes or stories; personalization; configuration (74). The addition of gaming features could support engagement, increasing motivation, creating a sense of empowerment and inducing positive emotional responses in users, such as a sense of pride.

The use of mobile applications for smartphones represents an interesting prospect for improving the engagement of FEP patients receiving care (75). A meta-analysis (76) assessing the opinions of 1,172 psychotic patients on mHealth services reports that 60.2% of users are in favor of using mobile phones to track and monitor their mental health and 51.1% to facilitate contact with health professionals. The study shows that this population is interested in this type of tool to facilitate the link between patient and healthcare department.

In a study assessing interest in new technologies among psychotic patients, the service of most interest to patients was the "contact alarm to clinicians in case of emergency" (77). Patients demand more personalized, more interactive and closer clinical attention. However, as noted in the studies, when it comes to the clinical implications associated with these interventions, it is very important to design these systems from the clinician's perspective. In a study exploring the attitude of mental healthcare

staff in England to digital health interventions, staff expressed concern about their moral, legal and professional obligations in relation to assessing information about risks such as suicidal ideas and behavior. They preferred patients to report symptoms themselves during consultations. Not only did staff feel that this would give patients control over the information they share, but also that their level of responsibility would be minimized. This somewhat contradicts the current focus of smartphone applications for symptom monitoring in this population, which, although they can be used by patients to share with their care team, tend to provide symptom reports to a central server that staff can use to identify early signs of relapse. Issues surrounding the legal and moral responsibilities of staff when viewing automatic symptom reports and their level of comfort in implementing such approaches in practice must be considered (78).

These various limitations need to be considered when jointly building new technologies with the people affected by FEP to ensure that the technologies are appropriate and that they will be used. Among the possible solutions identified to increase young people's interest in quality applications, the inclusion of users in the development process is essential, involving them in development of the objectives, the planned functions and the design of the application.

One prospect that shows promise concerns case management follow-up with a mobile application used jointly by patients and case managers. The Heal Your Mind application (79), currently under development, offers case management based on CBT techniques and symptom monitoring for young people with FEP. Surveys have shown that most participants use at least five of the six modules, find the application easy to use and express satisfaction with the tool. The feature that is most frequently used, most highly appreciated and perceived as most useful is communication with the case manager.

The French Plan-e-Psy project, led by Dr Frederic Haesebaert, aims to work with people affected by FEP and their families to jointly build a monitoring application in the context of *case management*. The protocol describes improvement in patient functioning as the primary endpoint (80). It aims to allow both the case manager and the patient to plan and monitor the achievement of individualized care goals. The assumption is that the use of such an application will improve the functioning of patients receiving care for FEP. This randomized, multi-center clinical trial will include 168 participants aged 18–30 with first-episode psychosis. The results are expected in January 2024.

5. Conclusion

Schizophrenia is one of the most severe psychiatric illnesses. It is frequent and still too often incapacitating. Clinical research in recent years has shown that early intervention leads to a more favorable evolution of this illness. Mobile health could also have a role to play in changing and enhancing the quality of care for psychosis. It could provide new opportunities to increase access to existing mental health resources, improve the quality of treatment and enhance the provision of mental health care. The future of mobile technology in mental health care is indeed gaining momentum in the literature. Preliminary data on efficacy is emerging in the literature.

Mobile health could help make users more autonomous and take greater responsibility for their own care, through monitoring and assessing symptoms and facilitating self-management strategies. This autonomy does not imply the replacement of health professionals, but would instead optimize their contribution by providing assistance in caring for patients. It could promote patient involvement in healthcare in general by encouraging them to be actors in their own care, enhancing their empowerment.

The use of technology for therapeutic purposes has the potential to increase access to standard treatments and to allow greater patient choice and control. It can offer the choice of a wide range of therapeutic interventions, personalized resources, psycho-education and various types of specialized therapy tools. These interventional applications can be personalized to address individual issues in real time and promote functional recovery. They could also facilitate peer support and social integration by providing secure social networking platforms.

Applications could be clinically incorporated into existing healthcare environments to provide patients with FEP with new tools and ways to engage in care by facilitating connections to clinical care. Smartphone-based symptom monitoring could be incorporated into electronic patient record systems and regular clinical monitoring to generate clinically usable information and predictions for preventive and personalized care. New models of healthcare could take advantage of these technologies while preserving the therapeutic relationship and including patients in the tool development process.

The literature highlights many of the challenges facing this new field of research, including ethical issues, cost, and the capacity of healthcare infrastructure, along with doubts about the quality of applications on the market. The rapid pace of technological development is at odds with the long scientific process required to develop a quality application. Clinical evidence for the efficacy of applications is currently limited. The lack of quality validation is one of the main problems. The rapid expansion of the mobile health sector makes it difficult for users to choose and for professionals to recommend the right application. On the other hand, these technological advances can make applications more attractive and improve results. To facilitate this, future research can explore barriers and potential solutions, focusing particularly on feedback from users and healthcare providers.

Mobile applications are emerging as interesting tools for better engagement in care, enhanced self-management of symptoms and better coordination of resources. This systematic review has several limitations due to the lack of randomized controlled studies. Overall, the studies to date suggest promising preliminary efficacy data on the use of mobile applications in early psychosis. Given the importance placed on early intervention in psychosis, the implementation of technologies for therapeutic purposes in young adult populations in the early stages of psychosis seems essential. While engagement is a challenge in traditional clinical practice, technological progress can enhance the engagement of young people in particular.

Data availability statement

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

Author contributions

CM and AC conceived the study and screened the titles of the publications identified in the databases using the search strategy defined above to identify potentially eligible studies. Both authors, first independently and then jointly, screened the studies based on their abstracts. All online abstracts were reviewed and full-text papers were retrieved where relevant. In case of disagreement, a AY was called on to arbitrate. CM wrote the initial draft and all tabular material. AC and AY supervised the study and critically revised the manuscript. All authors read and agreed to the published version of the manuscript.

Conflict of interest

AY received speaker's honoraria from AstraZeneca, Janssen, Lundbeck, Otsuka, Servier, and carried out clinical studies in relation to the development of medicine Janssen and Lundbeck medicine unrelated to this work.

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1137644/full#supplementary-material

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A retrospective database study on 2-year weight trajectories in first-episode psychosis

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Introduction: It is critical to focus on individual weight profiles in line with efforts to tailor treatment, given the heterogeneous nature of the clinical population. This study aims to identify and describe possible two-year weight trajectories among patients accepted to the Early Psychosis Intervention Programme (EPIP) in Singapore.

Methods: De-identified data was extracted from EPIP's standing database for patients accepted from 2014 to 2018 with a schizophrenia spectrum disorder. Data collected at fixed time-points (baseline, 1-year, and 2-year) included anthropometric measures (height and weight), and sociodemographic (age, sex, highest education level, and vocational status) and clinical (duration of untreated psychosis, number of inpatient admissions, and scores on the Positive and Negative Syndrome Scale and Global Assessment of Functioning) information.

Results: A total of 391 complete data sets were included for main analyses. Those with missing weight data were more likely to be males, older at baseline, have a highest education level of tertiary and above at baseline, and have a longer duration of untreated psychosis. The weight change across two years resulted in the following membership breakdown: 151 (38.6%) in super high risk; 133 (34.0%) in high risk mitigated; 17 (4.3%) in at risk; 34 (8.8%) in delayed risk; and 56 (14.4%) in low risk.

Discussion: The lack of pharmacological, dietary, and physical activity data is a significant limitation in this study; however, the results reinforce the justification for future studies to prospectively capture and examine the influence of these data, with the aim of early detection and weight intervention for high risk groups.

KEYWORDS

weight gain, first-episode psychosis, intervention, trajectories, outcomes

1. Introduction

It has been well-documented that people with psychosis are at risk of developing metabolic syndrome and cardiovascular diseases during the course of antipsychotic treatment. This can largely be explained by antipsychotic-induced weight gain, which has been associated with resulting higher body mass index (BMI), and increased rates of morbidity and mortality (1, 2). A prospective study of people with first-episode psychosis (3) identified that majority of the participants with schizophrenia (62%) and bipolar (50%) ended up obese 20 years after their first hospitalization for psychosis, with related physical health complications. A meta-analysis by Bak and colleagues (4) had shown robust findings that antipsychotic use was linked to significant weight gain in antipsychotic-naïve patients, and that this weight gain was independent of psychiatric diagnoses. In the local Singaporean context, antipsychotic-induced weight gain was observed to take place in the majority (79.2%) of a young adult population, in

a short span of 6 months from baseline (5). It was also found that upon matching healthy controls to patients receiving treatment at the Early Psychosis Intervention Programme (EPIP) in Singapore, the patients had a higher prevalence of diabetes even though they had lower BMI than controls at baseline (6). This, together with the low prevalence of obesity among the patients at illness onset, seems to suggest that the abnormal glucose metabolism was likely an associated result of the antipsychotic treatment.

However, while there has been literature examining antipsychotic-induced weight gain in drug-naïve patients, it is also critical to focus on individual weight profiles over time in line with efforts to tailor intervention. The heterogeneous nature of this clinical population has already been well-studied in terms of illness features; for example, a local study by Abdin and colleagues (7) had elicited among their sample of patients with first-episode psychosis, discrete trajectories of psychopathology and functioning over 2-years of follow-up, with certain trajectories associated with higher risk of deterioration as compared to the rest. Internationally, symptom trajectories over longer periods of time have also been identified (8, 9). Meanwhile, Zheng and colleagues (10) had derived latent BMI trajectories in a large non-clinical sample of retired older adults, which were found to be more effective at predicting mortality risk than static BMI status. It stands to reason that investigating distinct individual weight gain patterns in clinical populations would also be beneficial and yield significant information in preventing adverse physical health events, and maximizing treatment utility for these patients. Previous research suggest that the first year of antipsychotic treatment is often the most critical, as it is where majority of the weight gain happens and is sustained over the next few years (11, 12). These early weight changes were associated with persistent adverse metabolic effects later on, such as high triglyceride levels, and were able to predict further weight gain (13). An important qualitative study by Waite and colleagues (14) highlighted that weight gain profoundly impacted participants' sense of self-worth, and left them with a loss of control, hope, and motivation for interventions. Given their youth and the fact that antipsychotic treatment would potentially be required for a long period of time, the participants also shared their preference for early conversations on common weight gain trajectories to expect.

Weight interventions often have to be labor-and resource-intensive in order to be truly effective, which may result in costs too high to be implemented indiscriminately (15, 16). Therefore, such interventions may only be considered feasible when applied to patients identified to be in severe need of such weight management services. Even so, the type of intervention provided should be tailored accordingly. For those at-risk for severe weight gain, preventative measures such as psychoeducation and nutrition counselling should be supplied. Meanwhile, those already with severe weight gain should be titrated onto a lower-risk antipsychotic or prescribed with supplementary medication to mitigate weight gain, and at the same time, provided with more intensive support such as lifestyle intervention and specialist physical healthcare (17). As such, international guidelines have been published to improve routine monitoring of cardiometabolic parameters in patients newly initiated to antipsychotic treatment (18, 19). Timely monitoring of potential adverse metabolic events will aid clinicians in making optimal decisions to mitigate antipsychotic treatment side effects. Despite these concerns, challenges still impede efforts to conduct physical health monitoring regularly, and discrepancies still remain between recommended standards and clinical practice (20).

The primary aims of the current study are thus to: (a) identify and describe possible 2-year weight trajectory patterns among patients accepted to EPIP in Singapore; and (b) highlight sociodemographic differences, if any, between those with complete 2-years of weight data and those without. Implications and recommendations for future directions will also be discussed.

2. Materials and methods

EPIP is an intensive intervention program in Singapore for first-episode psychosis, led by a multidisciplinary team including psychiatrists and allied health professionals. Patients accepted into the program fulfil the following criteria: (a) age between 16 and 40 years inclusive, (b) first-episode psychotic disorder with no prior or minimal treatment, and (c) psychotic disorder that is not secondary to a general medication condition or substance use. As part of EPIP's service evaluation efforts, patient sociodemographic and clinical data are routinely collected at fixed time points (baseline, 1-year, and 2-year) and entered into a standing database (DSRB Reg. No.: IMH-2004-001) registered with the National Healthcare Group (NHG) Domain Specific Review Board (DSRB). The ratings used to collect each patient's data are completed by the case managers in charge of their care, as well as their treating clinicians. Patients receiving treatment attend follow-up sessions at the outpatient clinic at the Institute of Mental Health (IMH), where their anthropometric measures – such as height and weight, and the resulting calculated BMI – are usually taken prior to their consultation session. These anthropometric measures are also taken when they are warded as an inpatient, and are cross-captured in the standing database through the yearly sociodemographic assessment by the case managers.

For this retrospective database study, ethics approval was also obtained from NHG DSRB (Ref. No.: 2020/01388). De-identified data was extracted from the EPIP standing database for all patients accepted into the program between 01 Jan 2014 and 31 Dec 2018 inclusive. Patients were not re-contacted and no data was extracted from individual medical records. Sociodemographic variables of interest included age at baseline, gender, and highest education level at baseline, and vocational status at baseline and 2-year. Highest education level was regrouped into two levels: tertiary and above vs. below tertiary; similarly, vocational status was regrouped into two categories: meaningfully occupied in an age-appropriate role (e.g., gainfully employed, homemaker, students, etc.) vs. unemployed. Clinical variables collected included duration of untreated psychosis (DUP), number of inpatient admissions, Positive and Negative Syndrome Scale (PANSS) scores at baseline and 2-year, and Global Assessment of Functioning (GAF) disability scores at baseline and 2-year. Number of inpatient admissions was regrouped into three levels: no admissions vs. one admission vs. multiple admissions. Lastly, anthropometric measures extracted included height at baseline, and weight at baseline, 1-year, and 2-year. To ensure a homogenous sample for data analysis and compensate for the lack of medication data, only patients with a diagnosis of a schizophrenia spectrum disorder were included for analysis. Based on clinical experience, these patients would most likely be prescribed with only antipsychotics, as compared to patients with a diagnosis of affective

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psychosis, where prescriptions would likely include anti-depressants or mood stabilizers. They were also likely to be on longer term antipsychotics as compared to patients with brief psychotic disorder, who may be on a shorter course or lower dosage of antipsychotics.

Statistical analyses were conducted using IBM SPSS 23. Mean and standard deviations were computed for continuous variables, and frequencies and percentages were computed for categorical variables. To fulfil the study's main aims, baseline sociodemographic characteristics between those who did and did not have complete weight data for the first 2-years were compared using *t*- and chi-square tests. Subsequently, data sets with complete clinical and weight data were used for primary analyses. Clinically significant weight gain was defined as ≥7% for this study (21). Percentage weight changes between each time point were thus grouped into four categories: (a) increase severe, for weight gain ≥7%; (b) increase mild, for weight gain <7 and >1%; (c) maintain, for weight gain ≤1% and weight loss ≤1%; and (d) decrease, for weight loss >1%. Following, each included data set was assigned a weight profile according to their weight change categories across the first 2-years: (a) super high risk (e.g., increase severe across 2-years); (b) high risk mitigated (e.g., increase severe then decrease); (c) at risk (e.g., increase mild across 2-years); (d) delayed risk (e.g., maintain then increase severe); and (e) low risk (e.g., maintain across 2-years). The exact grouping matrix is presented in Table 1, while a simplified visual representation of each weight trajectory is depicted in Figure 1. Sociodemographic and clinical variables between the different groups of weight gain by the first year, and between those who continued to gain significant weight through to the second year and those who did not, were also compared using *t*-tests and one-way ANOVAs for continuous variables and chi-square tests for categorical variables, to explore if there were any other potential protective or risk factors to differentiate between these groups.

Separately, as part of secondary exploratory analyses, 2-year clinical (PANSS and GAF scores) and vocational (meaningfully occupied vs. unemployed) outcomes were compared between each separate weight gain trajectory using chi-square test or one-way ANOVAs, and linear regression and binary logistic analyses were used to evaluate the contribution of the weight trajectory classification on these outcomes, after accounting for other sociodemographic and clinical factors. This was conducted in the hopes of preliminarily validating differences in 2-year outcomes amongst the identified separate weight trajectories. Statistical significance was established at $p < 0.05$.

3. Results

A total of 686 patients were accepted into EPIP from 01 Jan 2014 to 31 Dec 2018 with a diagnosis of a schizophrenia spectrum disorder and completed at least 2-years of the program. However, only 445 (64.9%) had complete weight data for the first 2-years. Those with missing data were more likely to be males, χ^2 (1, $N = 686$) = 7.3, $p = 0.007$; older at baseline, t (684) = 3.491, $p = 0.001$; have a baseline highest education level of tertiary and above, χ^2 (1, $N = 678$) = 15.2, $p < 0.001$; and have a longer DUP, t (453) = 2.525, $p = 0.012$. There were no significant differences between those who had complete weight data for the first 2-years and those without, in terms of baseline vocational status, PANSS total and GAF disability scores, and number of inpatient admissions. The mean (SD) weight gain over the 2-years

TABLE 1 Grouping matrix and membership of the different weight trajectory profiles.

BL → 1-yr	1-yr → 2-yr				
	Increase severe (gain ≥7%)	Increase mild (1%<gain <7%)	Maintain (gain ≤1% & loss ≤1%)	Decrease (loss >1%)	Total (row)
Increase severe (gain ≥7%)	Super high risk 57 (14.6%)	Super high risk 79 (20.2%)	High risk mitigated 34 (8.7%)	High risk mitigated 99 (25.3%)	269 (68.8%)
Increase mild (1% < gain <7%)	Super high risk 15 (3.8%)	At risk 17 (4.3%)	Low risk 9 (2.3%)	Low risk 29 (7.4%)	70 (17.9%)
Maintain (gain ≤1% & loss ≤1%)	Delayed risk 5 (1.3%)	Delayed risk 3 (0.8%)	Low risk 3 (0.8%)	Low risk 3 (0.8%)	14 (3.6%)
Decrease (loss >1%)	Delayed risk 16 (4.1%)	Delayed risk 10 (2.6%)	Low risk 3 (0.8%)	Low risk 9 (2.3%)	38 (9.7%)
Total (column)	93 (23.8%)	109 (27.9%)	49 (12.5%)	140 (35.8%)	391 (100%)

BL, Baseline; 1-yr: 1-year; 2-yr: 2-year.

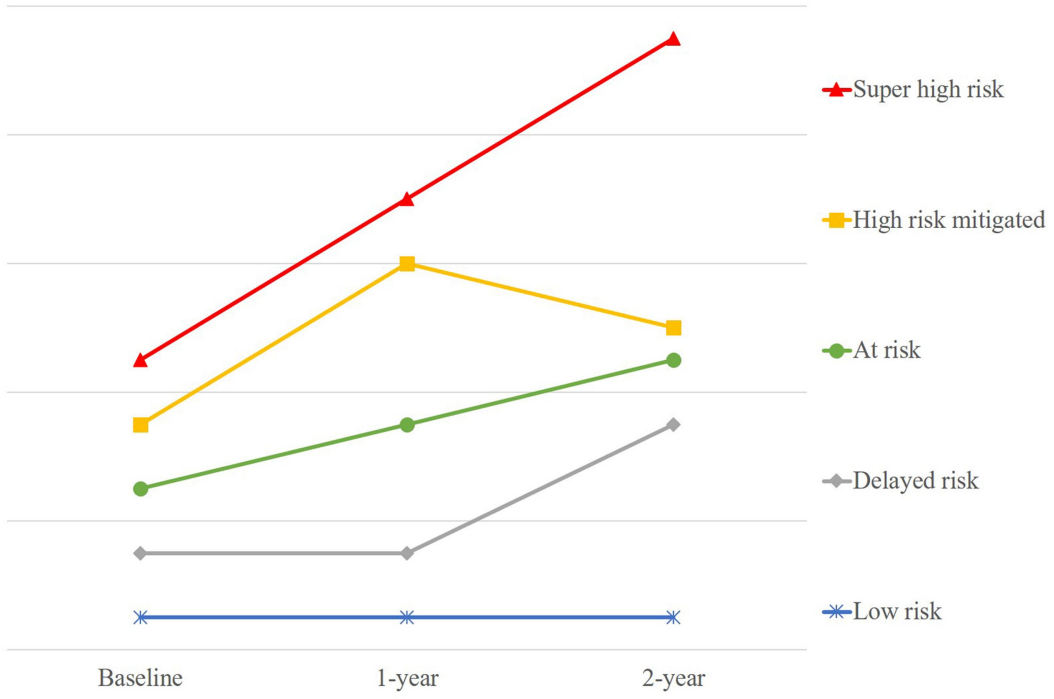

FIGURE 1
Simplified visual representation of the five different weight gain trajectories over 2-years.

was 9.7 (9.6) kg, with 42 (9.4%) participants gaining 40% and above of their baseline weight, and 124 (27.9%) gaining 20–40% of their baseline weight. Using the Asia-Pacific modified BMI classification by the World Health Organization (22), at the end of the 2-years, 210 (47.2%) were obese (BMI $\geq$25 kg/m^2), 65 (14.6%) were overweight (23 kg/m^2 $\leq$BMI <25 kg/m^2), 133 (29.9%) were normal (18.5 kg/m^2 $\leq$BMI <23 kg/m^2), and 37 (8.3%) were underweight (BMI <18.5 kg/m^2).

Of the 445 data sets with complete weight data for the first 2-years, 391 (87.9%) had complete clinical data and were included for the main analyses. Sociodemographic and clinical information of these are presented in Table 2. The recorded weight change across 2-years resulted in the following weight profile membership: 151 (38.6%) total in super high risk; 133 (34.0%) total in high risk mitigated; 17 (4.3%) total in at risk; 34 (8.8%) total in delayed risk; and 56 (14.4%) total in low risk. A detailed breakdown of the group membership had also been included in Table 1, and the actual mean weight of each group presented in Figure 2. Meanwhile, one-way ANOVAs and chi-square tests between the different groups of weight gain by the first year showed that there were no significant differences between these two groups, except for number of inpatient admissions, χ^2 (6, N = 391) = 23.6, p = 0.001. There were also no statistically significant differences found between those who continued to gain weight from the first to second year and those who did not, amongst those who had significant weight gain from baseline to the first year.

In addition, secondary exploratory analyses were conducted and the results are as follows. It was found that the delayed risk weight trajectory was consistently scoring higher on the 2-year PANSS positive and general psychopathology subscales and consistently scoring lower on the 2-year GAF disability scores as compared to the other groups (Supplementary Table S1). However, there was no significant difference in 2-year vocational status (meaningfully engaged in an age-appropriate role vs. unemployed) between the weight trajectory groups. Follow-up linear regressions revealed that belonging to the delayed risk weight trajectory group (vs. belonging to the super high risk, high risk mitigated, or at risk weight trajectory groups) and having multiple inpatient admissions significantly predicted 2-year PANSS total score (Supplementary Table S2) and lower GAF disability scores (Supplementary Table S3), after accounting for other variables (age, gender, highest education level, DUP, and baseline PANSS total and GAF disability scores).

4. Discussion

In a 2-year period of follow-up, majority of the study sample, made up of drug-naïve patients with a diagnosis of first-episode schizophrenia spectrum disorder, gained a significant amount of weight, which was congruent with pre-existing literature on the topic (5, 11, 23, 24). One of the primary aims of the present study was to identify and describe discrete 2-year weight trajectory patterns among patients accepted into EPIP in Singapore. It was revealed that majority of the patients with complete weight and clinical data belonged to the super high risk (38.6%) and high risk mitigated (34.0%) groups. The main difference between these two groups was that while both trajectories demonstrated clinically significant weight gain ($\geq$7%) in the first year, the high risk mitigated group managed to maintain or lose weight while the super high risk group continued to gain weight during the second year. Therefore, it was of interest to examine if there were potential sociodemographic differences between these two

TABLE 2 Sociodemographic and clinical information of datasets included for main analyses.

	Total (*n*=391)
Age at baseline – years, mean (SD)	25.8 (6.7)
Gender – no. (%)	
Male	193 (49.4)
Female	198 (50.6)
Highest education level at baseline – no. (%)	
Tertiary and above	204 (52.2)
Below tertiary	187 (47.8)
Vocational status at baseline – no. (%)	
Meaningfully occupied in an age-appropriate role	202 (51.7)
Unemployed	189 (48.3)
DUP – months, mean (SD)	14.4 (22.3)
No. of inpatient admissions in total – no. (%)	
No admissions	91 (23.3)
One admission	130 (33.2)
Multiple admissions	170 (43.5)
PANSS scores at baseline – mean (SD)	
Total	84.1 (22.5)
Positive	22.8 (6)
Negative	19 (8.6)
General psychopathology	42.4 (12.4)
GAF disability score at baseline – mean (SD)	42.6 (12.2)
Weight at baseline – kg, mean (SD)	60.0 (16.0)
BMI at baseline – kg/m^2, mean (SD)	22.1 (5.2)
Vocational status at 2-year – no. (%)	
Meaningfully occupied in an age-appropriate role	243 (62.1)
Unemployed	148 (37.9)
PANSS scores at 2-year – mean (SD)	
Total	42.7 (13.5)
Positive	9.2 (3.4)
Negative	11.3 (5.9)
General psychopathology	22.2 (6.6)
GAF disability score at 2-year – mean (SD)	71.4 (10.1)
Weight at 2-year – kg, mean (SD)	69.7 (19.0)
BMI at 2-year – kg/m^2, mean (SD)	25.5 (6.1)

DUP, duration of untreated psychosis; PANSS, Positive and Negative Syndrome scale; GAF, Global Assessment of Functioning; BMI, body mass index.

groups, in hopes of elucidating possible protective factors. There was a lack of significant differences found between these two groups; however, their differences may possibly lie beyond variables collected in this study. Zeroing in on weight gain patterns during the first year, those in the increase severe group (vs. increase mild, maintain, or decrease groups) were more likely to have one or multiple inpatient admissions instead of none. It is possible that patients with more severe psychopathology required more episodes of inpatient treatment, and the resultant increased use of psychotropic medications may have accounted for the significant weight gain. Conversely, significant weight gain may also be a surrogate marker heralding a more sinister course of illness in that patients with more severe psychopathology and who eventually have more inpatient episodes, may have had poorer self-care, dietary habits, and more sedentary lifestyles to begin with. Interestingly, we also found that the delayed risk group, out of the five trajectory groups, had the worst symptomatology and functioning at the end of the 2-years. We postulate that the delayed risk group may have had symptoms inadequately addressed in the first year of treatment, resulting in significant weight gain in the second year of treatment, and ultimately poorer clinical outcomes at the end of 2-years.

In the present study, there are hospital-wide processes in place for the collection of anthropometric data for patients in both the in-and out-patient settings. However, despite best efforts, these monitoring protocols are often not adhered to at the outpatient clinics for a variety of systemic and individual patient-/clinician-related reasons. This issue is not unique to our setting. A retrospective national audit in the United Kingdom of records of patients with schizophrenia or schizoaffective disorder revealed that BMI documentation was lacking even for those with established cardiovascular disease history (25). A recent commentary by Azfr Ali and colleagues (26) discussed some potential practical challenges in balancing cardiometabolic monitoring with antipsychotic treatment. Therapeutic response and risk of relapse are often primary drivers of the decision over which antipsychotic to use in treatment, which may result in overlooking of the antipsychotic's associated adverse profiles. Furthermore, treatment resistance is a major concern during early stages of psychosis treatment (27, 28), making addressing poor illness insight and adherence to treatment a priority over fulfilling the standards for cardiometabolic monitoring. The implications of the weight data for the first 2-years not missing at random include the possibility that analyses in this paper may have been biased, and the secondary exploratory results should be interpreted with caution. Despite these real-world limitations inherent in our naturalistic study, the weight data not missing at random provided some valuable insights into existing gaps in weight monitoring procedures and allowed us to better understand the types of patients who were less likely to have their anthropometric measurements monitored. Firstly, males were more likely to have missing data, which may be due to having less concerns about weight or image. However, this has important repercussions as males tend to engage in poorer lifestyle behavior (29) and develop cardiovascular disease at a younger age (30). Secondly, those older and having a highest education level of tertiary and above at baseline may be functioning better and less likely to attend outpatient appointments where the weight monitoring would occur. Conversely, those with a longer DUP may also be at high risk of defaulting outpatient appointments because of poorer illness insight or more severe symptoms. Work should be put into evaluating points of contact with the patient, and how to increase chances of successfully collecting data on their anthropometric measures (31, 32).

The lack of pharmacological, dietary, and physical activity data is a significant limitation in this study. Pillinger and colleagues (33) compared the effects of 18 antipsychotics on metabolic function, with olanzapine and clozapine ranked the worst, while others like aripiprazole ranked the most benign. Hence, the type of antipsychotic and dosage prescribed or compliance to medication could have had an impact on the resulting weight gain pattern experienced by an individual (34). Meanwhile, a scoping review described preliminary

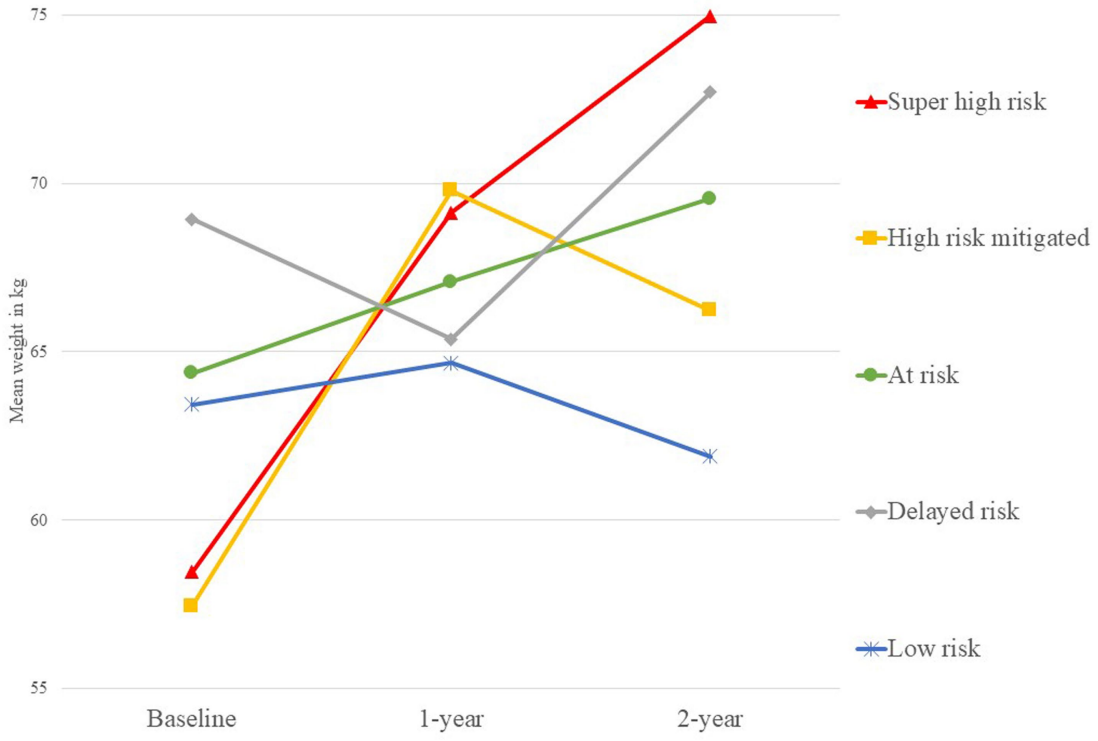

FIGURE 2
Actual mean weight of the five different weight gain trajectories over 2-years.

findings from food surveys and self-report questionnaires that antipsychotic exposure was associated with increased disinhibition in terms of appetite and snacking, leading to disturbed eating behaviors over longer periods of time (35). Another meta-analysis also found that people with severe mental illness were significantly more sedentary and spent less time doing moderate or vigorous physical activity than matched healthy controls (36). Therefore, in an attempt to control the undue influence of unmeasured variables, a homogeneous sample of patients of patients with a diagnosis on the schizophrenia spectrum was selected instead. Additionally, collection of clinical data in the current context also hinges on whether there was an outpatient follow-up appointment that coincided with the corresponding milestone of the patient's follow-up with EPIP; if the patient did not attend the appointment or an appointment was not scheduled, clinical data for that time point would not be captured. Future work should also look into the possibility and validity of extrapolating continuous data in order to overcome the rigidity of having fixed assessment time points.

