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Original Article

Temporal Dynamics of Electroencephalographic (EEG) Microstates as Predictors of Clinical Transition to Psychosis in Ultra-High Risk Individuals

Gulnihol Sharipova[1*], Jasur Rizaev[2], Shuxrat Boymuradov[3], Samadov Bakhodirjon[4, 5], Yulduz Urazbaeva[6]

Abstract

Objective: This study aimed to evaluate the potential of temporal parameters in electroencephalographic (EEG) microstates to serve as early biomarkers for the transition to psychosis in individuals at ultra-high risk (UHR). We specifically investigated whether alterations in the dynamics of canonical microstate classes could predict clinical outcomes over a 12-month period.
Method: Resting-state EEG was recorded from 48 UHR individuals and 48 age- and gender-matched healthy controls (HCs). Participants were followed longitudinally for 12 months to monitor clinical status. Microstate analysis was performed using a k-means clustering algorithm to identify the four canonical classes (A, B, C, and D). Temporal parameters, including mean duration, occurrence per second, and total time coverage, were extracted for each class. Cox regression and logistic regression analyses were conducted to identify predictors of transition, controlling for potential confounders such as baseline symptom severity and antipsychotic medication.
Results: Within the 12-month follow-up window, 14 UHR subjects (29.2%) converted to a full-threshold psychotic disorder. Converters exhibited a distinct pattern of temporal dysregulation compared to both non-converters and HCs. Specifically, the mean duration of microstate class C was significantly reduced in converters ($F(2, 93) = 8.45$, $P = 0.002$), with post-hoc tests confirming a difference compared with non-converters ($P = 0.003$). Conversely, the occurrence of microstate class D was significantly elevated in the converter group compared with both non-converters and HCs ($F(2, 93) = 5.21$, $P = 0.007$). Logistic regression identified that increased coverage of class D (OR = 1.85 per 1% increase, 95% CI: 1.22-2.81, $P = 0.004$) and decreased duration of class C (OR = 0.56 per 10 ms increase, 95% CI: 0.38-0.84, $P = 0.012$) were associated with transition. A combined predictive model yielded a sensitivity of 85.7% and a specificity of 82.4% (AUC = 0.89).
Conclusion: Specific temporal dynamics of EEG microstates, particularly shortened class C and increased occurrence of class D, are associated with clinical transition to psychosis in UHR individuals within a 12-month timeframe. However, given the small number of conversion events, these findings are preliminary and require replication in larger, independent cohorts before microstate parameters can be considered clinically useful predictive biomarkers.

Key words: *Biomarkers; Electroencephalography; Longitudinal Study; Psychosis; Prodromal Symptoms*

1. Department of Hygiene No.2, Bukhara State Medical Institute, Bukhara, Uzbekistan.
2. Department of Public Health and Healthcare Management, Samarkand State Medical University, Samarkand, Uzbekistan.
3. Boymuradov Shuxrat, Tashkent State Medical University, Tashkent, Uzbekistan.
4. Department of Clinical Sciences, Asia International University, Bukhara, Uzbekistan.
5. University of Tashkent for Applied Sciences, Tashkent, Uzbekistan.
6. Department of Psychology, Mamun University, Khiva, Uzbekistan.

***Corresponding Author:**
Address: Department of Hygiene No.2, Bukhara State Medical Institute, Bukhara, Uzbekistan.
Email: sharipova.gulnihol@bsmi.uz

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The identification of robust biomarkers capable of predicting the onset of psychosis remains a critical objective in contemporary psychiatric research. While clinical criteria have been established to define individuals at ultra-high risk (UHR) for developing a psychotic disorder (1-3), the conversion rate is variable, with approximately 20 to 35 percent transitioning to a full-threshold illness within a two-year window (4, 5). This diagnostic imprecision underscores the urgent need for objective, neurophysiological measures that can refine prognostic stratification and facilitate early, targeted intervention strategies (6, 7). Electroencephalography (EEG) offers a non-invasive window into the brain's spontaneous electrical activity, with resting-state paradigms providing unique insights into intrinsic neural network architecture (8). Traditionally, EEG research has focused on spectral power or functional connectivity; however, the analysis of EEG microstates has emerged as a promising alternative for mapping the spatiotemporal dynamics of large-scale brain networks (9). Microstates are defined as brief, quasi-stable periods of synchronized scalp potential fields that typically last between 80 and 120 milliseconds (10). These discrete states are thought to represent the sequential activation of underlying resting-state networks, such as the default mode or salience networks, and have been proposed as the atoms of thought (11).

