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EEG microstate D as psychosis-specific correlate in adolescents and young adults with clinical high risk for psychosis and first-episode psychosis

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ABSTRACT

Resting-state electroencephalography (EEG) microstates are brief periods (60–120 ms) of quasi-stable scalp field potentials, indicating simultaneous activity of large-scale networks. Microstates are assumed to reflect basic neuronal information processing. A common finding in psychosis spectrum disorders is that microstates classes C and D are altered. Whereas evidence in adults with schizophrenia is substantial, little is known about effects in underage patients, particularly in those at clinical high risk for psychosis (CHR) and first-episode psychosis (FEP). The present study used 74-channel EEG to investigate microstate effects in a large sample of patients with CHR ($n = 100$) and FEP ($n = 33$), clinical controls (CC, $n = 18$), as well as age-matched healthy controls (HC, $n = 68$). Subjects span an age range from 9 to 35 years, thus, covering underage patients as well as the most vulnerable period for the emergence of psychosis and its prodrome. Four EEG microstates classes were analyzed (A-D). In class D, CHR and FEP patients showed a decrease compared to HC, and CHR patients also to CC. An increase in class C was found in CHR and FEP compared to HC but not to CC. Results were independent of age and no differences were found between the psychosis spectrum groups. The findings suggest an age-independent decrease of microstate class D to be specific to the psychosis spectrum, whereas the increase in class C seems to reflect unspecific psychopathology. Overall, present data strengthens the role of microstate D as potential biomarker for psychosis, as early as in adolescence and already in CHR status.

1. Introduction

Psychotic disorders are severe illnesses with broad impact on personal and professional life as well as on society (Jääskeläinen et al., 2013). Schizophrenia is ranked third among the mental disorders causing disability-adjusted life years (DALYs) worldwide (GBD 2019 Mental Disorders Collaborators, 2022) and disease burden is growing (Charlson et al., 2018). Psychosis-spectrum disorders emerge early in life, with a peak of onset at 20.5 years and median onset at 25 years (Solmi et al., 2021). The period from late childhood to early adulthood spans a critical phase for conversion from clinical high-risk (CHR) states to full-blown psychosis and, at the same time, is a key stage for brain development. Importantly, duration of untreated psychosis was found to have a negative effect on the long-term outcome (Albert and Weibell, 2019), indicating that early detection and intervention has the potential to significantly alter the course of psychosis. The majority of first-episode psychosis (FEP) are preceded by a prodromal phase, in which CHR symptoms, a multitude of other mental health problems and psychosocial deficits occur (Fusar-Poli et al., 2013; Schultze-Lutter et al., 2015). This phase offers a unique point of intervention for the

Abbreviations: CHR, clinical high-risk; FEP, first-episode psychosis; CC, clinical controls; HC, healthy controls; BS, basis symptoms; GFP, global field power; CPZ, chlorpromazine.

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prevention or at least postponement of the transition to manifest psychosis by trying to reduce CHR, other symptoms, and associated distress (Schmidt et al., 2015). Thus, diagnosis at an early stage of psychosis has gained increased interest in recent decades, early detection centers have been established (Michel et al., 2022) and biomarkers have been proposed (Davison et al., 2018; de Bock et al., 2020; Kraguljac et al., 2021). Yet, early detection is still fully based on clinical markers (Fusar-Poli et al., 2013; Schultze-Lutter et al., 2015), whereas knowledge about biomarkers is sparse. These, however, might qualify as substantial tool in early detection and prevention.

One promising candidate for the development of a biomarker is electroencephalography (EEG). EEG is noninvasive, cost effective and relatively easy to perform. In psychosis, neuronal information processing is disturbed, leading to characteristic symptoms such as hallucinations, delusions and disorganization (Kahn et al., 2015). With its high temporal precision, EEG provides a powerful tool to study brain-related information processing. In resting-state EEG, microstates can be isolated, being brief temporal periods (60–120 ms), in which the scalp global field remains quasi-stable, before rapidly changing into another topographic state (Michel and Koenig, 2018). These stable periods suggest simultaneous activity of large-scale neuronal networks and have been suggested to correspond to basic building blocks of human information processing (Koukkou and Lehmann, 1983). Traditionally, data is decomposed into four microstate classes, labelled A-D, and the parameters Coverage (percentage of time covered by a microstate class), Duration (mean duration of a class in ms) and Occurrence (number of occurrences of a class per second) are investigated. The four classes explain 65–84 % of total EEG data variance (Michel and Koenig, 2018), template maps show a high degree of similarity across studies (Koenig et al., 2023) and microstates show good reliability and consistency across analytic methods (Khanna et al., 2014; Kleinert et al., 2023; Liu et al., 2020; Popov et al., 2023). Regarding the functional role of microstates, a recent review associated class A with both auditory and visual processing, class B with self-referential visual processing, class C with general self-referential processing and class D with executive functioning (Tarailis et al., 2023). Importantly, microstates have been linked to specific functional magnetic resonance imaging (fMRI) resting-state networks (Britz et al., 2010; Musso et al., 2010).

