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Automatic auditory processing features in distinct subtypes of patients at clinical high risk for psychosis: Forecasting remission with mismatch negativity

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Abstract

Individuals at clinical high risk (CHR) for psychosis exhibit a compromised mismatch negativity (MMN) response, which indicates dysfunction of pre-attentive deviance processing. Event-related potential and time-frequency (TF) information, in combination with clinical and cognitive profiles, may provide insight into the pathophysiology and psychopathology of the CHR stage and predict the prognosis of CHR individuals. A total of 92 individuals with CHR were recruited and followed up regularly for up to 3 years. Individuals with CHR were classified into three clinical subtypes demonstrated previously, specifically 28 from Cluster 1 (characterized by extensive negative symptoms and cognitive deficits), 31 from Cluster 2 (characterized by thought and behavioral disorganization, with moderate cognitive impairment), and 33 from Cluster 3 (characterized by the mildest symptoms and cognitive deficits). Auditory MMN to frequency and duration deviants was assessed. The event-related spectral perturbation (ERSP) and inter-trial coherence (ITC) were acquired using TF analysis. Predictive indices for remission were identified using logistic regression analyses. As expected, reduced frequency MMN (fMMN) and duration MMN (dMMN) responses were noted in Cluster 1 relative to the other two clusters. In the TF analysis, Cluster 1 showed decreased theta and alpha ITC in response to deviant stimuli. The regression analyses revealed that dMMN latency and alpha ERSP to duration deviants, theta ITC to frequency deviants and alpha ERSP to frequency deviants, and fMMN latency were significant MMN predictors of remission for the three clusters. MMN variables outperformed behavioral variables in predicting remission of Clusters 1 and 2. Our findings indicate relatively disrupted automatic auditory processing in a certain CHR subtype and a close affinity between these electrophysiological indexes and clinical profiles within different clusters. Furthermore, MMN indexes may serve as predictors of subsequent remission from the CHR state. These findings suggest that

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the auditory MMN response is a potential neurophysiological marker for distinct clinical subtypes of CHR.

KEYWORDS
event-related spectral perturbation, inter-trial coherence, mismatch negativity, remission, subtypes, ultra-high risk

1 | INTRODUCTION

Over the past two decades, great efforts have been exerted on understanding the symptoms and prognosis of individuals at clinical high risk (CHR) for psychosis. Those at CHR state typically manifest attenuated psychotic symptoms, functional deficits, and neurocognitive impairments (Salazar de Pablo et al., 2020). Moreover, CHR patients are at an increased risk of developing a psychotic disorder; 22% overall within 3 years (Fusar-Poli et al., 2020). However, psychotic experiences combined with depression and anxiety can be heterogenous, and the CHR concept has been criticized for observing multidimensional psychopathology in the youth (van Os & Guloksuz, 2017). To tackle this issue, our previous work has combined clinical symptom ratings with cognitive features to derive three CHR subtypes by applying canonical correlation analysis and cluster analysis (Zhang et al., 2020). The resulting subtypes showed promise for distinguishing clinical outcomes and might provide insights into the psychopathology of the CHR state. The three clusters generated are the following: Cluster 1, characterized by extensive negative symptoms and cognitive deficits, potentially has the highest risk for conversion to psychosis; Cluster 2, characterized by thought and behavioral disorganization, with moderate cognitive impairment; and Cluster 3, characterized by the mildest symptoms and cognitive deficits.

Elicited by infrequent deviant sounds within a sequence of repeated standard stimuli, auditory mismatch negativity (MMN) is an event-related potential (ERP) that occurs in the auditory cortex and frontal region. The MMN is thought to reflect pre-attentive detection of sound changes and the process of automatic attention shifts towards auditory deviance (Näätänen & Kähkönen, 2009). It has been consistently observed that compared with healthy controls, CHR individuals exhibit amplitude reductions in response to both frequency and duration deviants (Atkinson et al., 2012; Perez et al., 2014), which are associated with worse symptoms, impaired general and cognitive function, increased risk for conversion to psychosis, and decreased rate of remission from the CHR state (Bodatsch et al., 2011; Higuchi et al., 2013; Kim et al., 2018; Koshiyama et al., 2018; Shin et al., 2012). All these findings suggest that MMN is a core indicator of the pathophysiology of the CHR state.

While capturing stimulus-locked changes in the electroencephalogram (EEG) activities, analysis of MMN in the temporal domain tends to ignore the individual response and variability of activities across trials (Roach & Mathalon, 2008). In the meantime, with time-frequency (TF) decomposition, additional information including the magnitude of the EEG response (event-related spectral perturbation, ERSP) and phase-resetting of the activities (inter-trial coherence, ITC) can be obtained, which extends findings from the physiological aspect to the neural circuit level (Kantrowitz et al., 2016). The MMN response has been closely related to neural oscillations in theta and alpha bands, which may reflect local-circuit interactions involving somatostatin-type interneurons (Womelsdorf et al., 2014). A recent study has demonstrated an increased variability in response to deviant and standard stimuli in CHR individuals (Shin et al., 2015). Furthermore, a decrement in the theta and alpha ITC in deviant condition and a decreased theta ITC in response to the standard stimuli have also been noted in the CHR population (Sehatpour et al., 2020; Shin et al., 2015). Generally, previous studies have reported deficits in neural activities in the low frequency range, which may suggest impaired early stage information processing and local plasticity in response to auditory stimuli (Kantrowitz et al., 2016).

Since the validity of the CHR criteria, much attention has been paid to the prediction of the transition rate, which descended substantially from the initially reported 54% at 1 year (Miller et al., 2002) to 22% in 3 years (Fusar-Poli et al., 2020). Given the fact that a large proportion of CHR individuals do not convert to psychosis, and the nonconverters sustain long-term poor function despite the mitigation of attenuated symptoms (Addington et al., 2011), more recent studies have focused on predicting remission from the CHR status. Although the predictors of remission have not been adequately studied, research using neurocognitive profiles (Lee et al., 2014), neuroimaging data (Egerton et al., 2014; de Wit et al., 2017), or EEG measures (Fujioka et al., 2020; Hamilton et al., 2019) has shown potential and promise in predicting remission. Previous research has linked MMN with positive symptom scores

(Shin et al., 2009) and functional status (Revheim et al., 2014) and showed its capacity to predict remission from the CHR state (Fujioka et al., 2020). Taken together, MMN could be a reliable tool among the candidate biomarkers for predicting remission. By studying specific predictive indices of remission from the CHR state, it is possible to distinguish remitters who show resilience in the course of developing psychosis and hence provide insights into the mechanisms underlying the disease (Ferrarelli & Mathalon, 2020). In addition, the identification of nonremitters will facilitate the development of more active interventions and optimization for better individualized care.