Accumulating evidence suggests that the temporal parameters of microstates, including their duration, occurrence, and coverage, are altered in various neuropsychiatric conditions, including schizophrenia (12). Patients with established psychosis often exhibit specific abnormalities, such as a shortened duration of microstate class C and increased presence of class D (13, 14). However, it remains unclear whether these microstate alterations represent a consequence of chronic illness or a trait marker present prior to disease onset. Specifically, the utility of microstate dynamics in predicting the imminent transition to psychosis in UHR cohorts has not been fully elucidated. At the neurophysiological level, the UHR phase is characterized by a complex pattern of aberrant neural synchronization and disrupted connectivity, reflecting a brain in a state of dynamic instability (15). Structural and functional imaging studies have consistently demonstrated alterations in key neural circuits, particularly involving the prefrontal cortex, the limbic system, and the thalamocortical networks (16). These regions are critical for higher-order cognitive functions and sensory gating, processes that are frequently impaired during the prodromal phase (17). Specifically, UHR individuals often display a breakdown in the balance between excitation and inhibition (E/I balance), leading to inefficient synaptic pruning and dysregulated glutamatergic neurotransmission (18). This neurochemical dysregulation manifests electro physiologically as abnormal oscillatory activity and a failure to maintain stable functional network states. The brain's intrinsic connectivity networks, which normally operate with a high degree of temporal segregation and integration, become fragmented in UHR subjects (19). This fragmentation suggests that the neural systems responsible for maintaining coherent cognitive operations are already compromised before the formal onset of psychosis. Consequently, analyzing the rapid temporal dynamics of EEG microstates provides a high-resolution method to quantify this instability, as these microstates reflect the precise timing by which these distributed neural assemblies activate and deactivate.

The present study addresses this gap by longitudinally examining the temporal dynamics of EEG microstates in a well-characterized sample of UHR individuals. We hypothesized that distinct patterns of microstate instability at baseline would be significantly associated with clinical transition to psychosis over a 12-month follow-up period. By establishing a link between microstate syntax and disease trajectory, this research aims to validate a novel, electrophysiological biomarker for the early identification of individuals most likely to benefit from preventive therapeutic measures.

Materials and Methods

Participants

The study sample comprised 48 individuals identified as being at UHR for psychosis and 48 age- and gender-matched healthy controls (HCs). UHR participants were recruited from the outpatient psychiatric clinics of Bukhara, Uzbekistan, while HCs were recruited from the local community via advertisements. Inclusion criteria for the UHR group were defined by the comprehensive assessment of at-risk mental states (CAARMS), meeting the operationalized criteria for attenuated psychotic symptoms, brief limited intermittent psychotic symptoms, or trait vulnerability plus functional decline (20). Exclusion criteria for all participants included a history of a previous psychotic episode, major neurological disorders, head trauma with loss of consciousness, substance use disorder within the past six months, or any recent neurotherapy. All participants provided written informed consent after receiving a comprehensive description of the study aims. The protocol was approved by the local institutional review board and conducted in accordance with the Declaration of Helsinki.

Clinical assessment and follow-up

At baseline, all participants underwent a comprehensive clinical assessment including the Structured Clinical Interview for DSM-5 (SCID-5) to confirm the absence of a current psychotic disorder in UHR subjects and psychiatric history in controls. Symptom severity in the UHR group was assessed using the Scale of Prodromal Symptoms (SOPS) (21). Participants were then followed longitudinally for a period of 12 months. Clinical status

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was monitored through monthly follow-up interviews and bi-weekly phone check-ins. The primary outcome measure was transition to a full-threshold psychotic disorder, defined by the presence of psychotic symptoms lasting for more than one week or requiring hospitalization and antipsychotic treatment, as determined by the SCID-5. Transition to psychosis was operationalized according to the CAARMS-defined threshold for psychotic disorder (22). Specifically, transition was defined as the presence of at least one fully psychotic positive symptom (rating of 6 on the CAARMS positive symptom subscale for unusual thought content, non-bizarre ideas, perceptual abnormalities, or disorganized speech) occurring with a frequency and duration exceeding the UHR threshold (i.e., at least several times per week for more than one week, or daily for at least several hours per day, or if the symptom requires hospitalization). For each participant who transitioned, the time to transition was recorded in weeks from the baseline assessment to the date on which full-threshold criteria were first met, as confirmed by the monthly SCID-5 assessment. All baseline and follow-up CAARMS assessments were conducted by trained research clinicians who had completed formal CAARMS training and achieved inter-rater reliability (ICC > 0.80) on a set of training interviews. For participants who did not transition within the 12-month window, the follow-up time was recorded as the number of weeks from baseline to the final available assessment (censoring time). All 34 non-converters completed the full 12-month follow-up and were therefore censored at 52 weeks. The median time to transition among converters was 28.5 weeks (range: 6-48 weeks, interquartile range: 16-40 weeks). UHR individuals who did not meet these criteria within the 12-month period were classified as non-converters.