Despite the authors' best efforts, the lack of complete weight and clinical data of a portion of the data sets collected restricts the current study from developing beyond a descriptive paper, which in turn limits the generalizability of its findings and the extent of conclusions that can be drawn from it. Nevertheless, preliminary results still prove illuminating and worthy of discussion, and provide justification for future studies to prospectively capture and monitor metabolic activity according to international consensus standards, as well as pharmacological, dietary, and physical activity data. This will aid in early detection of risk for severe weight gain and understanding of its mechanisms, in order to tailor weight interventions effectively and maximize treatment outcomes beyond symptomatic remission. As reported by Garrido-Torres and colleagues (37), antipsychotic treatment may not be the only factor involved in altered metabolic outcomes; genetic factors and social adversity, or other variables not yet explored, may predispose or exert influence on patients towards obesity. For example, Alameda and colleagues found that patients who experienced psychological trauma during adolescence had a greater waist circumference after 1 year of antipsychotic treatment, compared to those who did not experience any trauma (38).

In conclusion, the present study described five different weight gain trajectory patterns over 2-years present in a sample of patients with a diagnosis of first-episode schizophrenia spectrum disorder, and contributed to the limited knowledge on individual weight profiles from treatment in a specialized early intervention service. Weight interventions are crucial for those at-risk for or already with severe weight gain, but are too costly to be implemented indiscriminately. As these interventions are only truly cost-effective when targeted at those who are at a greater need, identifying this group of high-risk patients as accurately and as early on as possible is imperative to minimize the side effects of antipsychotic medications while maximizing the treatment benefits for these patients (39). In addition, the present study found that existing metabolic monitoring standards were still discrepant from recommended guidelines, and further highlighted the impetus to minimize this gap. Future research directions should include prospectively evaluating challenges in implementing these monitoring practices in detail, such as qualitative interviews or focus group discussions from patients' and hospital staff's perspectives, using statistically robust methods (such as latent class group analysis) to elicit discrete weight gain trajectories with complete data sets which

include pharmacological, dietary, and physical activity data, and also continuing to explore the mechanisms behind antipsychotic-induced weight gain beyond type of antipsychotic prescribed.

Data availability statement

All the data from this study reside with the Office of Research, Institute of Mental Health. Data are not available for online access; however, readers who wish to gain access to the data can write to the Clinical Research Committee, Institute of Mental Health/Woodbridge Hospital Secretariat at IMHRESEARCH@imh.com.sg. Access can be granted subject to the Institutional Review Board (IRB) and the research collaborative agreement guidelines. This is a requirement mandated for this research study by our IRB.

Ethics statement

The studies involving human participants were reviewed and approved by National Healthcare Group Domain Specific Review Board (Ref. No.: 2020/01388). Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

YC and CT: conceptualization and investigation. YC and EA: methodology, data curation and formal analysis. YC: writing—original draft preparation and project administration. EA and CT: writing—review and editing and supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1185874/full#supplementary-material

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Perceptions and attitudes of users and non-users of mental health services concerning mental illness and services in Japan

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Objectives: There is a global movement to develop and implement community-based integrated mental health systems. The present study attempted to clarify the perceptions and attitudes of users and non-users of mental health services concerning mental illness and services in Japan.

Methods: A new questionnaire was developed for this internet survey. Data from 500 outpatients with depression and 500 healthy subjects were sampled according to the demographics of the Japanese population.

Results: Over 90% of healthy subjects and over 70% of patients were unaware of the common age of onset or lifetime prevalence of mental illness. Over 90% of the healthy subjects and about 70% of the patients could not describe any services where they would feel comfortable discussing mental health problems. In both groups, "adolescents and young adults" were ranked first as a target population for mental health and illness policies. The top requirement for the integrated care systems was the promotion and awareness of correct knowledge of mental illness in both the healthy subjects and patients.

Conclusion: Societal requirements could include disseminating correct knowledge, awareness-raising actions for society, and implementing services where people, especially young people, can easily consult and receive support in the community.

KEYWORDS

community, early intervention, integrated care system, mental health, perception, implementation research

Introduction

Mental illnesses have an enormous impact worldwide, including increased mortality rates and social and economic losses (1, 2). In 2013, the World Health Organization (WHO) adopted the Mental Health Action Plan 2013–2020 (3). The action plan has now been extended until 2030 (4). It takes a comprehensive and multisectoral approach, through coordinated services from the health and social sectors, with an emphasis on promotion, prevention, treatment, rehabilitation, care and recovery. One of the major objectives of this action plan was to provide comprehensive, integrated, and responsive mental health and social care services in community-based settings. Efforts to implement these services have been started in various countries (5).

In Japan, the number of people admitted to psychiatric hospitals has been much higher than in other industrialized countries, and the lengths of stays have also been relatively long (6, 7). The Japanese Ministry of Health, Labour and Welfare (MHLW) decided to address mental illness intensively as one of five priority diseases, along with cancer, stroke, acute myocardial infarction, and diabetes mellitus, in the sixth revision of the Medical Care Plan from 2013. In 2019, the MHLW also announced a vision of establishing a "Community-based Integrated Care System for Mental Disorders." The aims of this system were defined so as to ensure comprehensive medical care, welfare for disabilities, housing, social participation, employment, community cooperation, and education, enabling all individuals to live their own life as a member of a community with peace of mind, regardless of whether they have a mental illness or not and regardless of their level of disability. To promote the establishment of this system, fourteen operational items have been listed by the MHLW as of June 2022 (Table 1). Each local government can select the items and determine the contents of the services according to the actual situation in their area.

The establishment of a Community-based Integrated Care System for Mental Disorders in Japan is now in progress. The MHLW is currently reviewing operational items to ensure that they are consistent with the principles of this system. As indicated earlier in the aims of this system, this system targets the whole community, not just people with mental illness. In the present study, we aimed to clarify the perceptions and attitudes of users and non-users of mental health services regarding mental illnesses and services in Japan.

Methods

Study design and participants

This study had a cross-sectional design, in which data from 500 outpatients with depression and 500 healthy subjects were collected through a web-based, self-administered questionnaire survey. This survey was conducted in March 2021 by a professional agency with a large internet survey panel (Rakuten Insight, Inc., Tokyo, Japan; https://member.insight.rakuten.co.in/). A link to the online question form was distributed via email to those who had been registered on the agency's panel. People who had been previously enrolled in the survey panel as subjects with self-reported depression or with no self-reported history of mental illness were included in the present study. The registration information for this panel was regularly checked and updated by the agency.

The participants in both groups were between the ages of 20 and 59 years and lived in Japan. The patients with depression had received continuous outpatient treatment for at least 1 year and had no history of psychiatric hospitalization within 3 months of the survey. The healthy subjects had no history of a psychiatric visit. The exclusion criteria for both groups were a history of alcohol or substance abuse and a history of brain injury, convulsive seizure, or severe physical illness. To confirm these criteria, self-reported screening questions were set prior to the main survey instruments. For the patients with depression, we asked whether the participants had been informed by a clinician that he or she had depression; if they had not, they were excluded. For the healthy subjects, we asked whether the participant had ever visited a psychiatrist for their mental health problems; if they had, they were excluded. The other exclusion criteria mentioned above were also confirmed using appropriate questions. To lessen a selection bias, the age distribution and sex ratio of each group was selected to

TABLE 1 Operational items listed by the Japanese Ministry of Health, Labour and Welfare to promote the establishment of a "Community-based Integrated Care System for Mental Disorders" as of June 2022.

1.	Establishment of a conference platform for health, medical and welfare professionals
2.	Project related to dissemination and awareness-raising
3.	Project to support families of persons with mental disabilities
4.	Project to support the securement of housing for persons with mental disorders
5.	Project for the inclusion of peer support
6.	Project to support outreach methods
7.	Project to support the continuation of post-discharge medical care and other services for inpatients who are at risk of self-harm or violence
8.	Project for the utilization of supporters for the establishment of a care system
9.	Project for psychiatric treatment consultation
10.	Project for the establishment of a medical coordination system
11.	Project for training staff involved in the hospital discharge and community settlement of persons with mental disorders
12.	Project to support community life for inpatients with psychiatric disorders
13.	Project for the assessment of the development of a community-based integrated care system
14.	Other projects contributing to the establishment of a community-based integrated care system

TABLE 2 Results of questions regarding perceptions of current healthcare systems and knowledge of mental illness.

	Patient with depression group *N*=500	Healthy subject group *N*=500	*p* value
Q1. "When you have a mental health problem, such as anxiety, depressive mood, distress, etc., can you think of a service where you would feel comfortable discussing mental health problems?"	Yes 30.8% No 69.2%	Yes 6.2% No 93.8%	< 0.001
Q2. "Do you think the current system provides you with early access to consultation and support services when you have mental health problems or develop a mental illness?"	Yes 10.2% Not sure 47.4% No 42.4%	Yes 2.8% Not sure 66.2% No 31.0%	< 0.001
Q3. "Have you ever heard that about one in five people will experience a mental illness in their lifetime?"	Yes 28.4% No 71.6%	Yes 9.6% No 90.4%	< 0.001
Q4. "Have you ever heard that about 70% of individuals who develop a mental illness do so before the age of 25 years?"	Yes 12.4% No 87.6%	Yes 5.4% No 94.6%	< 0.001

reflect those of the latest Population Census of Japan.[1] In addition, we excluded respondents who provided the same answer to all the questions. Furthermore, similar to the methodology used in a previous internet survey study (8), we included a question designed to detect fraudulent responses.

This study was performed as part of a research project called MEICIS (Mental health and Early Intervention in the Community-based Integrated care System), which was supported by Health Labour Sciences Research Grants (19GC1015 and 22GC1001) (9–12). Informed consent was obtained before the participants responded to the questionnaire, and the participants were given the option to stop the survey at any point. The study protocol was approved by the Ethics Committee of the Faculty of Medicine, Toho University (A20076). The internet survey agency respected the Act on the Protection of Personal Information in Japan. This study was performed in accordance with the latest version of the Declaration of Helsinki.

Measures and data analysis

A survey questionnaire was developed by the members of the MEICIS project, which included the authors of the present report. The questionnaire was comprised of 6 fixed response or yes/no questions. The questions covered the following topics: Q1) whether the participants have knowledge of services where they can seek help comfortably; Q2) whether the participants think the current system provides early access to consultation and support services for mental health; Q3 and 4) whether the participants have knowledge of the common onset age and prevalence of mental illness; Q5) who the policy target for community-based integrated mental health services should focus on; and Q6) what specific services should be implemented in community-based integrated mental health systems. For Q6, the available choices were set to content related to early intervention in addition to choices for content specified in existing policies (Table 1). This questionnaire used simple Japanese to enable easy readability and comprehension.

The *t*-test was used to examine the differences in the ages and years of education between the groups. Regarding the results of questions about the perception of current healthcare systems and knowledge of mental illness, the chi-squared test was used to examine the differences between the two groups. Statistical differences were determined using two-tailed tests and a significance level of $p < 0.05$. A descriptive analysis was used to examine the characteristics of the answers. Data were analyzed using SPSS, version 26.0.

Results

A total of 1,000 subjects (500 patients with depression and 500 healthy subjects) were sampled by controlling the age distribution and sex ratio of each group to reflect the Japanese population, excluding 86 subjects (7.9%) who provided fraudulent responses. The mean (standard deviation) age of the patients was 41.4 (10.5) years in the patient group and 41.4 (10.6) years in the healthy subject group. There were no significant differences in age between the two groups. Each of the two groups consisted of 254 males and 246 females (50.8 and 49.2%, respectively). The mean (standard deviation) years of education was 14.1 (2.2) years in the patient group and 14.5 (2.0) years in the healthy subject group, being significantly longer in the healthy subject group ($p = 0.01$).

Table 2 shows the results of the questions about perception of current healthcare systems and knowledge of mental illness (i.e., Q1-4). For all questions, the patient group was significantly more likely to answer with a "yes" than the healthy subject group. Figure 1 shows the results of the question regarding policy targets for community-based integrated mental health systems (i.e., Q5). Table 3 shows the results of the question regarding specific methods that should be implemented in the community-based integrated mental health services (i.e., Q6).

Discussion

In the present internet survey, we investigated the perceptions and attitudes of people with depression and healthy residents in Japan towards mental illnesses and mental health services. The results of Q1 suggest that most participants could not describe any services where they would feel comfortable to discuss their mental health problems. This response may not simply represent the participants' knowledge about the available mental health services, but may also reflect their

1 https://www.stat.go.jp/english/data/kokusei/2020/summary.html

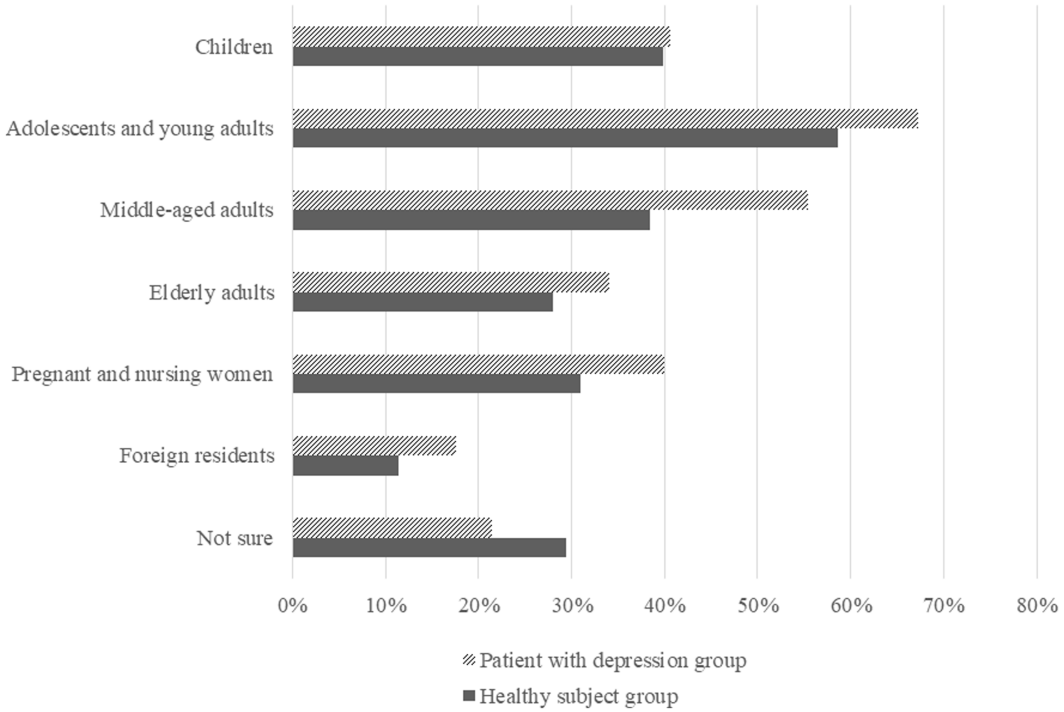

FIGURE 1
Results of the question regarding policy targets for community-based integrated mental health systems.

TABLE 3 Results of the question regarding specific methods that should be implemented in the community-based integrated mental health services.

Rank[a]	Patient with depression group (*N* =500)		Healthy subject group (*N* =500)	
	Choice	proportion	Choice	proportion
1	Promotion and awareness of correct knowledge of mental illness	65.4%	Promotion and awareness of correct knowledge of mental illness	51.6%
2	Employment support for people with mental illness	59.8%	Preventive support for mental health problems before the onset of illness	36.2%
3	Preventive support for mental health problems before the onset of illness	50.6%	Support for families of people with mental illness	34.2%
4	Support for people in the early years after illness onset	50.6%	Employment support for people with mental illness	33.6%
5	Support for families of people with mental illness	48.2%	Support for people in the early years after illness onset	32.4%
6	Support for people with mental illness who are at risk of self-injury or violence	44.2%	Support for people with mental illness who are at risk of self-injury or violence	27.4%
7	Securement of housing for people with mental illness	37.8%	Securement of housing for people with mental illness	23.2%
8	Support from peer staff	28.6%	Home visitation support (outreach) for people with mental illness	21.0%
9	Support after hospital discharge for people who have been hospitalized for a long time	28.0%	Support after hospital discharge for people who have been hospitalized for a long time	18.2%
10	Home visitation support (outreach) for people with mental illness	26.4%	Support from peer staff	17.6%

[a]Rank is based on the % of respondents who selected the choice.

attitudes towards approaching a mental health service when they do develop a mental health problem. A number of barriers to persons seeking help for mental health problems have been identified, a representative of which is stigma. Furthermore, it is known that the stigma attached to mental illnesses is greater in Asia than in the western countries (13, 14) and that the percentage of persons with mental illnesses that utilize mental health services is lower in Japan than in western countries (15, 16). Therefore, many participants may have answered that there are no services where they would feel comfortable to discuss their mental health problems because of stigma rather than because of an actual perception of the inadequacy of the services.

Nevertheless, since the proportion of the healthy group who answered that they could think of a service was very limited, this may be due to the minimal existing mental health services in Japan and the lack of knowledge about mental health and illness. Current Japanese policy does not include the implementation of consultation services, including those for young people, the most common age for mental illness (17, 18). Policies are needed to enable local governments to implement services where people can easily consult and receive support in the community. Consultations or medical services specializing in early intervention in mental health or illness have been provided only in a few, mainly university hospitals (19–22). This challenge is not unique to Japan. Even in many high-income countries, early intervention services are far from being sufficiently widespread (23). A lack of community services can lead to serious delays in treatment (24, 25). Many individuals not only with psychosis but also with depression and neurosis remain untreated; thus, early intervention remains a serious global challenge (26–28).

Regarding basic knowledge of mental illness, only about 10% of the patient group and 5% of the healthy group were aware of the common onset age and prevalence of mental illness. Regarding the required health care system, "adolescents and young adults" was ranked as the priority target of policies on mental health and illness, and the top requirements for community-based integrated mental health care systems were the promotion and awareness of correct knowledge of mental illness, preventive support for mental health problems before the onset of mental illness, and support for people in the early years after illness onset. These requirements were selected more frequently than those regarding existing policies. These findings suggest a high level of need and social interest in primary and secondary prevention for young people, together with the dissemination of correct knowledge and awareness-raising actions for society (29). These contents, which are likely to be desired by many people, should be included in the community-based integrated care systems that are currently being constructed in Japan. The MEICIS project in Japan, funded by the MHLW from 2019, is examining and making policy recommendations on specific early intervention services to address these unmet medical needs. For example, an integrated youth mental health service that has been implemented in other countries (e.g., "headspace" in Australia) was introduced in a metropolitan area of Japan from 2019 (9). The MEICIS project has also been working on developing a system for public health nurses to enhance their skills and provide mental health care for people in need in Akita Prefecture, which is a depopulated area of Japan, using Information and Communication Technology (ICT) (Akita Mental health ICT Network, AMIN), in addition to examining the effective placement of clinical psychologists in outreach teams and considering the development of an easy-to-access system for foreign residents, who are increasing in number in Japan (10–12, 30). Furthermore, the project has adopted the methods of dissemination and implementation science to identify promoting and hindering factors of these implementations and to facilitate evidence-based practices (31, 32). The Japanese government needs to consider policies to expand the implementation of necessary services based on epidemiological evidence, as well as further raise public awareness about mental health and illness and promote the use of appropriate services. Prior cases in other countries have reported the importance of building partnerships with local communities (33, 34), and this point needs to be taken into account in the development of policies of implementation strategies that have been adapted to Japan's unique context.

The limitations of the present study include the fact that all diagnoses were self-reported, and we were unable to investigate the severity of illness, patients with illnesses other than depression, or hospitalized patients. In addition, both groups did not include minors or elderly people. The participants in this study had relatively long years of education, given that the mean duration of education in the Japanese epidemiological study was 12.9 years. Furthermore, the healthy subjects had longer years of education than the patient group. The geographical location of the participants, which we were unable to examine in the present study, could have influenced the level of education of the subjects, as also their level of knowledge about mental illnesses. Although these limitations exist, the results were collected from a wide and large number of subjects through an internet survey, and the results were controlled for age and sex according to national demographics. In general, it is estimated that one in five persons would develop a mental illness in his/her lifetime (27, 35). However, Japan is considered to have lower income inequality than other countries, which could have influenced our estimated prevalence of mental illnesses in Japan (36). Therefore, the results of this study can only be extrapolated with caution to the situation in other countries.

In the present study, we included healthy subjects and patients with depression, however, further investigation is warranted on the perceptions about mental health services among patients with severe mental disorders (SMD), such as psychotic disorders. The social and economic losses associated with SMD are enormous, and patients with SMD are the main users of mental health services. Early interventions for psychotic disorders lead to both improved symptomatic and functional outcomes, and favorable evidence has been repeatedly reported for the effectiveness of early intervention services for these disorders (37). In addition, there is also growing evidence for a favorable cost-effectiveness of these services (38). The acceptability of these services to the patients is an important component of healthcare system development.

Conclusion

Societal requirements could include disseminating correct knowledge, awareness-raising actions for society, and implementing services where people, especially young people, can easily consult and receive support in the community. The Community-based Integrated Care System for Mental Disorders in Japan needs to take these services into account.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the study protocol was approved by the Ethics Committee of the Faculty of Medicine, Toho University (A20076). The patients/

participants provided their written informed consent to participate in this study.

Author contributions

TU and TN designed the study and wrote the protocol. EF, YT, MI, NK, NT, HI, CF, KT, and TS were involved in the conceptualization of the study. TU collected the data, undertook the statistical analysis, and wrote the first draft. TN revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

TU and TN belong to Department of Psychiatry and Implementation Science, Toho University Faculty of Medicine, that is funded by Nippon Life Insurance Company.

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

Publisher's note

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Mismatch negativity generation in subjects at risk for psychosis: source analysis is more sensitive than surface electrodes in risk prediction

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Background: Deficits of mismatch negativity (MMN) in patients with schizophrenia have been demonstrated many times and there is growing evidence that alterations of MMN already exist in individuals at risk for psychosis. The present study examines differences in MMN between subjects fulfilling ultra-high risk (UHR) or only basic symptoms criteria and it addresses the question, if MMN source analysis can improve prediction of transition to psychosis.

Methods: The MMN to duration, frequency, and intensity deviants was recorded in 50 healthy controls and 161 individuals at risk for psychosis classified into three subgroups: only basic symptoms (n=74), only ultra-high risk (n=13) and persons who fulfill both risk criteria (n=74). Based on a three-source model of MMN generation, we conducted an MMN source analysis and compared the amplitudes of surface electrodes and sources among the three groups.

Results: Significant differences in MMN generation among the four groups were revealed at surface electrodes Cz and C4 (p<0.05) and at the frontal source (p<0.001) for duration deviant stimuli. The 15 subjects from the risk groups who subsequently developed a manifest psychosis had a significantly lower MMN amplitude at frontal source (p=0.019) without showing significant differences at surface electrodes. Low activity at frontal MMN source increased the risk of transition to manifest disease by the factor 3.12 in UHR subjects.

Conclusion: MMN activity differed significantly between subjects presenting only basic symptoms and subjects which additionally meet UHR criteria. The largest differences between groups as well as between individuals with and without transition were observed at the frontal source. The present results suggest that source analysis is more sensitive than surface electrodes in psychosis risk prediction by MMN.

KEYWORDS

mismatch negativity, at risk for psychosis, EEG, source analysis, risk prediction

1. Introduction

Several studies suggest a continuum of severity of psychotic symptoms ranging from subclinical psychotic symptoms (SPS) without treatment indication up to manifest schizophrenia (1–3). While SPS are common in the general population (4), schizophrenia is a rare disease with a lifetime prevalence of 0.4–0.7% (5, 6). SPS often are temporary and subtle, and only a small amount of persons with those symptoms really develop a clinically relevant psychotic disorder (7). The prodromal period of psychosis is large and subtle psychopathological changes as well as cognitive impairment can occur years before a manifest schizophrenia is diagnosed (8).

Two approaches are especially common in the field of early recognition of psychosis. Basic symptoms (BS) as subtle, subclinical disturbances in amongst others thinking and stress tolerance are an integral part of psychosis and appear through several stages of the disorder (9). While they are not specific for psychosis, a meta-analysis (10) revealed a higher conversion rate than samples established by ultra-high risk criteria. Subjects with ultra-high risk (UHR) for conversion to psychosis show attenuated psychotic symptoms (APS), brief limited intermittent psychotic symptoms (BLIPS) or trait vulnerability criteria additionally to the basic SPS and are thus also selected by clinical criteria only in current practice. Individuals with UHR have a greatly increased risk of imminent transition to a manifest psychotic disorder. However, the exact risk of transition has varied across studies (11). A recent meta-analysis shows that approximately 15 to 25% of individuals at risk for psychosis will transition to a manifest psychotic disorder within 1 to 3 years (12).

The two risk approaches complement each other. The UHR criteria were designed to detect an imminent risk for transition into a manifest schizophrenic disease. Whereas basic symptom criteria were developed with the aim of identifying the potential risk for a psychotic illness as early as possible, ideally before functional impairments occur (10). It is assumed that in some affected persons basic symptoms occur earlier in the course of the disease and that additionally attenuated psychotic symptoms (APS) and brief limited intermittent psychotic symptoms (BLIPS) occur later in the course (11). However, there are also cases with no or only mild basic symptoms which still fulfil the UHR criteria and thus have also a high risk of transition. Thus, individuals with only basic symptoms are at lower risk of imminent transition to psychosis than individuals who meet both BS and UHR criteria and those who meet UHR criteria only.

At present, clinical early recognition – as usual in general clinical diagnostic in psychiatry – is mainly based on psychopathological symptoms. Thus, UHR criteria as well as basic symptom criteria are mainly based on psychopathological symptoms. Finding biomarkers that may help to identify individuals with an increased risk of conversion to psychosis at an early stage of disease is important, because early intervention may prevent or delay the conversion to psychosis (13).

The mismatch negativity (MMN) is a component of the auditory evoked event-related potential that occurs in response to any discriminable change in an ongoing uniform acoustic stimulation, typically in the range of 100–250 ms after the stimulus (14). The MMN can be observed even in the absence of attention or in sleeping subjects, as it is generally considered to reflect the outcome of a pre-conscious change detection mechanism (15).

MMN deficiency is one of the most robust findings in schizophrenia (16). Already in the at risk state of psychosis with impairment in cognitive functions and attenuated psychotic symptoms, a MMN deficiency can be observed (17). Bodatsch et al. (18) showed that in particular the amplitude of the duration MMN is reduced in at-risk subjects, which are later converted to a manifest psychosis compared with nonconverters. Shaikh et al. (19) found that the MMN amplitude of individuals with an "at-risk mental state" was reduced compared with healthy controls. A recent large study with 580 individuals at risk for psychosis found that MMN amplitude deficits were sensitive to future psychosis conversions, particularly those not taking antipsychotic medication at baseline (20).

Several studies found an association between decreased MMN in manifest psychosis and daily functioning, social functioning and cognitive impairment (21–23). Research has suggested that duration MMN amplitude correlates with global functioning already in early stages of psychosis (24). Only few studies found an association between psychotic symptoms and changes in MMN. For instance, Donaldson et al. (25) found transdiagnostic associations between reduced duration MMN and psychotic symptoms like auditory hallucinations and disorganization. A recent study of first-episode schizophrenic patients found a correlation between duration MMN at baseline and symptom severity after 3 years, thus MMN may also be used as a predictor of remission in schizophrenia (26).

Predictive coding theories suggest that the perceptual system is a set of hierarchically organized generative models where each model provides predictions about the state of the level below. The difference between model prediction and the actual input lead to a prediction error. Event-related potentials elicited by deviant stimuli are thought to be a correlate of prediction error at an intermediate level in the hierarchy. The repetition of standard stimuli leads to suppression of prediction error and reduction of the MMN wave. When a deviating stimulus is presented a prediction error is generated again and the MMN wave emerges (27, 28). MMN can thus be thought to reflect this underlying predictive coding process. The predictive coding framework can be used to explain both MMN reduction in psychosis and development of psychotic symptoms (25, 29).

There is also evidence that in individuals at ultra-high-risk for psychosis the amplitude of the MMN induced by a frequency-deviant sound decreases with transition to psychosis (30). It can be concluded that alterations in the MMN could be useful to determine which subjects at risk are most likely to develop a psychosis and to initiate risk-adapted prevention in the clinical work. Furthermore, it has been suggested by Kim et al. (31), that in subjects at clinical high risk MMN could be used not only as predictor of transition to psychosis but also as a predictor of remission regardless of transition.

The present non-invasive electrophysiological study examines MMN in subjects at risk for psychosis fulfilling ultra-high risk (UHR) or/and basic symptoms criteria. It addresses the questions if there are differences in MMN between the different risk criteria and if MMN source analysis can improve prediction of transition to psychosis.

2. Methods

2.1. Subjects and assessment

Individuals at risk for psychosis were recruited as part of the multimodal ZInEP (Zurich Program for Sustainable Development of Mental Health Services) early recognition study (32). Subjects were

recruited by a study website, advertisements in newspapers and flyers or a clinical therapist assigned the subjects to the study center. At study baseline amongst others psychopathology and neuropsychology were measured and EEG was recorded (33, 34). All interviews, cognitive testing and EEG measurement were administered by experienced and extensively trained psychologists and psychiatrists.

Inclusion criteria for the present study were individuals aged 13–35 years, sufficient German speaking ability, fulfilling at least one of the following psychosis risk criteria: (1) basic symptoms (BS), with at least one cognitive-perceptive (COPER) basic symptom or at least two cognitive disturbances (COGDIS) basic symptoms, assessed by the adult (35) or children-youth (36) version of the Schizophrenia Proneness Interview (SPI-A/SPI-CY), (2) ultra-high-risk status for psychosis (UHR) was rated by the Structured Interview for Prodromal Syndromes - SIPS (37), with at least one attenuated psychotic symptom, or at least one brief limited intermittent psychotic symptom, or a positive state–trait criterion (reduction in global assessment of functioning of >30% in the past year, plus either schizotypal personality disorder or first degree relative with psychosis).

The two groups were created to distinguish between individuals with a general risk (BS) and individuals with imminent risk (UHR) of transition to manifest schizophrenia (11, 38). All subjects at risk were followed up over 3 years as part of the ZInEP early recognition study (32, 39) to detect transitions in a manifest psychotic disorder. Transition to psychosis was defined according to ICD-10 criteria for schizophrenia. The diagnosis schizophrenia was made if at least one so-called Schneider's first rank symptom or at least two other symptoms of schizophrenia were present for most of the time during an episode lasting for at least 1 month.

Exclusion criteria were: estimated premorbid IQ < 80, meeting DSM-IV criteria for current substance dependence, any psychotic disorder confirmed by research diagnostic interviews, and/or any medical condition known to affect the brain.

Healthy controls matching age and gender were included in the study. A Mini-International Neuropsychiatric Interview (40) was used to assure the absence of any mental illness in control subjects.

The study was approved by the ethics committee of the canton Zurich and carried out in accordance with the Declaration of Helsinki. All participants gave their written informed consent after receiving a detailed description of the study and in case of minors the written informed consent was obtained from their parents too.

2.2. EEG recording

Subjects were tested in a quiet laboratory, sitting in a comfortable chair. EEG data were recorded using a BrainAmp amplifier and Brain Vision Recorder Software. Thirty-two Electrodes were applied to the scalp by well-trained professionals and held in position by a nylon cap (BrainCap MR32 standard; EASYCAP, Herrsching-Breitbrunn, Germany). EEG channels were referenced to FCz, scalp electrode impedance was kept below 10 k. An EOG electrode was positioned below the right eye and ground was positioned at AFz. The sampling rate was 500 Hz. A band-pass filter of 0.1 to 100.0 Hz (12 dB/ octave rolloff each) was applied to collect the data. 2,400 acoustic stimuli were presented binaurally by headphones and Presentation software (Neurobehavioral Systems, Inc., San Pablo, CA, United States). During recording, participants were instructed to relax and watch a soundless movie clip of "Mr. Bean" presented on an easily visible screen to distract attention away from the acoustic stimuli. The acoustic stimuli included 1896 standard (1,000 Hz, 100 ms, 80 dB; 79% of total stimuli), 168 duration-deviant (1,000 Hz, 50 ms, 80 dB; 7% of total stimuli), 168 frequency-deviant (1,200 Hz, 100 ms, 80 dB; 7% of total stimuli), and 168 intensity-deviant tones (1,000 Hz, 100 ms, 70 dB; 7% of total stimuli), which were applied in a pseudo-random sequence without recurring order as one continuous block. There were at least two standard stimuli between each deviant stimulus and the stimulus onset asynchrony was 500 ms. The participant was observed closely during the 20 min of EEG-recording.