Microstates have been shown to be altered in patients with chronic schizophrenia (da Cruz et al., 2020; Rieger et al., 2016), early-stage psychosis (Murphy et al., 2020; Sun et al., 2022), CHR states (Andreou et al., 2014; de Bock et al., 2020; Luo et al., 2020), and seem to predict later transition to psychosis (de Bock et al., 2020). Two meta-analyses revealed consistent changes in classes C and D in schizophrenia patients, with an increase of Coverage and Occurrence in class C and a decrease of Coverage and Duration in class D (da Cruz et al., 2020; Rieger et al., 2016). Thus, microstates were proposed as potential biomarker for psychotic disorders (de Bock et al., 2020) and as endophenotype for schizophrenia (da Cruz et al., 2020). Moreover, a recent study found that EEG microstates features outperform classical EEG features (e.g. power spectra, frequency domain, variability within the signal etc.) in differentiating schizophrenia patients from healthy controls, as demonstrated by machine-learning-based microstate analysis (Kim et al., 2021).

As introduced above, psychotic disorders emerge early in life, with a substantial proportion of patients being affected before reaching adulthood (Solmi et al., 2021). In contrast to findings in adults, knowledge about microstate dynamics in underage patients is sparse. Interestingly, microstates are not stable in their dynamics over the time course of healthy aging, but show a specific evolution, compatible with developmental stages (Koenig et al., 2002; Tomescu et al., 2018). Two studies investigated microstate dynamics in a sample of young patients with 22q11.2 deletion syndrome, which puts them at a very high genetic risk for psychosis. Similar to adult psychosis patients, these patients showed an increase of relevant microstate parameters of class C and a decrease of these parameters in class D (Tomescu et al., 2015, 2014).

However, no previous study directly investigated and compared microstate dynamics in adolescent and young-adult patients with CHR and FEP. Moreover, existing studies investigating microstate dynamics in CHR and FEP patients suffer from low sample size (Andreou et al., 2014; Luo et al., 2020) and did not include clinical control subjects, thereby rendering inconclusive evidence. Without comparison to a clinical control group, the specificity of psychosis related microstate effects remains unclear. Especially in CHR these might be related to general psychopathology and not be associated directly with the psychosis spectrum. This is because CHR reflects a heterogenous group, since only a subset of CHR will transition to psychosis, about 25 % in the first four and 35 % within ten years (Salazar de Pablo et al., 2021). CHR thus represents a wider range of psychopathology than solely prodromal stages of psychosis.

We therefore investigated EEG microstates in a large cohort of patients with CHR or FEP, clinical controls (CC) and healthy controls (HC), spanning a wide age range from 9 to 35 years, i.e., a period from late childhood to early adulthood. This is thus the first study to cover the entire main timeframe of psychosis manifestation. Besides investigating general microstate dynamics in CHR and FEP, we additionally target the question if these effects are influenced by age. Moreover, by including a clinical control group, we aim at assessing the specificity of altered psychosis associated microstate parameters. We hypothesize that established findings in adults with psychosis, such as increased microstate class C and decreased class D, can be replicated in underage patients, thereby possibly qualifying as a robust age-independent marker of psychosis.

2. Methods

2.1. Sample

Patients with CHR and FEP, as well as CC, were help-seeking individuals that were referred to the Early Detection and Intervention Center for Mental Crises (FETZ (Michel et al., 2022)) in Bern between 2011 and 2021. During this period, 514 patients presented to the FETZ, 164 of them (31.7 %) were classified as either CHR or FEP and received an EEG. CHR status was fulfilled (Fusar-Poli et al., 2013; Schultze-Lutter et al., 2015), when patients met any CHR criteria according to the ultra-high-risk (UHR) and/or basic symptoms approach (further details in Supplementary Methods). Criterion for assignment to FEP group was a first-time diagnosis of either schizophrenia ($n = 22$), bipolar disorder with psychotic symptoms ($n = 2$) or another manifest psychotic disorder ($n = 9$) according to ICD-10 (numbers after exclusion due to specific exclusion criteria, see below). Diagnoses were assessed by trained psychiatrists and psychologists at the FETZ (Michel et al., 2022). As CC we included those patients, which were referred to the FETZ and after thorough investigation were not classified as FEP or CHR, however were diagnosed with any other psychiatric disorder ($n = 18$ after exclusion).

Healthy controls (HC) were recruited and measured in Geneva (2010–2021), as part of the larger Synapsy project (Conus et al., 2011). HC were age-matched to CHR and FEP, which led to exclusion of 19 of 97 control participants.

Exclusion criteria for CHR, FEP and CC patients were current substance abuse, clinically abnormal MRI and/or EEG, neurological disease with relevant impact on cognitive functions, IQ below 70 and abortion of the FETZ assessment. Exclusion criteria for HC were psychiatric or neurological diagnosis (stated by a trained physician), general psychopathology, learning difficulties, premature birth, psychoactive medication and substance abuse. In all four groups, subjects who either did not follow task instructions (eyes closed resting-state), showed > 40 % EEG artefacts or heavily distorted microstate topographies were discarded. Initially, 126 CHR, 38 FEP, 30 CC and 78 HC (after age matching) were sampled. 26 CHR, 5 FEP, 12 CC and 10 HC had to be excluded, leaving a final sample of 100 CHR, 33 FEP, 18 CC and 68 HC (Table 1). 6 CHR, 6 FEP and no CC had a family history of a psychotic disorder (8 missing

Table 1
Sociodemographic and clinical characteristics of the sample.