EEG data acquisition and conditioning

Resting-state EEG data were acquired in a sound-attenuated, dimly lit room. Participants were instructed to sit comfortably, relax, fixate on a crosshair on a monitor, and minimize blinking and muscle movement. Continuous EEG was recorded using a 64-channel amplifier system (Brain Products, Gilching, Germany) with active Ag/AgCl electrodes positioned according to the international 10-20 system for eight minutes. Impedances were kept below 10 kΩ. Data were sampled at a rate of 1 kHz with an online bandpass filter of 0.1-100 Hz. An electrode placed on the tip of the nose served as the reference, and the ground electrode was positioned at FPz. Vertical and horizontal electrooculograms were recorded to monitor eye movements.

Data preprocessing was performed using the EEGLAB toolbox (23) and custom scripts in MATLAB. The continuous EEG data were down sampled to 250 Hz to reduce computational load. A bandpass filter (1-40 Hz, zero-phase FIR filter) was applied to remove slow drifts and high-frequency noise. A 50 Hz notch filter (bandwidth = 2 Hz) was also applied to attenuate power-line interference. Independent component analysis (ICA) was utilized to identify and remove artifacts resulting from eye blinks, eye movements, and cardiac activity (24). ICA was performed using the extended Infomax algorithm (25). Prior to decomposition, the data were re-referenced to a common average reference for ICA training only, and the final analyses used the average reference. The data were then visually inspected, and segments containing residual muscle artifacts or amplifier saturation were rejected. The cleaned data were re-referenced to the common average reference (26). Following filtering, ICA-based artifact removal, and visual inspection, the number of retained data segments (contiguous artifact-free periods of two seconds) was 52.6 ± 8.3 per participant. No participant was excluded on the basis of insufficient data quality. The number of retained segments was comparable across groups (converters: 51.2 ± 9.1; non-converters: 53.1 ± 7.9; HCs: 52.4 ± 8.2; $F(2, 93) = 0.45$, $P = 0.64$).

Microstate analysis

Microstate analysis was conducted following the methodology established by Koenig and colleagues. First, the global field power (GFP) was calculated for each time point, representing the standard deviation of potentials across all electrodes at a given instant. Local maxima in the GFP curve were identified using a standard peak-detection algorithm, with a minimum peak separation of 10 ms to avoid spurious peaks. Only GFP peaks were used for clustering, as these time points represent moments of maximal topographic stability and signal-to-noise ratio. No GFP amplitude threshold was applied, and all local maxima were retained regardless of absolute amplitude. Topographic maps at GFP peaks were clustered using a modified k-means clustering algorithm (27). The clustering was initialized using the standard approach in the EEGLAB Microstate plugin (28), in which initial cluster centroids are selected by randomly sampling maps from the GFP peak set. In the present study, we adopted a common group-level clustering solution, consistent with the majority of the microstate literature and with recommendations for between-group comparisons (29, 30). To avoid local minima, the algorithm was restarted 50 times with different random initializations, and the solution minimizing the intra-cluster distance (i.e., the sum of squared distances between maps and their assigned centroid) was selected. Microstate topographies were treated as having a fixed polarity (i.e., the sign of the map was preserved), and no polarity inversion was applied during clustering or back-fitting. The optimal number of clusters was determined based on a cross-validation criterion and the Krzanowski-Lai criterion (31), which consistently identified four distinct microstate classes (labeled A, B, C, and D) explaining the majority of the topographic variance. These four class maps were then back-fitted to the continuous EEG data using a winner-takes-all competitive fitting

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procedure, in which each time point was assigned the label of the microstate template with the highest spatial correlation (i.e., the smallest global map dissimilarity) to the instantaneous scalp topography (32). To eliminate spurious short segments, the resulting microstate sequence was smoothed by rejecting segments with duration < 30 ms. These segments were iteratively reassigned to the second-best-fitting microstate until no segments shorter than 30 ms remained. Boundary segments at the beginning and end of each EEG recording, as well as segments adjacent to artifact rejection boundaries, were excluded from temporal parameter calculation. For each microstate class, the following temporal parameters were computed: (I) Mean Duration (the average time a given microstate remains stable, in milliseconds), (II) Occurrence (the number of times a specific microstate appears per second), and (III) Coverage (the percentage of total recording time covered by a specific microstate class).