To date, most studies have examined MMN activity in individuals with CHR only in the temporal domain. Furthermore, previous research has not examined the contribution of neuro-oscillatory responses in MMN to remission from the CHR state. ERP and TF information, in combination with clinical and cognitive features, will probably shed light on the neurophysiological deficits and psychopathological alterations of the CHR state.

In the current study, we proposed to investigate MMN activity in both temporal and TF domains and explore the predictors of remission among our three clinical subtypes (Zhang et al., 2020). Just like the conventional ERP analysis, we obtained the MMN amplitude and latency. In TF decomposition, the ERSP and ITC in the theta and alpha frequency bands were acquired. Moreover, a correlation analysis was performed between the clinical profiles and EEG features, where significant group differences were observed. Lastly, we aimed to determine whether baseline characteristics and MMN features would predict remission from the CHR state. We predicted diminished MMN amplitude, theta, and alpha ERSP and ITC in Cluster 1 relative to the other two clusters. We also hypothesized that MMN features, where group differences existed, would predict later remission.

2 | METHODS

2.1 | Participants

Ninety-two CHR individuals aged 13–35 years and 41 demographically similar healthy control participants (HC) were recruited from the Shang-Hai At Risk for Psychosis extended program. All the CHR participants were drug-naïve before enrollment and met the criteria of prodromal states based on the Structured Interview for Prodromal Symptoms/Scale of Prodromal Symptoms (SIPS/SOPS) (Miller et al., 2002; Zheng et al., 2012). They fulfilled at least one of the following three syndromes: (1) attenuated positive symptom syndrome, (2) brief limited intermittent psychotic syndrome, or (3) genetic risk and deterioration syndrome. The overall level of functioning was evaluated using the Global Assessment of Functioning (GAF) (Jones et al., 1995). The drop GAF was measured as the baseline GAF score from the highest in the past year. The exclusion criteria included the diagnosis of psychotic disorders based on the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV), neurological disorders (such as delirium, dementia, stroke, and epilepsy), serious head injury, substance dependence or abuse, and severe somatic diseases (such as myocardial infarction and renal failure). The HC having a past or current DSM-IV Axis I disorder or a first-degree relative with a psychotic disorder were excluded. Further details of the recruitment procedure have been provided in previous publications (Wu et al., 2019; Zhang et al., 2014). This study was approved by the institutional review board of the Shanghai Mental Health Center (SMHC). The individuals signed the written informed consent prior to enrollment; individuals younger than 18 years of age provided informed consent signed by themselves and their legal guardians.

In the previous study, canonical variates were derived from a canonical correlation analysis of clinical symptoms and cognitive dysfunctions, and used for hierarchical clustering to produce CHR subtypes (Zhang et al., 2020). Three subtypes emerged. The 92 CHR samples in this study included 28 individuals from Cluster 1, 31 from Cluster 2, and 33 from Cluster 3. All participants were instructed to avoid strenuous exercises, cigarettes, alcohol, coffee, or others stimulants 4 h prior to the EEG recording.

After baseline assessment and EEG recording, the CHR participants were followed up routinely, wherein the research team did not interfere with the routine clinical treatment procedures at SMHC. They were reassessed by follow-up telephone calls semiannually and face-to-face interviews annually with SIPS. All participants received follow-up for at least 2 years, except for 1 participant from Cluster 1 who lost contact, 8 from Cluster 1, 2 from Cluster 2, and 2 from Cluster 3 who chose to discontinue contact within 1 year (of the 92 CHR individuals, 70 had a follow-up period of 2 years). Of these participants, 37 also repeated neurophysiological assessment (Supplementary Methods). Remission from the CHR state was defined as having a score of less than three on the SOPS-positive subscale and 60 or more on the GAF at the last follow-up. The clinical outcome was mainly determined by face-to-face interviews, partly by telephone interviews, and information from the clinician's reports. Among those from Cluster 1, 11 remitted from the CHR state, 21 from Cluster 2, and 22 from Cluster 3.

2.2 | Stimuli and procedure

The MMN paradigm consisted of 675 standard tones (1000 Hz, 50 ms), 75 frequency deviant tones (1500 Hz, 50 ms), and 75 duration deviant tones (1000 Hz, 100 ms). The auditory stimuli (75 dB sound pressure level) were presented randomly through headphones with a 500 ms stimulus onset asynchrony. Participants were instructed to ignore auditory stimuli while watching a silent cartoon.

The participants were seated in an acoustically attenuated and dimly lit chamber with electric shielding. EEG signals were recorded from an elastic cap containing 64 scalp electrodes, digitized at 1000 Hz, referenced to the tip of the nose, and filtered between 0.016 and 200 Hz (Brain Products Inc., Bavaria, Germany). The impedance of the electrodes was maintained below 5 kΩ.

2.3 | Preprocessing and ERP analysis

Data were preprocessed and analyzed offline using EEGLAB (Delorme & Makeig, 2004), ERPLAB (Lopez-Calderon & Luck, 2014), and customized MATLAB scripts (MathWorks, Inc., Natick, MA, USA).

EEG data were band-pass filtered between 0.1 and 30 Hz with a zero-phase-shift IIR Butterworth filter (24 dB/Oct) and re-referenced to averaged mastoid electrodes (TP9 and TP10). Ocular blink artifacts were also removed from the data using an independent component analysis.

Continuous data were segmented into epochs of −100 to 400 ms time locked to stimulus onsets and baseline corrected using the 100-ms pre-stimulus period. Epochs with voltages exceeding ±75 μV were rejected. The means and standard deviations of the numbers of remaining epochs for standard, frequency, and duration stimuli were as follows: Cluster 1 (582 ± 39.5, 65.1 ± 4.7, 65.1 ± 5.5), Cluster 2 (595 ± 33.1, 65.6 ± 5.0, 65.8 ± 5.0), and Cluster 3 (593 ± 23.2, 66.0 ± 3.5, 66.2 ± 3.5). There were no group differences in the number of epochs for three types of stimuli (all $p > .26$ for F). For each participant, separate averages were calculated for each stimulus type. MMN was obtained by subtracting ERP waves elicited by standard stimuli from the waves in response to the frequency stimuli (fMMN) or duration stimuli (dMMN), and its peak was identified as the most negative wave trough at Fz observed in the grand average. Based on grand average difference waves, individual MMN peak amplitude and latency were measured in the time window of 100–280 ms.