	CHR (n = 100)	FEP (*n* = 33)	CC (*n* = 18)	HC (*n* = 68)
Age (mean ± sd, range)	19.0 ± 4.3 (9–35)	20.0 ± 4.5 (13–33)	18.9 ± 5.7 (12–33)	18.6 ± 4.5 (9–30)
Age (underage/adult, n)	52/48	13/20	8/10	34/34
Sex (f/m, n)	45/55	16/17	4/14	33/35
CPZ equivalents (mean ± sd, range)	35.9 ± 135.5 (0–900)	67.9 ± 122.1 (0–480)	4.2 ± 17.7 (0–75)	None
Psychoactive medication (n, %)	28 (28 %)	19 (58 %)	5 (28 %)	None
Diagnoses and comorbidities (ICD-10), (n patients, % patients)				
F10-F19[a]	6 (6 %)	1 (3 %)	0	0
F20-F29[a]	3 (3 %)[b]	31 (94 %)[c]	2 (11 %)[b]	0
F30-F39[a]	50 (50 %)	10 (30 %)	7 (39 %)	0
F40-F49[a]	42 (42 %)	4 (12 %)	8 (44 %)	0
F50-F59[a]	3 (3 %)	0	1 (6 %)	0
F60-F69[a]	7 (7 %)	1 (3 %)	2 (11 %)	0
F80-F89[a]	2 (2 %)	0	2 (11 %)	0
F90-F99[a]	8 (8 %)	4 (12 %)	4 (22 %)	0
Distribution of CHR criteria (n, %)				
BS criteria only	26 (26 %)			
UHR criteria only	25 (25 %)			
BS and UHR criteria	49 (49 %)			

Legend for Table 1: [a]F10-F19: Mental and behavioral disorders due to psychoactive substance use; F20-F29: Schizophrenia, schizotypal and delusional disorders; F30-F39: Mood disorders; F40-F49: Neurotic, stress-related and somatoform disorders; F50-F59: Eating disorders (in this sample); F60-F69: Disorders of personality and behavior; F80-F89: Disorders of psychological development; F90-F99: Behavioral and emotional disorders with onset usually occurring in childhood and adolescence. [b]The three CHR and two CC subjects with F20–29 were diagnosed with schizotypal personality disorder (F21). [c]The two FEP patients without F20–29 diagnosis were diagnosed with bipolar disorder (F31). Abbreviations: CHR = clinical high risk, FEP = first-episode psychosis, CC = clinical controls, HC = healthy controls, f = female, m = male, sd = standard deviation, CPZ = chlorpromazine, BS = basic symptom, UHR = ultra-high-risk.

values) and 15 CHR, 6 FEP and 3 CC had a family history of any psychiatric disorder (13 missing values; family history was not assessed in HC).

The study was performed in agreement with the Declaration of Helsinki and all participants, and their parents in case of minors, gave informed consent. The study was approved by the ethical committee of the University of Bern (ID PB_2016–01,991) and the ethical committee of the University of Geneva (ID PB_2016–01470).

2.2. EEG recording

In Bern, the EEG was recorded with a 74-channel Nihon Kohden system (Neurofax 1100 amplifier, 500 Hz). Electrodes were placed according to an extension of the international 10–10 system (Ground: Fpz, reference: F3/F4). Impedance was kept below 20 kΩ. Electrocardiography (ECG) was additionally collected. During resting-state EEG recording (10 min) participants were comfortably seated in a separated room and instructed to close their eyes, stay awake, keep calm and relax. Every 120 s, they were told verbally to open their eyes for around 10–20 s and sit comfortably, in order to relax and stay awake.

In Geneva, the EEG was recorded by a high density, 256-channel HydroCel Geodesic Sensor Net (GES300/400 amplifier, 1000 Hz, reference: Cz, ground: between CPz and Pz). The impedance was kept below 10 kΩ for the reference and below 30 kΩ for other electrodes. The EEG (5 min) was recorded in a darkened, electrically shielded room and participants were instructed to close their eyes, stay awake, keep calm and relax. There were no breaks with open eyes.

2.3. EEG preprocessing

For preprocessing of all data, we used Brain Vision Analyzer 2.2. For data stemming from Bern, periods with eyes-open were excluded and noisy or otherwise bad channels were interpolated. Only for computation of an independent component analysis (ICA), data were filtered with a bandpass (2–20 Hz) and a notch (50 Hz) filter. ICA components for horizontal and vertical eyes movements, as well as ECG activity were visually identified and corrected. ICA-correction was then applied on unfiltered data. Subsequently, remaining artefacts were identified by visual inspection and removed. Finally, data were re-referenced to average reference.

Data from Geneva were first downsampled to 500 Hz, then bad channels were excluded and channels were interpolated to the 74 channel-montage from Bern. Subsequent preprocessing was similar to the procedure of data from Bern, however due to absent ECG channel we did not correct for this activity.