Statistical analysis

Statistical analyses were performed using SPSS (version 26.0) and R. Demographic and clinical variables were compared between groups using independent t-tests for continuous variables and Chi-square tests for categorical variables. To examine microstate parameters, a one-way analysis of variance (ANOVA) was conducted across the three groups (converters, non-converters, HCs), followed by Tukey's HSD post-hoc tests for pairwise comparisons (33). To identify predictors of transition, Cox proportional hazards regression models were employed, adjusting for baseline covariates including age, gender, antipsychotic medication status, and SOPS positive symptom score. The proportional hazards assumption was tested using Schoenfeld residuals, and no significant violations were detected (all $P > 0.05$), indicating that the assumption was tenable. A Kaplan-Meier survival curve was generated for the entire UHR cohort (n = 48) to descriptively characterize the timing of transition to psychosis over the 12-month follow-up period. Given that all non-converters were censored at 52 weeks and that the number of events was small (n = 14), a binary logistic regression was also conducted as a sensitivity analysis using the final conversion status as the dependent variable. The results of the Cox and logistic regression models were consistent in identifying the same two microstate parameters as significant predictors, supporting the robustness of the findings. Because survival times were available for all participants, the Cox model was retained as the primary analysis, with logistic regression providing a complementary confirmation. Additionally, binary logistic regression was utilized to calculate odds ratios (ORs) and 95% confidence intervals (CI) for significant microstate parameters. Receiver operating characteristic (ROC) curve analysis was performed to determine the predictive accuracy (area under the curve, AUC) of the microstate parameters, with sensitivity and specificity calculated at the optimal cut-off point determined by the Youden index. The threshold for statistical significance was set at a two-tailed $P < 0.05$.

Because three temporal parameters were computed for each of the four canonical microstate classes (12 candidate parameters), we pre-specified a hierarchical analytical strategy distinguishing confirmatory from exploratory analyses. Based on prior EEG microstate literature and the study hypotheses, class C duration and class D coverage were designated as the primary parameters of interest. These confirmatory comparisons were evaluated using a Bonferroni-adjusted significance threshold of $\alpha = 0.025$. The remaining microstate parameters were considered exploratory. Given the limited number of transition events (n = 14), multivariable models were restricted to the pre-specified primary microstate parameters and baseline covariates rather than to automated or outcome-driven variable-selection procedures. Multivariable Cox proportional hazards and binary logistic regression models were then used to examine associations with time to transition and final transition status, respectively. No automated feature selection or dimensionality-reduction procedure was applied.

Results

The groups were well-matched for age (UHR: 23.20 ± 4.12 years; HC: 23.86 ± 3.75 years, $P = 0.42$) and gender distribution (UHR: 58.3% male; HC: 54.2% male, $P = 0.68$). Within the 12-month follow-up period, 14 UHR participants transitioned to a full-threshold psychotic disorder (Converters), resulting in a conversion rate of 29.2%. The remaining 34 UHR participants did not transition (Non-converters). As expected, the UHR group (including both converters and non-converters) showed significantly higher baseline symptom severity on the SOPS total score compared to HCs ($t(94) = 12.34$, $P < 0.001$). Demographic and clinical baseline data are summarized in Table 1.

Table 1. Baseline Demographic and Clinical Characteristics of 48 Individuals at Ultra-High Risk (UHR) for Psychosis and 48 Healthy Controls

Characteristic	UHR Group (n = 48)	Healthy Controls (n = 48)	Statistic	P-value
Age, years (mean ± SD)	23.2 ± 4.1	23.8 ± 3.7	$t(94) = 0.81$	0.42
Gender, Male (n, %)	28 (58.3%)	26 (54.2%)	$\chi2(1) = 0.17$	0.68
SOPS Total Score (mean ± SD)	39.5 ± 8.3	8.2 ± 5.1	$t(94) = 22.34$	< 0.001

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Characteristic	UHR Group (n = 48)	Healthy Controls (n = 48)	Statistic	P-value
SOPS Positive Symptoms (mean ± SD)	14.0 ± 3.0	0.5 ± 0.8	t(94) = 30.15	< 0.001
SOPS Negative Symptoms (mean ± SD)	12.8 ± 4.2	1.1 ± 1.3	t(94) = 18.76	< 0.001
SOPS Disorganization (mean ± SD)	7.5 ± 2.9	0.8 ± 1.0	t(94) = 15.87	< 0.001
SOPS General Symptoms (mean ± SD)	5.2 ± 2.1	5.8 ± 3.2	t(94) = 1.05	0.30
Antipsychotic Medication Use (n, %)	14 (29.2%)	-	-	-
Duration of UHR Symptoms, months (mean ± SD)	14.6 ± 9.8	-	-	-
CAARMS Criteria-Attenuated Psychotic Symptoms (n, %)	35 (72.9%)	-	-	-
CAARMS Criteria-Brief Limited Intermittent Psychotic Symptoms (n, %)	8 (16.7%)	-	-	-
CAARMS Criteria-Trait Vulnerability + Functional Decline (n, %)	5 (10.4%)	-	-	-