2.4 | TF decomposition

For TF analysis, EEG data were divided into epochs of 1.5 s (0.5 s pre-stimulus to 1 s post-stimulus) and baseline corrected using 0.1 s pre-stimulus. Segments with amplitudes exceeding ±75 μV were rejected. A Morlet wavelet-based technique was used to decompose the data to extract the ERSP and ITC. The number of wavelet cycles varied from 3 at 4 Hz to 15 at 40 Hz. One hundred log-spaced frequencies and 200 timepoints were generated, and the window size used was 417 samples wide. ERSP and ITC were computed for frequency band activities including theta (4–7 Hz) and alpha (8–12 Hz) in Fz, as they were demonstrated to play a major role in MMN dysfunction (Lee et al., 2017). The data were averaged separately over the two distinct frequency bands in a 100 ms time interval centered around 200 ms (standard tones), 100 ms (frequency deviants), and 180 ms (duration deviants), thus yielding a mean value for each participant per band.

2.5 | Neurocognitive assessment

All participants completed the neurocognitive assessments at baseline using the Chinese version of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) (Shi et al., 2013). The validated Chinese version of the MCCB (Shi et al., 2015) performed in the current study covered six cognitive domains: speed of processing, attention/vigilance, working memory, verbal learning, visual learning, and reasoning and problem solving. Since most of the participants were less than 18 years old, the social cognition domain was excluded from the analysis.

2.6 | Statistical analysis

All statistical analyses were conducted using SPSS version 25 (SPSS Inc., Chicago, IL, USA). Group differences in the MMN amplitude and latency were examined via a two-way repeated measures analysis of variance (ANOVA), with group (Cluster 1, Cluster 2, and Cluster 3) as the between-participants factor and deviant type (frequency and duration) as the within-participants factor. Repeated measures ANOVA was also performed to assess group effects in ERSP and ITC in the theta and alpha frequencies. Statistical tests were 2-tailed, with an alpha level of $p = 0.05$. Partial eta squared (η_p^2) was reported for the group effect sizes. Bonferroni adjustment was used for multiple comparisons in the post hoc analysis. Moreover, EEG variables with group differences were associated with clinical symptoms and functional levels using Pearson's correlations. Since the correlation analysis aimed to provide broader information about the relationships between research variables within distinct clinical subtypes, we reported the traditional Pearson's r and p values without multiple comparison adjustment. Bonferroni-corrected p values ($p_{adjusted}$) were provided as well. To further identify the predictive value of MMN in CHR remission, baseline MMN variables were entered into binary logistic regression models with the forward selection method. For comparison, we also performed logistic regressions with baseline behavioral variables, including clinical and neurocognitive characteristics. The analysis of MMN variables at follow-up is described in the Supplementary Methods.

3 | RESULTS

3.1 | Participant characteristics

The characteristics of the 92 individuals with CHR are shown in Table 1. Sex, age, and years of education matched well between the groups. At baseline, GAF differed significantly, with Cluster 1 being worse than Cluster 2 and Cluster 3. For symptom ratings, Cluster 1 had more serious negative symptoms than the other two clusters and experienced greater disorganization symptom severity than Cluster 3. For neurocognitive assessment, Cluster 1 performed significantly worse than Cluster 2 and Cluster 3 in all six MCCB domains. Regarding the follow-up characteristics, the three clusters did not differ in terms of the medications prescribed or the olanzapine equivalent dosages. However, Cluster 1 had a significantly shorter follow-up duration than Cluster 2 and Cluster 3. Moreover, Cluster 1 had more severe positive symptoms and functional impairment than the other two clusters at the 1-year and 2-year timepoints. CHR-R did not differ from CHR-NR in terms of demographic, clinical, and neurocognitive measures within each subtype at baseline, nor did they differ in the medication use during the follow-up period (see Table S1, all $p > .05$ for χ^2 or t). Comparison of HC and three clusters are shown in Table S2 and Supplementary Results.

TABLE 1 Baseline demographic, clinical, neurocognitive, and follow-up characteristics of three clinical subtypes