2.4. Microstate feature extraction

Microstates were analyzed using the Microstates Toolbox by Thomas Koenig (Version 1.2, https://www.thomaskoenig.ch/index.php/software/microstates-in-eeglab) implemented in EEGLAB (Delorme and Makeig, 2004) in MATLAB R2020a. First, data were band-pass filtered (2–20 Hz) following previous microstate studies in schizophrenia (Kikuchi et al., 2007; Kindler et al., 2011; Koenig et al., 1999; Lehmann et al., 2005). Then global field power (GFP) was computed for each moment in time. All maps at momentary peaks of the GFP were selected and submitted to a modified k-means clustering algorithm (Pascual-Marqui et al., 1995). The k-means clustering was re-initialized 20 times, and the best solution was retained. The backfiring was limited to the moments of momentary GFP peaks, and the assignment of the remaining time was based on a nearest neighbor interpolation. A set of four microstate classes was chosen, in line with most previous psychosis-related microstate studies (Andreou et al., 2014; da Cruz et al., 2020; de Bock et al., 2020; Murphy et al., 2020; Tomescu et al., 2015, 2014). Separate group means for each of the four groups (and for every class) were computed using a permutation algorithm that minimizes common variance across subjects (Koenig et al., 1999). The four group means were aggregated into an overarching mean, which was class-labelled based on model map norms (Koenig et al., 2002) using minimal Global Map Dissimilarity. This labelled overarching mean was then used to label the four maps of the group means. Class-labelled group means were used to sort microstate means in every individual subject. Microstates in individual subjects were labelled to its corresponding class based on these sorted individual means (for the rationale behind this proceeding see Supplementary Methods). Only non-truncated microstate parameters were computed, thus first and last segments were ignored. Finally, for each class the parameters Coverage, Duration and Occurrence were computed. For outlier detection, Mahalanobis distance was computed, which is a multidimensional measure of the distance of a given datapoint from the mean of all datapoints. The distance was computed with the stats package in R and included the crucial parameters of interest of this study (group, age, sex, explained variance, length of EEG sampling, percentage of artefacts, GFP, as well as Coverage, Duration and Occurrence in each class). The cut-off for exclusion was defined as those five subjects who beside showing the greatest distance, simultaneously displayed heavily distorted microstate topographies on visual inspection (4 CHR, 1 HC).

2.5. Statistical analysis of group characteristics

Groups were compared for sex and psychoactive medication using the Chi-Square test in R. For comparison of age and chlorpromazine

equivalents between groups, we used the Kruskal-Wallis test in R. For post-hoc testing the pairwise proportions test (psychoactive medication) and the pairwise Wilcoxon test (chlorpromazine equivalents) were used. HC did not receive psychoactive medication, therefore this group was not included in statistical tests regarding medication.

2.6. Statistical analysis of microstates

Group differences for the three microstate parameters (Coverage, Duration, Occurrence) were assessed using a linear model with the fixed factors microstate class (A-D), group (FEP, CHR, CC, HC), age, sex, chlorpromazine equivalents and the following interactions: class × group, class × age, class × sex, class × chlorpromazine equivalents and class × group × age. Importantly, the linear model can account for age-related effects on microstate parameters. Model parameters were estimated using the restricted maximum likelihood in package lme4 in R (Bates et al., 2015), and degrees of freedom were calculated by Satterthwaite's approximation. Post-hoc tests were carried out with the package lsmeans in R (Lenth, 2016). All models were corrected for multiple comparisons using the Bonferroni-Holm method ($n = 24$ in every microstate parameter). Effect sizes for post-hoc paired *t*-tests were computed as Cohen's d, using the emmeans package in R (Lenth, 2021). To further explore possible effects of age, the above linear model was repeated including an age-split (underage, adult) instead of age as factor. The linear model was also repeated with psychoactive medication status instead of chlorpromazine equivalents as factor (psychoactive medicated vs. unmedicated patients) to detect possible effects of general psychoactive medication.

In addition to classical statistics, we performed Bayesian statistics to allow statements not only for the alternative hypothesis but also for the null hypothesis. Bayes Factors (BF) were computed using the R packages rstanarm (Goodrich et al., 2020) and bayestestR (Makowski et al., 2019). The Bayesian model included the factors group, age, sex, chlorpromazine equivalents and the interaction of group × age. Bayesian statistics were computed only for significant effects in the linear model in classes C and D, as our main hypotheses are focused on these. Priors were set manually, so that a substantial effect would mean that the observed group difference (5 % for Coverage; 10 ms for Duration and 0.5/s for Occurrence) would disappear over a time-period of 20 years, which reflects the age-range including > 95 % of the present sample (further details in Supplementary methods).

Chlorpromazine equivalents were computed using the chlorpromazineR package for R (Brown et al., 2022; Gardner et al., 2010). Computing Kendall-rank correlation in R, we assessed whether any microstate parameter was correlated with chlorpromazine equivalents.

2.7. Analysis of topographic differences between microstate maps

Using the MATLAB tool Randomization Graphical User interface (Ragu) (Habermann et al., 2018; Koenig et al., 2011), we performed a topographic analysis of variance (TANOVA), testing for topographic differences between groups (further details in Supplementary Methods). Also, using Pearson's linear correlation, we computed correlations between mean group topographies.