2.3. Data preprocessing and analysis

The recorded EEG files were edited using Brain Electrical Source Analysis (BESA) software, version 5.3. The EEGs were re-referenced to an average reference. Before averaging the EEGs, a filter with the low cut-off of 1 Hz and a high cut-off of 20 Hz (both 12 dB/ octave) was applied. Then each EEG file was divided into 500 ms epochs including a 100 ms pre-stimulus baseline interval and blinking artefacts were eliminated. All trials with amplitudes exceeding 120 V were discarded, all EEG files were visually examined and if the horizontal or vertical EOG channels detected eye movement, the corresponding EEG epoch was declined. Subject providing less than 60% accepted trials were excluded from the study. The included trials were averaged individually for each subject and each condition (standard and deviant in duration, frequency or intensity). Afterwards individual standard and MMN average waveforms were calculated for every subject and every condition. The standard average waveform was subtracted from the particular deviant waveforms, namely duration, frequency or intensity, resulting in the respective MMN waveforms. The MMN waveforms at six centrally positioned surface electrodes (Fz, F3, F4, Cz, C3, and C4) (41) were examined and the peak MMN amplitude and latency were determined. Peak amplitude was detected within a window of 150–250 ms post-stimulus. This was performed for each group of subjects and each condition separately.

2.4. Source analysis

For the Source Analysis we used the BESA spatiotemporal source analysis tool in accordance with the BESA tutorial by Hoechstetter et al. (42). We assumed a source model with two symmetric regional sources temporal in the auditory cortex, based on knowledge that MMN is generated in the primary auditory cortex, and a third regional source located in the frontal cortex, as it is suitable for MMN (43, 44), assuming a contribution in generating MMN made by the right frontal cortex. We used MRI image CLARA ("Classical LORETA Analysis Recursively Applied"), an iterative application of the LORETA ("Low-resolution electromagnetic tomography") algorithm, in which the source space is implicitly reduced in each iteration. Using the grand average of all subjects a source model was created for each condition. Then the event related potentials of each subject were used together with the source model acquired before out of the grand averages to asses individual MMN source activity for each participant and each condition so that potential differences among the study groups could be evaluated.

2.5. Statistical analysis

Demographic and clinical characteristics were analyzed using Chi-square statistics for categorical variables and one-way analysis of variance (ANOVA) for continuous variables. Distribution of MMN surface activity (Fz, F3, F4, Cz, C3, and C4) and MMN source activity (RS1, RS2, and RS3) were compared across groups using one-way ANOVAs. Pairwise group comparisons were performed using Bonferroni post-hoc comparisons for continuous data. Unadjusted and adjusted (for demographic and clinical variables) logistic regression models were conducted for subjects meeting the UHR criteria to estimate transition probability according to MMN source activity in the duration condition. For regression analyses measures of MMN source activity were inverse coded and, as well as other continuous variables, centered to sample mean (*z*-transformed).

All statistical analyses were performed using STATA/SE 16.0 (StataCorp LP, TX, United States).

3. Results

3.1. Sample

One-hundred sixty-one individuals at risk for psychosis could be included in the study. Of these, $n = 74$ subjects fulfilled only the basic symptom (BS) criteria and $n = 13$ were classified as only ultra-high risk (UHR), while $n = 74$ met both UHR and BS criteria. The control group consisted of 50 healthy controls matched by age and gender (see Table 1). The UHR only and the combined UHR&BS group were significant younger and reported more positive symptoms on the SIPS than the only BS group. The combined UHR&BS group had more SIPS negative symptoms and lower functioning than the BS group.

3.2. MMN surface amplitudes

Grand average MMN surface waveforms for duration, frequency and intensity deviants are displayed in Figure 1. Mean peak amplitudes (±standard deviation) for the duration deviant condition are presented for the six examined electrodes in Table 2. No significant differences in MMN surface amplitudes were found when comparing the whole risk group with the control group. In comparison across all subgroups, significant amplitude differences were found at electrodes Cz and C4. Bonferroni-corrected pairwise post-hoc comparisons revealed significantly lower amplitude in the BS group compared with the UHR&BS group (significant for electrode Cz). No significant group differences at surface electrodes were found for the two other deviant conditions intensity and frequency.

3.3. MMN source activity

The BESA source localization revealed three regional sources (RS): one in the left superior temporal lobe (RS1), one in the right superior temporal lobe (RS2), and a third in the anterior cingulate gyrus (RS3). Transferred to the Talairach space, the first two sources were based in the primary auditory cortices (Brodmann 41) on the left and right transverse temporal gyri and the third source in the anterior cingulate area (Brodmann 24).

Comparing MMN Source activity between individuals at risk and healthy controls group differences were found only in the duration condition for the activity of the frontal regional source (RS3; Table 2). Source activity was significantly lower in individuals at risk compared to controls (RS3-posthoc: CON > BS, $p < 0.001$; CON > UHR&BS, $p < 0.001$; CON > UHR, $p = 0.024$).

Correlation analyses between demographic variables, functioning and MMN source activity in the duration condition found gender to be linked to lower activity in the right temporal source (RS2), while age was linked to lower activity in the left temporal source (RS1; Table 3). Higher activity in the left temporal source (RS1) was positively associated to activities in the two other sources (RS2 & RS3). Baseline global functioning (GAF) was not bi-variately related to any other study variable.

3.4. Transition versus no transition

The fifteen individuals with transition to manifest schizophrenia did not differ from subjects at risk without transition

TABLE 1 Demographic and clinical characteristics of the study sample.

	Controls		At-risk			Group comparisons	
	CON	All at-risk (BS, UHR & BS, UHR)	BS	UHR & BS	UHR	CON vs. at-risk value of *p*	Across subgroups overall value of *p*
n	50	161	74	74	13		
Gender male	27 (54.0%)	97 (60.25%)	46 (62.16%)	41 (55.41%)	10 (76.92%)	$p = 0.433$	$p = 0.402$
Age	21.00 ± 5.55	20.70 ± 5.65	23.11 ± 5.69	18.91 ± 4.86	17.15 ± 3.98	$p = 0.741$	**$p < 0.001$** BS > UHR&BS***; UHR*
SIPS positive	–	7.94 ± 4.62	4.58 ± 3.29	10.86 ± 3.68	10.44 ± 2.68	–	**$p < 0.001$**[a] UHR&BS; UHR > BS***
SIPS negative	–	11.94 ± 6.13	10.46 ± 5.95	13.32 ± 6.01	12.46 ± 6.36	–	**$p = 0.016$** [a] UHR&BS > BS*
GAF	–	55.61 ± 13.67	58.92 ± 14.75	52.01 ± 12.19	57.67 ± 10.51	–	**$p = 0.008$** [a] BS > UHR&BS***
CPZ-equivalent	–	26.29 ± 142.9	10.03 ± 37.81	47.18 ± 206.12	0 ± 0	–	$p = 0.227$ [a]
Transition F20 (n/%)	–	15 (9.32%)	3 (4.05%)	10 (13.51%)	2 (15.38%)	–	$p = 0.104$ [a]

CON, control group; BS, only basic symptoms criteria; UHR&BS, fulfilling basic symptoms criteria and ultra-high-risk criteria; UHR, only ultra-high-risk criteria; SIPS, structured interview for prodromal syndromes; GAF, global assessment of functioning; CPZ-equivalent, chlorpromazine equivalent; Transition F20, transition into manifest schizophrenia.[a](comparisons were done without CON), *($p < 0.05$) and ***($p < 0.001$).

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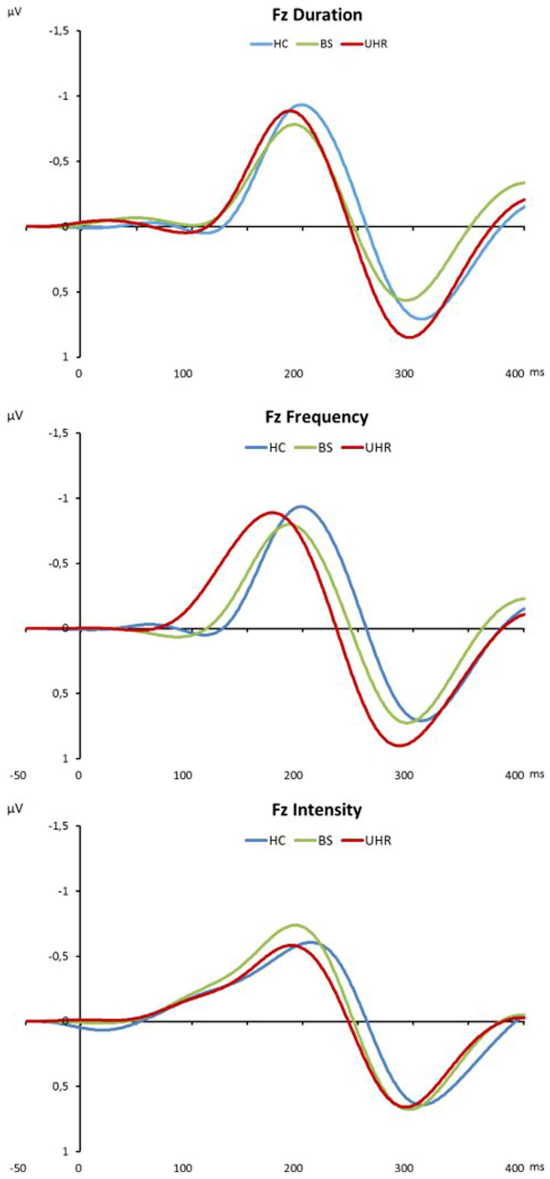

FIGURE 1
Grand average MMN surface waveforms for duration, frequency and intensity deviants in microvolts at electrode Fz. HC, healthy controls; BS, basic symptom group; UHR, ultra-high-risk group (UHR&BS+only UHR).

in MMN activity at surface electrodes. With respect to MMN source activity, a significant difference was found only at the frontal source (RS3) in the duration condition with a lower MMN source activity in subjects with transition ($F = 5.601$; $p = 0.019$) (Figure 2).

Table 4 shows the results from logistic regression models estimating the transition probability in subjects fulfilling the UHR criteria according to MMN source activity in the duration condition, sex, age, psychopathology and global functioning. Unadjusted models revealed lower frontal source (RS3) activity to increase the likelihood for F20 transition by the factor 3.12, while no other predictor was linked to F20 transition. Effect for RS3 increased after adjusting for all other variables, while age as well as SIPS positive symptoms were also found to be linked to transition in the adjusted model.

4. Discussion

In recent years, several studies have shown the predictive value of MMN for assessing the risk of transition in individuals at risk for psychosis (18–20, 45–49). The present study extends the existing knowledge by examining differences in MMN between different risk groups, subjects fulfilling only basic symptoms, subjects who meet both BS and UHR criteria and subjects only at ultra-high-risk for psychosis. In addition, a source analysis of MMN was performed to determine whether evaluation of source activity can improve risk assessment. Three different deviant stimuli (duration, frequency, intensity) in a traditional constant standard MMN paradigm involving the same high probability standard stimulus throughout the whole sequence were used in the study. Significant differences could be detected only for duration deviants.

Subjects from the only basic symptoms group had a significantly lower MMN amplitude compared to the group fulfilling both UHR & BS in the analysis of the surface electrodes. No significant differences were found between persons at risk for psychosis and controls at surface electrodes. However, when the underlying source activity of MMN was examined, significant differences were found at the frontal source between controls and all three risk groups.

Dipole modeling studies as well as fMRI and PET investigations have shown that in addition to both temporal generators, a frontal generator is also involved in the development of MMN (50–55). Some authors assign the frontal components of MMN the role of directing attention on detection of changes in sensory processing areas (56, 57). Within the framework of hierarchical predictive coding theory, it is assumed that the MMN reflects an error signal. This error signal occurs when a sensory input does not match the prediction for that input (58). Frontal mechanisms are thought to underlie the coding of the predicted representation, which then acts on sensory processing regions (59).

The results of the present study suggest that particularly the frontal components of MMN are disturbed in the risk state for psychosis. All three risk groups showed significantly lower MMN activity at frontal source compared to healthy controls. The fact that this change was already detectable in the only BS group indicates that changes in MMN occur already early in the course of the disease. Disturbances of frontal brain functions belong to the typical characteristics of the schizophrenic disease (60, 61). Consistent with this is the finding that individuals with transition to manifest schizophrenia showed the strongest alterations at the frontal MMN source already in the risk state.

During the observation period of 3 years after MMN examination, 15 participants developed a manifest schizophrenic disorder. Individuals with transition already differed at the time of study inclusion by significantly lower activation of the frontal MMN source from individuals in the risk state of psychosis who did not develop manifest schizophrenia during the observation period. Due to the limited follow-up period of 3 years, only a very small number of transitions ($n = 3$) could be observed in the only BS group. The analysis of transition probability was therefore limited to those individuals who met UHR criteria. The logistic regression model showed that low activity at the frontal MMN source more than tripled the probability of transition in UHR subjects. Transferred to the average transition risk of 15 to 25% within 3 years (12), this could mean that individuals who are at risk for psychosis and additionally have low activity at the frontal

TABLE 2 MMN peak amplitudes (μV) and source activity (nAm)±standard deviation.

	Controls		At-risk (sub groups)			Group comparison	
	CON	All at risk (BS, UHR, UHR & BS)	BS	UHR & BS	UHR	CON vs. all	Across subgroups (CON, BS, UHR, UHR & BS)
Surface electrodes (μV mean ± SD)						Value of *p*	overall value of *p*
Fz	−1.32 ± 0.56	−1.31 ± 0.55	−1.19 ± 0.51	−1.41 ± 0.56	−1.40 ± 0.64	$p = 0.920$	$p = 0.109$
F3	−1.15 ± 0.53	−1.17 ± 0.54	−1.09 ± 0.49	−1.25 ± 0.58	−1.20 ± 0.50	$p = 0.816$	$p = 0.338$
F4	−1.29 ± 0.63	−1.36 ± 0.55	−1.25 ± 0.51	−1.44 ± 0.55	−1.44 ± 0.76	$p = 0.491$	$p = 0.187$
Cz	−1.16 ± 0.51	−1.05 ± 0.47	−0.94 ± 0.43	−1.15 ± 0.48	−1.15 ± 0.54	$p = 0.173$	$\mathbf{p = 0.022}$ BS > UHR & BS*
C3	−1.03 ± 0.40	−0.97 ± 0.50	−0.87 ± 0.43	−1.08 ± 0.55	−0.90 ± 0.52	$p = 0.441$	$p = 0.052$
C4	−1.12 ± 0.56	−1.00 ± 0.48	−0.89 ± 0.48	−1.10 ± 0.48	−1.05 ± 0.37	$p = 0.130$	$\mathbf{p = 0.028}$ no sig. *Post hoc*
Sources (nAm mean ± SD)							
Left temporal (RS1)	14.71 ± 8.51	16.11 ± 7.45	14.86 ± 7.48	16.96 ± 7.13	18.33 ± 8.47	$p = 0.266$	$p = 0.159$
Right temp. (RS2)	13.08 ± 5.54	14.69 ± 7.35	13.66 ± 6.38	15.74 ± 7.79	14.56 ± 9.51	$p = 0.156$	$p = 0.150$
Frontal (RS3)	13.95 ± 7.17	8.34 ± 4.42	7.72 ± 4.16	8.80 ± 4.42	9.23 ± 5.65	$\mathbf{p < 0.001}$	$\mathbf{p < 0.001}$ CON > BS*** CON > BS & UHR*** CON > UHR*

CON, control group; BS, only basic symptoms criteria; UHR&BS, fulfilling basic symptoms criteria and ultra-high-risk criteria; UHR, only ultra-high-risk criteria; RS, regional source; *($p < 0.05$) and ***($p < 0.001$).

TABLE 3 Correlation analysis of the three MMN sources activity in the duration condition with age, sex, and global functional level.

	1. Sex	2. Age	3. RS1 (duration)	RS2 (duration)	RS3 (duration)	GAF Baseline
Sex	–					
Age	0.086	–				
RS1 duration	−0.085	**−0.169***	–			
RS2 duration	**−0.141***	−0.108	**0.407*****	–		
RS3 duration	−0.130	−0.073	**0.236*****	0.088	–	
GAF baseline	0.001	0.100	−0.027	0.003	0.000	–

RS1, left temporal source; RS2, right temporal source; RS3, frontal source; GAF, global assessment of functioning (only available for subjects at risk). *$p < 0.05$ and ***$p < 0.001$.

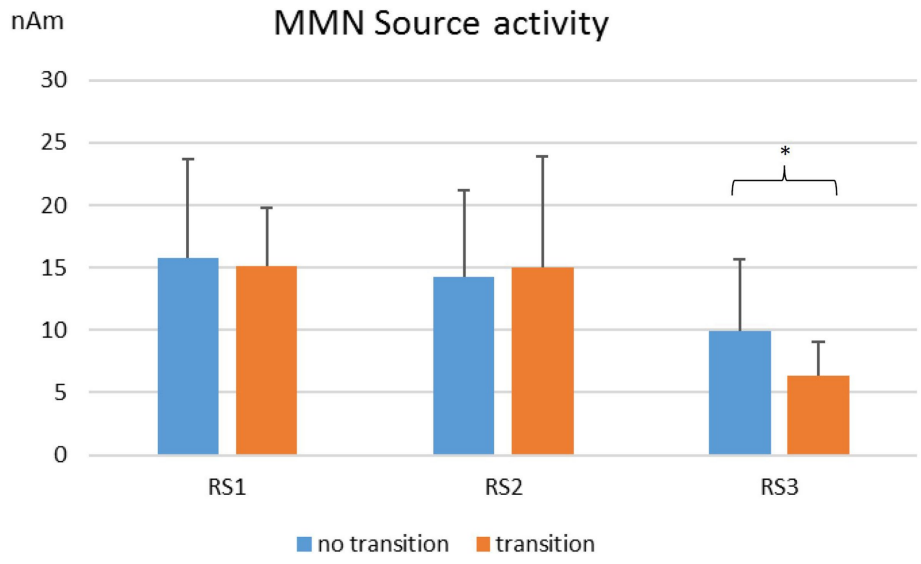

FIGURE 2
MMN source activity in nAm for duration deviants. Comparison of individuals with (*n*=15) and without transition (*n*=146) to manifest schizophrenia. RS1, left regional source; RS2, right regional source; RS3, frontal regional source. *$p<0.05$.

TABLE 4 Results of logistic regression models estimating transition probability in UHR individuals.

	No Transition (*n*=75)	Transition F20 (*n*=12)	Unadj. OR (95%CI)	Adj. OR (95%CI)
Sex Male (*n*/%)	43 (57.3%)	8 (66.7%)	1.49 (0.41–5.38)	1.35 (0.25–7.34)
Age	18.37 ± 4.52	20.33 ± 6.00	1.55 (0.80–2.99)	**2.97 (1.18–7.45)***
RS1 duration (invers coded)	−16.62 ± 7.55	−13.34 ± 4.92	1.80 (0.81–4.00)	1.45 (0.43–4.87)
RS2 duration (invers coded)	−14.38 ± 7.87	−15.66 ± 9.20	0.87 (0.52–1.46)	0.53 (0.25–1.13)
RS3 duration (invers coded)	−8.29 ± 4.68	−5.21 ± 2.89	**3.12 (1.08–9.07)***	**5.34 (1.16–24.60)***
GAF baseline	52.69 ± 11.93	53.64 ± 13.57	1.09 (0.53–2.26)	1.89 (0.77–4.64)
SIPS positive	10.57 ± 3.48	12.23 ± 3.69	1.79 (0.83–3.87)	**3.21 (1.09–9.41)***
SIPS negative	12.88 ± 5.81	15.17 ± 7.25	1.49 (0.78–2.85)	0.90 (0.38–2.10)

OR, odds ratio; 95%CI, 95% confidence interval; GAF, general assessment of functioning; RS, regional source; SIPS, structured interview for prodromal syndromes; *$p < 0.05$.

MMN source might have a risk of about 45 up to over 75% of transition into manifest psychosis.

A limitation of the study is that localization of sources by EEG is imprecise. This may account for the different localization of frontal MMN source in various studies [e.g., middle frontal gyrus, left, right, or bilateral inferior frontal gyrus and anterior cingulum (50–52, 62, 63)]. However, this variability in the location of the frontal source could also stem from variations in the degree of attentional focus on the stimuli (59). A further limitation arises from the circumstance that some of the individuals in the at-risk state were already receiving antipsychotic medication. However, the average chlorpromazine equivalent was relatively low at 26.3 mg per day. Another limitation is the relatively low transition rate of 9.3 percent, which is still in line with other early recognition studies (12, 39).

The present study found significant changes only for duration deviant stimuli. This is in line with other studies which reported stronger MMN changes in individuals at risk for psychosis to duration deviant stimuli compared to frequency deviant stimuli (18, 64). A possible explanation could be that processing of duration changes requires more complex brain functions than processing of frequency changes, and more complex processes can already be affected by discrete brain dysfunctions as they are present in risk states for psychosis.

5. Conclusion

Consistent with the existing literature, the present study was able to confirm MMN alterations in individuals at risk for psychosis. Through analysis of the underlying source activity, these changes could be attributed primarily to the frontal MMN source. Alterations in the frontal components of MMN appear to be particularly relevant for predicting a transition to manifest schizophrenic disorder. Even if MMN is not suitable as a sole biomarker of psychosis, it may contribute additional information about the risk of transition in individuals fulfilling ultra-high risk (UHR) for psychosis.

Data availability statement

The datasets presented in this article are not readily available because they are not publicly available. Requests to access the datasets should be directed to the the corresponding author karsten.heekeren@uzh.ch.

Ethics statement

The study was reviewed and approved by the Ethics committee of the canton of Zurich (KEK-ZH-Nr. E-63/2009). Written informed consent was obtained from all participants and participants' parents/legal guardians for their participation in this study.

Author contributions

TA, AT, SW, WR, WK, and KH designed the study and wrote the protocol. TA and FH collected the data. TA, MM, and KH analyzed the data. TA drafted the manuscript. TA, MM, AT, FH, ES, SW, WR, WK, and KH discussed the results and reviewed the manuscript, making critical revisions. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Analysis of polyunsaturated fatty acids in antipsychotic-free individuals with at-risk mental state and patients with first-episode schizophrenia

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Introduction: Abnormalities in membrane phospholipids are considered one of the pathophysiological backgrounds for schizophrenia. This study, explores the fatty acid composition of erythrocyte membranes and its association with clinical characteristics in two groups: individuals with an at-risk mental state (ARMS) and patients experiencing their first-episode of schizophrenia (FES).

Materials and methods: This study measured erythrocyte membrane fatty acids in 72 antipsychotic-free individuals with ARMS, 18 antipsychotic-free patients with FES, and 39 healthy volunteers. Clinical symptoms and cognitive and social functions were assessed using the Positive and Negative Syndrome Scale (PANSS), Brief Assessment of Cognition in Schizophrenia (BACS), Schizophrenia Cognition Rating Scale (SCoRS), and Social and Occupational Functioning Assessment Scale (SOFAS).

Results: Eicosapentaenoic and docosapentaenoic acid levels were lower in the ARMS and FES groups than in the healthy control group. In contrast, nervonic acid (NA) levels were markedly higher in the ARMS and FES groups than in the controls, while only the FES group showed higher levels of arachidonic acid. Oleic acid and NA levels were significantly associated with PANSS scores in both the FES and ARMS groups, particularly for the negative and general subscores. However, the patient groups had no significant associations between the fatty acid composition and the BACS, SCoRS, and SOFAS scores. Furthermore, the baseline fatty acid composition did not differ between the ARMS individuals who later developed psychosis ($N = 6$) and those who were followed for more than 2 years without developing psychosis onset ($N = 30$).

Discussion: The findings suggest that abnormal fatty acid compositions may be shared in the early stages of schizophrenia and the clinical high-risk state for psychosis and may serve as vulnerability markers of psychopathology.

KEYWORDS

polyunsaturated fatty acid, omega-3 polyunsaturated fatty acid, omega-6 polyunsaturated fatty acid, n-3 polyunsaturated fatty acid, n-6 polyunsaturated fatty acid, nervonic acid, at-risk mental state, first-episode schizophrenia

1. Introduction

Altered compositions of membrane phospholipids, which reflect the fluidity and elasticity of cell membranes (1, 2), have been implicated in the pathogenesis of schizophrenia (3–6). Specifically, decreased omega-3 (*n*-3) polyunsaturated fatty acid (PUFA) (7) in the erythrocyte membrane may reflect a core trait characteristic of the illness. Erythrocyte membrane PUFA level was estimated to better reflect neural cell membrane fatty acid composition than plasma PUFA level shown by several studies conducted on humans (8–10), and animal (11, 12). Decreased erythrocyte membrane PUFA levels exists even in the first-episode of schizophrenia (1, 6) and may also be associated with cognitive impairments (13, 14) and negative symptomatology (15, 16). However, the concentration of essential PUFAs, which cannot be synthesized *de novo* and require dietary intake (3, 5), is considerably affected by environmental factors such as physical condition, dietary habits, and antipsychotic medication (1, 7, 17). Furthermore, a few previous studies of erythrocyte membrane nervonic acid (NA), an n-9 monounsaturated fatty acid (FA) that is a major component of the myelin membrane (17), have reported both increased (18) and decreased (19) levels in medicated patients with schizophrenia. Thus, further comprehensive (i.e., saturated, monounsaturated, and PUFA) analyses in antipsychotic-free patients and well-controlled (e.g., physical condition, general biochemical data) comparison subjects are required to clarify the role of FA in the pathophysiology of schizophrenia.

Recently, studies have demonstrated reduced erythrocyte (20) or plasma (21) n-3 PUFAs in individuals with a clinical high-risk state for psychosis, known as the at-risk mental state (ARMS) (22, 23), of which approximately 30% develop psychosis within 2 years (24, 25). These findings suggest that deficits in PUFAs may be present prior to psychosis onset, serving as a potential trait marker. These findings may support the hypothesized relationship between PUFAs and early neurodevelopment (26), where low nutrition exposure during the brain's neurodevelopmental period may cause epigenetic changes (27), leading to various neuropsychiatric disorders, including psychosis. Similar to schizophrenia, decreased membrane n-3 PUFAs seem to contribute to negative symptoms (28) and cognitive deficits (such as impaired verbal fluency) (29, 30) in individuals with ARMS who are less affected by antipsychotics. High-risk individuals may also be characterized by an increased proportion of NA (20), associated with a range of prodromal symptomatology (28, 31). However, conflicting results, such as normal n-3 PUFA [docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA)] levels (32), have also been reported in individuals with ARMS. Furthermore, it remains largely unknown whether the FA findings in ARMS are associated with clinical outcomes, such as later psychosis onset. Amminger et al. (33) demonstrated that "decreased" NA but not PUFA levels predicted the future transition into psychosis in ARMS individuals. Therefore, FA composition in ARMS and its relationship with clinical characteristics, including symptoms, cognitive and social functions, and outcome, require further investigation compared to overt schizophrenia.

This study comprehensively measured erythrocyte membrane FAs in antipsychotic-free individuals with ARMS, antipsychotic-free patients with first-episode schizophrenia (FES), and healthy control subjects. The examined FAs included saturated FAs [palmitic acid (PA) and stearic acid (SA)], n-9 monounsaturated FAs [oleic acid (OA) and NA], n-3 PUFAs [eicosapentaenoic acid (EPA), DPA, and DHA], and n-6 PUFAs [linoleic acid (LA), dihomogammalinolenic acid (DGLA), and arachidonic acid (AA)]. The incorporation of these fatty acids was essential for a comprehensive analysis due to their significance as major constituents, comprising over 90% of the total fatty acid content in erythrocytes and the brain (1, 34). Based on previous findings, we predicted that both clinical groups would have an altered FA composition (especially a decreased n-3 PUFA and increased NA) and that such alterations would contribute to their symptom severity and cognitive functions. We also explored whether FA findings in the patients were associated with the illness stages of psychosis (ARMS vs. FES) and outcome of high-risk individuals (ARMS with vs. without later psychosis onset).

2. Materials and methods

2.1. Participants

Ninety Japanese patients from the University of Toyama Hospital participated in this study. They were diagnosed with either ARMS (34 males and 38 females; mean age ± standard deviation = 18.8 ± 4.4 years) or FES (11 males and 7 females; 24.5 ± 8.2 years). None of the patients took antipsychotic medications within 2 weeks of blood sampling; 61 of 72 ARMS patients and 11 out of 18 FES patients were antipsychotic-naïve. Thirty-nine healthy volunteers (21 males and 18 females; 28.9 ± 5.5 years) were recruited from university students, hospital staff, and acquaintances. Table 1 presents the demographic and clinical data.

Patients diagnosed with schizophrenia underwent diagnostic interviews using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) Patient Edition (35). FES was defined as an illness duration of fewer than 2 years and a single psychotic episode, following previous studies (36, 37). Recent-onset patients who had multiple psychotic episodes within 2 years were excluded. ARMS individuals were identified using the Comprehensive Assessment of At-Risk Mental State (CAARMS) (23), with diagnoses performed by experienced psychiatrists. ARMS individuals were further sub-grouped based on clinical outcomes during the follow-up period, as described in previous reports (24). Conversion to psychosis was defined according to the "psychotic disorder criteria" in CAARMS: (i) hallucinations, unusual thoughts, and suspiciousness exceed defined severities, or delusion with strong conviction, or conceptual disorganization exceeds moderate level, (ii) frequency of symptoms is at least several times a week, and (iii) the episode is longer than 1 week (23). In the subgroup analyses of the ARMS individuals, 36 subjects were excluded due to an insufficient short follow-up period (<2 years). During the follow-up period, six ARMS subjects developed psychosis (ARMS-P), with five developing schizophrenia and one developing delusional disorder. Thirty participants who did not develop psychosis were defined as ARMS-non-psychosis (ARMS-NP). The transition rate was 16.7%.

The study collected information on clinical history through interviews with the participants, their families, or medical records. Physical examination and standard laboratory tests confirmed that participants were physically healthy. Exclusion criteria included a history of substance abuse or dependence, seizures, head injury, and an estimated premorbid IQ of less than 70 based on the Japanese Adult Reading Test (38). Additional criteria for healthy controls were; (i) no Axis I disorders based on the SCID-I Non-patient Edition (35), and (ii) no personal or family (within first-degree relatives) history of psychiatric disorders.

TABLE 1 Demographic and clinical data for patients.

	H	ARMS	FES	Statistics	Group difference[a]
	$n = 39$	$n = 72$	$n = 18$		
Age (years)	28.9 (5.5)	18.9 (4.5)	24.5 (8.1)	$\chi^2 = 56.6$	$p < 0.001$**, H > FES > ARMS
Gender (female/male)	21/18	34/38	11/7	$\chi^2 = 1.27$	$p = 0.52$
Age at onset (years)	–	–	23.8 (8.3)	–	–
Duration of illness (years)			0.7 (0.4)	–	–
Socioeconomic status	6.6 (0.6)	3.6 (1.5)	4.4 (1.4)	$\chi^2 = 34.7$	$p < 0.001$**, H > ARMS, FES
Parental socioeconomic status	6.2 (0.8)	4.9 (0.9)	5.1 (0.9)	$\chi^2 = 20.1$	$p < 0.001$**, H > ARMS, FES
BMI (kg/m^2)	20.1 (1.6)	21.1 (4.5)	22.4 (3.5)	$\chi^2 = 3.8$	$p = 0.15$
JART	–	96.5 (9.9)	99.6 (9.0)	$U_{70,17} = 487.5$	$p = 0.25$
PANSS					
: positive	–	12.0 (2.9)	17.1 (3.4)	$U_{70,16} = 128.5$	$p < 0.001$**, ARMS < FES
: negative	–	15.3 (6.4)	16.7 (6.1)	$U_{70,16} = 473.5$	$p = 0.34$
: general psychopathology	–	30.2 (7.8)	33.4 (7.0)	$U_{70,16} = 418.0$	$p = 0.12$
: total	–	57.5 (14.1)	67.3 (13.1)	$U_{70,16} = 343.0$	$p = 0.02$*, ARMS < FES
BACS[b]	–	−0.62 (0.91)	−1.37 (1.09)	$U_{72,17} = 348.0$	$p = 0.006$**, ARMS > FES
SCoRS[c]	–	5.5 (2.2)	6.9 (2.0)	$U_{70,16} = 351.5$	$p = 0.02$*, ARMS < FES
SOFAS[d]	–	48.5 (10.3)	44.6 (12.5)	$U_{57,16} = 365.5$	$p = 0.23$

Values represent mean (S.D.). ARMS, at-risk mental state (ARMS); BACS, brief assessment of cognition in schizophrenia; BMI, body mass index; FES, first-episode schizophrenia; H, healthy control; JART, Japanese Adult Reading Test; PANSS, positive and negative syndrome scale; SCoRS, schizophrenia cognition rating scale; SOFAS, social and occupational functioning assessment scale.