	Cluster 1(A) ($n = 28$)	Cluster 2(B) ($n = 31$)	Cluster 3(C) ($n = 33$)	χ^2/F[d]	p value	Post hoc contrast[e]
Baseline characteristics						
Sex, male [n (%)]	12 (42.9)	12 (38.7)	15 (45.5)	0.301	.860	
Age, years [mean (SD)]	18.8 (5.3)	18.1 (5.0)	19.5 (5.3)	0.615	.543	
Education, years, [mean (SD)]	9.5 (2.4)	9.7 (2.5)	10.9 (2.8)	2.736	.070	
Family history[a] [n (%)]	2 (7.1)	3 (9.7)	3 (9.1)	0.129	1.000	
Structured interview of prodromal syndromes (SIPS/SOPS) [mean (SD)]						
Highest GAF in past year	77.1 (2.6)	78.9 (3.1)	78.8 (6.0)	1.517	.225	
Baseline GAF	49.9 (7.5)	54.4 (7.8)	56.4 (5.4)	6.914	.002*	B*, C* > A
Drop GAF[b]	27.3 (6.6)	24.5 (6.4)	22.4 (5.8)	4.648	.012*	A > C*
Positive symptoms total	10.1 (3.9)	9.3 (3.3)	9.3 (3.0)	0.650	.524	
Negative symptoms total	16.2 (6.0)	11.6 (5.6)	11.3 (5.1)	7.267	.001*	A > B*, C*
Disorganization symptoms total	8.0 (3.2)	6.7 (3.4)	5.1 (2.7)	6.521	.002*	A > C*
General symptoms total	8.6 (3.2)	10.2 (2.5)	9.4 (2.8)	2.284	.108	
SIPS/SOPS total	42.9 (11.5)	37.7 (10.2)	35.1 (8.8)	4.641	.012*	A > C*
MATRICS consensus cognitive battery (MCCB) domains[c] [mean (SD)]						
Speed of processing	41.0 (6.5)	54.0 (5.9)	56.5 (6.8)	49.424	<.001**	B**, C** > A
Attention/vigilance	37.2 (7.0)	48.7 (7.2)	57.2 (7.0)	56.822	<.001**	B**, C** > A; C > B**
Working memory	38.6 (10.5)	45.0 (8.6)	52.6 (6.5)	20.261	<.001**	B*, C** > A; C > B*
Verbal learning	39.0 (8.7)	48.5 (9.4)	49.6 (9.0)	12.250	<.001**	B**, C** > A
Visual learning	45.6 (7.0)	60.5 (5.3)	56.5 (6.8)	42.269	<.001**	B**, C** > A; B > C*
Reasoning and problem solving	45.2 (9.5)	53.4 (9.4)	58.0 (10.7)	12.811	<.001**	B*, C** > A
Follow-up characteristics						
Months follow-up [mean (SD)]	18.3 (8.6)	23.2 (7.3)	22.9 (4.3)	4.729	.011*	B*, C* > A
Conversion [n (%)]	12 (44.4)	7 (22.6)	4 (12.1)	9.516	.045*	
Remission [n (%)]	11 (40.7)	21 (67.7)	22 (66.7)			
Medication use						
Antipsychotics [n (%)]	25 (92.6)	26 (83.9)	29 (87.9)	1.022	.610	
Antidepressants [n (%)]	3 (11.1)	8 (25.8)	9 (27.3)	2.664	.264	
Olanzapine equivalents [mean (SD)]	5.4 (3.4)	4.3 (5.7)	3.9 (3.0)	1.085	.342	
Positive symptoms total [mean (SD)]						
One-year	7.4 (4.9)	3.7 (3.1)	3.8 (3.6)	8.747	<.001**	A > B**, C**
Two-year	6.3 (3.8)	3.7 (3.0)	2.2 (1.7)	15.430	<.001**	A > B*, C**
GAF [mean (SD)]						
One-year	60.3 (10.6)	68.6 (10.8)	70.7 (9.4)	8.468	<.001**	B*, C** > A
Two-year	60.9 (7.0)	69.4 (8.7)	75.6 (4.8)	33.922	<.001**	B**, C** > A; C > B*

[a]Family history: having at least one first-degree relative with psychosis.
[b]Drop GAF: GAF (Global Assessment of Functioning) score baseline from highest in the past year.
[c]MCCB Domains: T scores.
[d]χ^2/F: Analyzed with Pearson χ^2 tests, one-way analysis of variance.
[e]Adjustment for multiple comparisons: Bonferroni.
*$p < .05$; **$p < .001$.

3.2 | Response to deviants

3.2.1 | ERP analysis

Grand average topographic maps, waveforms, and mean amplitude values for fMMN and dMMN for the three clusters are shown in Figure 1. Repeated measures ANOVA of MMN amplitude revealed a significant group effect ($F_{2,89} = 35.982$, $p < .001$, $\eta_p^2 = 0.447$) that was qualified by a significant group × deviant type interaction ($F_{2,89} = 4.330$, $p = .016$, $\eta_p^2 = 0.089$). Significant differences among the three clusters were found in the frequency deviant ($F_{2,89} = 14.404$, $p < .001$, $\eta_p^2 = 0.245$), with Cluster 1 showing