3. Results

3.1. Group characteristics

The four groups did not differ significantly in gender ($\chi^2 = 4.3$, $p = 0.233$) and age ($\chi^2 = 3.0$, $p = 0.394$). General psychoactive medication differed between groups ($\chi^2 = 10.0$, $p = 0.007$), as it was increased in FEP (58 %) compared to CHR (28 %, $p = 0.004$) and tended to be increased in FEP compared to CC (28 %, $p = 0.08$). Dosage of chlorpromazine equivalents was higher in FEP compared to CHR and CC ($\chi^2 = 13.2$, $p = 0.001$; FEP vs. CHR: $p = 0.002$; FEP vs. CC: p = 0.001). For details see Table 1.

3.2. Microstates

3.2.1. Topographies of microstates

In each of the four groups, microstate maps resemble the four maps consistently reported in previous literature (Michel and Koenig, 2018) (Fig. 1).

The TANOVA revealed different microstate topographies between groups (group × class: $p < 0.001$). Specifically, different group means were observed for all four microstate classes (all $p = 0.001$). Correlations of the different group means showed slightly increased correlation coefficients when comparing mean topographies from Bern (CHR, FEP, CC) to each other in contrast to comparing mean topographies from Bern to mean topographies from Geneva (HC; see Table S1 in Supplementary Material). An additional age regression of microstate topographies over all subjects revealed a tendency towards a significant effect in class B (A: $p = 0.290$; B: $p = 0.087$; C: $p = 0.276$; D: $p = 0.364$). There were no effects in single groups when correcting with Bonferroni-Holm.

3.2.2. Group differences in microstate parameters

As EEG was recorded in separate locations, we tested whether GFP differed between groups, which was not the case ($F_{2,215} = 0.4$, $p = 0.955$). Explained variance was high in all groups (CHR: 80 %, FEP: 81 %, CC: 80 %, HC: 76 %) but differed between locations, being slightly higher in CHR and FEP compared to HC ($F_{2,215} = 4.8$, $p = 0.003$; CHR vs. HC: $t_{166} = 3.2$, $p = 0.008$, d = 0.502; FEP vs. HC: $t_{99} = 3.2$, p = 0.008, d = 0.679; no differences between CHR and FEP as well as between CC and all other groups).

Significant effects were found for the interactions of group × class for Coverage ($F_{6,836} = 11.8$, $p < 0.001$), Duration ($F_{6,836} = 2.9$, $p = 0.002$) and Occurrence ($F_{6,836} = 4.2$, $p < 0.001$), (Fig. 2). An overview of effects on the group level can be found in Table 2.

Post-hoc comparisons revealed that Coverage was decreased in class D in FEP and CHR compared to HC (FEP vs. HC: $t_{99} = -3.8$, p = 0.003, d = −0.839; CHR vs. HC: $t_{166} = -7.5$, $p < 0.001$, d = −1.193) and in CHR compared to CC ($t_{116} = -4.5$, p < 0.001, d = −1.173). In class A Coverage was increased in CHR compared to CC ($t_{116} = 3.4$, $p = 0.010$, d = 0.891) and in class B, Coverage was increased in CHR compared to HC ($t_{166} = 4.1$, $p = 0.001$, d = 0.647).

Duration was increased in classes A-C in CHR and FEP compared to HC (Class C: CHR vs. HC: $t_{166} = 4.3$, p < 0.001, d = 0.679, FEP vs. HC: $t_{99} = 3.2$, $p = 0.022$, d = 0.716; Class B: CHR vs. HC: $t_{166} = 5.2$, p < 0.001, d = 0.836, FEP vs. HC: $t_{99} = 4.1$, p < 0.001, d = 0.917; Class A: CHR vs. HC: $t_{166} = 4.8$, p < 0.001, d = 0.773, FEP vs. HC: $t_{99} = 3.4$, $p = 0.012$, d = 0.755). In class B Duration was increased in CC compared with HC ($t_{84} = 4.6$, p < 0.001, d = 1.245).

Occurrence was decreased in class D in both CHR and FEP compared to HC (CHR vs. HC: $t_{166} = -7.9$, p < 0.001, d = −1.261, FEP vs. HC: $t_{99} = -4.9$, p < 0.001, d = −1.084) and in CHR compared to CC ($t_{116} = -3.1$, $p = 0.046$, d = −0.795). In Class A Occurrence was decreased in FEP vs. HC ($t_{99} = -3.3$, $p = 0.023$, d = −0.727) and tended to be deceased in CHR vs. HC and in CC vs. HC (CHR vs. HC: $t_{166} = -3.0$, $p = 0.052$, d = −0.482; CC vs. HC: $t_{84} = -3.0$, p = 0.052, d = −0.807).

No significant effect for age (all $F_{1,218} < 0.4$, $p > 0.563$), the interaction of age × class (all $F_{3,216} < 1.2$, $p > 0.343$) or of age × group × class (all $F_{6,836} < 1.3$, $p > 0.262$) was found in any microstate parameter. This negative result was maintained when we performed an age-split, comparing adults with underage subjects (adulthood: all $F_{1,218} < 0.5$, $p > 0.501$; adulthood × class: all $F_{3,216} < 1.4$, $p > 0.250$; and adulthood × group × class: all $F_{6,836} < 1.4$, $p > 0.201$). The course of the microstate effects over the age range of the present sample can be found in the Supplementary material (Fig. S1).