[a]Demographic differences between groups were examined by Kruskal–Wallis test (age), qui-square test (gender), or Mann–Whitney U test (others). **$p < 0.01$ and *$p < 0.05$.

[b]BACS composite score was calculated by averaging all z-scores of the six primary measures from the BACS.

[c]Data are ranging from 0 to 10, with larger numbers representing more worse functions.

[d]Data are ranging from 0 to 100. Generally, Healthy subjects generally have a scores ranging from 90 to 100.

This study was conducted following the principles of the Declaration of Helsinki and was approved by the Committee on Medical Ethics of Toyama University (no. I2013006) on February 5, 2014. Written informed consent was obtained from all participants after a full explanation of the study's purpose and procedures were provided. For participants under 20, written consent was also obtained from their parents or guardians.

2.2. Clinical assessment

Experienced psychiatrists or psychologists evaluated clinical symptoms, cognitive function, and social function using the Positive and Negative Syndrome Scale (PANSS) (39), Brief Assessment of Cognition in Schizophrenia (BACS) (40, 41), Schizophrenia Cognition Rating Scale (SCoRS) (42, 43), and the Social and Occupational Functioning Assessment Scale (SOFAS) (44). BACS composite scores were obtained by averaging the z-scores of the six subtests (41). Clinical assessments were performed on the same day as blood collection or within 2 weeks of blood collection.

2.3. FA analysis

Blood samples were collected from study participants between 08:30 and 10:00 after at least 2 hours of fasting for FA measurements and general blood and biochemical examinations (Supplementary material 1 for detailed results). Erythrocyte membrane FA levels were analyzed using gas chromatography based on an established method (14, 34, 45). Briefly, 1 mL of red blood cells obtained from the subjects was collected into a 15 mL screw cap vial. The vial received 4.0 mL of 0.6 N methanolic HCl containing 4 μL of 0.5% butyl hydroxytoluene (BHT) as an internal standard and was then sealed and incubated at 80°C for 2 hours. Methylated FAs were extracted twice with hexane, and the layers were separated by centrifugation in a swinging rotor at 3000 g for 15 min at room temperature. The hexane layer was carefully removed and collected in separate vials. The hexane extract was dried entirely by passing through argon and stored at −40°C until use. The methylated FAs were resuspended in 150 μL hexane, and aliquots (1 μL) were used for FA analysis with a Shimadzu gas chromatograph (Model GC-2010, Japan), using a capillary column of dimensions 30 m × 0.32 mm × 0.20 μm (Supelco, United States). A flame ionization detector was used with a column oven temperature of 160°C for 10 min, programmed at 10°C rise/min up to 175°C, and held at 220°C for 10 min. The injector and detector temperatures were set to 240°C and 275°C, respectively. The column was calibrated by injecting a standard FA mixture at approximately equal proportions. The peaks in the recorded data were identified based on the retention time of standard FAs run under identical conditions.

The FA data were categorized into four groups: (i) saturated FAs (PA, SA), (ii) n-9 series monounsaturated FAs (OA, NA), (iii) n-3 PUFAs (EPA, DPA, DHA), and (iv) n-6 series PUFAs (LA, DGLA, AA). FA levels were expressed as relative values measured as 100% of the 11 FAs, which included the 10 FAs mentioned above and BHT as

an internal standard (1). We calculated the following parameters based on the previous literatures: (i) n-3 total (EPA + DPA + DHA), (ii) n-6 total (LA + DGLA + AA), (iii) n-6/n-3 ratio (AA/[EPA + DHA]) as an index to assess the inflammatory response (46, 47), and (iv) omega-3 index (EPA + DHA) as a potential index to predict vulnerability to several neuropsychiatric conditions and functional outcome of ARMS (28, 48, 49).

2.4. Statistical analysis

Statistical analyses were performed using Statistical Package for Social Sciences version 25 (SPSS Japan Inc.) and Jamovi Software[1]. As most demographic/clinical data (age, scores for PANSS subscales, BACS, SCoRS, and SOFAS) had skewed distributions, nonparametric Mann–Whitney U (for two-group comparisons) or Kruskal–Wallis (for three-group comparisons) tests were used to compare group differences. Similarly, nonparametric tests were employed for group differences in FA compositions, which were found to have non-normal distributions. Spearman's rho with semi-partial correlation was used to calculate the correlation between FA composition and clinical data, with FA indices being controlled by age, because significant age differences among the groups and age significantly affected NA, EPA, and DPA in our data (data not shown). To correct for multiple comparisons, post-hoc Dwass–Steel–Critchlow–Fligner tests were used for group comparisons. For correlation analyses between FA composition and clinical variables, the Benjamini–Hochberg false discovery rate (FDR) procedure was used because there were many items to be compared (50). Significance was set at a value of p less than 0.05. In the cases of FDR-adjusted p-values, significance was set at less than 0.1 according to the previous literatures (51–53) where screening many items was done.

3. Results

3.1. Subjects' profile

The gender ratios of the groups were matched, but there were significant differences in age (controls > FES > ARMS) and personal/parental socioeconomic status (Table 1). Body mass index did not differ between the groups. Japanese Adult Reading Test scores did not differ between the ARMS and FES groups. As expected, the FES group had lower BACS scores, higher SCoRS scores, and higher PANSS positive symptom scores than the ARMS group. The ARMS and FES groups had relatively high alkaline phosphatase levels, which fell within the normal range for adolescents (Supplementary material 1). Prolactin (PRL) levels were examined in 78 patients, of which 12 (10 males and 2 females, 15.4%) exceeded the normal range. Prolactin levels can be elevated even in antipsychotic-free schizophrenia patients without apparent physical illness (54, 55), so patients with high levels were not excluded from this study. Some of the patients were taking anxiolytics (15.6%), hypnotics (11.1%) and antidepressants (8.9%). However, these medications did not affect clinical or cognitive indices, or fatty acids composition (data not shown).

3.2. FA composition

Table 2 and Figure 1 present the results of FA composition analysis. EPA and DPA levels were significantly lower in the ARMS and FES groups than in healthy controls. The NA level was markedly higher in the ARMS and FES groups, while the AA level was significantly higher only in the FES group compared to the controls. Regarding summary values, the FES group had significantly lower n-3 total and higher n-6 total scores than the controls. These findings remained consistent even when we analyzed only antipsychotic-naïve FES/ARMS subjects (data not shown).

3.3. Relationships between FA component and clinical variables

The correlation results are presented in Table 3; Supplementary material 2. A significant positive correlation was found between NA level and PANSS scores in the ARMS group, particularly for negative syndrome and general psychopathology scores. A significant positive correlation was found between OA level and total PANSS score in the FES group. No significant correlation was found between FA levels and BACS, SCoRS, or SOFAS scores.

3.4. FA levels and diagnostic outcome of ARMS

Baseline FA levels did not differ significantly between the ARMS-P ($N = 6$) and ARMS-NP ($N = 30$) subgroups (Supplementary material 3).

3.5. Potential role of antipsychotics and illness chronicity on FA levels

We compared the FA levels between the current antipsychotic-free patients and an independent cohort receiving antipsychotics (Supplementary material 4). The medicated group had significantly higher n-3 PUFA levels in the ARMS and FES groups (Supplementary material 5). Correlation analyses showed a strong effect of antipsychotics on FA composition in the FES group but not in the ARMS group (Supplementary material 6). Furthermore, illness duration did not correlate with FA composition in the FES group (Supplementary material 7).

4. Discussion

To our knowledge, this is the first comprehensive study to investigate the erythrocyte membrane FA composition in antipsychotic-free patients with both ARMS and FES in comparison with healthy controls, as well as its relationship with symptom severity, social and cognitive functions assessed by the BACS, SOFAS, and SCoRS, and other clinical characteristics. Our findings showed

1 https://www.jamovi.org

TABLE 2 Fatty acid composition.

		H	ARMS	FES	χ^2	p
		$n = 39$	$n = 72$	$n = 18$		
Saturated	PA	21.14 (0.99)	21.17 (0.98)	20.86 (1.08)	0.91	0.64
	SA	19.74 (0.65)	19.57 (0.75)	19.68 (0.88)	3.70	0.16
n-9 monounsaturated	OA	14.74 (1.08)	14.84 (1.11)	15.31 (1.19)	2.86	0.24
	NA	0.54 (0.07)	0.92 (0.29)	0.89 (0.29)	61.27	<0.0001***, H < ARMS, FES
n-3 polyunsaturated	EPA	1.30 (0.46)	1.04 (0.40)	0.87 (0.23)	14.92	0.0006***, H > ARMS, FES
	DPA	3.00 (0.31)	2.79 (0.27)	2.80 (0.25)	15.28	0.0005***, H > ARMS, FES
	DHA	8.29 (1.22)	8.22 (1.33)	7.56 (0.86)	5.99	0.05
n-6 polyunsaturated	LA	10.24 (0.97)	10.10 (1.03)	10.20 (1.12)	0.68	0.71
	DGLA	1.43 (0.19)	1.53 (0.26)	1.49 (0.30)	4.78	0.09
	AA	15.22 (1.43)	15.77 (1.13)	16.36 (1.57)	10.63	0.005**, H < FES
Summary value	n-3 total	12.60 (1.79)	12.05 (1.72)	11.22 (1.11)	9.65	0.008**, H > FES
	n-6 total	26.89 (1.72)	27.40 (1.24)	28.05 (1.20)	7.06	0.03*, H < FES
	n-6/n-3 ratio[a]	1.65 (0.46)	1.77 (0.41)	1.98 (0.38)	9.67	0.008**, H < FES
	Omega-3 Index[b]	9.59 (1.57)	9.26 (1.63)	8.42 (0.97)	8.62	0.01*, H > FES

Values represent mean (S.D.) of the percentage of the total fatty acids. AA, arachidonic acid (20:4 n-6); ARMS, at-risk mental state; DGLA, dihomogammalinolenic acid (20:3 n-6); DHA, docosahexaenoic acid (22:6 n-3); DPA, docosapentaenoic acid (22:5 n-3); EPA, eicosapentaenoic acid (20:5 n-3); FES, first-episode schizophrenia; H, healthy control; LA, linoleic acid (18:2 n-6); NA, nervonic acid (24:1 n-9); OA, oleic acid (18:1 n-9); PA, palmitic acid (16:0); SA, stearic acid (18:0). Differences between groups were examined by Kruscal–Wallis test with post-hoc comparisons. ***$p < 0.001$, **$p < 0.01$, and *$p < 0.05$.
[a]n-6/n-3 ratio = AA/(EPA + DHA).
[b]Omega-3 index = EPA + DHA.

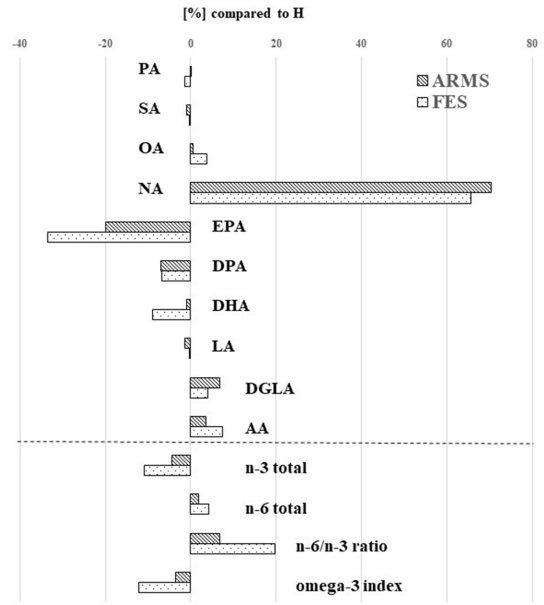

FIGURE 1
Percentage of fatty acid levels in the at-risk mental state (ARMS) and first-episode schizophrenia (FES) groups compared to the healthy control (H) group. AA, arachidonic acid (20:4 n-6); DGLA, dihomogammalinolenic acid (20:3 n-6); DHA, docosahexaenoic acid (22:6 n-3); DPA, docosapentaenoic acid (22:5 n-3); EPA, eicosapentaenoic acid (20:5 n-3); LA, linoleic acid (18:2 n-6); NA, nervonic acid (24:1 n-9); OA, oleic acid (18:1 n-9); PA, palmitic acid (16:0); SA, stearic acid (18:0).

that both clinical groups had decreased n-3 PUFAs (EPA and DPA) and increased NA, an n-9 monounsaturated FA, compared to the controls, regardless of the outcome of the ARMS group. We also found that n-9 monounsaturated FA (OA and NA) levels were predominantly associated with symptoms in the FES and ARMS groups, while the FA composition was not significantly related to their social and cognitive functions. These results suggest that the ARMS and FES groups may share FA abnormalities as a potential vulnerability factor, which could contribute to symptomatology.

4.1. n-3 PUFAs

These findings of decreased EPA and DPA levels in the current ARMS and FES groups are consistent with previous research in FES (6, 7, 34) and ARMS (20, 32), indicating that these changes may be a trait characteristic in the early stages of psychosis and not solely explained by antipsychotic medication (1, 15) or other environmental factors such as smoking or dietary intake after the onset of psychosis (56). While the exact role of membrane PUFAs in the pathophysiology of psychosis remains unclear, animal and experimental studies have suggested that PUFA abnormalities can affect membrane properties in the central nervous system (e.g., fluidity, elasticity, and thickness) (2) and dopaminergic transmission (57). Our findings may also support the animal vulnerability model of psychosis (27). PUFA deficiency during early neurodevelopmental stages could cause epigenetic changes, such as DNA methylation, which affect the expression of developmentally regulated genes (58) and increase the risk of psychosis in adulthood.

TABLE 3 Relationships between fatty acid levels and clinical/cognitive indices.

		PANSS total		PANSS positive		PANSS negative		PANSS general psychopathology		BACS		SCoRS		SOFAS	
		ARMS	FES	ARMS	FES	ARMS	FES	ARMS	FES	ARMS	FES	ARMS	FES	ARMS	FES
Saturated	PA	0.18	0.05	0.03	−0.01	0.22	0.25	0.14	−0.16	0.02	−0.03	−0.14	0.20	−0.03	−0.64†
	SA	−0.14	−0.46	−0.13	−0.58†	−0.14	−0.37	−0.05	−0.34	−0.19	0.26	0.23	−0.13	−0.16	0.06
n-9 monounsaturated	OA	−0.12	**0.71***	−0.07	0.25	−0.10	0.63†	−0.17	0.61†	0.11	−0.60†	0.11	0.08	−0.06	−0.14
	NA	**0.43***	0.17	0.19	−0.27	**0.36***	0.13	**0.36***	0.33	−0.05	−0.17	−0.17	−0.09	0.20	0.19
n-3 polyunsaturated	EPA	0.04	−0.17	0.11	0.15	0.09	−0.18	−0.04	−0.17	0.03	−0.05	−0.22	0.12	0.25	−0.20
	DPA	0.12	0.03	0.18	−0.14	0.13	0.01	0.05	0.17	0.13	−0.39	−0.10	−0.20	0.08	0.25
	DHA	0.20	0.01	0.14	0.10	0.18	−0.05	0.15	0.15	0.02	−0.29	−0.20	0.27	0.24	0.21
n-6 polyunsaturated	LA	−0.19	0.04	−0.05	0.54†	−0.22	−0.28	−0.17	0.16	0.01	0.15	0.11	−0.27	−0.10	0.55†
	DGLA	0.08	0.07	0.09	0.38	0.00	−0.11	0.07	0.13	−0.21	−0.04	0.10	−0.14	−0.13	0.43
	AA	−0.05	−0.21	−0.04	−0.40	−0.04	−0.16	0.00	−0.18	0.03	0.19	−0.07	−0.03	−0.08	−0.23
summary value	n-3 total	0.18	−0.08	0.17	−0.09	0.18	−0.06	0.11	0.07	0.04	−0.32	−0.22	0.22	0.25	0.25
	n-6 total	−0.17	−0.07	−0.03	0.29	−0.23	−0.30	−0.09	−0.02	−0.04	0.54†	0.12	−0.38	−0.24	0.13
	n-6/n-3 ratio[a]	−0.16	−0.10	−0.13	−0.27	−0.16	−0.05	−0.09	−0.12	−0.02	0.29	0.18	−0.29	−0.22	−0.13
	omega-3 index[b]	0.17	−0.01	0.15	0.06	0.18	−0.01	0.11	0.09	0.01	−0.26	−0.22	0.33	0.25	0.10

Values are Spearman's rho, calculated using semi-partial correlation analysis that only fatty acid indices were controlled by age as a covariate. *False discovery rate adjustment p value < 0.1 (written in bold letters). †There was a significant correlation between fatty acid composition and clinical/cognitive indices, however, they did not survive after post-hoc analysis for multiple comparison. AA, arachidonic acid (20:4 n-6); ARMS, at-risk mental state; BACS, brief assessment of cognition in schizophrenia; DGLA, dihomogammalinolenic acid (20:3 n-6); DHA, docosahexaenoic acid (22:6 n-3); DPA, docosapentaenoic acid (22:5 n-3); EPA, eicosapentaenoic acid (20:5 n-3); FES, first-episode schizophrenia; H, healthy control; LA, linoleic acid (18:2 n-6); NA, nervonic acid (24:1 n-9); OA, oleic acid (18:1 n-9); PA, palmitic acid (16:0); PANSS, positive and negative syndrome scale; SA, stearic acid (18:0); SCoRS, schizophrenia cognition rating scale; SOFAS, social and occupational functioning assessment scale.

[a]n-6/n-3 ratio = AA/(EPA + DHA).

[b]omega-3 index = EPA + DHA.

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4.2. n-6 PUFAs

We observed increased levels of n-6 PUFA, particularly AA, in the FES group compared to controls. Previous studies have reported increased (18) and decreased (1, 6, 20) n-6 PUFA in the early stages of psychosis. The reasons for this discrepancy are unclear, but the FA composition of erythrocyte membranes is influenced by various factors, including dietary FA composition, age, ethnicity, physical condition, genes, and gene-by-diet interactions (59). Nonetheless, these studies consistently found an increased n-6/n-3 ratio in schizophrenia (1, 6, 18) and ARMS (20) groups. n-6 PUFAs have a high turnover rate and compete with n-3 PUFAs through the same enzyme (60). Because AA-derived eicosanoids have more prominent inflammatory activity than n-3 PUFAs, the imbalance between n-6 and n-3 PUFAs, indicated by the increased n-6/n-3 ratio, may cause neuroinflammatory pathology in neuropsychiatric disorders (58, 59). Although the increase in the n-6/n-3 ratio was prominent in the FES group, it did not reach statistical significance in the ARMS group (Table 2). This may be due to that ARMS is not as severe as schizophrenia in terms of neuroinflammation as mentioned above. Future longitudinal studies, especially before and after the onset of psychosis in ARMS patients, must investigate whether the putative n-3/n-6 imbalance progresses during psychosis.

4.3. n-9 monounsaturated FAs

The most robust finding of this study was the increased level of n-9 monounsaturated FAs (especially NA) and its relationship with PANSS negative and general subscale scores in both the ARMS and FES groups. Increased levels of OA were also associated with the severity of cognitive deficits in the FES group (rho = −0.60), although this did not survive multiple comparison corrections. Since NA is abundant in brain white matter and plays a crucial role in myelin maturation and integrity (17), our results may be partly in line with neuroimaging evidence that abnormalities in brain connectivity contribute to trait characteristics of psychosis, such as negative symptomatology (61) and cognitive deficits (62) in ARMS (63) and schizophrenia (64). Previous studies on FAs in ARMS and FES have also demonstrated an increased NA level (18, 20) and its relationship with symptom severity (18, 28, 31). However, some of them showed the association of NA level also with positive symptomatology (28, 31). No statistically significant correlation between FA levels and positive symptoms in this study might be attributable to relatively low scores of the positive subscales in our sample. Conflicting results have also shown that lower NA levels contributed to impaired white matter integrity and severe negative symptoms in recent-onset psychosis (46). Therefore, these findings on n-9 monounsaturated FAs require replication in combination with imaging studies of brain connectivity.

4.4. Diagnostic outcome and PUFAs in ARMS

This study did not observe any significant differences in FAs between the ARMS-P ($N = 6$) and -NP ($N = 30$) groups at baseline, indicating that the erythrocyte membrane FA composition may reflect general vulnerability to psychopathology but does not predict future onset of psychosis. However, this study may not have had sufficient statistical power due to small sample size of ARMS-P subjects. In contrast, Amminger et al. (33, 47) reported that lower NA and n-3 PUFAs may predict psychosis in high-risk individuals ($N = 40$, transition rate = 28%). However, the relationship between NA and psychosis risk is complex, as ARMS and psychosis patients, including Amminger's own ARMS cohort (20), are generally reported to have increased NA levels compared to healthy controls. The most recent study by Amminger et al. (65) that examined EPA, DHA and omega-3 index found no significant predictor for transition at both month 6 and 12 (65). Given the relatively small sample size of this study and previous studies, as well as the potential influence of various factors on both FA and transition rate, including FA supplementation (66, 67) and antipsychotic medication (1, 68), the potential use of FAs as a predictive marker for psychosis remains unclear and requires further investigation.

4.5. Limitations

This study has several limitations. First, the small sample size, especially for the FES and ARMS-P groups, may have limited the statistic power of our results. Additionally, there was a significant age difference between groups (control > FES > ARMS), which we statistically controlled for in our analyses. However, future studies with larger age-matched samples must confirm our findings. Second, we did not control for the dietary habits of our participants. Although all participants had standard body mass indices (Table 1) and laboratory data (Supplementary material 1), environmental factors such as dietary habits may have influenced our FA results. However, one of the strengths of the study may be that there were no race differences, which is considered a limiting factor in other international collaborative studies (20). Third, as our study is cross-sectional, future longitudinal studies are needed to confirm the role of FA changes as a trait marker and to investigate the influence of illness stages. Fourth, as FA abnormalities have been reported in other neuropsychiatric disorders such as major depression (69), further research is necessary to confirm our findings' disease specificity and investigate the potential influence of comorbid anxiety/depressive symptoms in patients with ARMS. Fifth, we failed to investigate the duration of symptom of ARMS that might have affected the results. Lastly, tobacco use should have been checked, however, we lacked this information.

4.6. Conclusion

This study found that the ARMS and FES groups exhibited similar FA abnormalities, including decreased n-3 PUFAs (EPA and DPA) and increased n-9 monounsaturated FA (NA) levels, regardless of previous antipsychotic exposure. Additionally, we found that the altered n-9 monounsaturated FA levels were associated with symptoms, measured by PANSS especially negative symptom and general psychopathology but not social or cognitive functions in the early stages of psychosis. Our findings support the notion that an altered composition of membrane phospholipids may be a characteristic of psychosis. We observed no significant influence of illness stages or outcomes of high-risk individuals on the FA composition. However, the potential for FA changes during psychosis and the neural substrates associated with these findings should

be examined in future longitudinal studies that employ neuroimaging methods.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Committee on Medical Ethics of the University of Toyama. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

TS, MS, TT, YH, and AL conceived the idea and design of this study. TS, YH, TT, DS, and MS recruited subjects and were involved in the clinical assessments. HI was used to measure the fatty acid components. YH, DS, and AL were involved in data collection. YH, AL, and DS were responsible for entering data and data analyses. MS, YH, and AL interpreted the results. AL wrote the manuscript. MS, TS, TT, and YH contributed to the writing, checking, and editing of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1188452/full#supplementary-material

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Cognitive subgroups and the relationships with symptoms, psychosocial functioning and quality of life in first-episode non-affective psychosis: a cluster-analysis approach

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Introduction: Prior research examining cognitive heterogeneity in psychotic disorders primarily focused on chronic schizophrenia, with limited data on first-episode psychosis (FEP). We aimed to identify distinct cognitive subgroups in adult FEP patients using data-driven cluster-analytic approach, and examine relationships between cognitive subgroups and a comprehensive array of illness-related variables.

Methods: Two-hundred-eighty-nine Chinese patients aged 26–55years presenting with FEP to an early intervention program in Hong Kong were recruited. Assessments encompassing premorbid adjustment, illness-onset profile, symptom severity, psychosocial functioning, subjective quality-of-life, and a battery of cognitive tests were conducted. Hierarchical cluster-analysis was employed, optimized with k-means clustering and internally-validated by discriminant-functional analysis. Cognitive subgroup comparisons in illness-related variables, followed by multivariable multinominal-regression analyzes were performed to identify factors independently predictive of cluster membership.

Results: Three clusters were identified including patients with globally-impaired (n=101, 34.9%), intermediately-impaired (n=112, 38.8%) and relatively-intact (n=76, 26.3%) cognition (GIC, IIC and RIC subgroups) compared to demographically-matched healthy-controls' performance (n=50). GIC-subgroup was older, had lower educational attainment, greater positive, negative and disorganization symptom severity, poorer insight and quality-of-life than IIC- and RIC-subgroups, and higher antipsychotic-dose than RIC-subgroup. IIC-subgroup had lower education levels and more severe negative symptoms than RIC-subgroup, which had better psychosocial functioning than two cognitively-impaired subgroups. Educational attainment and disorganization symptoms were found to independently predict cluster membership.

Discussion: Our results affirmed cognitive heterogeneity in FEP and identified three subgroups, which were differentially associated with demographic and

illness-related variables. Further research should clarify longitudinal relationships of cognitive subgroups with clinical and functional outcomes in FEP.

KEYWORDS

cognitive heterogeneity, cognitive clusters, cognitive impairment, first-episode psychosis, functional outcome

Introduction

Cognitive impairment is a core feature of schizophrenia and other psychotic disorders (1, 2). It is a major determinant of deterioration in functioning in everyday life including vocational functioning, independent living skills and social functioning (3–5). However, it is considered less recognizable and less manageable than positive symptoms of psychotic disorders as it cannot be improved effectively by antipsychotic treatment (1, 2). In fact, although early intervention service significantly improves functional outcome in patients with first-episode psychosis (FEP) (6), a substantial proportion of FEP patients still exhibit pronounced functional disability even in the presence of symptom remission (7–9). Hence, cognitive impairment constitutes an unmet therapeutic need in patients with psychotic disorders, particularly in relation to promoting early functional recovery.

An extant of literature has demonstrated deficits across multiple cognitive domains among patients with psychotic disorders relative to healthy controls, encompassing attention, processing speed, memory and executive functions (5, 10, 11). On the other hand, evidence has revealed cognitive heterogeneity in patients with psychotic disorders in terms of the severity and patterns of cognitive impairment (12). A growing body of research has utilized data-driven approach, e.g., cluster analysis, in an at attempt to identify homogeneous cognitive subgroups in psychotic disorders. Previous studies reported a 2- to 5-cluster solution on cognition, with the majority indicating three discrete cognitive subgroups characterized by patients with relatively-intact cognitive function, intermediate (i.e., moderately-severe deficits) and global cognitive impairment (i.e., widespread and severe deficits) (12–14). Some other studies also identified cognitive subgroups with more selective impairment in certain domains (12, 15, 16). Prior research has further explored differential associations of cognitive subtypes with clinical and functional characteristics of psychotic disorders. Although relatively mixed findings were observed across studies, accumulating data have suggested that a globally-impaired subgroup is generally associated with lower educational attainment, greater symptom severity (particularly negative symptoms) and worse psychosocial functioning compared with other cognitive subgroups (13, 14). Discrepant findings regarding the number, profiles and correlates of cognitive clusters derived might partly be attributable to cross-study methodological variations such as stages of illness (early vs. chronic or mixed) [e.g., (17)], clinical status (acute vs. clinically-stabilized), diagnostic categories included (non-affective psychoses only vs. both affective and non-affective psychoses) [e.g., (16, 18–20)], patient sample size, and adoption of different cognitive assessments, to name a few. Notably, the majority of earlier studies examining cognitive clusters focused on patients with chronic schizophrenia, which are confounded by clinical heterogeneity, illness chronicity and prolonged medication exposure. Until now, relatively few studies have applied data-driven approach to specifically delineate cognitive variability in FEP patients (18–22), with relatively modest sample size (ranged:105–204 patients, mostly with $n < 150$).

Better understanding and delineation of cognitive heterogeneity in the early course of psychotic disorders would facilitate elucidation of neurobiological mechanisms underlying various cognitive subtypes, and prediction of cognitive impairment trajectories, treatment response and illness outcome. To this end, we report a study conducted in a large representative cohort of Chinese adult patients presenting with first-episode non-affective psychosis to a specialized early intervention program with an aim to identify distinct cognitive subgroups using a cluster-analytic approach. In addition, we examined differential relationships of identified cognitive subgroups with a comprehensive array of illness-related variables encompassing premorbid adjustment, onset profile, various symptom domains, psychosocial functioning, and subjective quality of life (QoL). Based on prior literature in both FEP and chronic schizophrenia, we hypothesized that three cognitive subgroups would be identified by cluster analysis, including a relatively-intact, intermediately-impaired, and globally-impaired subgroups along a continuum of severity of cognitive impairment. We also anticipated that educational attainment, symptom severity and psychosocial functioning would be differentially associated with cognitive cluster membership.

Materials and method

Participants and setting

This study was conducted as part of the Jockey Club Early Psychosis (JCEP) Project (23), a territory-wide early intervention service which provided phasic-specific case management to adult individuals aged 26–55 years presenting with first-episode DSM-IV schizophrenia, schizophreniform disorder, schizoaffective disorder, brief psychotic disorder, delusional disorder, or psychotic disorder not otherwise specified (NOS) in Hong Kong. A total of 355 patients were recruited from publicly-funded generic adult psychiatric outpatient units. Patients with intellectual disability, neurological diseases and history of head injury that may compromise cognitive performance, substance-induced psychosis or psychotic disorder due to general medical condition were excluded. Data of this study were derived from baseline assessments (conducted with a mean of 119.7 days (median: 88 days) after treatment initiation) of a JCEP 4-year follow-up study, and baseline findings regarding depressive symptoms, duration of untreated psychosis (DUP), primary negative symptoms, and psychopathological network analysis have been reported

elsewhere (24–27). The study was approved by local institutional review boards and written informed consent was obtained from all participants. Of the initial cohort, 289 patients who had completed all assessments including cognitive tests were retained as the study sample for the current report. Comparison between the study sample and the excluded participants ($n = 66$) revealed no significant differences in age at entry, gender and diagnostic categories. Excluded patients had significantly lower educational level than patients included in the current analysis ($p < 0.01$).

Study assessments

Diagnostic ascertainment of each patient was based on reviewing all available information including Chinese-bilingual Structured Clinical Interview for DSM-IV (CB-SCID-I/P) (28) administered by senior research psychiatrists at intake, informant histories and medical records. Premorbid adjustment was evaluated using the Premorbid Adjustment Scale (PAS) (29). The overall PAS score encompassing developmental stages of childhood, early and late adolescence was derived according to the scoring method developed by Cannon-Spoor et al. (29). As in previous studies, we subdivided premorbid adjustment into social and academic functional domains (30, 31). An overall score for each of the two functional domains was computed by averaging the ratings of the relevant subscales across developmental stages (32). An overall premorbid adjustment score for each of the three developmental stages was also calculated by summing up all subscale scores and dividing by the maximum possible score. Interview for Retrospective Assessment of the Onset of Schizophrenia (IRAOS) (33) was employed to confirm the first-episode status and to determine age DUP and age at onset of psychosis. Positive and disorganization symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) (34) and were based on previous factor-analysis conducted in early psychosis sample (35). Negative symptoms were examined by the Scale for the Assessment of Negative Symptoms (SANS) (36). Calgary Depression Scale for Schizophrenia (CDSS) (37) was used to assess depressive symptoms. Insight was evaluated by PANSS G12 item score. Global psychosocial functioning was measured with the Social and Occupational Functioning Assessment Scale (SOFAS) (38). Subjective QoL was measured using a self-rated 12-Item Short Form Survey (SF12) (39). Data on treatment characteristics including use of second-generation antipsychotic and dose of antipsychotic medication (chlorpromazine equivalent doses were computed for analysis) (40) were obtained. A brief battery of cognitive assessments was administered comprising the following: a digital symbol subtest from the Wechsler Adult Intelligence Scale Revised (WAIS-R) (41) for processing speed; digit span from the WAIS-R for working memory; logical memory and visual reproduction subtests from the Wechsler Memory Scale Revised (WMS-R) (42) for verbal and visual memory, respectively; and category verbal fluency and Modified Wisconsin Card Sorting Test (MWCST) (43) for executive functioning. A group of healthy controls ($n = 50$), matched by age (mean = 36.4 years, SD = 12.7), gender (male: 30.0%) and educational level (mean = 10.3 years, SD = 1.9), was recruited in the community via advertisements. Controls were evaluated with the same battery of cognitive assessments as patients. Standardized z-score for each of the cognitive tests of individual patients was computed based on performance of healthy controls by subtracting the mean of controls' score from each patient's score and divided by the standard deviation of controls. All of the study assessments (other than diagnostic evaluation), including cognitive tests, were administered by research assistants who had received intensive training in the use of these assessments prior to participant recruitment.