Significant group differences were found for specific temporal parameters of the canonical microstate classes A, B, C, and D (one-way ANOVA results shown in Table 2). Post-hoc analyses revealed that the significant group effect for the mean duration of microstate class C ($F(2,93) = 8.45$, $P = 0.002$) was driven by a significantly shorter duration in converters compared to both non-converters ($P = 0.003$) and HCs ($P = 0.002$). There was no significant difference in class C duration between non-converters and HCs ($P = 0.87$). A significant group effect was also observed for the occurrence per second of microstate class D ($F(2,93) = 5.21$, $P = 0.007$). Post-hoc tests indicated that converters exhibited a higher occurrence of class D compared to non-converters ($P = 0.01$) and HCs ($P = 0.04$). No significant differences were found between non-converters and HCs for this parameter ($P = 0.31$). The total time coverage of microstate classes showed a significant group effect only for class D ($F(2,93) = 6.18$, $P = 0.003$), with converters demonstrating increased coverage relative to the other two groups. Other temporal parameters (e.g., mean duration and occurrence of classes A and B) did not differ significantly across groups (Table 2).

Table 2. One-Way ANOVA Comparisons of Resting-State EEG Microstate Temporal Parameters Among UHR Individuals Who Converted to Psychosis (Converters, n = 14), UHR Non-Converters (n = 34), and Healthy Controls (n = 48)

Microstate Parameter	Group Means (ms or /s or %)	F(2,93)	P-value	Significant Post-hoc Comparisons (Tukey HSD)
Class A Duration (ms)	C: 68.2, NC: 71.5, HC: 70.1	1.23	0.30	-
Class B Duration (ms)	C: 72.8, NC: 75.3, HC: 73.9	0.95	0.39	
Class C Duration (ms)	C: 61.4, NC: 74.1, HC: 73.5	8.45	0.002	C < NC, C < HC
Class D Duration (ms)	C: 79.6, NC: 76.9, HC: 78.2	0.78	0.46	-
Class A Occurrence (/s)	C: 3.12, NC: 3.05, HC: 3.08	0.11	0.90	-
Class B Occurrence (/s)	C: 2.98, NC: 2.87, HC: 2.91	0.45	0.64	-
Class C Occurrence (/s)	C: 2.45, NC: 2.51, HC: 2.48	0.21	0.81	-
Class D Occurrence (/s)	C: 3.41, NC: 2.82, HC: 2.95	5.21	0.007	C > NC, C > HC
Class D Coverage (%)	C: 21.8, NC: 17.2, HC: 18.1	6.18	0.003	C > NC, C > HC

C = Converter, NC = Non-converter, HC = Healthy Control, UHR = Ultra-High Risk

The median follow-up duration was 52 weeks (range: 6-52 weeks). Among the 14 converters, the median time to transition was 28.5 weeks (interquartile range: 16-40 weeks; range: 6-48 weeks). The majority of transitions (10 of 14, 71.4%) occurred between weeks 12 and 40, with the earliest transition at week 6 and the latest at week 48. Three transitions occurred in the first 12 weeks, seven between weeks 12 and 24, three between weeks 24 and 36, and one after week 36. The Kaplan-Meier curve for the entire UHR cohort (n = 48) is presented in Figure 1. The estimated probability of remaining free from transition at 12 months was 0.71 (95% CI: 0.58-0.84). The median time to transition was not reached, as more than 50% of participants remained free from transition at the end of follow-up. The proportional hazards assumption was tested using Schoenfeld residuals and was satisfied for all predictors (all $P > 0.05$).

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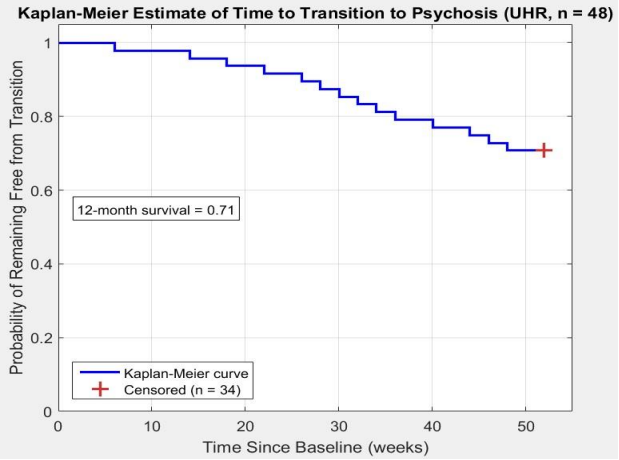


Figure 1. Kaplan-Meier Estimate of Time to Transition to a Full-Threshold Psychotic Disorder among 48 Individuals at Ultra-High Risk (UHR) for Psychosis during the 12-Month Follow-Up Period