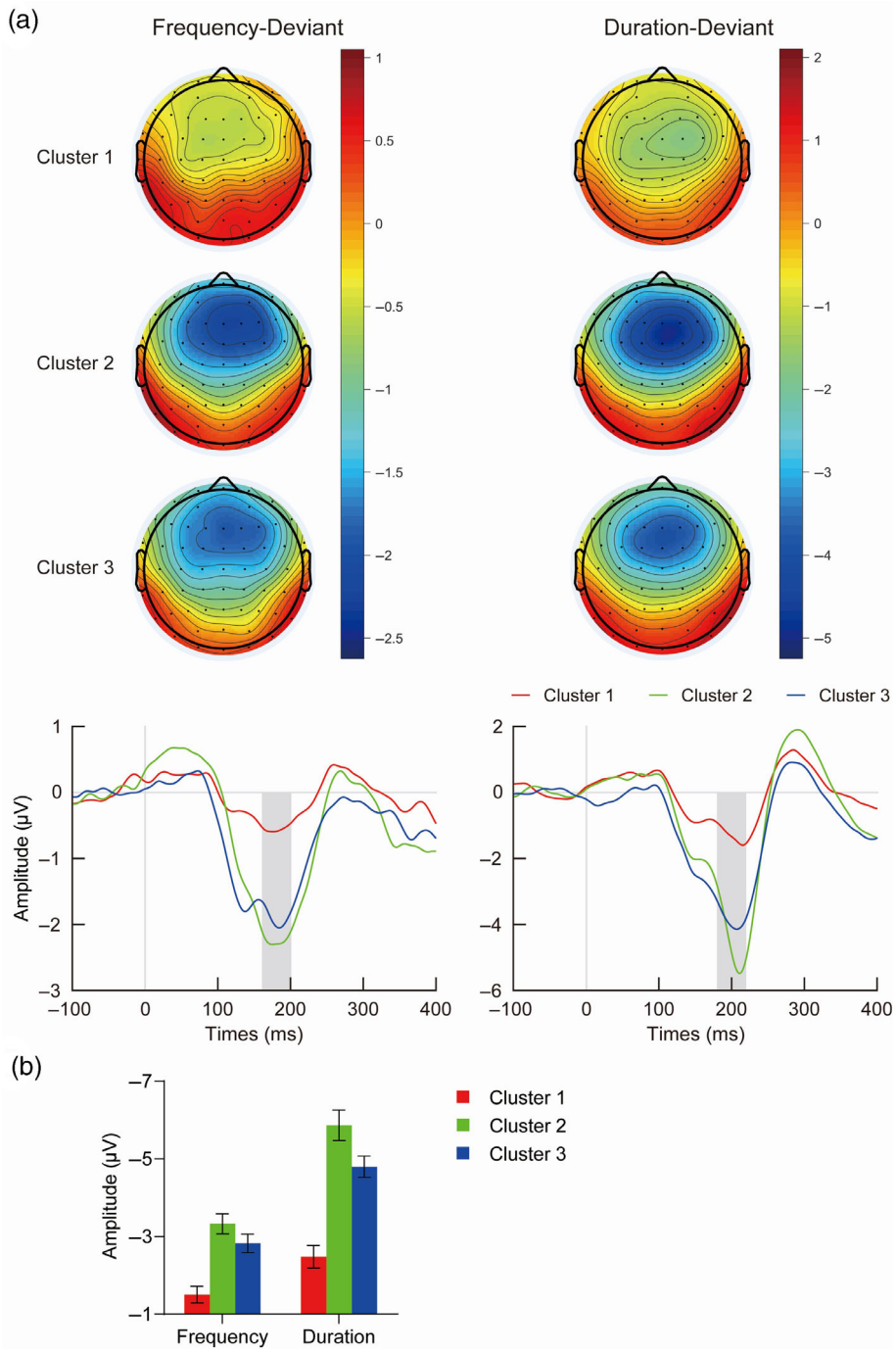

FIGURE 1 (a) Scalp topography demonstrating mean mismatch negativity (MMN) voltage around the peak latency ±20 ms (indicated by the shaded regions in the waveform plots) for three clusters. MMN difference waveforms at Fz for each deviant type. (b) Means and standard errors for MMN amplitudes at Fz

reduced amplitude relative to Cluster 2 ($p < .001$) and Cluster 3 ($p = .001$). In addition, there was a significant group effect in the duration deviant ($F_{2,89} = 27.262$, $p < .001$, $\eta_p^2 = 0.380$), and the amplitude of Cluster 1 was smaller than that of Cluster 2 ($p < .001$) and Cluster 3 ($p < .001$). Regarding the MMN latency, the repeated measures ANOVA demonstrated a significant group effect ($F_{2,89} = 3.288$, $p = .042$, $\eta_p^2 = 0.069$) with no group × deviant type interaction ($F_{2,89} = 2.468$, $p = .091$, $\eta_p^2 = 0.053$). The MMN latency was shorter for Cluster 1 than for Cluster 2 ($p = .013$). The MMN measures are presented in Table 2.

3.2.2 | TF decomposition

Grand average plots and mean theta and alpha values of ITC and ERSP are presented in Figures 2, S1, and S2. Concurrent with the conventional decomposition results, auditory stimulus-related activity was most prominent within the theta (4–7 Hz) and alpha (8–12 Hz) frequency bands. In theta ITC analysis, a significant group effect was found ($F_{2,89} = 8.454$, $p < .001$, $\eta_p^2 = 0.160$) with no group × deviant type interaction ($F_{2,89} = 1.473$, $p = .235$, $\eta_p^2 = 0.032$), and Cluster 1 showed a lower ITC than Cluster 2 ($p < .001$) and Cluster

3 ($p = .026$). Similarly, there was a significant group effect for alpha ITC ($F_{2,89} = 3.889$, $p = .024$, $\eta_p^2 = 0.080$) with no group × deviant type interaction ($F_{2,89} = 1.889$, $p = .157$, $\eta_p^2 = 0.041$), and Cluster 1 had decreased ITC compared to Cluster 2 ($p = .025$). In the ERSP analysis, there was a group difference ($F_{2,89} = 3.167$, $p = .047$, $\eta_p^2 = 0.066$) with no group × deviant type interaction ($F_{2,89} = 1.143$, $p = .324$, $\eta_p^2 = 0.025$) in the theta band, and the theta ERSP in Cluster 1 was trend-level lower than in Cluster 2 ($p = .075$). No significant group effect was found in alpha ERSP ($F_{2,89} = 2.390$, $p = .098$, $\eta_p^2 = 0.051$). The TF values are summarized in Table 2.

3.3 | Response to standards

3.3.1 | ERP analysis

In accordance with prior research, there was a P1 response (Sehatpour et al., 2020) that did not reach significance among groups ($F_{2,89} = 0.381$, $p = .684$) in response to standard tones in the time domain.

3.3.2 | TF decomposition

No significant between-group difference was found regarding standard ITC in the theta band ($F_{2,89} = 0.677$, $p = .511$) or alpha band ($F_{2,89} = 0.663$, $p = .518$). There were no significant group differences in the standard ERSP in the theta band ($F_{2,89} = 0.005$, $p = .995$) or alpha band ($F_{2,89} = 0.008$, $p = .992$). When responses to standards were added to the stimulus types with deviants, neither standard ERSP nor ITC in two bands contributed to difference among three subtypes.

Grand average topographic maps, waveforms, and plots of ERSP and ITC for HC at baseline, and three clusters at follow-up are depicted in Figures S3–S5. Analysis of MMN at follow-up in three clusters is presented in Tables S3 and S4, and Supplementary Results.

3.3.3 | Correlation and regression

In Cluster 1, fMMN amplitude was trend-level associated with GAF at baseline ($r = -0.365$, $p = .056$) ($p_{adjusted} = 1$) and drop GAF ($r = 0.364$, $p = .057$) ($p_{adjusted} = 1$). Moreover, fMMN amplitude was

TABLE 2 Baseline descriptive statistics for MMN and time-frequency values in three clinical subtypes

Mean (SD)	Cluster 1	Cluster 2	Cluster 3
Amplitude (μv)			
Standard	1.16 (1.07)	1.38 (1.03)	1.32 (1.01)
fMMN	−1.50 (1.14)	−3.33 (1.45)	−2.82 (1.39)
dMMN	−2.48 (1.54)	−5.86 (2.18)	−4.80 (1.57)
Latency (ms)			
fMMN	178.71 (42.87)	185.23 (32.07)	176.42 (36.79)
dMMN	187.43 (34.09)	213.55 (10.12)	203.70 (20.32)
Event-related spectral perturbation (dB)			
Theta			
Standard	0.35 (0.60)	0.36 (0.62)	0.37 (0.53)
Frequency	0.35 (1.23)	0.39 (0.75)	0.58 (0.79)
Duration	0.31 (0.95)	0.98 (1.24)	0.73 (1.07)
Alpha			
Standard	0.20 (0.56)	0.18 (0.64)	0.22 (0.37)
Frequency	0.04 (0.93)	0.30 (0.82)	0.44 (0.89)
Duration	0.64 (0.68)	1.00 (1.34)	0.32 (0.92)
Inter-trial coherence			
Theta			
Standard	0.18 (0.11)	0.20 (0.08)	0.21 (0.07)
Frequency	0.21 (0.11)	0.26 (0.10)	0.24 (0.09)
Duration	0.25 (0.10)	0.36 (0.10)	0.32 (0.12)
Alpha			
Standard	0.14 (0.07)	0.15 (0.09)	0.16 (0.08)
Frequency	0.19 (0.10)	0.23 (0.09)	0.25 (0.10)
Duration	0.25 (0.10)	0.33 (0.14)	0.28 (0.11)

Abbreviations: dMMN, duration mismatch negativity; fMMN, frequency mismatch negativity.