Statistical analysis

Hierarchical agglomerative cluster analysis (HCA) using squared Euclidean distance and Ward's linkage method was performed to identify cognitive subgroups in FEP patients, based on the standardized z-scores of the six cognitive tests. Case similarity (i.e., distance between data points) was computed using squared Euclidean distance. Ward's linkage method was applied as agglomeration procedure specification, and the distance between two clusters was defined by the increase of the sum of squares when merging them. The appropriate number of clusters was determined by collaborative inspection of the dendrogram and the agglomeration schedule coefficients in scree plot (as indicated by a sharp increase in the agglomeration coefficient). Then a k-means clustering (iterative partitioning) technique was applied to optimize the retained clusters, with initial partitions in the k-means solution defined using the cluster means derived from the hierarchical clustering procedure. A discriminant function analysis (DFA) was conducted to evaluate the internal validity of the cluster solution and to determine the predictive power of the cognitive performance in differentiating patients into discrete cognitive subgroups. Leave-one-out classification was used for assessing the reliability of the model generated by DFA. We then compared the identified cognitive subgroups on individual cognitive test scores, demographics, premorbid adjustment, onset profile, symptom domains, global functional status and subjective QoL, and treatment characteristics using a series of analysis of variance (ANOVAs), followed by post-hoc Turkey HSD test (with adjusted $p < 0.01$ indicating statistical significance) and chi-square tests as applicable. Those variables that were found to be statistically significant in preceding analyzes were also included in multivariate multinominal regression models to determine which factors independently predicted cognitive cluster membership. All analyzes were conducted using SPSS24.0 with significance level as $p < 0.05$, except post-hoc contrasts.

Results

Characteristics of the sample

Of the 289 participants in the study, 43.3% were male. The mean age of the sample was 38.2 years (SD = 8.3) and the median of DUP was 13 weeks (mean = 74.6, SD = 156.0). The majority (64.0%) were diagnosed with schizophrenia-spectrum disorder (schizophrenia: $n = 134$; schizophreniform disorder: $n = 48$; schizoaffective disorder: $n = 3$). For other non-affective psychoses, 12.8% ($n = 37$) of the cohort had brief psychotic disorder, 19% ($n = 55$) had delusional disorder and 4.2% ($n = 12$) had psychotic disorder NOS.

Cluster analysis and cognitive profiles across clusters

Inspection of the agglomeration scree plot and dendrogram revealed a three-cluster solution (Supplementary Figure S1). The discriminant plot of the final k-means cluster solution indicated relatively cohesive clusters with a concentration of cases around each of the three distinct centroids (Figure 1). The DFA yielded two discriminant functions which explained 92.4 and 7.6% of the variance, respectively (Wilks' lambda = 0.197, χ^2 (12) = 460.6, $p < 0.001$; Wilks' lambda = 0.799, χ^2 (5) = 63.68, $p < 0.001$), and the significant results indicated that the corresponding function explained the group membership well. The analysis also demonstrated that 86.5% of the cases were correctly classified in the respective group membership.

Cognitive profiles of three clusters are shown in Figure 2. Cluster 1 ($n = 101$, 34.9%) referred to globally-impaired cognitive (GIC) subgroup which displayed impairment in all of the six cognitive measures within 0.5–1.5 SD below the mean of controls' performance, with more marked impairment in digit span, verbal fluency and MWCST (within 1.0–1.5 SD below the mean of controls). Cluster 2 ($n = 112$, 38.8%) was termed as intermediately-impaired cognitive (IIC) subgroup which exhibited mixed patterns of cognitive impairment including mild deficits in digit symbol and verbal fluency (i.e., within 1 SD below the mean of controls' performance) and near-normal performance in the remaining cognitive measures (within 0.5 SD above the mean of controls). Cluster 3 ($n = 76$, 26.3%) referred to relatively-intact cognitive (RIC) subgroup which showed within 1 SD above the mean of controls' performance in all cognitive measures. Table 1 summarizes the results of comparisons on the performance of individual cognitive measures across three clusters. There were significant differences in all of the six cognitive test scores between three cognitive subgroups. Post-hoc pairwise comparisons found that patients in GIC subgroup had significantly poorer performance than those in IIC and RIC subgroups in all cognitive measures. Patients in IIC subgroup significantly underperformed than those in RIC subgroup in digit symbol, logical memory, visual reproduction and verbal fluency. All of these between-cluster differences in cognitive test performance remained statistically significant after controlling for age at study entry and educational levels.

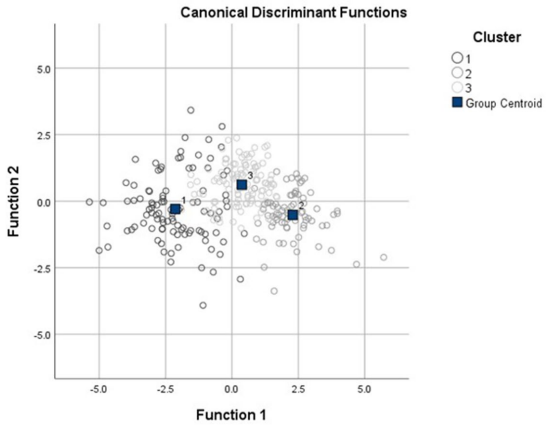

FIGURE 1
Discriminant plot of *k*-means three-cluster solution. The three clusters are (1) globally-impaired cluster, (2) intermediately-impaired cluster, and (3) relatively-intact clusters.

Subgroup comparisons on demographics, clinical and functional characteristics

As shown in Table 2, significant differences between three subgroups were observed in age at study entry, educational levels, age at onset, PANSS positive and disorganization symptom scores, SANS total scores, PANSS insight item scores, antipsychotic dose, SOFAS and SF12 total scores. There were no significant between-group differences in premorbid adjustment measures and DUP. Post-hoc pairwise comparisons revealed that patients in GIC subgroup were significantly older at entry and onset of psychosis, had fewer years of education, more severe positive, disorganization and negative symptoms, poorer insight and subjective QoL than those in IIC and RIC subgroups, and had higher antipsychotic dose than RIC subgroup. Patients in IIC subgroup had significantly fewer years of education and more severe negative symptoms than those in RIC subgroup. The RIC subgroup had significantly better global psychosocial functioning than both GIC and IIC subgroups. Multivariate multinominal regression analyzes (using GIC subgroup as a reference category) revealed that patients in GIC subgroup had significantly fewer years of education ($p < 0.001$) and greater disorganization symptom severity ($p < 0.001$) than those in RIC and IIC subgroups (Supplementary Table S1). Additionally, patients in GIC subgroup received higher dose of antipsychotic medication than those in RIC subgroup, with the group difference approaching statistical significance ($p = 0.05$).

Discussion

To our knowledge, this is the largest study to examine cognitive heterogeneity in FEP patients using a data-driven cluster-analytic approach and to comprehensively assess differential relationships of cognitive subgroups with various illness-related characteristics. The current investigation is also the first of its kind conducted in non-Western regions and in the Chinese population. Two major findings emerged from the study. First, we identified three discrete cognitive subgroups, characterized by global impairment, intermediate impairment and relatively-intact cognitive functioning. Second, these cognitive clusters exhibited significant between-group differences in educational attainment, symptom severity, treatment characteristics, psychosocial functioning and subjective QoL.

Our finding of three-cluster solution concurs with the majority of previous studies which derived three distinct cognitive subgroups based on cluster analysis in both FEP (19, 20, 22) and chronic schizophrenia samples (14). Specifically, we found that patients classified as RIC subgroup accounted for 26.3% of our FEP sample, which is consistent with a recent systematic review showing that one-fourth of patients with schizophrenia-spectrum disorder displayed relatively-preserved cognitive functioning compared to healthy controls (14). For the two cognitively-impaired subgroups, 34.9 and 38.8% of patients were categorized as GIC and IIC subgroup, respectively. Patients in GIC subgroup showed deficits across all cognitive tests with 0.5–1.5 SD below the mean of healthy participants'

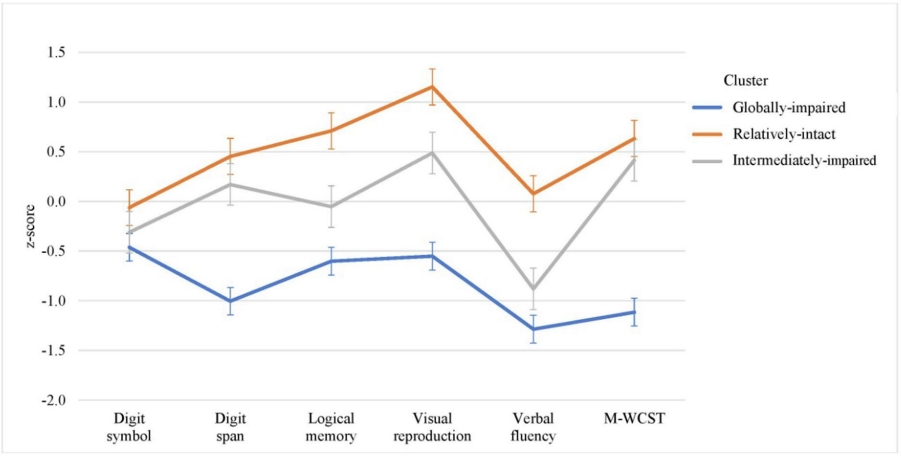

FIGURE 2
Cognitive performance among three cognitive clusters on each of the cognitive measures.

TABLE 1 Comparisons of cognitive performance among three cognitive subgroups in each of the cognitive measures.

Cognitive measures	Relatively-intact (n = 76)	Intermediately-impaired (n = 112)	Generally-impaired (n = 101)	F	P	Post-hoc comparison
Digit symbol	−0.06 (0.17)	−0.31 (0.13)	−0.46 (0.16)	152.20	<0.001	GIC < RIC GIC < IIC IIC < RIC
Digit span	0.45 (1.09)	0.17 (0.84)	−1.01 (0.97)	61.61	<0.001	GIC < RIC GIC < IIC
Logical memory	0.71 (0.83)	−0.05 (0.91)	−0.60 (0.91)	47.34	<0.001	GIC < RIC GIC < IIC IIC < RIC
Visual reproduction	1.15 (0.47)	0.49 (1.32)	−0.55 (1.61)	40.17	<0.001	GIC < RIC GIC < IIC IIC < RIC
Verbal fluency	0.08 (0.79)	−0.88 (0.76)	−1.29 (0.86)	64.33	<0.001	GIC < RIC GIC < IIC IIC < RIC
Modified Wisconsin Card Sorting Test	0.63 (0.52)	0.42 (0.71)	−1.12 (1.15)	118.95	<0.001	GIC < RIC GIC < IIC

GIC, globally-impaired cognitive subgroup; IIC, intermediately-impaired cognitive subgroup; RIC, relatively-intact cognitive subgroup.

performance, whereas those in IIC subgroup displayed mixed pattern of cognitive dysfunction which comprised mild degree of deficits in digit symbol and verbal fluency as well as near-normal performance in the other cognitive measures. Our results thus affirm cognitive heterogeneity in first-episode population. Of note, our cognitively-impaired subgroups had comparatively milder degree of cognitive deficits than those with chronic schizophrenia. Prior cluster-analysis research on chronically-ill samples generally found that patients classified as having global cognitive impairment were characterized by widespread and more severe deficits of >1.5 SD below healthy control comparison (14). Conversely, most first-episode studies reported less severe overall cognitive deficits. For instance, Uren et al. (19) found 27.8% FEP patients with preserved cognitive functioning and 54.9% with "moderate cognitive impairment" of <0.5 SD below the mean of healthy controls, while Amoretti et al. (21) and Wenzel et al. (44) classified a large proportion of patients with FEP (43.9%) and recent-onset psychosis (62%) as having relatively-intact cognitive functioning, respectively.

Upon examining the patterns of cognitive profile of individual cognitive clusters, we found that the GIC subgroup displayed more pronounced deficits in verbal fluency, MWCST and digit span compared with the other cognitive tests. This finding thus suggested that, among various cognitive domains, executive functioning and working memory (albeit to a lesser extent) were relatively more impaired in patients with GIC subgroup. It is noted that some previous research has also conceptualized working memory as one of the separable cognitive components subsumed under executive functioning (45). Executive dysfunction, particularly impaired

TABLE 2 Comparisons among three cognitive subgroups in demographics, premorbid adjustment, clinical and functional characteristics.

Variables of interest	Relatively-intact (RIC) (n = 76)	Intermediately-impaired (IIC) (n = 112)	Globally-impaired (GIC) (n = 101)	F/X^2	P	Post-hoc comparison
Demographics						
Male gender, n (%)	32 (42.11)	50 (44.64)	43 (42.57)	0.15	0.929	
Age at entry, mean (SD)	35.16 (7.76)	37.77 (8.02)	40.89 (8.13)	11.39	**<0.001**	GIC > IIC, GIC > RIC
Years of education, mean (SD)	13.28 (2.82)	11.36 (3.65)	9.08 (3.29)	35.32	**<0.001**	GIC < IIC < RIC
Premorbid and onset profiles						
Premorbid adjustment measures, mean (SD)						
PAS overall score	0.15 (0.15)	0.18 (0.16)	0.18 (0.17)	0.95	0.389	
PAS childhood score	0.17 (0.17)	0.14 (0.15)	0.16 (0.16)	0.46	0.630	
PAS early adolescence score	0.20 (0.19)	0.15 (0.15)	0.19 (0.17)	1.72	0.181	
PAS late adolescence score	0.18 (0.21)	0.16 (0.15)	0.17 (0.18)	0.37	0.690	
PAS academic domain score	0.21 (0.15)	0.15 (0.15)	0.19 (0.20)	0.42	0.655	
PAS social domain score	0.17 (0.21)	0.15 (0.18)	0.17 (0.18)	2.27	0.105	
Age at onset of psychosis, mean (SD)	33.47 (7.85)	36.13 (8.45)	39.09 (8.96)	9.65	**<0.001**	GIC > IIC, GIC > RIC
Log DUP, mean (SD)	1.90 (0.97)	1.85 (0.94)	2.07 (0.88)	1.67	0.190	
Diagnosis of schizophrenia-spectrum disorder,[a] n (%)	46 (60.53)	71 (63.39)	68 (67.33)	0.90	0.637	
Symptom severity						
PANSS positive symptom score, mean (SD)	8.24 (3.99)	8.42 (3.26)	9.90 (4.60)	5.11	**0.007**	GIC > IIC, GIC > RIC
PANSS disorganization score, mean (SD)	7.46 (1.28)	8.19 (2.38)	9.77 (3.45)	18.86	**<0.001**	GIC > IIC, GIC > RIC
SANS total score, mean (SD)	3.03 (5.37)	5.62 (8.41)	8.77 (10.94)	9.53	**<0.001**	GIC > IIC > RIC
CDSS total score, mean (SD)	1.79 (3.25)	2.03 (3.62)	2.78 (3.68)	1.97	0.141	
Good insight,[b] n (%)	63 (82.89)	94 (83.93)	69 (68.31)	4.69	**0.010**	GIC < IIC, GIC < RIC
Psychosocial functioning and subjective quality of life						
SOFAS score, mean (SD)	65.37 (13.97)	59.80 (12.72)	56.70 (11.94)	10.02	**<0.001**	GIC < RIC, IIC < RIC
SF12 total score, mean (SD)	132.89 (46.69)	132.83 (42.06)	115.07 (47.73)	5.03	**0.007**	GIC < IIC, GIC < RIC
Treatment characteristics						
Use of second-generation antipsychotics, n (%)	56 (73.7)	78 (69.6)	71 (70.30)	6.27	0.353	
Chlorpromazine equivalents, mg/day, mean (SD)	140.86 (131.40)	157.16 (113.76)	196.53 (164.43)	3.97	**0.020**	GIC > RIC

CDSS, Calgary Depression Scale for Schizophrenia; DUP, Duration of untreated psychosis; PANSS, Positive and Negative Syndrome Scale; PAS, Premorbid Adjustment Scale; SANS, Scale for the Assessment of Negative Symptoms; SD, Standard deviations; SF12, 12-Item Short Form Survey; SOFAS, Social Occupational Functioning Assessment Scale.

[a]Schizophrenia-spectrum disorder included schizophrenia, schizophreniform and schizoaffective disorder, while other non-affective psychoses included brief psychotic disorder, delusional disorder and psychosis not otherwise specified.

[b]Good insight was defined as PANSS G12 (Insight) item score ≤ 3.

The blod values indicate $p < 0.05$, i.e., statistically significant.

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switching and flexibility, has been found to predict poor vocational outcome in FEP patients (46). One recent study even indicated that executive functioning performance specifically delineated the two clusters of chronic schizophrenia patients with intermediate cognitive impairment (47). Given that executive functioning comprises multiple individual cognitive processes, which were not comprehensively assessed in the current study, further research adopting a fractionated approach in examining executive functioning (45, 48) would facilitate clarification of whether there is any potential selective association of executive functioning profile with cognitive cluster membership in FEP patients. Nevertheless, in line with earlier cognitive-cluster studies in first-episode samples (19, 20, 22), our results indicate that cognitive cluster membership was primarily based on quantitative rather than qualitative difference in cognitive performance (with most of the cognitive tests showing graded pattern of impairment, i.e., RIC < IIC < GIC), thereby suggesting that cognitive impairment in FEP may represent a continuum of severity instead of the presence of distinct, domain-specific subtypes of the disorder. Owing to the relative paucity of existing data on cognitive subgrouping in FEP patients, further investigation is required to delineate cognitive variability in the early stage of illness.

Our results noted that years of education significantly decreased with increasing severity of impairment across cognitive subgroups (i.e., GIC < IIC < RIC). This is in line with past research on both chronic schizophrenia and early psychosis showing that patients with relatively-intact cognitive functioning had higher educational attainment than those in cognitively-impaired clusters (14, 17, 19, 22, 44). Substantial body of research also recognized close association between educational attainment and cognitive abilities across a lifespan (49). Contrary to a recent study revealing that relatively-intact subgroup displayed better premorbid scholastic performance than cognitively-impaired counterparts with first-episode schizophrenia (22), we failed to observe any significant differential associations between cognitive subgroups and various measures of premorbid adjustment. It should be noted that premorbid adjustment has rarely been investigated in cognitive cluster-analytic research on psychotic disorders. Nonetheless, evidence has indicated that poorer premorbid adjustment is related to worse cognitive impairment in psychotic disorders, particularly premorbid academic functioning (32, 50). Previous research examining cognitive developmental trajectories before onset of schizophrenia has also demonstrated that patients with long-term compromised premorbid cognition (with low premorbid and current intelligence) had significantly lower educational attainment than patients exhibiting cognitively-stable trajectory with normative premorbid intelligence (51, 52). Thus, the consistency between premorbid adjustment/intelligence and educational attainment regarding their relationship with cognitive impairment demonstrated in some past studies on psychotic disorders was not evident in our analyzes. Of note, our negative finding might partly be attributable to the nature of our FEP sample comprising only adult patients aged 26–55 years (i.e., over-represented by adult-onset psychosis), which contrasts with those earlier first-episode studies that also included patients at younger age or focused solely on adolescent and young adult patients (e.g., 15–25 years) (19, 22). Given that young age at onset (especially adolescent-onset) is in general associated with poorer premorbid adjustment relative to older age at onset, our sample might had comparatively lower degree of and less variance in premorbid functional impairment, thereby obscuring its potentially significant yet subtler association with cognitive subgroups. Moreover, premorbid functional assessment in our relatively older-aged sample may be more susceptible to recall bias, compared with younger-onset patients, due to a more prolonged duration between premorbid stage and illness onset, which in turn may result in less accurate evaluation of premorbid adjustment. Alternatively, most prior studies reported no association between age and cognitive clusters in FEP patients (18–20, 22), while one first-episode study found that later age at onset was linked to relatively-intact subgroup relative to the cognitively-impaired subgroup (21). Our result that "younger" age at onset was significantly related to GIC subgroup relative to IIC and RIC subgroups contrasts to the aforementioned findings, but should be treated with caution owing to an older age range of our sample compared with previous first-episode studies. Results of our multivariable multinominal regression analyzes also indicated that age or age at onset was not independently predictive of cognitive cluster membership.

We found that patients in GIC subgroup had significantly more severe positive and disorganization symptoms and poorer insight than counterparts in IIC and RIC subgroups. In particular, negative symptoms were differentially related to cognitive cluster membership, with symptom levels increased with patient subgroups of increasing severity of cognitive impairment (i.e., GIC > IIC > RIC). Our results thus accord with most previous studies showing that severely-impaired cognitive cluster experienced the greatest overall symptom severity, especially negative symptoms (14, 17–21). Recent data have further suggested that cognitive cluster membership at baseline was associated with negative symptom severity at 6- to 12-month follow-up in FEP patients (19, 20). These findings echo with a large body of evidence demonstrating significant associations between negative symptoms and cognitive deficits in both chronic and early course of illness (48, 53, 54), with accumulating data further indicating that baseline cognitive dysfunction predicts subsequent development of early-stage persistent negative symptoms in first-episode patients (55, 56). It is posited that cognitive impairment could affect the manifestations of negative symptoms as more preserved cognitive function is essential for individuals' ability to plan, initiate and execute goal-directed behaviors. Alternatively, diminished motivation (or termed amotivation), a core subdomain of negative symptoms, was found to adversely influence cognitive performance in schizophrenia patients (57). Accumulating evidence demonstrated that schizophrenia patients exhibited effort-based decision-making impairment, with reduced willingness to expend effort for reward being associated with more severe amotivation (58). Our recent report further indicated significant association between decreased "cognitive" effort expenditure and higher levels of amotivation in FEP patients (59). Thus, amotivation and poor effort of patients may moderate and compromise their cognitive performance.

Consistent with the literature on cognitive subgrouping in psychotic disorders (14, 17–22), our results noted that the two cognitively-impaired subgroups exhibited significantly lower levels of psychosocial functioning than RIC subgroup. This is in agreement with substantial evidence showing that cognitive impairment is critically linked to poor functional outcome in early psychosis (48, 60–62). Furthermore, our study is the first to demonstrate differential relationship between cognitive clusters and subjective QoL in FEP, with RIC subgroup having significantly better subjective QoL than the two cognitively-impaired subgroups. Although existing data mostly

found lack of significant association between subjective QoL and cognitive deficits in psychotic disorders (63), recent studies using structural equation modeling approach revealed that cognitive dysfunction was indirectly linked to subjective QoL via the mediation of psychosocial functioning (64, 65). Notably, our multinominal regression analysis showed that the difference between GIC and RIC subgroups on receipt of antipsychotic dose (with higher CPZ dose in GIC subgroup relative to RIC subgroup) approached statistical significance suggested that antipsychotic treatment may affect and potentially confound the study results. Previous research revealed that antipsychotics, particularly at high dose, may have negative effect on cognitive performance in schizophrenia patients (66). Evidence also observed that such negative effect varies with individual antipsychotics and specific cognitive domains (67). The finding of higher CPZ dose in GIC-subgroup patients might, on the other hand, reflect the need for increased intensity of antipsychotic treatment for their greater symptom severity, relative to those in RIC subgroup. Future investigation in medication-naïve FEP patients may help differentiate the effect of antipsychotics and illness on cognitive clustering and subgroup comparison. Taken together, our cluster-analysis results of three distinct cognitive subgroups in FEP patients were empirically supported by their significant differential associations with educational attainment, symptom severity, psychosocial functioning and subjective QoL. Multivariate multinominal regression analyzes, which took into consideration various significant variables, further showed that (fewer) years of education and (greater) severity of disorganization symptoms significantly delineated patients in GIC subgroup from those in RIC and IIC subgroups.

The study has several methodological limitations. First, the cross-sectional study design precludes us from establishing the causality between cognitive cluster membership and illness-related variables. Prospective research is warranted to clarify the longitudinal relationships of cognitive subgroups with clinical and functional outcomes in FEP. Second, we used a relatively brief battery of cognitive assessments which may not adequately capture the breadth and degree of impairment across multiple cognitive domains. Moreover, social cognition, which was found to be impaired in first-episode populations (68), was not evaluated in the study. Third, our finding that a relatively large proportion of our patients were categorized as relatively-intact or intermediately-impaired may indicate possible selection bias. Results of attrition analysis that patients retained in the current analysis had higher educational attainment than the excluded participants also suggest that our study sample may have potential bias of including FEP patients with less severe cognitive impairment. Nonetheless, several past cluster-analytic studies have also classified a large proportion of FEP or early psychosis patients (ranged: 43.9–62%) as cognitively-preserved subgroup (17, 21, 44). Fourth, age difference was found between cognitive subgroups, even though it was not independently predictive of cognitive cluster membership based on multivariable multinominal regression analyzes. This suggests that the effect of age on cognitive performance could be better accounted for in future studies on cognitive cluster analysis in early psychosis patients. Fifth, the cognitive assessment (alongside other study assessments) was undertaken when patients were clinically-stabilized with antipsychotic treatment, which may affect cognitive performance and confound the study results. Fifth, the relatively older mean age of our sample (age range of 26–55 years) may render our findings less comparable to the literature of first-episode research which mainly recruited younger patients with more typical age of onset (i.e., late adolescence or early adulthood) (69).

In conclusion, the current cluster analysis affirmed cognitive variability in a large cohort of adult FEP patients and identified three discrete cognitive subgroups with relatively-intact, intermediately-impaired (and mixed patterns of) and globally-impaired cognitive functioning. These cognitive subgroups were differentially associated with educational attainment, symptomatology, functional impairment and subjective QoL. Our findings thus suggest the potential utility of examining distinct cognitive subtypes to unravel their neurobiological underpinnings and genetic risk factors. Emerging data have in fact revealed that cognitive subgroups of schizophrenia are characterized by differences in neuroanatomical abnormalities (44, 70, 71). Additionally, our results underscore potential clinical implications of incorporating early identification of and provision of cognitive remediation (72, 73) to a subgroup of first-episode patients with global and severe cognitive impairment into the early psychosis service framework. This will facilitate improvement in cognitive deficits, psychosocial functioning and subjective QoL in first-episode patients during the early phase of illness.

Data availability statement

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

Ethics statement

The study involved human participants and was approved by the local institutional review boards, and written informed consent was obtained for all participants.

Author contributions

EC designed the study. WC and CK conceptualized the research question and the analysis approach. CK performed statistical analyzes, interpreted the results and wrote the first draft of the manuscript. WC and VF interpreted the results, critically revised and finalized the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1203655/full#supplementary-material

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Association between suicidal ideation and cognitive function in young patients with schizophrenia spectrum disorder

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Introduction: Suicide is a major concern for patients with recent-onset schizophrenia. We hypothesized that preserved cognitive function might be associated with a higher level of suicidality in patients with schizophrenia. We investigated the associations between cognitive function and suicidal ideation (SI) in young patients recently diagnosed with a psychotic disorder.

Methods: This study analyzed data from a naturalistic clinical cohort study that comprised 402 patients with schizophrenia spectrum disorder. Patients with a treatment duration of ≤5 years and an age range of 15–39 years were enrolled. Participants were categorized into two groups based on SI as assessed by the Columbia Suicidal Severity Rating Scale. We collected demographic and clinical data and administered psychiatric, neurocognitive, and social cognitive measures.

Results: Among participants, 52% reported experiencing SI. Patients with SI were significantly younger and had a longer duration of untreated psychosis (DUP) than those without it. The Positive and Negative Syndrome Scale-general psychopathology score was significantly higher in the SI group. Scores on the Calgary Depression Scale for Schizophrenia, Perceived Stress Scale, Beck Depression Inventory (BDI), and Beck Hopelessness Scale were significantly higher among patients with SI, while scores on the Subjective Well-being Under Neuroleptics-Short Form and Brief Resilience Scale were significantly lower compared to those without it. Patients with SI demonstrated significantly higher scores on the verbal and visual learning test, false belief task, picture stories task, and Controlled Oral Word Association Test. They also completed the Trail Making Test (TMT) parts A and B in significantly less time than those without it. After adjusting for age, DUP, and scores on the BDI, group differences in scores on the verbal and visual learning tests, TMT (parts A and B), and the false belief task, and the picture story task remained significant.

Discussion: Our results suggest that along with traditional risk factors, better cognitive function may also be a major risk factor for suicidality in patients with schizophrenia. Providing psychological support and cognitive interventions is essential for young patients with recent-onset schizophrenia spectrum disorders, particularly those with high levels of depression, hopelessness, perceived stress, low resilience, and good cognitive function.

KEYWORDS

suicide, cognitive function, schizophrenia, early psychosis, depression

Introduction

Suicide ranks as the fifth leading cause of death in South Korea (1) and imposes a significant socioeconomic burden (2). In individuals with schizophrenia, suicide is a tragic outcome, accounting for early mortality in nearly 5% of patients, with 25–50% attempting suicide during their lifetime (3, 4). Despite the gravity of this issue, the relatively low incidence of completed suicide in this population makes comprehensive investigation challenging (5). Suicidal behaviors, encompassing both suicide attempts and suicidal ideation (SI), are prevalent among individuals with schizophrenia and are recognized as substantial risk factors for suicide (6, 7). Hence, the identification of factors associated with suicidal behavior in patients with schizophrenia plays a crucial role in suicide prevention efforts. Previous research has revealed that factors such as previous suicide attempts, the choice of more lethal methods, feelings of hopelessness, and the presence of depressive symptoms significantly contribute to suicide risk in individuals with schizophrenia, and these results are similar to those found in the general population (8–14).

Cognitive function is one of the domains predominantly affected in patients with schizophrenia spectrum disorder (14). Cognitive functions, such as attention, executive function, working memory, and episodic memory, are impaired in patients with schizophrenia (15). Previous studies have reported that preserved cognitive function in schizophrenia is a risk factor for suicidality (16, 17). However, these studies were conducted in patients with chronic schizophrenia. Young patients with schizophrenia face a significantly higher risk of suicidality (18–23). Additionally, the highest risk of suicide occurs within the first 5 years after diagnosis (4, 24). Therefore, it is crucial to identify the risk factors for suicidality in young patients with recently diagnosed schizophrenia.

In young patients with psychotic disorders, suicidal thoughts are strongly linked to actual suicidal behavior and even death by suicide (20–22). When patients experience SI, they may be at an elevated risk of taking further steps toward suicide. Furthermore, SI is a crucial element in the overall understanding of how individuals progress from having thoughts of suicide to engaging in suicidal behaviors. Thus, for effective suicide prevention in patients with early psychosis, it is necessary to investigate the pathogenesis of SI.

We hypothesized that preserved cognitive function might be associated with a higher level of suicidality in patients recently diagnosed with schizophrenia. Most previous studies examining the relationship between neurocognitive function and suicidality were conducted in patients with chronic schizophrenia and did not incorporate measures assessing social cognition and theory of mind. Therefore, in this study, we investigated the associations between cognitive function, including social cognition, and SI in young patients recently diagnosed with a schizophrenia spectrum disorder.

Materials and methods

Study design

We analyzed the data from a naturalistic clinical cohort study conducted at the Gwangju Early Treatment and Intervention Team of Chonnam National University Hospital (25). All participants were consecutively recruited from patients who recently developed psychotic symptoms and visited Chonnam National University Hospital. In this study, inclusion criteria were a treatment duration of ≤5 years and an age range of 15–39 years. Furthermore, a qualified research psychiatrist established the clinical diagnosis for each participant, ensuring that all patients met the criteria for 'Schizophrenia Spectrum Disorder and Other Psychotic Disorders' in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (26). Patients with a substance-or medication-induced psychotic disorder, psychotic disorder due to another medical condition, or severe neurological or medical disorder were excluded. The study was conducted from September 2015 to December 2022, during which a total of 402 participants met the inclusion criteria. This study was approved by the Chonnam National University Hospital Institutional Review Board, and all subjects provided written informed consent before participating.