Cox proportional hazards regression, adjusting for baseline covariates (age, gender, antipsychotic medication, and SOPS positive symptom score), identified class C duration and class D coverage as significant independent predictors of transition. Greater class C duration was associated with a lower hazard of transition (HR = 0.61, 95% CI: 0.45-0.83, P = 0.001), whereas greater class D coverage was associated with a higher hazard of transition (HR = 1.72, 95% CI: 1.21-2.45, P = 0.003). Thus, shorter class C duration and greater class D coverage were associated with increased transition risk. Results from the binary logistic regression analysis, confirming these two parameters as predictors, are presented in Table 3. For each 10 ms increase in class C duration, the odds of transitioning decreased by 44% (OR = 0.56, 95% CI: 0.38–0.84, P = 0.012). Equivalently, each 10 ms decrease in class C duration was associated with a 79% increase in the odds of transition (OR = 1.79). Conversely, for each 1% increase in the total time covered by class D, the odds of transitioning increased by 85% (OR = 1.85, 95% CI: 1.22–2.81, P = 0.004). Sensitivity analysis using binary logistic regression with final conversion status as the dependent variable yielded consistent results: decreased class C duration (OR = 0.56, 95% CI: 0.38-0.84, P = 0.012) and increased class D coverage (OR = 1.85, 95% CI: 1.22-2.81, P = 0.004) remained significant predictors. The concordance between Cox and logistic models supports the robustness of the findings.

Table 3. Binary Logistic Regression Predicting 12-Month Transition to a Full-Threshold Psychotic Disorder from Baseline EEG Microstate Parameters in 48 Ultra-High Risk (UHR) Individuals (14 Converters, 34 Non-Converters)

Predictor	β (SE)	Wald	Odds Ratio (OR)	95% CI for OR	P-value
Class C Duration (per 10 ms increase)	-0.58 (0.23)	6.32	0.56	0.38 – 0.84	0.012
Class D Coverage (per 1% increase)	0.61 (0.21)	8.45	1.85	1.22 – 2.81	0.004
Constant	-3.45 (1.12)	9.51	0.03	-	0.002

Of the 48 UHR participants, 14 (29.2%) were receiving antipsychotic medication at baseline. Medicated participants did not differ significantly from unmedicated participants in age (t (46) = 0.82, P = 0.42), gender distribution ($\chi 2(1) = 0.34$, P = 0.56), SOPS total score (t (46) = 1.24, P = 0.22), or duration of UHR symptoms (t (46) = 0.95, P = 0.35). Among medicated participants, 4 of 14 (28.6%) transitioned, compared with 10 of 34 (29.4%) among unmedicated participants ($\chi 2(1) = 0.003$, P = 0.96). In the sensitivity analysis restricted to unmedicated participants (n = 34; 10 converters, 24 non-converters), the pattern of results was consistent with the primary analysis. Class C duration remained significantly shorter in converters than in non-converters (F (1, 32) = 6.42, P = 0.016), and class D coverage remained significantly higher in converters (F (1, 32) = 5.87, P = 0.021). In Cox regression adjusted for age, gender, and SOPS positive symptoms, decreased class C duration (HR = 0.63, 95% CI: 0.44-0.90, P = 0.011) and increased class D coverage (HR = 1.68, 95% CI: 1.14-2.48, P = 0.009) remained significant predictors of transition. In logistic regression, the corresponding ORs were 0.58 (95% CI: 0.37-0.91, P = 0.018) for class C duration and 1.79 (95% CI: 1.13-2.84, P = 0.013) for class D coverage. The magnitude and direction of these effects were comparable to those observed in the full sample, suggesting that the findings were not driven by antipsychotic medication. However, due to the reduced sample size (n = 34) and the smaller number of conversion events (n = 10), the CIs in the sensitivity analysis were wider than in the primary analysis, and the results should be interpreted with caution.

The ROC curve analysis evaluated the discriminative power of the two significant microstate parameters, individually and in combination. The results are summarized in Table 4. As shown, the mean duration of class C achieved an AUC of 0.78 (95% CI: 0.64-0.92) for distinguishing converters from non-converters. The coverage of class D achieved an AUC of 0.76 (95% CI: 0.62-0.90). Moreover, a combined model (using the linear predictor from the logistic regression) yielded superior predictive accuracy, with an AUC of 0.89 (95% CI: 0.80-0.98). At the optimal cut-off point determined by the Youden index, this model achieved a sensitivity of 85.7% and a specificity of 82.4%.