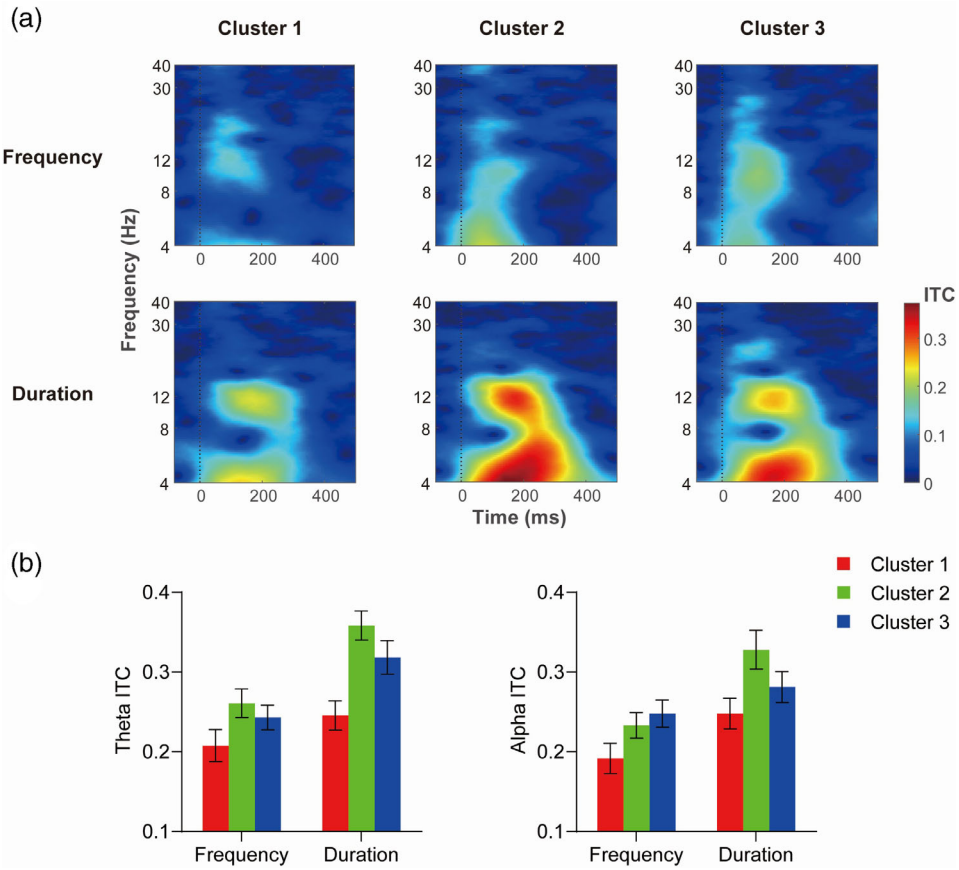

FIGURE 2 (a) Grand-averaged plots of inter-trial coherence (ITC) in response to frequency and duration deviant stimuli at Fz. (b) Means and standard errors for theta and alpha ITC at Fz

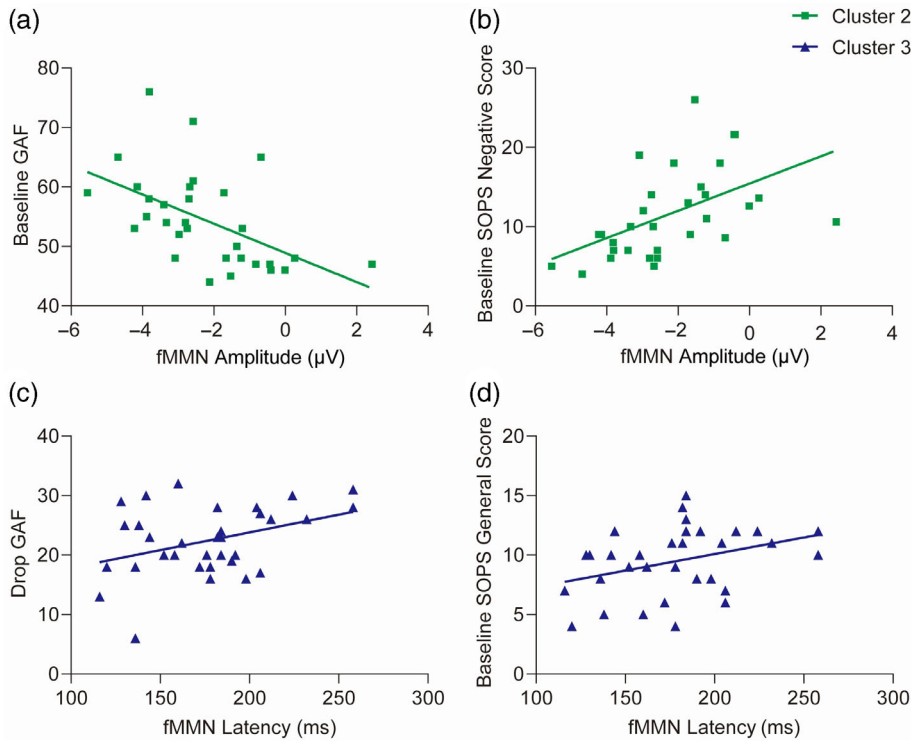

FIGURE 3 (a) Correlation between frequency MMN (fMMN) amplitude and baseline Global Assessment of Functioning (GAF). (b) Correlation between fMMN amplitude and baseline scale of prodromal symptoms (SOPS) negative score. (c) Correlation between fMMN latency and drop GAF. (d) Correlation between fMMN latency and baseline SOPS general score

significantly correlated with baseline GAF ($r = -0.601$, $p < .001$) ($p_{adjusted} = .022$) (Figure 3a), drop GAF ($r = 0.598$, $p < .001$) ($p_{adjusted} = .025$), baseline negative symptoms ($r = 0.542$, $p = .002$) ($p_{adjusted} = .056$) (Figure 3b), and baseline SOPS total scores ($r = 0.461$, $p = .009$) ($p_{adjusted} = 0.252$) in Cluster 2. In addition, dMMN amplitude in Cluster 2 was correlated with GAF at baseline