Demographic and clinical measures

Baseline sociodemographic and clinical data were collected, including age, sex, education level, occupation, body mass index (BMI), duration of treatment, diagnosis, and duration of untreated psychosis (DUP; time between the appearance of the initial psychotic symptoms and the start of antipsychotic treatment or psychiatric hospitalization) (27). The doses of prescribed antipsychotics were converted into chlorpromazine (CPZ)-equivalent dose (28).

Suicidal behavior was assessed using a semi-structured interview with the Columbia Suicidal Severity Rating Scale (C-SSRS) administered by a trained researcher (29, 30). At the baseline assessment, the C-SSRS was used to evaluate lifetime suicidal behavior. Patients who responded affirmatively to any item indicative of suicidal ideation (SI) were categorized into the SI group. Psychiatric symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS) (31, 32). We utilized three subscales (positive, negative, and general psychopathology) as well as total scores as variables. For exploratory analysis, we also examined the 12th item of the general psychopathology subscale (lack of insight and judgment; G12). Other objective psychiatric measures included Social and Occupational Functioning Assessment Scale (SOFAS; used to evaluate general functioning) (33) and Calgary Depression Scale for Schizophrenia (CDSS; used to analyze depressive symptoms) (34, 35).

We employed several subjective self-report measures, including the Beck Depression Inventory (BDI; used to assess depressive symptoms) (36, 37), Beck Hopelessness Scale (BHS; used to evaluate hopelessness) (38, 39), Perceived Stress Scale (PSS; used to assess subjective stress) (40, 41), Brief Resilience Scale (BRS; used to quantify the ability to recover from stress) (42), and Subjective Well-being Under Neuroleptics-Short Form (SWN-K; used to evaluate subjective health-related quality of life) (43). Higher scores on the BRS and SWN-K, and lower scores on the BHS, BDI, and PSS, indicate better outcomes.

Neurocognitive measures

We assessed neurocognitive function using a computerized neurocognitive test battery standardized for the Korean population, including individuals with psychotic disorders. Research nurses, who

were unaware of the study's objectives, administered six neurocognitive tests. The Digit Span test was used to assess attention span; higher scores indicate superior attention and vigilance (44–46). The modified Rey Auditory Verbal Learning Test was used to assess immediate and delayed verbal memory; the outcome measure is the total number of recalls (46, 47). The visual learning test was administered to assess immediate and delayed visual memory. The outcome measure was the total number of recalls, and a higher score indicated better memory (48). The Wisconsin Card Sorting Test was administered to assess executive function; the outcome measure is the number of categories completed, and a higher score indicates better executive function and cognitive flexibility (49–51). The Continuous Performance Test (CPT) was administered to measure the ability to sustain attention (vigilance) to a stimulus; the outcome measures are reaction time and number of correct responses, where faster reaction times and more correct responses indicate superior attention (52–54). Finally, the Trail Making Test (TMT) was used to assess visuomotor coordination. The TMT consists of two parts that measure executive function and visuospatial working memory (A and B, respectively), and the outcome measure is the time taken (in seconds) to complete both parts (54–56). In addition, we used the Mini-Mental Status Examination (MMSE) to assess global cognitive function (57–59) and the Controlled Oral Word Association Test (COWAT) to evaluate verbal fluency and cognitive speed (60, 61).

Social cognitive measures

The false belief task of Wimmer and Perner was administered to assess social cognition (62, 63). Patients are required to infer the thoughts of characters in four stories. The maximum total score is 12 points, and higher scores indicate the superior theory of mind (ToM) and social cognition. Picture stories task developed by Brüne were used to assess ToM, which is the ability to infer others' mental states and emotions (64, 65). Six cartoons are presented to the patient without a background story description, and the patient is then required to answer questions related to ordering and mind-reading. This task represents a more complex and higher-order ToM test. Total ordering (36 points) and mind-reading (23 points) scores are calculated; higher scores indicate superior ToM (65).

Statistical analysis

The dependent variable in this study was lifetime suicidal ideation, assessed using the C-SSRS. Participants were divided into two groups based on the presence of SI. Sociodemographic and clinical characteristics, as well as cognitive function, were compared between these two groups. We used the chi-square test for categorical variables, the independent t-test for normally distributed variables, and the Mann–Whitney *U* test for variables that did not follow a normal distribution, as appropriate. To control for the potential confounding effects of age, DUP, and BDI scores, which showed significant associations with SI in the univariate analyses, we included them as covariates in logistic regression analysis along with each cognitive measure that demonstrated a significant association with SI in the univariate analyses. DUP and BDI scores, which were not normally distributed, were log-transformed before entering them into the model. TMT part A and B times, also not normally distributed, were transformed into 10-point scales based on ten percentiles before inclusion in the logistic regression analysis. For exploratory analysis, we calculated Pearson's or Spearman's correlation coefficients between the PANSS G12 score and measures of clinical status and ToM. All statistical tests were two-tailed, and $p < 0.05$ was taken to indicate statistical significance. The statistical analysis was performed using SPSS software (version 25.0; IBM Corp., Armonk, NY, United States).

Results

In total, 402 patients (males, 49.2%; females, 50.2%) with recent-onset psychosis were included in the analysis. The mean (standard deviation) age at baseline was 24.4 (5.7) years. The most common diagnosis was schizophrenia ($n = 244$, 65.9%), followed by schizophreniform disorder ($n = 78$, 21.1%), other specified schizophrenia spectrum disorder ($n = 34$, 9.2%), and schizoaffective disorder ($n = 14$, 3.8%). Approximately half of the patients (52.0%) reported experiencing SI.

Table 1 shows the participants' sociodemographic and clinical characteristics according to the presence of SI. Patients with SI were significantly younger and had longer DUP than those without it. There was no significant group difference in sex, marital status, education level, occupation, BMI, duration of treatment, diagnosis, or CPZ equivalent dose.

The PANSS positive, negative, G12, and total scores did not differ according to SI, but the general psychopathology score was significantly higher in the SI group. Scores on the CDSS, PSS, BDI, and BHS were significantly higher in patients with SI compared to those without it, whereas scores on the SWN-K and BRS were significantly lower. There were no significant associations found between G12 and other clinical measures (data not shown). However, the PANSS G12 score was significantly correlated with scores on the picture stories task and the false belief task ($r = -0.130$, $p = 0.009$, and $r = -0.117$, $p = 0.019$, respectively).

Table 2 shows the neurocognitive and social-cognitive outcomes according to the presence of SI. The patients with SI had significantly higher scores on the verbal and visual learning test, false belief task, picture stories task, and COWATT, and took significantly less time to complete TMT parts A and B, than those without it. They also completed more categories, although the difference was not statistically significant ($p = 0.084$). The two groups had no significant differences in scores on the digit span test, CPT, or MMSE.

Table 3 shows the results of adjusted logistic regression analyses. After controlling for age, DUP, and scores on the BDI, significant differences between groups remained evident in scores on the verbal and visual learning tests, TMT (parts A and B), the false belief task, and the picture story task. However, the group differences in COWATT scores lost statistical significance after adjusting for the confounding variables.

Discussion

This study investigated the risk factors for SI in young patients with recent-onset schizophrenia and examined their association with cognitive function. Patients with SI had superior neurocognitive and

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TABLE 1 Comparison of the sociodemographic and clinical characteristics of participants according to the presence of suicide idea.

	Total (N = 402)	Suicide idea (+) (*N* = 209, 52.0%)	Suicide idea (–) (*N* = 193, 48.0%)	Statistical value	*p*-value
Age, mean (SD) years	24.4 (5.7)	23.5 (5.2)	25.4 (6.1)	$T = -3.229$	0.001
Gender, *N* (%) women	202 (50.2)	107 (51.2)	95 (49.2)	$\chi^2 = 0.156$	0.693
Marital status, *N* (%) married	22 (5.5)	7 (3.3)	15 (7.8)	$\chi^2 = 3.794$	0.051
Education, median (IQR) year	14.0 (12.0–16.0)	13 (12–16)	14 (12–16)	$Z = -1.331$	0.183
Occupation, *N* (%) Employed	95 (23.6)	51 (24.4)	44 (22.8)	$\chi^2 = 0.143$	0.705
Duration of treatment, median (IQR) month	1.0 (0.8–3.2)	1.0 (0.9–3.2)	1.0 (0.8–3.5)	$Z = -0.229$	0.819
DUP, median (IQR) month	3.2 (1.0–15.0)	6.0 (1.0–18.0)	2.0 (1.0–8.75)	$Z = -2.979$	0.003
Diagnosis, *N* (%) Schizophrenia	244 (65.9)	116 (61.7)	128 (70.3)	$\chi^2 = 6.596$	0.086
Schizophreniform	78 (21.1)	40 (21.3)	38 (20.9)		
Schizoaffective disorder	14 (3.8)	8 (4.3)	6 (3.3)		
Other specified SSD	34 (9.2)	24 (12.8)	10 (5.5)		
CPZ equivalent dosage, median (IQR) mg/day	400 (200–600)	325 (200–600)	400 (200–650)	$Z = -1.580$	0.114
Body Mass Index, median (IQR)	22.2 (20.0–24.9)	21.9 (20.0–25.2)	22.2 (20.6–24.7)	$Z = -0.094$	0.925
PANSS, Positive, mean (SD)	15.1 (4.8)	15.4 (4.8)	14.7 (4.8)	$T = 1.294$	0.197
Negative, mean (SD)	16.2 (4.7)	16.0 (4.6)	16.4 (4.8)	$T = -0.836$	0.404
General psychopathology, mean (SD)	33.8 (7.5)	34.9 (7.5)	32.6 (7.4)	$T = 3.152$	0.002
Total, mean (SD)	65.0 (14.6)	66.1 (14.6)	63.8 (14.6)	$T = 1.540$	0.124
G12 (lack of insight), mean (SD)	3.1 (1.2)	3.1 (1.1)	3.2 (1.2)	$T = -1.267$	0.206
SOFAS, mean (SD)	60.3 (9.9)	60.7 (10.2)	59.8 (9.6)	$T = 0.913$	0.362
CDSS, median (IQR)	4.0 (10–7.0)	5.0 (2.0–9.0)	2.0 (0.75–5.0)	$Z = -6.810$	<0.001
SWN-K, mean (SD)	75.5 (17.4)	70.4 (17.4)	81.3 (15.6)	$T = -6.147$	<0.001
Brief Resilience Scale, mean (SD)	17.1 (4.9)	16.1 (4.9)	18.3 (4.5)	$T = -4.445$	<0.001
Perceived Stress Scale, mean (SD)	20.3 (6.5)	21.9 (6.3)	18.5 (6.2)	$T = 5.015$	<0.001
Beck Depression Inventory, median (IQR)	7.0 (3.0–16.8)	12.0 (5.0–23.0)	5.0 (1.0–10.0)	$Z = -6.822$	<0.001
Beck Hopelessness Scale, mean (SD)	3.1 (1.0)	3.3 (1.0)	2.9 (1.0)	$T = 3.200$	0.001

SD, standard deviation; IQR, Inter-Quartile Range; DUP, Duration of Untreated Psychosis; SSD, Schizophrenia Spectrum Disorder; PANSS, CPZ, chlorpromazine; Positive and Negative Syndrome Scale; SOFAS, Social and Occupational Functioning Assessment Scale; CDSS, Calgary Depression Scale for Schizophrenia; SWN-K, Subjective Well-being Under Neuroleptics-Short Form. All *p*-values are empirical.

social-cognitive function than those without it. In addition, they showed higher levels of depression, perceived stress, and hopelessness and lower levels of resilience and subjective well-being. These results suggest that, along with traditional risk factors such as depression, perceived stress, and hopelessness (8, 9), better cognitive function may also be a major risk factor for suicidality. A better understanding of SI may help prevent suicidal behavior in patients with recent-onset schizophrenia.

The SI group in this study was significantly younger than the group without SI. This finding aligns with the nationwide Danish OPUS trial, which investigated the effectiveness of early intervention programs for schizophrenia spectrum disorders and demonstrated that younger age was a risk factor for suicidality (21). Notably, there is a trend toward a higher risk of suicide at a younger age in patients with schizophrenia compared to the general population, where the risk for suicide tends to be higher among older individuals (23). Individuals diagnosed with schizophrenia often undergo a mourning process as they grapple with the losses experienced upon the onset of their illness (66). The risk of suicide may increase when young individuals with schizophrenia experience demoralization stemming from their pessimistic outlook on a future characterized by long-term treatment demands. Additionally, individuals experiencing their first episode of schizophrenia in life often find themselves in a more unstable situation, as they are unfamiliar with the disorder and, as adolescents, face the typical problems and conflicts that come with beginning a new phase in life (18). Therefore, it is crucial to assess the risk of suicidality when treating young patients with early psychosis, particularly those in their late teens and early twenties.

Longer DUP, a prognostic factor associated with poorer overall outcomes in patients with schizophrenia (67, 68), was observed in the group with SI in this study. SI may occur as a result of protracted psychotic symptoms when the DUP is extended (22). Several studies have demonstrated that a long DUP is a risk factor for suicidality (69, 70), and this association may be mediated by depressive symptoms (71, 72). Furthermore, patients with an extended DUP might experience great distress due to psychotic symptoms, which, in turn, could increase the risk of SI.

As in previous studies of patients with schizophrenia and the general population, the individuals in this study who had experienced SI showed significantly higher levels of depression and

TABLE 2 Comparison of neurocognitive and social cognitive outcomes of participants according to the presence of suicide idea.

	Suicide idea (+) (*N* = 209, 52.0%)	Suicide idea (–) (*N* = 193, 48.0%)	Statistical value	*p*-value
Digit Span, Forward, mean (SD)	7.2 (1.5)	7.1 (1.4)	$T = 0.554$	0.580
Digit Span, Backward, mean (SD)	5.5 (1.7)	5.3 (1.4)	$T = 1.447$	0.149
Verbal Learning Test, total mean (SD)	89.8 (18.5)	85.9 (20.1)	$T = 2.018$	0.044
Visual Learning Test, total mean (SD)	73.3 (12.1)	69.6 (13.8)	$T = 2.773$	0.006
WCST, Categories completed, median (IQR)	6.0 (4.0–6.0)	6.0 (4.0–6.0)	$Z = -1.725$	0.084
CPT, Correct Response, mean (SD)	116.6 (21.2)	115.7 (20.2)	$T = 0.413$	0.680
CPT, Reaction Time, mean (SD) millisecond	682.6 (70.5)	686.6 (64.5)	$T = -0.592$	0.554
TMT, Part A, median (IQR) second	22.0 (18.0–27.0)	23.0 (19.0–30.0)	$Z = -2.089$	0.037
TMT, Part B, median (IQR) second	38.0 (30.0–49.0)	42.0 (34.0–58.0)	$Z = -3.407$	0.001
False Belief Task. mean (SD)	8.3 (2.7)	7.6 (2.3)	$T = 2.728$	0.007
Picture Stories Task. mean (SD)	50.3 (8.4)	48.1 (9.1)	$T = 2.572$	0.010
Controlled Oral Word Association Test, mean (SD)	69.4 (20.7)	65.1 (17.9)	$T = 2.226$	0.027
Mini-Mental Status Examination, mean (SD)	28.5 (1.6)	28.5 (1.6)	$T = -0.157$	0.875

SD, standard deviation; IQR, Inter-Quartile Range; WCST, Wisconsin Card Sorting Test; CPT, Continuous Performance Test; TMT, Trail Making Test.

TABLE 3 Adjusted analysis for associations between neurocognitive and social cognitive outcomes and suicidal ideation.

	B	Odds ratio (95% confidence interval)	Adjusted *p*-value*	Nagelkerke R^2
Verbal Learning Test, 1 score increase	0.012	1.012 (1.000–1.024)	0.047	0.206
Visual Learning Test, 1 score increase	0.028	1.028 (1.010–1.046)	0.002	0.223
TMT, Part A, 10 percentile increase	−0.090	0.914 (0.846–0.987)	0.021	0.200
TMT, Part B, 10 percentile increase	−0.116	0.890 (0.823–0.963)	0.004	0.212
False Belief Task, 1 score increase	0.089	1.093 (1.000–1.194)	0.049	0.193
Picture Stories Task, 1 score increase	0.026	1.026 (1.001–1.052)	0.043	0.194
Controlled Oral Word Association Test, 1 score increase	0.009	1.009 (0.998–1.021)	0.121	0.193

*Adjusted for age, duration of untreated psychosis, and the Beck Depression Inventory scores by pairwise logistic regression analysis. All *p*-values are empirical.

hopelessness (11, 73–76). A higher general psychopathology PANSS score in patients with SI might be associated with depressive symptoms. Depression is common in patients with schizophrenia (77), and it should be managed to prevent suicide (78). Hopelessness is a major psychological risk factor and a clinical endophenotype for suicidality in the general population. Hopelessness plays a role in the development of suicidal thoughts and behaviors, and it also mediates the relationship between SI and suicidality (75). Demoralization, which is associated with hopelessness (79), is important in the context of the current study, which explored the link between cognitive function and SI. People who experience hopelessness tend to isolate themselves and not seek help (75). Life stressors can reduce the will to live, and it is intuitive that hopelessness plays an important role in the suicidality of patients with schizophrenia (79).

In recent studies, perceived stress was found to be significantly associated with suicidality in patients with schizophrenia spectrum disorder (80, 81), and resilience is a major protective factor for suicidality. In one study, early psychosis patients with comorbid depression showed lower resilience. Resilience in patients with schizophrenia spectrum disorders was associated with symptom remission, recovery, better social and interpersonal functioning, and higher quality of life, all of which may have reduced SI (82).

In this study, the group with SI demonstrated better performance on several neurocognitive and social-cognitive tasks. Higher levels of verbal and visual learning ability, visuospatial working memory, and ToM were observed in individuals with high suicidality, while attention span, sustained attention, and verbal fluency showed no significant differences between groups. These findings suggest that complex cognitive processes, such as working memory and social cognition, are more strongly associated with suicidality than simple attention.

ToM refers to the ability to understand and represent another person's mental state and use these representations to explain and predict human interactions (83). It is associated with cognitive flexibility (84, 85), which generally exhibits an inverse association with suicidality (86). However, in this study, the SI group displayed superior ToM even after adjusting for confounding variables. It is possible that patients with high mental reasoning abilities were more aware of the difficulties that can arise during interpersonal and social situations, which could lead to psychological strain (12, 66). This aligns with the significant increase in suicide attempts observed among patients

shortly after discharge, when real-world life challenges may escalate (87). Clinical insight, which refers to an individual's awareness of having a mental illness that requires treatment, can be associated with ToM (88). In this study, ToM was significantly linked to higher levels of insight and judgment, even though there was not difference based on the presence of SI.

Higher levels of insight in patients with schizophrenia can also be connected to increased severity of depression and hopelessness (16, 89). While this study did not demonstrate these associations, it can be inferred that SI may manifest in patients who recognize their own condition, especially those who struggle to maintain social relationships. Providing care for individuals with schizophrenia who are aware of their condition is essential to help them adapt to society, mitigate depressive responses, and reduce the risk of suicide (78). Cognitive therapy and psychological support for patients with early psychosis, particularly those with good cognitive function, are essential to prevent suicidality.

No significant differences in indicators of disease severity, such as the PANSS positive symptoms score, medication dosage, and social functioning, were observed between the groups in this study with and without SI. In previous studies, severe psychotic symptoms such as command hallucinations were associated with suicidality in patients with schizophrenia (23, 90). Relatively low scores on the PANSS among our patients in the early stages of schizophrenia might explain this discrepancy.

This study had some limitations. First, it used a cross-sectional design such that causal relationships could not be established. Therefore, longitudinal studies are needed. Second, a control group of healthy individuals was not included; doing so may have helped us achieve a deeper understanding of the impact of social cognition on suicidality in patients with schizophrenia through comparison with the general population. Third, the generalizability of the results to chronic schizophrenia patients with more severe cognitive impairment may be limited. Fourth, in this study, we used lifetime SI as a key variable for assessing suicidality. Future research should consider incorporating the severity of suicidal behavior. Finally, the potential type I errors should be considered because this study employed empirical value of p-values without correction for multiple testing. Nevertheless, our results serve as a basis for future investigations into the relationship between suicidality and cognitive function in young patients with psychosis. We believe that our study contributes to a deeper understanding of suicidal behavior in young patients going through their first episode of schizophrenia and can aid in the development of suicide prevention strategies for this population.

In conclusion, our findings suggest that patients with recent-onset psychosis, who exhibit relatively high cognitive abilities, especially in complex functions and social cognition, are more prone to experiencing suicidal thoughts, potentially leading to increased suicidality. It is crucial to pay greater attention to suicidality among younger patients who demonstrate a better ability to understand others' perspectives and adapt to social situations. Moreover, providing psychological support with empathy and cognitive interventions is essential for young patients with recent-onset schizophrenia spectrum disorders, particularly those with elevated levels of depression, hopelessness, perceived stress, low resilience, and good cognitive function.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Chonnam National University Hospital Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

JSK: Writing – original draft, Data curation, Investigation. SHB: Data curation, Investigation, Methodology, Writing – review & editing. HK: Data curation, Investigation, Writing – review & editing. JWK: Data curation, Investigation, Writing – review & editing. HJK: Writing – review & editing, Conceptualization, Supervision. SR: Supervision, Writing – review & editing, Data curation, Formal analysis. JYL: Supervision, Writing – review & editing. JMK: Supervision, Writing – review & editing. SWK: Writing – review & editing, Conceptualization, Formal analysis, Funding acquisition, Methodology, Writing – original draft.

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Conflict of interest

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

Publisher's note

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Predictors of positive outcomes from 'Early Intervention in Psychosis': protocol for a national retrospective cohort study

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Background: Psychotic disorders are severe and prevalent mental health conditions associated with long-term disability, reduced quality of life, and substantial economic costs. Early Intervention in Psychosis (EIP) services aim to provide timely and comprehensive treatment for psychotic disorders, and EIP service input is associated with improved outcomes. However, there is limited understanding of the specific components of EIP care that contribute to these improvements. There is significant nationwide variability in the commissioning and delivery of EIP, with individuals receiving different packages of components from different services. In this study, we seek to explore associations between EIP components and clinically significant outcomes, in order to understand the mechanisms underlying improved psychosis care.

Methods: This national retrospective cohort study will utilize data from the 2019 National Clinical Audit of Psychosis (NCAP), examining the care received by 10,560 individuals treated by EIP services in England. Exposure data from the NCAP, capturing the components of care delivered by EIP services, will be linked with outcome data from routine NHS Digital datasets over a three-year follow-up period. This will be the first study to use this method to examine this population in England. The primary outcomes will be surrogate measures of relapse of psychosis (hospital admission and referral to community-based crisis intervention services). Secondary outcomes include duration of admissions, emergency hospital attendances, episodes of detention under the Mental Health Act, and all-cause mortality. We will use multilevel regression to examine associations between exposures and outcome events. We will handle missing data using appropriate imputation techniques.

Discussion: This study aims to provide valuable insights into the long-term effects of variations in EIP service delivery. The study involves a large, diverse cohort including individuals treated by every EIP service in England. While there are limitations inherent in the observational nature of the study, any associations identified will be of great relevance to clinicians, researchers, and policymakers seeking to optimize EIP care. The results will enable more targeted treatment planning, resource allocation, and potential innovations in EIP care, ultimately leading to improved prognoses for people experiencing psychosis.

KEYWORDS
early intervention, psychosis, schizophrenia, family therapy, CBTp, carer support

1. Introduction

Psychotic disorders are highly prevalent, severe mental health conditions that are associated with long-term disability, reduced quality of life and premature mortality (1, 2). They are major contributors to the global burden of disease, and a significant source of expenditure for the United Kingdom economy and National Health Service (3). Current models of care for psychotic disorders stress the importance of intervention early in the course of illness to optimize long-term prognosis (4). Specialized 'Early Intervention in Psychosis' (EIP) services were developed to facilitate proactive management of psychotic disorders at an early stage, and have been widely implemented in the UK (5) and internationally (6). These services aim to provide timely and comprehensive treatment, including psychosocial interventions, carer support and medication management with the goal of promoting recovery, reducing hospitalization, and improving outcomes (7).

Despite the widespread adoption and advancement of EIP services, there remains a significant gap in our understanding of the factors within these services that contribute to their observed benefits (8). Individual EIP services differ in the components of care that they deliver, and little is known about how this variation influences outcomes (9, 10). Some components have also been associated with positive results when delivered outside of the typical EIP service framework – for example 'one-stop network' services, which are attracting increasing attention as an alternative model of early access mental health service (11).

It is crucial that these associations between specific components of care and favorable outcomes are examined in order to continue to improve the quality of psychosis care. An advanced understanding of these processes would allow for more targeted treatment planning and resource allocation. It may also guide researchers in developing further innovations to enhance the delivery of EIP, and ultimately lead to improved prognoses for individuals experiencing psychosis.

The primary objective of this study is to identify which components of EIP services are associated with improved clinical outcomes for people with psychotic disorders. We will link exposure data from the National Clinical Audit of Psychosis (NCAP) (12) with outcome data from routine NHS Digital datasets, examining the outcomes of 10,560 individuals who were treated by EIP services in England in 2019. There is significant nationwide variability in the commissioning and delivery of EIP, with individuals receiving different packages of components from different services. This project aims to use this variation to examine the effect of specific components of care on outcomes.

2. Methods and analysis

This protocol is compliant with the 'Strengthening the Reporting of Observational Studies in Epidemiology' (STROBE) statement for observational studies (13).

2.1. Study design

This is a national retrospective cohort study. The cohort in question comprises 10,560 individuals for whom data were collected via case-note review as part of the 2019 NCAP (12).

The NCAP is a multi-cycle quality improvement program commissioned by the Health Quality Improvement Partnership (HQIP) on behalf of NHS England. The NCAP has been established as an effective tool to examine the quality of care for people with psychosis. Since 2017 it has been progressively refined over multiple rounds of data collection with input from users and providers of psychiatric services, and provides high quality data on participant demographics (e.g., age, gender, ethnicity, employment/education status) and the components of care that they receive.

In 2019, the NCAP specifically examined all EIP services in England and identified marked variation in components of care at both service and participant levels (12). Individuals received differing packages of treatments (e.g., psychological therapies, carer support). Services also differed in organizational aspects (e.g., waiting times, total caseload, average caseload per care coordinator). The 2019 NCAP received HRA (s215) approval to record patient identifiable data (NHS number/date of birth), enabling linkage with other datasets held by NHS Digital.

We intend to link exposure data from the 2019 NCAP (relating to the components of care delivered by EIP services) with outcome data recorded in routine NHS Digital datasets over the following 3 years. These are the 'Mental Health Services Data Set' (MHSDS) recording secondary mental health care provided by NHS Trusts; the 'Emergency Care Data Set' (ECDS), and its precursor 'Hospital Episode Statistics Accident and Emergency' (HES A&E) recording acute general hospital attendance; the 'Hospital Episode Statistics Admitted Patient Care' (HES APC) recording inpatient hospital episodes; and the 'ONS Civil Registration Death' recording non-hospital mortality. This linked dataset is currently in production, but not yet available for analysis at the time of publication of this protocol – hence the need for an *a priori* analysis plan.

Using the linked dataset, we will describe the cohort in terms of patient demographics, clinical characteristics, components of care received and outcomes. We will then examine for associations between specific exposures (components of care) and outcomes using appropriate statistical methods. This study has been informed by consultations with service users and carers and their priorities for research.

2.2. Exposure variables

Our exposures are specific components of the care provided by EIP services, all of which are specified by NICE as necessary constituents of comprehensive treatment for psychosis (14, 15): receipt of an antipsychotic, receipt of 'cognitive behavioral therapy for psychosis' (CBTp), receipt of a family intervention, receipt of

vocational support, receipt of a carer focused intervention, offer and initiation of clozapine where appropriate, whether monitoring was conducted with validated outcome measures, receipt of NICE-approved EIP physical health interventions (smoking cessation, weight reduction), EIP service caseload size, care coordinator caseload size, and waiting time (whether waiting time standard was met prior to initiation of treatment).

2.3. Outcome variables

Our primary outcome will be time to relapse as indicated by inpatient admission. Secondary outcomes will include time to relapse as indicated by referral to a community-based crisis intervention service, number and length (bed days) of inpatient admissions during the 3-year follow-up period, number of acute general hospital attendances (type 1 emergency departments) during this period, whether any admissions were subject to detention under the Mental Health Act, and all-cause mortality.

2.4. Covariates

In preparation for this analysis, we have constructed a Directed Acyclic Graph (DAG) to visually represent hypothesized causal relationships among the variables and covariates in our data (as well as potential unobserved mediators/confounders), in order to guide inclusion in regression models (see Figure 1). This process was informed based on the theoretical expertise of co-authors (including experts in this field and experts by experience) and previous research evidence. Potential confounders which we will be able to adjust for include participant age, sex, ethnicity, employment status and duration of EIP care (at individual level) and EIP service and socioeconomic status of local region (at service level).

2.5. Study population

Our sample comprises 10,560 individuals for whom data were collected via case-note review as part of the 2019 NCAP. Data were collected from all 155 EIP teams and from all mental health trusts across all regions in England between June–October 2019. All participating EIP teams provided a complete list of eligible patients to the NCAP audit team, who selected a random sample of 100 patients from each team (where the total caseload included less than 100 eligible patients, all patients were selected).

2.5.1. Inclusion criteria

All participants in the case-note review which was conducted as part of the 2019 National Clinical Audit of Psychosis. Eligibility criteria for the NCAP were as follows:

- Recorded diagnosis of a 'first episode' of any 'non-organic' psychotic disorder (including affective and substance-induced psychosis).
- Under the care of an EIP service for more than 6 months on 1 April 2019.
- Aged 14–65 – this broad age range reflects current access standards for EIP services recommended by the United Kingdom Royal College of Psychiatrists (16).

2.5.2. Exclusion criteria

Potential participants were excluded from the NCAP if they had a recorded diagnosis of psychosis due to an 'organic cause', for example, neurological disorders such as Huntington's and Parkinson's disease, dementia, or infections.

2.6. Data linkage and storage

We will utilize two sources of data: exposure data from the NCAP and outcome data from NHS Digital (MHSDS, HES, ONS mortality records). Exposure data from the NCAP will be transferred directly to NHS Digital by the Royal College of Psychiatrists (current data controller) and linked to outcome data. The resulting dataset will then be pseudonymized and minimized by NHS Digital to ensure that no patients are identifiable prior to access by our research team. The pseudonymized dataset will be stored within the Office of National Statistics Secure Research Service (ONS SRS).

2.7. Statistical analyses

All analyses will be performed using 'R' (17). This study involves a comprehensive analysis of the associations between exposure variables and primary and secondary outcomes while accounting for potential confounding factors.

Initially, descriptive statistics will be generated for all exposure variables, outcome measures and covariates as appropriate. Unadjusted tests will then be used initially to explore relationships between the exposure variables, covariates and primary and secondary outcomes.

We will examine associations between exposures and the frequency of outcome events (e.g., number of hospital admissions or acute hospital attendances) using negative binomial regression, in order to account for overdispersion commonly observed in such data. If the frequency of outcome events is small, we will instead dichotomize outcomes and examine associations using logistic regression. We will examine associations between exposures and time to first outcome events (e.g., time to relapse as indicated by admission or referral to crisis support team) using Cox regression. Cox regression allows for the analysis of time-to-event data while accommodating censoring effects, which may occur if participants do not experience the event of interest during the study period.

Multilevel regression models will be used to account for the clustering effects (participants are grouped within EIP services). This approach acknowledges the potential correlation between individuals within the same service, ensuring appropriate adjustments are made to obtain unbiased estimates. All regression models will be adjusted for potential confounding variables as specified in the DAG (participant age, gender, ethnicity, employment/education status and duration of EIP care).