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Table 4. Receiver Operating Characteristic (ROC) Curve Analysis of Baseline EEG Microstate Parameters for Predicting 12-Month Transition to Psychosis in 48 Ultra-High Risk (UHR) Individuals

Predictive Model	Area Under Curve (AUC)	95% CI	Sensitivity (%)	Specificity (%)	Youden Index (J)
Class C Duration	0.78	0.64 – 0.92	78.6	73.5	0.521
Class D Coverage	0.76	0.62 – 0.90	71.4	79.4	0.508
Combined Model	0.89	0.80 – 0.98	85.7	82.4	0.681

Discussion

The present study investigated whether temporal parameters of EEG microstates could serve as predictive biomarkers for the imminent transition to psychosis in individuals at ultra-high risk. Our longitudinal findings demonstrate that specific patterns of microstate dysregulation (i.e., a shortening of microstate class C and an increase in the occurrence and coverage of microstate class D) distinguish those who subsequently develop full-threshold psychosis from those who do not. These results corroborate prior observations of microstate abnormalities in established schizophrenia and position microstate analysis as a promising neurophysiological tool for risk stratification in the prodromal phase. One of the most striking findings was the significantly reduced mean duration of microstate class C in individuals who subsequently transitioned to psychosis. This shortening was specific to converters, as non-converting UHR individuals and HCs exhibited comparable class C durations. Microstate class C has been associated with the salience network, particularly the anterior cingulate cortex and bilateral insular regions, which are critically involved in the detection of salient stimuli and the switching between large-scale networks (34, 35). Our data extend prior observations by demonstrating that such alterations are present prior to the onset of frank psychosis, suggesting that microstate dysregulation represents a vulnerability marker rather than merely a consequence of chronic illness or medication exposure. A recent meta-analysis synthesized data from 23 studies examining EEG microstates in schizophrenia and reported that patients consistently exhibited reduced class C duration (standardized mean difference = -0.68) and increased class D coverage (standardized mean difference = 0.54) relative to HCs (12). The effect sizes observed in our study for these same parameters (comparing converters to non-converters and HCs) were of comparable magnitude, lending external validity to our results. Importantly, the specificity of these abnormalities to converters in our sample suggests that the microstate alterations observed in chronic schizophrenia are not merely epiphenomena of illness chronicity, antipsychotic exposure, or institutionalization, but rather reflect a neurobiological process that is already underway in the pre-psychotic phase.

In contrast, microstate class D was significantly more prevalent in converters, as evidenced by both increased occurrence per second and greater total time coverage. Class D has been associated with the default mode network, including the posterior cingulate cortex and medial prefrontal regions (36). An increased dominance of class D in the microstate sequence suggests that the default mode network exerts an abnormally large influence on the brain's spontaneous activity in individuals on the cusp of psychosis (37). This pattern may reflect a compensatory mechanism in which the brain, confronted with mounting network instability, defaults to a more internally oriented mode of processing (38). Consistent with our findings, prior research in chronic schizophrenia has documented increased class D parameters, including longer duration and higher coverage, though the literature is somewhat heterogeneous (39). Some studies have reported that class D is the most frequently occurring microstate class in patients with schizophrenia, displacing the typical dominance of class A observed in healthy individuals (40, 41). Our data suggest that this shift toward class D dominance may be a progressive phenomenon, becoming most pronounced in those who are about to develop frank psychosis.

The sensitivity analysis excluding medicated participants supported the robustness of the primary findings. Effect sizes for class C duration and class D coverage were comparable in direction and magnitude to those in the full sample, suggesting that the observed microstate abnormalities are unlikely to be solely attributable to antipsychotic medication. This is consistent with prior evidence that microstate alterations are present in antipsychotic-naïve individuals at clinical high risk for psychosis (42) and in first-episode patients before treatment initiation (43). Nevertheless, because the sensitivity analysis was based on a smaller sample and fewer events, these results should be interpreted as supportive rather than definitive.

The combination of microstate class C duration and class D coverage yielded an apparent AUC of 0.89, with sensitivity of 85.7% and specificity of 82.4%. While these values are numerically higher than many existing predictors, they must be interpreted with substantial caution due to the small number of conversion events (n = 14). With such a limited number of events, predictive models are highly susceptible to overfitting, and the apparent performance is likely optimistic. However, the results obtained in our preliminary study are considerable. For instance, meta-analyses of structural MRI findings in UHR cohorts have reported more modest predictive accuracies, with hippocampal volume reductions and basal ganglia alterations showing AUC

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values typically in the range of 0.65-0.75 (6, 44). Similarly, neurocognitive measures (45), while useful, rarely achieve the discriminative power observed in our combined microstate model. The ORs derived from our logistic regression analysis provide a clinically interpretable metric of risk. A decrease in class C duration of 10 milliseconds was associated with a 44% increase in the odds of transition, while a 1% increase in class D coverage was associated with an 85% increase in the odds of transition. These effect sizes suggest that even modest alterations in microstate dynamics carry meaningful prognostic information.