Additionally, performing Bayesian statistics to check for presence or absence of a meaningful impact of age on significant effects in classes C and D, results pointed overall towards an absence. For Coverage in class

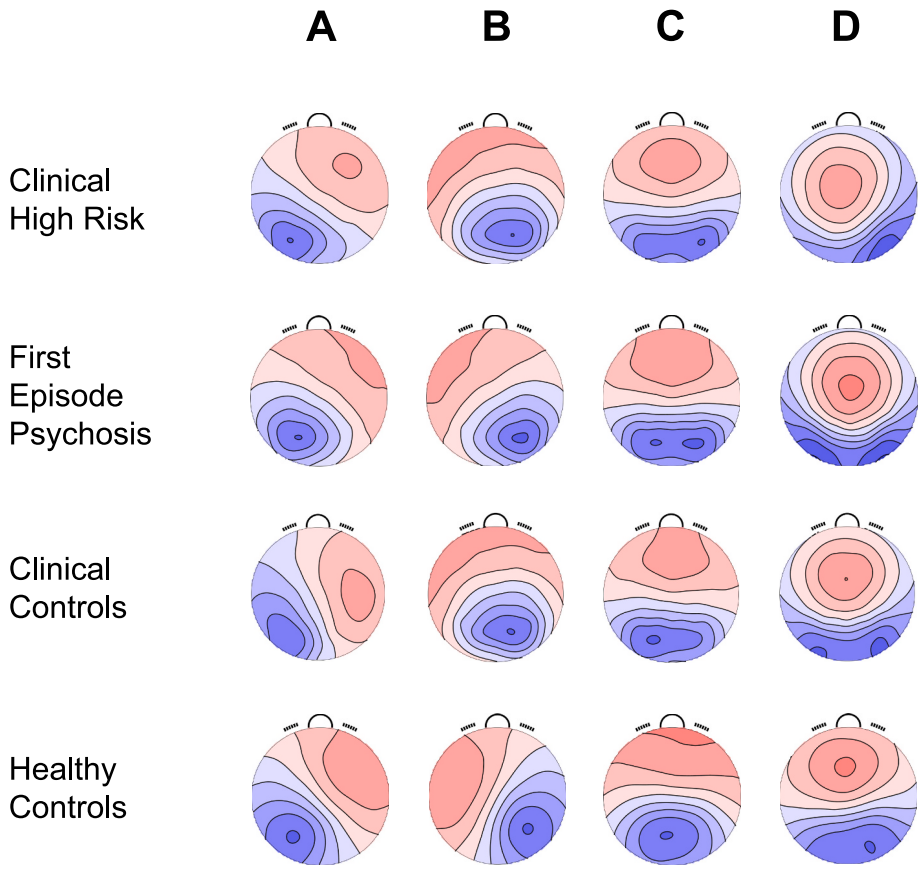

Fig. 1. Mean microstate maps for the four different groups clinical high risk (CHR), first-episode psychosis (FEP), clinical controls (CC) and healthy controls (HC) for microstate classes A-D.

D, moderate evidence against an age effect in CHR (BF = 0.178) and HC (BF = 0.206) but not in FEP (BF = 0.639) and CC (BF = 0.894) was found. For Duration in class C, weak evidence against an age effect in CHR (BF = 0.394), FEP (BF = 0.558), HC (BF = 0.530) and CC (BF = 0.560) revealed. Finally, for Occurrence in class D evidence against an age effect was moderate in CHR (BF = 0.253), weak-to-moderate in HC (BF = 0.328) and weak in FEP (BF = 0.545) and CC (BF = 0.568).

In our statistical analysis, we controlled for antipsychotic medication, adding chlorpromazine equivalents as covariate to the linear model. Additionally, we computed if any of the microstate parameters correlated with chlorpromazine equivalents. No significant correlations were detected for any parameter (Coverage, Duration and Occurrence) in any microstate class (all $z < 1.96$, $p > 0.051$, uncorrected). Above stated analyses were repeated with psychoactive medication status instead of chlorpromazine equivalents as factor, comparing medicated and unmedicated patients (CHR and FEP, see also Table 1). There were no effects of medication status (all $F_{1,218} < 3.5$, $p > 0.064$) nor of medication status × class (all $F_{3,216} < 1.1$, $p > 0.352$), suggesting no general effect of psychoactive medication on above reported results.

4. Discussion

In this unique study spanning an age range of 9 to 35 years, we investigated EEG microstate dynamics and their potential age-dependence in a large cohort of 100 patients with a clinical high risk (CHR) state for psychosis, 33 patients with first-episode psychosis (FEP) as well as 18 clinical controls (CC) and 68 age-matched healthy controls (HC). A psychosis-specific decrease in microstate class D was found in both groups of patients compared to HC, as well in CHR compared to CC. Importantly, this result was independent of age, thus, adding substantial evidence to the notion that this microstate signature may qualify as a robust age-independent biomarker of risk stages and psychosis.