TABLE 3 Significant predictors of remission in three clinical subtypes

Remission	Significant predictors	R^2	Wald (1)	Exp (*B*)	p	95% CI	
						Lower	Upper
Part 1: MMN variables							
Cluster 1	dMMN latency	0.578	6.267	1.070	.012	1.015	1.128
	Alpha ERSP to duration deviants		4.127	0.127	.042	0.017	0.930
Cluster 2	Theta ITC to frequency deviants	0.625	6.913	1.9e−9	.009	6.3e−16	0.006
	Alpha ERSP to frequency deviants		5.016	6.729	.025	1.269	35.692
Cluster 3	fMMN latency	0.175	3.729	0.977	.053	0.955	1.000
Part 2: Behavioral variables							
Cluster 1	SOPS disorganization score	0.408	4.587	2.219	.032	1.070	4.601
Cluster 2	SOPS positive score	0.630	4.341	0.558	.037	0.323	0.966
Cluster 3	SOPS positive score	0.240	3.560	0.689	.059	0.468	1.015

Abbreviations: dMMN, duration mismatch negativity; ERSP, event-related spectral perturbation; fMMN, frequency mismatch negativity; ITC, inter-trial coherence; SOPS, scale of prodromal symptoms.

TABLE 4 Performances of logistic regressions using MMN or behavioral variables alone in three clinical subtypes

Subtype	Sensitivity	Specificity	Accuracy
Part 1: MMN variables			
Cluster 1	0.818	0.875	0.852
Cluster 2	0.952	0.800	0.903
Cluster 3	0.909	0.273	0.697
Part 2: Behavioral variables			
Cluster 1	0.636	0.750	0.704
Cluster 2	0.857	0.800	0.839
Cluster 3	0.909	0.455	0.758

Abbreviation: MMN, mismatch negativity.

($r = -0.419$, $p = .019$) ($p_{adjusted} = .532$). In Cluster 3, significant associations were also observed in fMMN latency with drop GAF ($r = 0.379$, $p = .030$) ($p_{adjusted} = .84$) (Figure 3c) and baseline general symptoms ($r = 0.361$, $p = .039$) ($p_{adjusted} = 1$) (Figure 3d).

In the binary logistic regression models, there were distinct predictive variables for the remission of each cluster. The significant predictors are presented in Table 3. In models with MMN variables, dMMN latency (Exp (B) = 1.070, $p = .012$) and alpha ERSP to duration deviants (Exp (B) = 0.127, $p = .042$) produced a prediction effect in the remission of Cluster 1. Theta ITC to frequency deviants (Exp (B) = 1.9e − 9, $p = .009$) and alpha ERSP to frequency deviants (Exp (B) = 6.729, $p = .025$) were predictors for Cluster 2. fMMN latency (Exp (B) = 0.977, $p = .053$) was the only predictor for Cluster 3. Table 4 summarizes the performances of the logistic regressions. In Cluster 1, models with MMN variables outweighed models with behavioral variables regarding sensitivity (0.818), specificity (0.875). MMN variables also outperformed behavioral variables by higher sensitivity (0.952) in predicting remission of Cluster 2. However, prediction using MMN variables had a disadvantage in specificity (0.273) in Cluster 3. The ROC curves for each cluster are plotted in Figure 4.

4 | DISCUSSION

This study investigated automatic auditory processing using temporal and TF analysis, and its contribution to predicting subsequent remission from the CHR state within three CHR clinical subtypes. As expected, in response to frequency and duration deviants, Cluster 1 showed deficits in MMN amplitude, along with a decrease in theta ITC compared with the other two clusters. Moreover, a shorter MMN latency and a smaller alpha ITC were observed in Cluster 1, in contrast to Cluster 2. As for responses to standard stimuli, no significant differences in ERPs or TF domain were found between clusters. We also found certain MMN variables related to GAF scores and clinical symptoms among the three clusters. Furthermore, there were distinct MMN predictors of remission for each cluster, that is, dMMN latency and alpha ERSP to duration deviants for Cluster 1, theta ITC and alpha ERSP to frequency deviants for Cluster 2, and fMMN latency for Cluster 3. MMN variables outperformed behavioral variables in predicting remission of Clusters 1 and 2.

Cluster 1, the group with the highest transition rate, had reduced fMMN and dMMN amplitudes compared to the other two clusters. This is consistent with previous studies in the CHR population, demonstrating the relationship between reduced MMN amplitude and increased likelihood of converting to frank psychosis (Bodatsch et al., 2011; Lavoie et al., 2018). We identified the fMMN amplitude in Cluster 1 trend-level correlated with the GAF score at baseline. The fMMN and dMMN amplitude of Cluster 2 also correlated with the baseline GAF. These findings are in line with previous work suggesting correlations between MMN and global functioning in the CHR population (Friedman et al., 2012; Salisbury et al., 2017). The deficits in the MMN response of Cluster 1 may indicate the impaired process of encoding the NMDAR-mediated "prediction" (Wacongne, 2016), or discriminating frequency and duration deviance from the sensory-memory traces formed by the repeated stimuli (Näätänen et al., 2011). Resting-state functional connectivity studies suggested that fMMN correlates with local circuits within the primary and secondary