Our findings can be situated within several influential theoretical frameworks of psychosis pathophysiology. The dysconnectivity hypothesis, originally articulated by Friston and colleagues (46), posits that schizophrenia is characterized by a disruption in the functional integration across distributed brain regions. EEG microstates, by virtue of their whole-head topographic representations, are inherently suited to capture such dysconnectivity, as they reflect the momentary synchronization of large-scale neural assemblies (47). The shortened duration of class C and increased dominance of class D in future converters may thus be electrophysiological signatures of a brain that is progressively losing its capacity for coordinated, stable network activation. The E/I balance model provides another informative lens through which to interpret our data. A growing body of evidence suggests that the UHR state is characterized by a disruption in the balance between excitatory glutamatergic and inhibitory GABAergic neurotransmission, leading to aberrant neural synchronization (48). This imbalance may manifest as a failure to maintain stable microstates, resulting in more rapid transitions between states (reflected in shortened durations) and a predominance of certain states over others (49). The specific pattern observed in our study (i.e., reduced class C stability and increased class D prominence) may reflect the particular ways in which E/I dysregulation affects the salience and default mode networks, respectively. Finally, the synaptic pruning hypothesis, which has gained considerable traction in recent years, proposes that excessive pruning of dendritic spines during adolescence and early adulthood leads to a progressive disconnection of cortical circuits (50). This process, thought to be mediated in part by immune activation and dysregulated microglial function, could disrupt the large-scale synchronization that underlies microstate stability (51). Our finding that microstate abnormalities are already present in the UHR phase is consistent with the view that pruning-related disconnection is well underway before the onset of frank psychosis (52). However, it should be noted that microstate parameters reflect the temporal dynamics of whole-head topographic configurations, and their interpretation in terms of specific large-scale networks remains indirect. False-positive classification in the UHR population carries substantial clinical and ethical weight. Individuals incorrectly identified as likely to transition may experience heightened anxiety, stigma, and altered self-concept, particularly when the prediction concerns a severe mental illness. Some may receive unnecessary interventions, including antipsychotic medication, with metabolic and neurological side effects that are especially concerning in young people. False positives also consume scarce early intervention resources, potentially diverting specialized care from those who would actually transition. These harms must be weighed against the benefits of true-positive detection, and any future clinical application of predictive markers should be embedded within comprehensive risk assessment, shared decision-making, and adequate psychological support for all individuals identified as high risk, regardless of eventual outcome.

Limitation

Several limitations should be acknowledged. First, the sample size was relatively modest (n = 48 UHR participants, of whom 14 transitioned), and replication in larger independent cohorts is essential. Second, the 12-month follow-up period may have missed later converters who develop psychosis beyond this window. Third, although we controlled for medication status in all regression models and conducted a sensitivity analysis excluding medicated participants that supported the robustness of the findings, the possibility that antipsychotic medication influences microstate parameters cannot be entirely excluded. Future research should aim to replicate these findings in multi-site designs, incorporate microstate parameters into existing multivariate prediction models, and track microstate dynamics longitudinally to determine whether they are sensitive to therapeutic interventions.

Conclusion

This longitudinal study provides compelling evidence that the temporal dynamics of EEG microstates are significantly altered in UHR individuals who subsequently transition to psychosis. Specifically, a shortening of microstate class C and an increase in the occurrence and coverage of microstate class D at baseline independently predict clinical transition within a 12-month period. The combined predictive model achieved an AUC of 0.89, with a sensitivity of 85.7% and specificity of 82.4%, values that compare favorably with existing neurobiological and clinical predictors. These findings suggest that microstate analysis captures a fundamental aspect of brain dysfunction operative in the pre-psychotic phase, potentially reflecting the progressive breakdown of large-scale network coordination underlying the emergence of psychotic symptoms. The specificity of these abnormalities to converters indicates that microstate parameters provide incremental prognostic information beyond clinical assessment alone. From a clinical perspective, EEG

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microstates represent a non-invasive, cost-effective, and widely accessible technique. However, before microstate parameters can be integrated into early intervention programs for risk stratification, they must be validated in larger, independent cohorts with adequate numbers of conversion events. At present, the clinical utility of microstate-based prediction remains unproven, and no recommendation for clinical implementation can be made. In summary, specific temporal parameters of EEG microstates, particularly class C duration and class D coverage, were associated with psychosis transition in UHR individuals, warranting replication in larger cohorts and suggesting significant promise as a neurophysiological biomarker for early identification of individuals at highest risk for developing full-threshold psychotic disorder.

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None.

Authors' Contribution
All authors contributed equally in all aspects of this study, such as conception and design, data collection, data analysis and interpretation, drafting and critical revision of the manuscript.

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