We found a decrease of class D (Coverage, Occurrence) in both patient groups (FEP, CHR) compared to HC (Fig. 2). Also, class D was decreased in CHR compared to CC (and in FEP compared to CC, but this result did not survive correction for multiple comparisons). This finding is in line with two recent meta-analyses comparing adult schizophrenia patients to controls (da Cruz et al., 2020; Rieger et al., 2016), as well as with results on samples at genetically increased risk for psychosis, i.e., patients with 22q11.2 syndrome (Tomescu et al., 2015, 2014) and relatives of patients with psychosis (da Cruz et al., 2020). All of these studies attribute a decrease in class D (and an increase in class C) to be specific to schizophrenia, psychosis and risk for psychosis. There are two studies investigating FEP and CHR, which do not report general differences between patients and healthy controls in classes C and D (Andreou et al., 2014; de Bock et al., 2020). However, it should be noted that sample size was small in the first study (Andreou et al., 2014). In the second (de Bock et al., 2020), EEG recordings were conducted with a low resolution of 19 channels compared to the 74-channel montage used in our study. Moreover, the CHR state was defined by UHR criteria only in that study, thus missing basic symptom (BS) criteria, which are assumed to more directly reflect aberrations in brain processes than UHR (Schultze-Lutter et al., 2020).

Importantly, above mentioned studies (da Cruz et al., 2020; Rieger et al., 2016; Tomescu et al., 2015, 2014) report aside a decrease in class D, also an increase in class C to be specific to risk for psychosis and manifest psychosis. Here, we show a similar finding in CHR and FEP compared to HC. However, only class D differentiates patients from CC, but not class C. This is a crucial finding, since it suggests that the increase in class C is rather related to general psychopathology than specific to the psychosis spectrum. On the basis of the present data we are not able to specify the type of psychopathology that might be associated with