Regarding missing data, our chosen outcomes (e.g., hospitalizations, referrals and use of the Mental Health Act) are

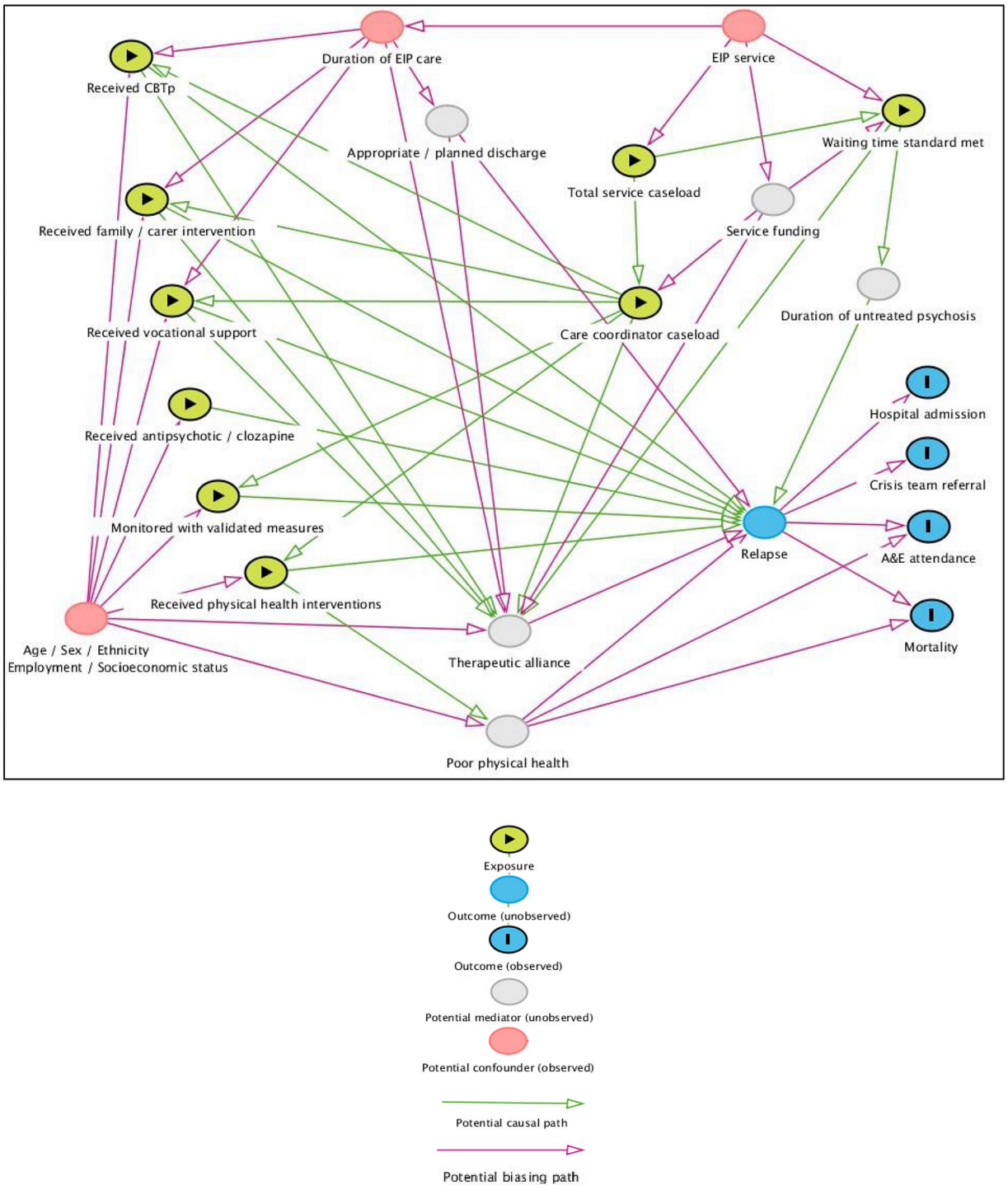

FIGURE 1
Directed acyclic graph of variables for the proposed analysis.

considered mandatory submissions for NHS Digital and we anticipate relatively little missing data. Nonetheless, we plan to examine the distribution of any missing data compared with complete data utilizing descriptive statistics and statistical tests, and identify the mechanism of missingness (completely at random, missing at random, not at random).

Following this analysis, we will select an appropriate data handling technique to address missing values from the following options: complete case analysis only; multiple imputation; substituting missing values with mean/modal observed values; using dummy variables as an indicator for missing values. We will perform sensitivity analyses to assess the impact of missing data by comparing the results obtained from different missing data handling techniques. We will transparently report our approach for handling missing data and acknowledge the potential influence of missing data on any interpretations from our findings.

2.8. Study power

Considering the dependent variable of 'hospital admission', from prior data we estimate that two-thirds of patients treated by EIP teams will have one or more admissions in the 3 years following their referral to EIP (18). As an example, one of our exposure variables would have 5,221 experimental subjects and 5,339 control subjects – data from the NCAP case note audit indicate that 5,221 (49.4%) of patients received CBTp.

For this example, using a 5% level of statistical significance (giving a Type I error probability of 0.05), we estimate that we will have 95% power to detect a small difference in the likelihood of admission to hospital among those who do and do not receive CBTp (equivalent to an odds ratio of 1.05). For reference, the NICE evidence review of CBTp vs. standard care found a RR of 0.76 for rehospitalization up to 18 months following treatment (14).

3. Discussion

This study seeks to explore associations between specific components of EIP care and clinically significant outcomes, using a retrospective cohort design. The results of this study will provide valuable insights into the long-term effects of variations in EIP service delivery.

Currently, the literature examining different EIP components is sparse, and there are no comprehensive experimental comparisons of specific components of EIP care. Previous observational comparison studies of EIP services have included relatively few different service models, restricting the opportunity to differentiate components of care (19–21). These studies have also lacked data on real-world outcomes, and been limited by relatively short follow-up times. Although they identified significant variation in outcomes between differing EIP programs, they were ultimately not able to identify any components which accounted for this.

Our cohort is a large, diverse sample encompassing every EIP service in England, and we will have the opportunity to examine a range of clinically relevant, real-world outcome measures over a substantial follow-up period. As such, we would anticipate that results would be widely generalizable with high external validity, and that any associations identified will provide significant information relevant to clinicians, researchers and policymakers seeking to optimize EIP care. To the best of our knowledge, this study is the first to capture and link national audit data with routine outcome data on service use in individuals with mental disorders in England.

This study does have several important limitations. For our exposure variables (i.e., the components of care that were delivered), we are reliant on data provided by the services via the NCAP. However, the NCAP was subject to a vigorous quality assurance process including random data-checking visits to participating trusts by NCAP team members, accompanied by impartial clinicians. Data are therefore of verifiable quality and good reliability. Our primary and secondary outcome measures are surrogate markers of mental wellbeing/relapse (rather than, for example, validated measures of psychotic symptoms). However, they are also objectively important outcomes with clear causal links to mental wellbeing, and clear relevance to patients and clinicians.

As an observational study, this project is also obviously susceptible to inherent limitations such as potential unmeasured confounding and the inability to establish causality. Specific unmeasured confounders include funding variations between services – although we would expect that some of the beneficial effects of improved funding would be mediated by variables that we are examining (waiting times, caseload per care coordinator and availability of interventions). The retrospective design also carries risks of incomplete or missing information. However, we plan to address these limitations through appropriate data handling techniques, and we will transparently report any implications for the conclusions we draw from the results.

In conclusion, this cohort study will provide significant novel data about the processes and outcomes of EIP care. This will help to optimize treatment pathways for people with psychosis and improve quality of life for this vulnerable group.

Ethics statement

This study was reviewed and approved by y the London Queens Square Research Ethics Committee (REC), part of the NHS Health Research Authority (HRA) – REC reference 22/PR/0602. Written informed consent to participate was not required.

Author contributions

RW: Conceptualization, Funding acquisition, Methodology, Writing – original draft. EP: Writing – review & editing. VG: Writing – review & editing. AT: Writing – review & editing. PF: Writing – review & editing. BL: Writing – review & editing. AB: Methodology, Supervision, Writing – review & editing. MC: Conceptualization, Methodology, Supervision, Writing – review & editing.

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Conflict of interest

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

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Cognitive deficits profiles in the first-episode of schizophrenia, clinical high risk of psychosis, and genetically high-risk of psychosis

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Background: Cognitive deficits are core characteristics of schizophrenia, presenting before the emergence of psychotic symptoms. Individuals with a clinical high-risk for psychosis (CHR) and those with genetically high-risk of psychosis (GHR) also exhibit cognitive impairments. Nonetheless, it remains uncertain in which domains of cognitive impairments in these two groups were more similar to those of schizophrenia patients. Moreover, it is unclear which domains of impairment are caused by quality factors and which are more related to the state of disease. This research initiative aimed to extensively examine the distinct cognitive impairment profiles among the CHR, GHR, and first-episode schizophrenia (FES) cohorts.

Methods: We compared the cognitive functions of the three groups and a healthy control group (HCs) using the MATRICS Consensus Cognitive Battery (MCCB). The participants for this study were recruited from the Beijing Anding Hospital of Capital Medical University. Our sample consisted of 56 patients with FES, 42 with CHR, 26 with GHR, and 62 HCs. The participants across all groups were matched in terms of gender, age, and level of education.

Results: Individuals with FES, GHR, and CHR showed significant impairment across the majority of MCCB domains, with the exception of visual learning, in comparison to HCs. None of the MCCB domains demonstrated a discerning ability to accurately differentiate between individuals with CHR and those with GHR. In the speed of processing and attention/vigilance domains, individuals with GHR and CHR exhibited scores between those of FES and HCs, with all group differences reaching statistical significance. This pattern of results indicates an intermediate level of cognitive function in individuals with GHR and CHR. Conversely, the levels of impairment observed in working memory and verbal learning were relatively consistent across all three groups: FES, CHR, and GHR. Notably, individuals in the CHR group exhibited performance akin to that of the HCs in the reasoning/problem-solving domain, while showing significant differences from the FES group, with the CHR individuals demonstrating better performance. Additionally, individuals with GHR displayed performance in social cognition similar to that of the HCs, while also demonstrating significant distinctions from the FES group, with the GHR individuals demonstrating better performance.

Conclusion: Significant cognitive deficits exist in individuals with CHR, GHR, and FES, and these deficits vary across domains. Processing speed and attention/vigilance could potentially serve as robust biomarkers for identifying individuals

at a risk of psychosis. The impairment observed in reasoning/problem-solving abilities might signify a qualitative trait, whereas deficits in social recognition could indicate a state characteristic specific to schizophrenia.

KEYWORDS

clinical high-risk for psychosis, genetically high-risk of psychosis, first episode schizophrenia, cognitive deficits, MCCB

1 Introduction

Cognitive deficits are core characteristics of schizophrenia (1), and affect all aspects of neuropsychological functioning. Specifically, executive function, memory, and sustained attention seem to be particularly affected (2). Evidence suggests that cognitive decline precedes the emergence of psychotic symptoms (3), followed by a period of relative cognitive stability until later life (4).

Prior to the emergence of schizophrenia, many individuals experience non-specific symptoms such as perceptual disturbances, unusual beliefs or magical thinking, attentional disruptions, and symptoms of anxiety and depression. These manifestations are collectively denoted as clinical high-risk for psychosis (CHR) (5). Approximately one-third of individuals identified with CHR undergo a transition into psychosis within the subsequent 2–3 years (6). Compared to healthy controls (HCs), CHR individuals exhibit significant cognitive impairments, suggesting that neurocognitive dysfunction could serve as a potential biomarker for early detection and prognosis in this population (7).

Individuals who are first-degree relatives of schizophrenia patients, but currently show no clinical symptoms and function normally, are typically classified as genetically at high risk for psychosis (GHR). Individuals who are GHR demonstrate moderate cognitive deficits compared to healthy controls, and their cognitive profiles were similar to those observed in patients with schizophrenia (8, 9). Furthermore, those who are GHR for schizophrenia typically demonstrate poorer cognitive functioning than those at risk for affective psychosis. This observation implies that the genetic predisposition for schizophrenia, as marked by a positive GHR, exerts a significant influence on cognitive abilities (8).

Evidence indicates that considerable cognitive impairment among individuals with CHR is largely attributable to their transition to psychosis (CHR-T) (6). Therefore, neurocognitive deficits in CHR cohorts should be interpreted with caution, especially when considering psychosis or even CHR status as the specific clinical syndrome of interest, as these impairments likely signify a transdiagnostic or psychosis-specific vulnerability (10). It is important to note that the majority of CHR individuals do not develop psychosis (6). Consequently, the decrease in cognitive function might arise from either a subgroup genuinely at an elevated risk for psychosis who exhibits more pronounced impairments, or it might reflect generalized distress, psychopathology, or other psychiatric issues within CHR subjects (11). This highlights the importance of considering cognitive impairment among CHR subjects not solely as an exclusive marker for emerging psychosis, but potentially as a reflection of a broader range of underlying factors (12). Certain domains of cognitive impairment could potentially reflect qualitative traits associated with schizophrenia, rather than being indicative of current states. In these domains, the impairment in individuals with GHR may be more akin to that in the patient population than that observed in CHR individuals. Conversely, in domains where cognitive impairment represents a state characteristic, the impairment in CHR individuals could be more analogous to that in the patient population than in GHR individuals.

While existing literature generally acknowledges that both CHR and GHR individuals exhibit cognitive impairments compared with HCs, there is a paucity of studies that directly compare cognitive functioning across CHR, GHR, first-episode schizophrenia (FES) patients, and HCs (13, 14). Furthermore, previous research has not consistently utilized standardized cognitive assessment tools such as the MATRICS Consensus Cognitive Battery (MCCB) (13), or has only employed four of the seven cognitive domains assessed by the MCCB (14). MCCB was developed to provide a comprehensive assessment of cognitive functioning in patients with schizophrenia or schizoaffective disorder for the purposes of conducting clinical trials (15). Previous findings showed that the MCCB is a sensitive instrument to detect cognitive impairments in patients with schizophrenia (16–20).

In this study, we leveraged the MATRICS Consensus Cognitive Battery (MCCB) to compare the cognitive functions of individuals with FES, those at CHR, those with GHR, and HCs. Our objective was to explore the differences in cognitive profiles across these four groups. We aimed to pinpoint the shared domains of impairment across all three at-risk groups, and to highlight which domains of impairment are more pronounced within a particular group.

2 Materials and methods

This cross-sectional study was conducted between January 2015 and January 2018 at Beijing Anding Hospital of Capital Medical University. The study was reviewed and approved by the institutional ethics committee. All participants or their guardians in applicable cases provided their voluntary consent by signing written informed consent forms.

2.1 Participants

The study included individuals aged between 17 and 40 years, all of whom had completed at least an elementary education. FES patients were sourced from either outpatient services or inpatient wards, while those at the CHR were identified among the hospital's help-seeking population. Individuals in the GHR and HCs were recruited through advertisements.

Patients with FES met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for schizophrenia, with a first episode of disease and a duration of less than 3 years (21). These patients had either no history of medication or had used antipsychotics for no more than one continuous month since the onset of the disorder (22).

Individuals with CHR were screened using the Structured Interview for Psychosis-risk Syndromes (SIPS), qualifying if they met one or more of three conditions: Brief Intermittent Psychotic Symptoms Syndrome (BIPS), Attenuated Psychotic Symptoms Syndrome (APSS), or Genetic Risk and Deterioration Syndrome (GRD) (23).

Individuals with GHR were defined as first-degree relatives (siblings or children) of individuals diagnosed with schizophrenia. Any psychiatric disorders in individuals with GHR and HCs were ruled out using the Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID-I/P) and SIPS. If a GHR individual meets the criterion of more than 30% functional deterioration in the past year as defined by the SIPS, they are included in the CHR group.

Participants were excluded if they had a severe physical illness or had undergone modified electroconvulsive therapy within the past 6 months. Substance-induced schizophrenia and patients with organic brain disorders were excluded from the study.

2.2 Measures

2.2.1 Clinical assessment

The severity of symptoms in patients with FES was evaluated using the Positive and Negative Syndrome Scale (PANSS). This scale consists of 30 items, each with a defined criterion and a specific seven-level operational scoring standard (ranging from 1 to 7) (24).

To assess symptom scores for CHR, GHR, and HC individuals, we used the Scale of Prodromal Symptoms (SOPS) included in the Structured Interview for Psychosis-risk Syndromes (SIPS). The SOPS comprises 19 fundamental items, each rated on a seven-point scale (ranging from 0 to 6) (23).

2.2.2 Cognitive function assessment

The MATRICS Consensus Cognitive Battery (MCCB) was utilized to assess the neurocognitive levels of the participants (25). It encompasses 10 subtests that measure seven cognitive domains: information processing speed, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem-solving, and social cognition. This study employed the Chinese version of the MCCB (26). The assessors conducting the evaluations underwent training from the staff at the Institute of Mental Health of Peking University, who participated in the development of the Chinese version of the MCCB. Subsequently, the raw scores were converted into T-scores using gender and age corrections based on the Chinese cognitive norms, with higher T-scores indicating superior cognitive function.

2.2.3 Statistical analysis

The data were analyzed using IBM SPSS Statistics 23.0 for Windows (SPSS, Inc., Chicago, IL, United States). Continuous variables are presented as means and standard deviations, while categorical variables are presented as frequencies and percentages. Differences in demographic data between groups were assessed using the chi-square test or one-way ANOVA. Differences in cognitive domains among the four groups were analyzed using a Multivariate Analysis of Covariance (MANCOVA), with gender, age, years of education, and unemployment status as covariates. Analysis of Covariance (ANCOVA) was used to compare the overall composite scores among the four groups. *Post hoc* comparisons were conducted using Bonferroni correction. Effect sizes (Cohen's *d*) were calculated to identify differences in cognitive performance levels. A value of p of less than 0.05 was deemed to represent statistical significance.

3 Results

3.1 Demographics and clinical characteristics

During the initial screening, five individuals with FES and two individuals with CHR were excluded because of non-cooperation with cognitive testing. Ultimately, a cohort of 186 Chinese participants was enrolled, consisting of 56 FES patients, 42 CHR individuals, 26 GHR individuals, and 62 HCs (Refer to Table 1). No significant differences were observed across the four groups in terms of age, years of education, sex ratio, marital status, or smoking status. However, the FES group had a significantly higher unemployment rate than the other three groups ($\chi^2 = 28.51$, $p < 0.001$). Additionally, all SOPS scores in the CHR group were significantly higher than those in the GHR and HC groups ($\chi^2 = 94.06$, $p < 0.001$).

3.2 Comparison of cognitive performance among study groups

3.2.1 FES, CHR, and GHR groups vs. healthy controls

No significant differences were observed in the MANCOVA of the visual learning domain ($F = 1.96$, $p = 0.12$). However, significant differences between the groups were noted in the remaining cognitive domains and overall composite scores (Table 2).

Post hoc comparisons demonstrated that the performance of individuals with FES was significantly inferior to that of HCs in six of the seven cognitive domains, with the exception of visual learning (*Cohen*' $d = 0.71–1.71$). Compared to the HCs, both the CHR (*Cohen*' $d = 0.47–1.46$) and GHR (*Cohen*' $d = 0.36–1.80$) groups exhibited significantly worse performance in the domains of information processing speed, attention/vigilance, working memory, verbal learning, and the overall composite score. The cognitive profiles of the FES, CHR, and GHR groups compared to those of the HC group are shown in Figure 1.

3.2.2 Comparison between FES group and CHR group

First-episode schizophrenia patients scored lower than CHR individuals in the domains of information-processing speed ($p = 0.008$, *Cohen'd* = 0.73), attention/vigilance ($p < 0.001$, *Cohen'd* = 1.00), and reasoning/problem solving ($p = 0.018$, *Cohen'd* = 0.57).

TABLE 1 Demographics and clinical features of the participants.*

	FES	CHR*	GHR	HCs	Total	*F*	*p*
Subjects, *n*	56	42	26	62	186	—	—
Age, years	25.7 ± 6.5	23.8 ± 4.8	26.7 ± 4.8	25.1 ± 3.6	25.2 ± 5.1	2.07	0.11
Education, years	12.9 ± 3.2	14.3 ± 2.9	13.2 ± 3.2	14.2 ± 3.3	13.7 ± 3.2	2.60	0.05
Duration of illness, months	27.4 ± 26.2	26.3 ± 27.8	—	—	27.0 ± 26.7	0.04	0.84
SIPS							
Positive	—	9.4 ± 4.1	0.3 ± 0.5	0.3 ± 1.2	—	96.55	< 0.001
Negative	—	9.0 ± 5.2	0.7 ± 1.6	0.2 ± 0.8	—	95.49	< 0.001
Disorganization	—	4.7 ± 3.4	0.5 ± 0.8	0.1 ± 0.5	—	84.72	< 0.001
General	—	4.9 ± 3.5	0.8 ± 1.5	0.1 ± 0.5	—	83.59	< 0.001
Total score	—	28.0 ± 12.4	2.2 ± 3.7	0.8 ± 2.6	—	94.06	< 0.001
PANSS							
Positive	22.8 ± 6.1	—	—	—	—	—	—
Negative	21.0 ± 8.3	—	—	—	—	—	—
General psychopathology	41.9 ± 6.7	—	—	—	—	—	—
Total score	84.3 ± 15.0	—	—	—	—	—	—
						χ^2	*p*
Men	30 (53.6)	26 (61.9)	15 (57.7)	35 (56.5)	106 (57.0)	0.69	0.88
Married	11 (19.6)	5 (11.9)	8 (30.8)	10 (16.1)	34 (18.3)	4.12	0.25
Family history*	9 (16.1)	12 (28.6)*	26(100.0)	0(0%)	47 (25.3)	100.61	< 0.001
Smoking	8 (14.3)	6 (14.3)	3 (11.5)	9 (14.5)	26 (14.0)	0.16	0.98
Unemployed	24 (42.9)	6 (14.3)	4 (15.4)	3 (4.8)	37 (19.9)	28.51	< 0.001
Medication	48 (85.7)	24 (57.1)	—	—	72	—	—
Unmedicated	8 (14.3)	18 (42.9)	—	—	26	—	—
Only AP*	44 (78.6)	13 (31.0)	—	—	57	—	—
Only AD*	0	5 (11.9)	—	—	5	—	—
AD + AP	1 (1.8)	4 (9.5)	—	—	5	—	—
Unspecified	3 (5.3)	2 (4.7)	—	—	5	—	—

*Data are reported as *n* (%), unless indicated otherwise. 37 cases of APS, two cases of BLIPS, and three cases of GRD were included in the CHR group. The family history refers to the presence of mental illness in the relatives of the subjects in two families and three generations. The 12 people listed in the family history of CHR are "first-degree relatives who had a family history of psychosis." AD, Antidepressant; AP, Antipsychotic.

3.2.3 Comparison between FES group and GHR group

First-episode schizophrenia patients performed worse than GHR individuals in the domains of information processing speed ($p = 0.04$, *Cohen'd* = 1.09), attention/vigilance ($p = 0.001$, *Cohen'd* = 1.02), and social cognition ($p = 0.004$, *Cohen'd* = 0.73).

3.2.4 Comparison between CHR group and GHR group

No significant differences were observed in the performance across all cognitive domains between the CHR and GHR groups.

4 Discussion

In this study, cognitive performance in the FES, GHR, CHR, and HC groups was investigated. Our findings indicate that individuals in the FES, GHR, and CHR groups exhibited notably poorer performance across the majority of domains assessed by the MCCB, in contrast to the HC group. While cognitive impairment was evident in both GHR and CHR individuals, its severity was milder than that observed in patients with FES.

In our study, cognitive functioning in individuals with CHR occupied an intermediate position between that of HCs and FES, which is consistent with previous research (14, 27). CHR individuals exhibited lower performance than HCs across all MCCB domains except for visual learning, especially in the domains of processing speed and attention/vigilance. Previous meta-analyses have consistently noted that CHR subjects lag behind HCs in all MCCB cognitive domains, particularly processing speed, attention/vigilance, and working memory (28). The cognitive deficit domains identified in the CHR group in our study echo those found in previous studies.

Several studies have compared cognitive impairment among the FES, CHR, and GHR groups (13, 14, 29). In a previous study

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TABLE 2 Cognitive functions of the FES, CHR, GHR, and HCs.

Domains	FES	CHR	GHR	HCs	Total	Statistic[a]		Pairwise comparison [b]		
						F	*p*		*p*	*Effect size* [c]
Speed of processing	33.0 ± 8.9	39.0 ± 7.6	40.6 ± 5.1	45.2 ± 6.9	39.5 ± 8.9	15.72	< 0.001	FES < CHR	0.008	0.73
								FES < GHR	0.04	1.09
								FES < HC	< 0.001	1.54
								CHR < HC	< 0.001	0.86
								GHR < HC	0.006	0.77
Attention/ Vigilance	30.1 ± 10.1	40.8 ± 11.3	39.4 ± 8.1	46.0 ± 8.5	39.3 ± 11.5	18.69	< 0.001	FES < CHR	< 0.001	1.00
								FES < GHR	0.001	1.02
								FES < HC	< 0.001	1.71
								CHR < HC	0.03	0.53
								GHR < HC	0.004	0.80
Working memory	38.5 ± 9.7	39.1 ± 3.4	42.3 ± 17.0	46.6 ± 6.9	41.9 ± 11.6	5.88	0.001	FES < HC	0.001	0.98
								CHR < HC	0.001	1.46
								GHR < HC	0.016	0.36
Verbal learning	38.7 ± 9.0	42.2 ± 9.6	40.8 ± 6.2	46.9 ± 10.6	42.5 ± 9.9	5.15	0.002	FES < HC	0.001	0.84
								CHR < HC	0.007	0.47
								GHR < HC	0.005	0.73
Visual learning	39.3 ± 14.1	42.8 ± 11.8	44.9 ± 9.9	47.1 ± 10.3	43.5 ± 12.2	1.96	0.12	—	—	—
Reasoning/ problem solving	34.4 ± 11.0	40.7 ± 11.3	37.6 ± 8.4	43.4 ± 10.5	39.3 ± 11.2	3.87	0.01	FES < CHR	0.018	0.57
								FES < HC	0.002	0.84
Social recognition	31.4 ± 12.3	36.6 ± 8.1	39.7 ± 10.4	39.3 ± 9.8	36.4 ± 10.8	3.92	0.01	FES < GHR	0.004	0.73
								FES < HC	0.003	0.71
Overall composite	35.4 ± 6.4	40.6 ± 5.8	41.2 ± 3.0	45.0 ± 5.7	40.7 ± 6.9	7.00	< 0.001	FES < HC	< 0.001	1.59
								CHR < HC	0.004	0.77
								GHR < HC	0.031	0.87

[a]Multivariate analysis of covariance. [b]Bonferroni correction applied to *post hoc* pairwise comparisons analyses. [c]After significant pairwise comparisons, effect sizes were calculated using *Cohen's d*.

(12), no significant differences were observed in the cognitive performances between the ultra-high risk (UHR) for psychosis and familial high-risk group (FHR) groups. The cognitive deficits in the UHR and FHR groups were largely similar to those in the FES group. Nonetheless, another study reached a different conclusion, suggesting that the performance in psychomotor speed, attention, processing speed and working memory, and verbal memory gradually decreased from the HC, first-degree relatives (FDR), UHR to FES groups (14). This implies that cognitive functioning in the UHR group was intermediate between that in the FES and FDR groups. The findings of our study appear to be more aligned with the first study mentioned earlier (13). Our study and the first study mentioned share similarities in the distribution of sample sizes across groups (our sample sizes: FES = 56, CHR = 42, and GHR = 26; the first study's sample sizes: FES = 53, CHR = 52, and GHR = 29). However, the latter study mentioned had a larger sample size in the GHR group (FES = 40, CHR = 40, and GHR = 40) compared to ours (14). We wonder if our smaller GHR group size might have masked a potentially modest difference between the GHR and CHR groups, which warrants further investigation to confirm.

In our study, we detected impaired processing speed, attention/vigilance, working memory, and verbal learning in the GHR group, with the most significant impairments observed in the attention/vigilance domain. This finding aligns with previous studies that have suggested that individuals with GHR exhibit cognitive impairments resembling their affected siblings and demonstrate moderate deficits compared with HCs (8, 30–32). A quantitative and qualitative review has reported larger effect sizes for measures of full-scale IQ, vocabulary, and single-word reading tests, while measures of declarative memory, sustained attention, and working memory showed more modest effect sizes (8). The differences observed in the cognitive impairment domains between our study and previous studies may be attributed to variations in the assessment tools used. Different assessment tools measure various domains, or the same assessment item may be considered to reflect different domains in different assessment toolkits. For instance, in the aforementioned review, the IQ measures are typically composed of more elemental measures such as processing speed, working memory, language ability, and visual–spatial ability. The mentioned severe impairment in full-scale IQ in these studies also implies serious impairments in processing speed and working memory. These apparent differences

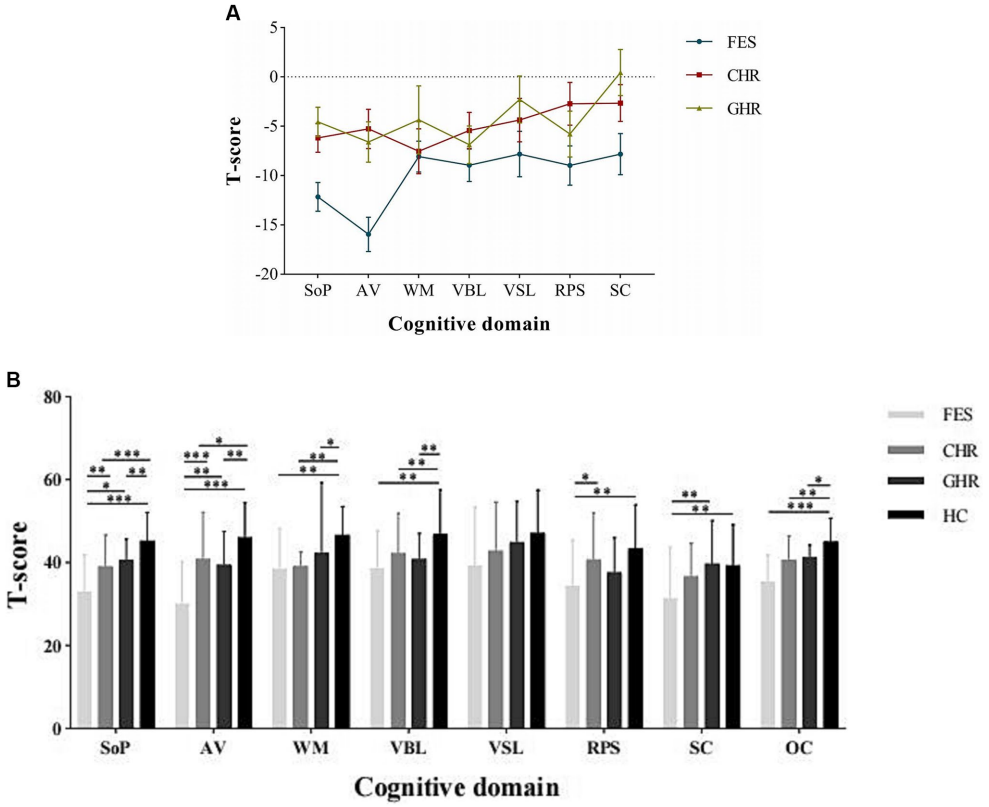

FIGURE 1
Cognitive profiles of the FES, CHR, and GHR groups against HC group. FES, First-episode schizophrenia; CHR, Clinical high-risk for psychosis; GHR, Genetically high-risk of psychosis; HC, healthy control. SoP, Speed of processing; AV, Attention/Vigilance; WM, Working memory; VBL, Verbal learning; VSL, Visual learning; RPS, Reasoning and problem solving; SC, Social cognition; and OC, Overall composite. The Y-axis in presents the mean and standard error of the difference between the study group and HC group.

might essentially be the same at their core. Similarly, the systemic review also mentions severe impairment in vocabulary, which actually corresponds to verbal learning in our study. This is also a key reason why recent studies have increasingly standardized the use of the MATRICS Consensus Cognitive Battery (MCCB), as it allows for comparability between research findings.

Among the three groups (FES, CHR, and GHR), processing speed and attention/vigilance were consistently impaired, with CHR and GHR individuals exhibiting milder impairments than FES individuals. This finding is in line with those of previous studies (29, 33). These results suggest that processing speed and attention/vigilance could potentially serve as promising biomarkers for early detection and severity assessment of schizophrenia. We hypothesized that genetic factors, current symptoms, or other unknown factors may influence these cognitive domains, with their effects potentially accumulating over time. Consequently, the most pronounced impairment in these particular domains was noted within the FES group.