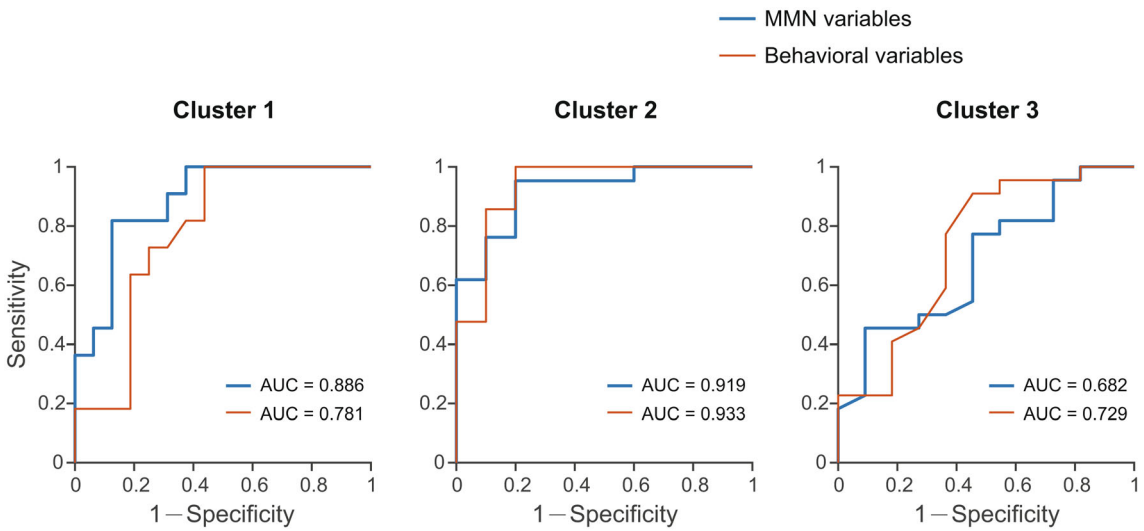

FIGURE 4 ROC curves of logistic regressions using MMN or behavioral variables alone in three clinical subtypes

auditory cortex, while somatomotor networks are involved in processing timing and thus the dMMN activity (Cacciaglia et al., 2015; Kantrowitz et al., 2015). Hence, the dysfunction of the MMN response can hint at the corresponding disrupted functional connectivity between the distinct cortical regions in Cluster 1. Furthermore, the relative reduction of fMMN and dMMN amplitudes may be associated with the loss of gray matter in Heschl's gyrus (Rasser et al., 2011), which has been linked to thalamic glutamate levels (Stone et al., 2009).

For TF measures, Cluster 1 showed a compromised theta and alpha ITC under the deviant condition relative to the other clusters, while no significant group difference was found in ERSP. This suggests that ITC better captured the group effect of the neural response to deviants than the overall activity power, and it has been illustrated before that ITC was sensitive even to small power differences (van Diepen & Mazaheri, 2018). According to previous studies (Jones, 2009; Lakatos et al., 2020), thalamic afferents to the auditory cortex can be divided into the core (lemniscal) and the matrix (nonlemniscal) projections. The core neurons project narrowly to layer 4 and drive inputs to induce activity power and reset phase and may primarily be involved in the fMMN generation. By comparison, the matrix neurons project mainly into the superficial cortical layers and modulate cortical activation to change the ITC and probably play an important role in the generation of dMMN (Viaene et al., 2011). Therefore, the relative decrease in the ITC in Cluster 1 may be associated with disturbances in the core versus matrix inputs from the thalamus to the auditory cortex. In addition, a deficit in theta band activity may preferentially involve cortico-cortical interaction in the MMN response (Recasens et al., 2014), while a deficit in the alpha activity reflects activity in the thalamo-cortical pathway (Potes et al., 2014). The impaired neural activities of Cluster 1 in the two frequencies may thereby signify a dysfunction in both afferent and interactive processes.

In analyzing responses to standard stimuli, we did not observe differences between clusters in ERPs or in the TF decomposition. Response to standards is deemed to play a crucial part in the mnemonic template underlying the early stage of auditory processing (Näätänen et al., 2007). Furthermore, it is deemed to reflect inputs to the auditory cortex (Näätänen & Kähkönen, 2009). In this scheme, the current result may be tentatively interpreted as a similar function level of the three clusters in memory trace creation and initial input processing.

In a previous study, Kim et al. (2018) explored predictors of prognosis in individuals in the CHR state using demographic, clinical, and MMN amplitude data. Logistic regression analysis indicated that MMN amplitude at Fz was a significant predictor of remission among CHR individuals. Given the lack of TF information, our study extended previous reports by performing TF analysis and entering these values into the regression. We found distinct predictors for each cluster, namely dMMN latency and alpha ERSP to duration deviants for Cluster 1, theta ITC to frequency deviants and alpha ERSP to frequency deviants for Cluster 2, and fMMN latency for Cluster 3. Interestingly, the fMMN amplitude, which showed a close affinity with global functioning, failed to act as a significant variable in the predictive models. We tentatively attributed this to the adopted remission criteria incorporating both symptom amelioration and functional improvement in the current study. In predicting remission within clusters, MMN indexes performed better than behavioral variables in Clusters 1 and 2, with satisfactory sensitivity and specificity (all greater than or equal to 0.8). The MMN index also had a high sensitivity in Cluster 3 despite the low specificity. These results indicate that within the framework of clinical subtypes, MMN variables could be powerful objective markers for later remission, which may facilitate optimization of clinical management in the CHR population. However, since there are distinct MMN generators neuro-anatomically (Rissling et al., 2014) and functional connectivity statuses between cortical regions (MacLean & Ward, 2014), which may contribute to heterogeneity across CHR patients, further prediction of remission should also take into account the neural circuits triggering the MMN response.

This study has several strengths and limitations. Strengths include its complete clinical data, psychotropic medication-naïve sample before enrollment, a relatively long time granularity to document clinical outcomes, and novelty in exploring automatic auditory processing in distinct CHR subtypes across temporal and frequency domains. However, this study also has several limitations. First, the relatively small to medium sample size restricted our ability to generalize the findings, including the predictive values. Moreover, the follow-up period varied among CHR individuals, which may be attributed to early withdrawal of the high function individuals; this could cause potential bias in the prediction, and thus, the results should be interpreted with caution. In addition, other important measures, including structural and functional magnetic resonance imaging and biochemical indices of blood, are required to further elucidate the neural mechanisms associated with the pathogenesis of the CHR state.

In summary, our study observed relatively diminished responses to deviant stimuli during automatic auditory processing in Cluster 1. Additionally, temporal and frequency EEG profiles of distinct clinical subtypes were related to important clinical aspects, including global functioning, negative symptoms, and general symptoms. Moreover, we found distinct MMN indexes of three clusters to predict the subsequent remission from the CHR state. The findings of this study will help to identify more specific neurophysiological and neurocognitive targets for effective therapy, and in turn, allow the scope of the target population at the CHR stage to be specified for active intervention.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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