Interestingly, the severity of impairment in the reasoning/problem-solving domain was comparable between GHR and FES (with no statistically significant difference), while CHR exhibited milder impairment than FES (with a statistically significant difference). On the other hand, the severity of impairment in social recognition was similar between CHR and FES (with no statistically significant difference), while GHR displayed less impairment than FES (with a statistically significant difference). Previous studies have consistently reported impaired social cognition in in individuals with CHR (34). Research on social cognition in individuals with GHR has been limited and inconsistent. However, previous findings have indicated that social cognitive impairments are significantly associated with psychopathology in young relatives of individuals with schizophrenia (35). Building on these insights, we propose that social recognition could potentially be more closely tied to an individual's current state, while reasoning/problem-solving may be more indicative of qualitative differences.

The utilization of the MCCB in this study contributed to standardized cognitive testing and domains. Nevertheless, it is crucial to interpret these results with caution because of several limitations. First, the sample size was relatively small, which may have limited the generalizability of the findings. Second, the cross-sectional design of the study prevented the determination of predictive neuropsychological markers for the transition to psychosis in at-risk individuals. Third, the family history of the 12 individuals with CHR may serve as a confounding factor. Subsequent analyses could benefit from an expanded sample size and the incorporation of longitudinal observations from clinical and genetic high-risk psychosis cohorts to fortify the robustness of the findings. Additionally, antipsychotic medications may potentially account for the cognitive impairments. We were unable to exclusively collect data from unmedicated patients and have strived to minimize the impact of medications by including patients who have not been on regular medication for over 1 month.

5 Conclusion

Our study provides evidence supporting the existence of cognitive deficits in individuals at high risk for schizophrenia, both in clinical (CHR) and genetic (GHR) predispositions, prior to the onset of the first episode. Notably, processing speed and attention/vigilance emerged as shared domains that exhibited progressive impairment across the three groups, indicating their potential as biomarkers for schizophrenia. The observed impairment in reasoning/problem solving might signify a qualitative trait, whereas social recognition could potentially reflect an individual's current state. However, it is crucial to emphasize that additional rigorous research is necessary to validate and substantiate these findings.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Beijing Anding Hospital Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

FD: Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. ZM: Data curation, Formal analysis, Investigation, Software, Writing – review & editing. YD: Formal analysis, Writing – review & editing. LW: Writing – review & editing. QB: Methodology, Project administration, Supervision, Writing – review & editing. FL: Investigation, Writing – review & editing. FW: Investigation, Writing – review & editing. CW: Project administration, Resources, Supervision, Writing – review & editing.

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Conflict of interest

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

Publisher's note

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Exploring the impact of biological alterations in the superior thalamic radiations on exploratory eye movements in attenuated psychosis syndrome

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Introduction: Aberrant fixation and scan paths in visual searches have been repeatedly reported in schizophrenia. The frontal eye fields (FEF) and thalamus may be responsible for fixation and scan paths. These two regions are connected by superior thalamic radiation (STR) in humans. Studies have reported reduced fixation numbers and shortened scan path lengths in individuals with attenuated psychosis syndrome (APS) and schizophrenia. In this study, we hypothesized that STRs in the white matter fiber bundles of impairments underlie abnormalities in fixation and scan path length in individuals with APS.

Methods: Twenty-one individuals with APS and 30 healthy controls participated in this study. All participants underwent diffusion tensor imaging, and fractional anisotropy (FA) values of the left and right STR were analyzed using the novel method TractSeg. The number of eye fixations (NEF), total eye scanning length (TESL), and mean eye scanning length (MESL), derived using the exploratory eye movement (EEM) test, were adopted to evaluate the fixation and scan path length. We compared the FA values of the bilateral STR and EEM parameters between the APS and healthy control groups. We investigated the correlation between bilateral STR and EEM parameters in the APS and healthy control groups.

Results: NEF, TESL, MESL, and the FA values of the left STR were significantly reduced in individuals with APS compared to healthy controls. The left STR FA value in the APS group was significantly positively correlated with the MESL (r = 0.567, p = 0.007). In addition, the right STR FA value of the APS group was significantly correlated with the TESL (r = 0.587, p = 0.005) and MESL (r = 0.756, $p = 0.7\times10^{-4}$).

Discussion: These results demonstrate that biological changes in the STR, which connects the thalamus and FEF, underlie abnormalities in fixation and scanning.

Recently, aberrations in the thalamus–frontal connection have been shown to underlie the emergence of psychotic symptoms. STR impairment may be a part of the biological basis of APS in individuals with subthreshold psychotic symptoms.

KEYWORDS

attenuated psychosis syndrome, superior thalamic radiation, fixations, scan path lengths, exploratory eye movement, diffusion tensor imaging, TractSeg

1 Introduction

Approximately 80% of patients with schizophrenia and 66% of patients with the first episode before antipsychotic administration are reported to have genuine motor abnormalities (1, 2). These motor abnormalities and psychiatric symptoms observed in patients with schizophrenia may be caused by the disruption of neural networks in the brain. Therefore, investigating the biological background of motor abnormalities in schizophrenia may clarify part of the pathology of the aberrant neural networks in the brain underlying schizophrenia.

In 1908, Diefendorf and Dodge reported abnormal eye movements in schizophrenia (3). Abnormalities in saccades, smooth pursuit, and visual search have been identified as characteristics of eye movements in schizophrenia (4). Repeated short stops of eye movement between scanning objects are defined as fixations, and the set of fixations connected by saccades is defined as the scan path (4, 5). In studies on visual search in schizophrenia, a reduced number of fixations and shortened scan path lengths have been repeatedly reported by several studies (5–7). In the latest study in 336 patients with schizophrenia and 1,254 healthy controls, a significant reduction in the scan path length and number of fixations has been reported using the free viewing test (8). This reduction corroborates with the reduced number of fixations and shortened scan path lengths observed in patients with schizophrenia. Considering that the pathway connecting fixations comprises the scan path, impairment of the function of fixation is shown to provoke abnormalities in the scan path and fixation.

Fixation neurons in the frontal eye field (FEF) are responsible for maintaining fixation and discharge during fixation. Conversely, a reduction in the activity of fixation neurons within the FEF increases the activity of saccade-related movement neurons (9). Spontaneous eye movements are controlled by motor and fixation cells in the FEF (10), which play a critical role in the early stages of visual search (11, 12).

The localization of the FEF, which may include fixation neurons, varies depending on the differences in studies and methods. In general, the FEF is more widely distributed posteriorly in humans than in primates, including the precentral cortex (13–15). The frontal cortex is thought to have hierarchical anatomical and functional gradients along its rostral-to-caudal axis. The pathological changes in the lowest layer of the frontal cortex underlie the impairment of a broad range of the frontal cortex, including the prefrontal cortex, which is in the upper layer (16).

Several regions other than the frontal cortex are also responsible for fixation (17). Mounting evidence shows a relationship between fixation and the thalamus. Rafal et al. (2004) investigated patients with thalamic lesions and reported that the thalamus was involved in the control of fixation for visually triggered saccades (18–20). Furthermore, several studies reported a relationship between fixation abnormality and thalamic impairments in schizophrenia (19, 20). Fukumoto-Motoshita et al. (2009) proposed high activation of the thalamus in fixation tasks in schizophrenia (19). The thalamus has a neural connection with the cerebral cortex and the thalamocortical pathway. McAvoy et al. (2012) have reported a relationship between fixation and thalamocortical connectivity (21). Recently, converging evidence has corroborated that impairment of the thalamocortical pathway is central to the pathophysiology of schizophrenia (22, 23). The FEF that includes fixation neurons is distributed in the posterior part of the frontal cortex, including the precentral cortex in humans (13–15), and these regions have a neural connection with the thalamus via superior thalamic radiation (STR) (24, 25). Few studies have directly investigated the precise impairment of the STR in schizophrenia *in vivo* because of methodological difficulties. However, the STR is included in the corona radiata, and reduced fractional anisotropy (FA) values in the corona radiata among patients with schizophrenia have been reported using diffusion tensor imaging (DTI) (24, 26). FA values obtained through DTI are regarded as a measure of white matter fiber bundle integrity that facilitates communication between different brain regions. Additionally, in a longitudinal study of individuals at risk of developing psychosis (ARMS group), a noteworthy reduction in FA values within the left superior corona radiata was observed among those who eventually developed psychosis compared to those who did not (27). These findings imply that biological alterations within the corona radiata, including the STR, become evident in individuals at risk for psychosis and in those with established schizophrenia.

Attenuated psychosis syndrome (APS) affects 85% of ARMS individuals (28). Shido et al. investigated abnormal eye movements in individuals with APS using an exploratory eye movement (EEM) test. The EEM test comprises the following parameters: number of

eye fixations (NEF), total eye scanning length (TESL), mean eye scanning length (MESL), and responsive search score (RSS), calculated from the point of gaze and movement distance of eye movements (29), all of which have been reported to be significantly reduced in schizophrenia compared to other mental disorders, such as depression and anxiety disorders (6). In this study, the NEF, TESL, and RSS were significantly lower in the APS group than in the healthy control group (30). Regarding fixation and scan path length, these results are in line with the reduction in total eye scanning length, that is, TESL reduction and significant NEF reduction, which were repeatedly reported in previous reports on EEM tests in schizophrenia (6, 7). Kojima et al. (2019) focused on the subjectivity disorder in schizophrenia and reported that EEM tasks, including comparison matching and reminder tasks, can assess the disorder in schizophrenia (31). Subjectivity disorder or self-disorder is the core feature of schizophrenia. Thus, there is a possibility that investigating the EEM disturbance clarifies the core pathophysiology of APS as well as schizophrenia. Meanwhile, due to the methodological difficulty in investigating the precise structure of the STR *in vivo*, whether the biological changes of the STR underlie the abnormality of visual search in the APS group remains unclear.

The advent of a new method, TractSeg, enables the analysis of white matter tract segmentation using a direct approach that provides complete and accurate segmentation of the entire brain, including the STR (32). In this study, we hypothesized that biological changes in the STR are associated with EEM abnormalities in individuals with APS. We used TractSeg to investigate the FA values in the STR and examined the differences in the FA values of the STR and EEM parameters (NEF, TESL, MESL, and RSS) between the APS and healthy control groups. Furthermore, we examined the relationship between changes in STR and EEM parameters in the APS and healthy control groups.

2 Materials and methods

2.1 Participants

All individuals who visited the Department of Psychiatry at Toho University Omori Medical Center underwent The Prevention Through Risk Identification, Management, and Education (PRIME) Screen-Revised (PS-R) program to screen potential individuals with APS. Subsequently, the Japanese versions of the Structured Interview for Prodromal Syndromes and the Scale of Prodromal Symptoms (SIPS/SOPS) were assessed to identify individuals with APS criteria (33–35). APS individuals were native Japanese of 16–40 years of age and had no history of alcohol dependence, substance abuse, or neurological illnesses. Healthy control participants were recruited from independent sources in the community and were interviewed in detail by experienced psychiatrists. Similar to the APS group, healthy controls were native Japanese of 16–40 years of age, and none had a history of alcohol dependence, substance abuse, or neurological illnesses. The Edinburgh Handedness Inventory was used to determine handedness in both the healthy controls and the APS group, and all analyses were performed with right-handed participants (36). The study procedure was explained, and written informed consent was obtained from all participants. For participants under 20 years of age, we explained the contents of this research to their parents or legal representatives and obtained their written informed consent. This study was performed in accordance with the Declaration of Helsinki of the World Medical Association and approved by the Ethics Committee of Toho University Omori Medical Center (A19078).

2.2 Exploratory eye movements

The dominant eye was identified using the Miles test Prior to testing exploratory eye movements (37). The participants were first asked to extend their arms out in front of them. Secondly, they were asked to create a triangle between their thumbs and forefingers by placing their hands together at a 45-degree angle. They were then asked to center this triangle on a wall clock with both eyes open. Finally, they were asked to close either the right or left eye. If the object stays centered, the opened eye is determined to be the dominant eye. If the object is no longer framed by their hands, the closed eye is considered the dominant eye. We acquired four EEM parameters, NEF, TESL, MESL, and RSS, using a digital eye-mark recording system (Nac Image Technology, EMR-NS, Tokyo, Japan). The device includes an eye camera that detects the corneal reflection of infrared light and a 15-inch LCD monitor that displays figures for EEM tasks to identify eye movements (38). A computer automatically recorded and analyzed the eye movements.

First, the original S-shaped figure (Figure 1A) was displayed on the LCD monitor, and the participants were asked to observe it for 15 s. Subsequently, participants were asked to "Please draw the next figure after finishing this test," and once again, the original S-shaped

FIGURE 1
S-shaped figure. **(A)** Original target figure; **(B, C)** two figures are slightly different from the target.

figure was displayed for an additional 15 s. Eye movements were continuously tracked while the participants gazed at the figure, and the fixation point of view was recorded when the eye movements stopped for more than 0.1 s at a specific location. The number of fixations of the participants was recorded as NEF, total eye scanning length as TESL, and mean eye scanning length as MESL.

For the comparison task, the participants were asked to look at a figure featuring a single bump located in a different position (Figure 1B) for 15 s. Following this observation period, participants were asked whether this figure differed from the original one, and if their response was affirmative, they were asked to specify the observed difference. Participants were also prompted to identify any additional discrepancies. Subsequently, the responsive search score (RSS) was automatically calculated based on the number of fixation locations within a 5-s window. The figure was divided into seven segments, and the maximum attainable RSS score for this task was seven. The same procedure was repeated using another figure, which was identical to the original (Figure 1A). Participants were expected to report no differences.

Subsequently, a comparison task was performed using a figure without bumps (Figure 1C). Similar to the initial comparison task, eye movements were automatically recorded after the posing question, and the RSS was calculated. The maximum RSS for the entire test was 14. Finally, the participants were asked to draw a target figure on the paper. Participants with NEF below 11 or whose RSS was 0 were excluded from the analysis, as their responses were considered unreliable for accurate measurements.

As a sample, we show the results of an EEM performed by a control subject (Supplementary Figure 1).

2.3 Acquisition conditions for magnetic resonance imaging

Magnetic Resonance Imaging (MRI) data were obtained using a 1.5-T scanner (Signa HDxt, GE Medical Systems, Waukesha, WI, USA) with a single-shot, spin-echo echo-planar imaging sequence. Diffusion MRI data were acquired with b = 1000 s/mm^2 along 30 noncollinear directions and a single b = 0 s/mm^2 volume. The other scan parameters included TE = 77 ms, TR = 13000 ms, 3 mm^3 isotropic voxel, FOV = 240 × 240 mm, and 60 slices.

2.4 Image processing

Raw images were denoised and corrected for Gibbs ringing. Eddy currents and motion corrections were performed using the eddy tool in the FMRIB Software Library (FSL Version 6.0.4). Finally, the images were minimally smoothed using a Gaussian kernel with sigma = 1 mm to suppress the effects of residual noise and Gibbs artifacts. The DTI FA map was computed using a standard weighted least-squares fit implemented in MRTrix3.

Segmentation of the white matter tracts was performed using TractSeg (32), which allows semi-automatic reconstruction of fiber bundles in the individual's native space. In this study, we focused on the STR (Figure 2).

2.5 Statistical analysis

In the initial step, demographic comparisons were made using a t-test for age and a chi-square test for sex and dominant eye. In the second step, we conducted a comparison between the individuals with APS and healthy controls. We compared the FA values of the left and right STR and EEM parameters (NEF, TESL, MESL, and RSS) using analysis of covariance, adjusting for values that were significantly different between the APS and healthy control groups in the first step.

Finally, the relationships between FA values of bilateral STR and parameters of saccades were evaluated using correlation analysis with Pearson's correlation coefficient in both groups. We ensured the normality of the saccade parameter and FA value distributions by confirming skewness values below 2 and kurtosis

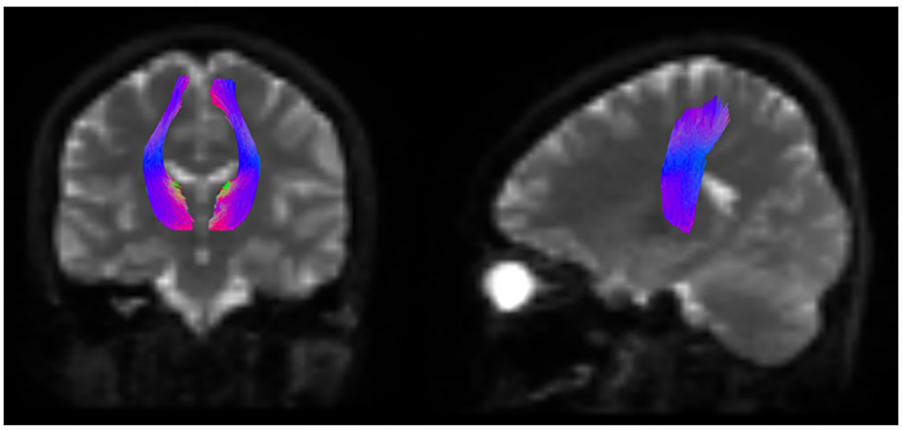

FIGURE 2
Schematic representation of the white matter tract segmentation in the STR. Schema of segmentation of the white matter tracts of STR using TractSeg. STR, superior thalamic radiation.

values below 4 for all items (39). Statistical significance was set at $p < 0.05$. The analysis was performed using SPSS for Windows (version 23.0; IBM Corp., Armonk, NY, USA).

3 Results

In this study, 21 participants were diagnosed with APS. Among them, 5 were males, and 16 were females, with a mean age of 21.4 (SD = 5.8) years. Among the 21 individuals with APS, 12 were receiving antipsychotic treatment, with a mean daily chlorpromazine-equivalent dosage of prescribed antipsychotics of 122.9 (SD = 112.5) mg (40). Additionally, we recruited 30 healthy controls (19 males and 11 females) from independent community sources.

The demographic data and SOPS scores are presented in Table 1. Notably, the t-test for age (t = -2.965, p = 0.004) and the chi-square test for sex ($\chi 2$ = 7.746, p = 0.005) both revealed statistically significant differences.

The chi-square test for the dominant eye ($\chi 2 = 2.375$, p = 0.12) revealed no significant differences between the APS group and the healthy control group. The EEM parameters and FA values in the left and right STR are presented in Table 2. After adjusting for age and sex, the analysis of covariance revealed that the FA value of left STR (F [1, 47] = 5.713, p = 0.021), NEF (F [1, 47] = 4.419, p = 0.041), TESL (F [1, 47] = 4.967, p = 0.031) and MESL (F [1, 47] = 4.378, p = 0.042) were lower in the APS group compared to the healthy control group.

In the APS group, Pearson's correlation analysis revealed significant positive correlations between the FA values of the left STR and the MESL (r = 0.567, p = 0.007). Although the reduction in the FA value of the right STR was not significant in the APS group, significant correlations between the right STR and TESL (r = 0.587, p = 0.005) and MESL (r = 0.756, $p = 0.7\times10^{-4}$) were observed (Table 3). The SOPS items were not significantly correlated with EEM parameters or bilateral STR FA values (for detailed results, refer to Supplementary Table 1).

TABLE 1 The demographic data.

Characteristic	APS (SD)	HC (SD)	$t/\chi 2$	p
Participants (Male/Female)	21(5/16)	30(19/11)	7.746	0.005**
Age (years, mean)	21.4 (5.8)	25.9 (4.9)	-2.965	0.004**
Dominant eye (right/left)	11/10	22/8	2.375	0.12
Mean scores of SOPS items				
positive symptom (mean)	13.6 (2.4)	–		
Negative symptom (mean)	14.9 (6.4)	–		
Disorganized symptom (mean)	5.8 (3.2)	–		
General symptom (mean)	9.2 (3.6)	–		

Age is compared using Student's t-test. Sex and dominant eyes are compared using the chi-square test.
SOPS, Scale of Prodromal Symptoms; SD, standard deviation; HC, healthy control group; APS, attenuated psychosis syndrome.
**p < 0.01.

TABLE 2 Analyses of covariance with EEM parameters and FA value of STR.

	APS (SD)	HC (SD)	F	p
EEM Parameters				
NEF	28.3 (8.6)	32.6 (7.7)	4.419	0.041*
TESL (mm)	1286.0 (670.9)	1646.44 (725.6)	4.967	0.031*
MESL (mm)	43.6 (15.3)	49.7 (14.7)	4.378	0.042*
RSS	6.0 (2.7)	6.7 (2.6)	0.200	0.657
FA value				
STR_left	0.395 (0.021)	0.403 (0.020)	5.713	0.021*
STR_right	0.389 (0.018)	0.394 (0.016)	0.862	0.358

The FA values of the bilateral STR and EEM parameters are compared using an analysis of covariance that is adjusted for age and sex.
EEM, exploratory eye movement; NEF, number of eye fixations; TESL, total eye-scanning length; MESL, mean eye-scanning length; RSS, responsive search score; FA, fractional anisotropy; STR, superior thalamic radiation; SD, standard deviation; HC, healthy controls; APS, attenuated psychosis syndrome.
*p < 0.05.

4 Discussion

4.1 EEM parameters and STR changes in APS

Consistent with previous studies on schizophrenia, our study revealed significant reductions in NEF, TESL, and MESL in the APS group. These results are also consistent with those of Shido et al. (30), who reported a significant reduction in NEF and TESL in the APS group compared with the healthy control group. Notably, our study additionally revealed a significant reduction in MESL in the APS group, a finding that differs from Shido's study (30). This difference may have resulted from using an analysis of covariance to compare the APS and healthy control groups while adjusting for age and sex.

MESL has been associated with attention (41), perceptual reasoning (29), and particularly negative symptoms in schizophrenia (6, 41–44). Negative symptoms, rather than positive symptoms, have been proposed to have a biological basis, including genetic factors (45–47). As MESL is calculated by dividing TESL by NEF, that is, MESL = TESL/NEF (37), a reduction in TESL can consequently lead to a decrease in MESL. A reduction in TESL in patients with schizophrenia (6), which is negatively correlated with the severity of negative symptoms, has also been reported (44). McAvoy et al. (2012) revealed the relationship between fixation and thalamocortical connectivity in humans (21). Zhang et al. (2021) reported lower NEF values in patients with schizophrenia compared to healthy controls, with a further reduction in patients with schizophrenia with pronounced negative symptoms (48).

The FA values of the left STR were significantly lower in the APS group than in healthy controls. The STR is a part of the thalamocortical pathway, which has been repeatedly reported in

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TABLE 3 Correlations between fractional anisotropy value of superior thalamic radiation and EEM parameters.

	Pearson	NEF	TESL	MESL	RSS
APS (n = 21)					
FA value of left STR	*r*	0.052	0.328	0.567	0.186
	p	0.823	0.146	0.007**	0.419
FA value of right STR	*r*	0.286	0.587	0.756	0.277
	p	0.209	0.005**	0.7×10^{-4}**	0.223
HC (n = 30)					
FA value of left STR	*r*	0.301	0.278	0.141	-0.109
	p	0.107	0.137	0.459	0.568
FA value of right STR	*r*	-0.067	0.081	0.122	-0.426
	p	0.724	0.672	0.521	0.019*

EEM, exploratory eye movements; NEF, number of eye fixations; TESL, total eye scanning length; MESL, mean eye scanning length; RSS, responsive search score; FA, fractional anisotropy; STR, superior thalamic radiation; HC, healthy controls; APS, attenuated psychosis syndrome.
*p < 0.05. **p < 0.01.

ARMS and schizophrenia (49). Carletti et al. (2012) reported changes in FA values in the left superior corona radiata in the ARMS (27). These studies corroborate the pathological changes on the left side of the white matter fiber bundles connecting the frontal cortex and thalamus. The decrease in FA values in the STR on the left side in the APS group in this study is consistent with the results of previous studies. In terms of laterality, cross-dominance, which is the crossover among the dominance of the left and right side of the eye, hand, and foot, is associated with treatment resistance in schizophrenia (50). This association indicates that cross-dominance as a biological background relates to differences in schizophrenia, such as prognosis and/or other symptoms. In this study, all participants were right-handed, while left-eye dominance (i.e., cross-dominance) was observed in 47.6% of the APS group and 26.7% of the healthy group. However, no significant differences in cross-dominance were observed between the two groups ($\chi2$ = 2.375, p = 0.12). Unlike the previous study (50), the sample size was small, and the dominant foot was not identified in this study. These factors possibly affected the non-findings of cross-dominance in the APS group. Meanwhile, several recent studies revealed that APS does not necessarily transition to schizophrenia but various psychiatric disorders such as depression, bipolar disorder, and personality disorder (transdiagnostic psychiatry) (51). Thus, it is indicated that the biological backgrounds of APS are more heterogeneous, and it may not necessarily coincide with the biological trait of schizophrenia.

4.2 Relationship between changes of STR and fixations and scan path lengths

The thalamus plays a pivotal role in multiple brain networks responsible for processing sensory input, and it is intricately linked to various higher-order cognitive and emotional functions (52). Dysfunctions in the electrophysiological coordination of cortico-thalamic connections have been associated with cognitive impairments (53, 54). Aberrant neural connections between the thalamus and cortex have been repeatedly reported in schizophrenia (55). However, whether biological changes in corticothalamic disconnection underlie aberrant eye movement and subthreshold psychotic symptoms in APS remains unclear.

In this study, we hypothesized that biological changes in the STR might be associated with aberrant eye movements, including fixation and scan path length abnormalities, among individuals with APS. Our analysis aimed to explore the potential correlation between STR FA values and the NEF, TESL, and MESL values within both the APS and healthy control groups.

In the APS group, a significant reduction in the FA value in the left STR was observed compared with that in the healthy group, and the FA value of the left STR was significantly correlated with the MESL. Although no reduction in the FA value in the right STR was observed compared to that in the healthy group, significant correlations between the FA values of the right STR, TESL, and MESL were observed. Considering that TESL and MESL are parameters of the scanning length, our findings raise the possibility that impairment of the white matter fiber bundles of the STR causes aberrant scanning in APS. This study is the first to report an association between STR, fixation, and scan path length in an APS group.

Qiu et al. (2018) reported that the severity of hallucination was negatively correlated with RSS and grey matter volume of bilateral precentral gyri and left supplementary motor area in schizophrenia (56). This report suggests that biological changes in STR appear in schizophrenia and are involved in auditory hallucinations and abnormalities of exploratory eye movements because the STR originated from the precentral gyri and supplementary motor area.

Transition to schizophrenia is defined by the expression of prominent positive symptoms, and sub-threshold psychotic symptoms gradually develop before the onset of schizophrenia.

Our study shows reduced white matter integrity of STR and abnormalities in EEM in the APS group of those who reveal sub-threshold psychotic symptoms. Therefore, we considered that biological changes in the STR and abnormalities in the EEM precede prominent psychotic symptoms, such as positive and negative symptoms.

4.3 Thalamus-related anomalies as candidate mechanism-based biomarkers for psychosis

Regarding the pathogenesis of schizophrenia, mounting evidence shows that abnormal connections within several brain

circuits, including the thalamus, progress during the prodromal period, resulting in worse functional outcomes and the emergence of psychosis (22).

Yao et al. (2019) reported a relationship between decreased FA values in the thalamus-FEF pathway and the severity of psychotic symptoms in schizophrenia (49). Additionally, abnormal thalamocortical structural connectivity has been reported during the prodromal phase (57). In this study, we unveiled an anomaly in the STR, a component of the thalamocortical pathway, which correlated with shortened scan path lengths, representing a parameter of visual search in APS.

From the viewpoint of whole-brain networks, thalamo-cortical networks are part of the cortico-striatal-thalamic circuits. Abnormalities in the cortico-striatal-thalamic circuit may cause impairments in self-relevance processing and induce aberrant salience, which is proposed to be the biological background of self-disorder, the core symptom of schizophrenia (58). Moreover, abnormal neural connections between the cortex and thalamus lead to a hyperdopaminergic state in the striatum, resulting in psychiatric symptoms (59, 60). This study demonstrates that the scan path length in APS is associated with STR impairment, a component of the cortico-striatal-thalamic circuit, in individuals with APS exhibiting subthreshold psychotic symptoms. Kojima et al. (2019) predicted that EEM is a parameter of a subjective disorder, which is a core symptom of schizophrenia (31).

Finally, our results indicate that the scan path length may be a potential parameter of STR alterations in APS. In other words, there is a possibility that the reduction of scan path lengths could be predictive of STR impairment, which is presumed to be a part of the cortico-thalamic pathway associated with several psychotic symptoms, including self-disorder, in individuals with APS.

4.4 Limitations

This study has some limitations. First, the use of antipsychotic medication by some participants may have influenced both white matter fiber integrity and eye movement test outcomes. A more comprehensive investigation of biological changes would necessitate an analysis involving individuals who are not receiving antipsychotic medication. Second, the use of a 1.5-T scanner in this study could potentially limit the precision of the MRI data. Future analyses utilizing images obtained from 3-T MRI scanners would be preferable to enhance data quality. Third, in this study, the demographic data of the individuals in the APS and healthy control groups were significantly different in age and sex, which may have influenced the comparison of the two groups. Although we adjusted for age and sex to minimize this effect, in the follow-up study, it would be desirable to compare groups that are matched in age and sex. Fourth, this was a cross-sectional study. In a follow-up study, it would be necessary to examine the differences in longitudinal changes in STR and/or eye movement between individuals who developed psychosis and those who did not in the APS group to elucidate whether and how these biological changes are related to the emergence of psychotic symptoms.

5 Conclusion

Abnormalities in fixation and scan-path lengths have been observed as specific features associated with schizophrenia. Investigating the underlying biological basis of visual search in schizophrenia can clarify the etiology of aberrant neural networks in the brain, which are implicated in the development of schizophrenia. However, whether the abnormality of fixations and scan path lengths emerge before the onset of schizophrenia and what contributes to the abnormality of visual search remain unclear. In this study, we identified significant correlations between biological changes in the STR, including neural connections between the thalamus and the FEF, and anomalies in fixation and scanning in the APS group. The STR is a crucial component of the frontal–striatal–thalamic circuit and is responsible for broad mental activity in humans. An impairment of this circuit is supposed to cause psychotic symptoms partly. Possibly, impairment of the STR is related to the biological background of subthreshold psychotic symptoms as well as oculomotor disturbances. Furthermore, our findings, which demonstrated that biological changes in the STR correlated negatively with MESL, reveal that MESL can serve as an indicator of STR alterations in individuals with APS.

Data availability statement

The datasets presented in this article are not readily available because the Ethics Committee of Toho University Omori Medical Center has not authorized to provide any data. Requests to access the datasets should be directed to ktgrnoyk@med.toho-u.ac.jp.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Toho University Omori Medical Center (A19078). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

YA: Writing – original draft, Methodology, Funding acquisition, Formal Analysis, Data curation, Conceptualization. NK: Writing – review & editing, Writing – original draft, Supervision, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. HT: Writing – review & editing, Methodology, Data curation. TU: Writing – review & editing, Methodology, Data curation. JS: Writing – review & editing, Methodology, Data curation. YS: Writing – review & editing, Methodology, Data curation. KK: Writing – review & editing, Software, Methodology. MH: Writing – review & editing, Supervision,

Software, Methodology. MM: Writing – review & editing, Supervision, Conceptualization. TN: Writing – review & editing, Supervision, Conceptualization.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2024.1323786/full#supplementary-material

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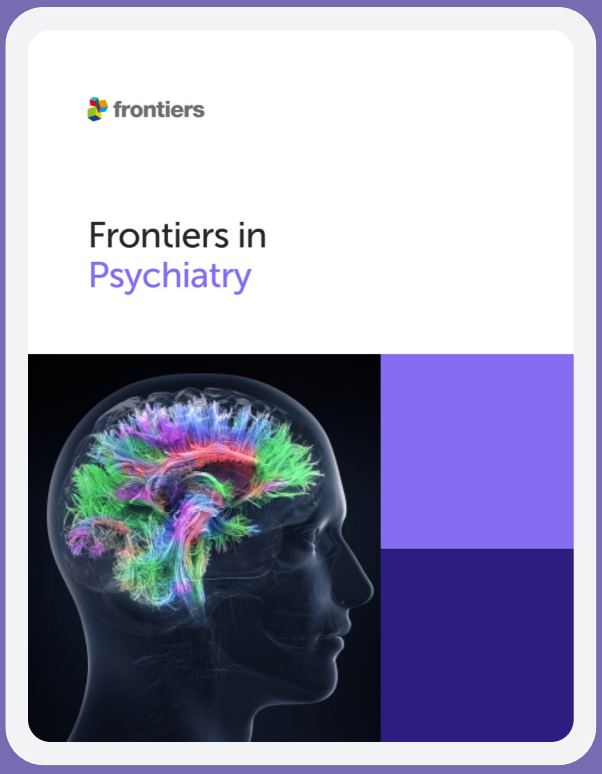

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