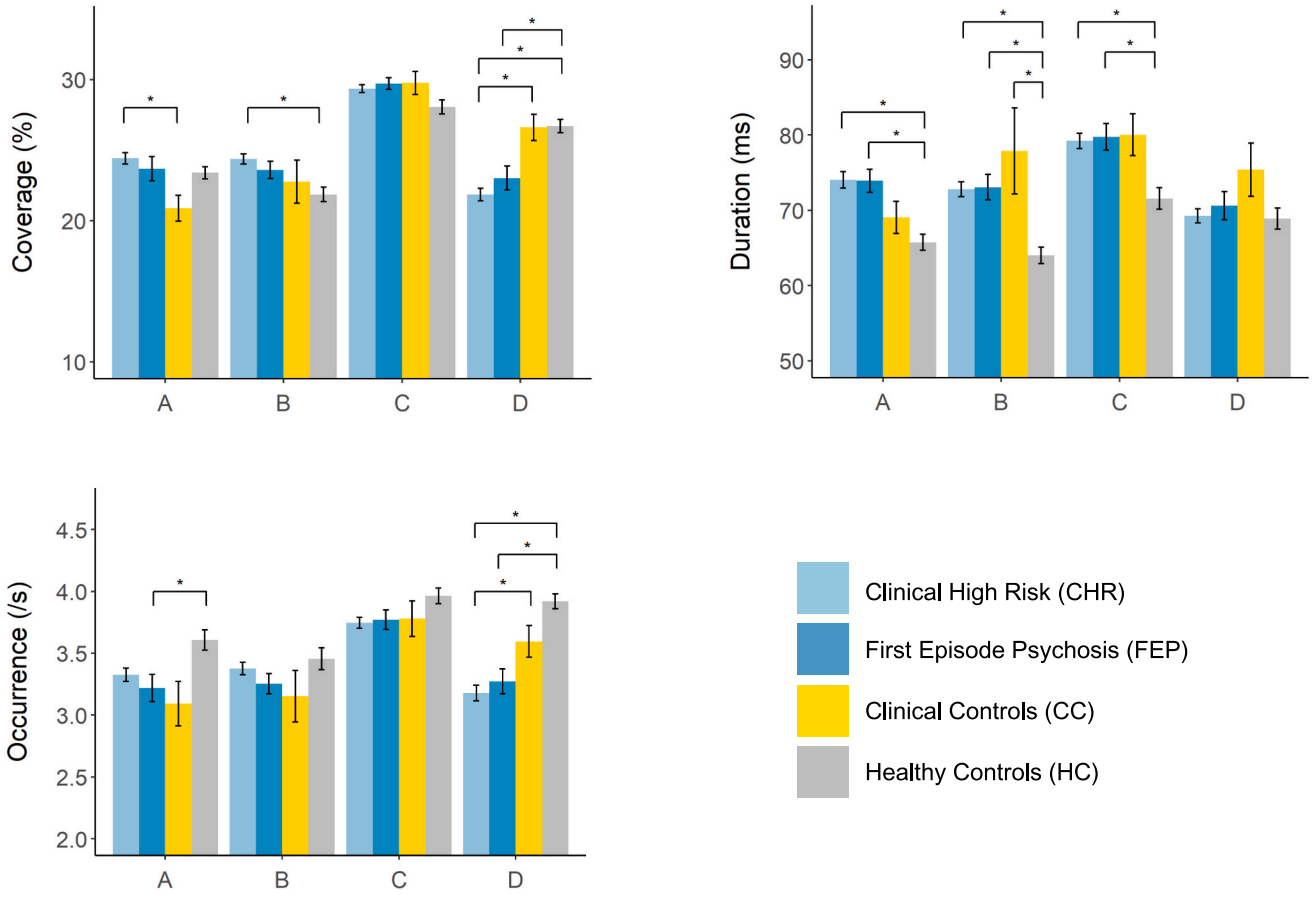

Fig. 2. Microstate dynamics (coverage, duration, occurrence) in microstate classes A-D, in the four investigated groups (CHR, FEP, CC, HC). Error bars display the standard error of the mean (SEM). Asterisks indicate significant comparisons after Bonferroni-Holm correction. Note that values on y-axis do not initiate from zero.

Table 2
Microstate group level effects.

	F	p	Significant post-hoc comparisons
Coverage (%)			
A	4.1	0.007	CHR > CC
B	5.1	0.002	CHR > HC
C	3.1	0.029	
D	19.8	<0.001	CHR < CC, CHR < HC, FEP < HC
Duration (ms)			
A	10.9	<0.001	CHR > HC, FEP > HC
B	11.7	<0.001	CHR > HC, FEP > HC, CC > HC
C	8.3	<0.001	CHR > HC, FEP > HC
D	1.9	0.125	
Occurrence (/s)			
A	5.4	0.001	FEP < HC
B	1.6	0.197	
C	2.9	0.035	
D	23.7	<0.001	CHR < CC, CHR < HC, FEP < HC

Legend for Table 2: Displayed are effects on the group level (F- and *p*-values) and significant post-hoc comparisons after correction for multiple comparisons with the Bonferroni-Holm method ($n = 24$ in every microstate parameter) in clinical high risk (CHR), first-episode psychosis (FEP), clinical controls (CC) and healthy controls (HC).

class C, this however is important be clarified in future studies. The specific finding in class D is in line with one study associating auditory verbal hallucinations (AHV) with a decrease in class D, but not with altered class C (Kindler et al., 2011). Moreover, a recent study found a significant difference in topography only in class D between schizophrenia patients and healthy controls, also speaking for a specificity of this class (Kim et al., 2021). Finally, specifically a decrease in class D has been associated with transition to psychosis from risk state, further underpinning the exclusive role of class D (de Bock et al., 2020). In terms of its functional significance, the class D decrease might point to a dysfunctional role of executive functioning (Tarailis et al., 2023). One possibility is that core cognitive functions such as attention, context updating and cognitive inhibition are less under cognitive control, thereby leading to typical psychotic symptoms. This however is speculative and needs to be clarified in future work.

In present data microstates C and D did not differentiate patients with a CHR state from those with manifest psychosis. This speaks against a dependency of these microstate signatures on disease progression. Similarly, a recent study did not report differences in classes C and D between schizophrenia patients and their siblings, who face increased risk for psychosis (da Cruz et al., 2020). Moreover, in the same study no different effects between patients with FEP and chronic schizophrenia were found, as well as no evolution in follow-up measurements in FEP patients over a period of one year. Also, in a further study microstates in classes C and D did not differ between patients with first-episode of schizophrenia and patients with a CHR state (Luo et al., 2020). In contrast, a recent study found a decrease of microstate D in patients who

transformed to psychosis within UHR state (de Bock et al., 2020). It also has to be taken into account that, as mentioned above, only a subset of CHR patients face transition to psychosis and CHR therefore represents a heterogenous pluripotent risk marker with multiple possible outcomes such as psychosis, depression, bipolar disorder or borderline disorder (Hartmann et al., 2021). Summing up, more longitudinal studies are needed to answer the question of disease stability of microstate markers. Present findings point carefully in the direction that altered microstate patterns are present from at risk stage and remain stable over the time course of the disease.

The main objective of this study was to investigate microstate dynamics across age groups from early adolescence to adulthood. Our analyses suggest that the finding of a decrease of microstate D in patients (FEP and CHR) is independent of age within the developmentally important age range from late childhood to young adulthood. This conclusion is supported by Bayesian statistics, in particular in CHR states, although support for absence of an age effect was not strong. However, priors were set rather conservative and sample size of FEP patients was relatively small. Moreover, we did not find any indication for a presence of age effects in any microstate class. This is in contrast to previous data speaking for an evolution of microstates with developmental stages (Koenig et al., 2002; Tomescu et al., 2018). In patients this might be due to an impaired dysfunctional neurodevelopment (Lewis and Levitt, 2002; Pino et al., 2014), the absence of this effect in healthy controls is however unclear. Nevertheless, the translation of microstate effects in class D to underage patients has two important implications. First, it suggests microstates as potential biomarker for psychosis, as it seems applicable as early as in adolescence and already in CHR status. This is of importance, as psychotic disorders generally remain untreated in children and adolescents for extended periods (Howes et al., 2021; Penttilä et al., 2014), which might convey the commonly assumed more negative outcome of early-onset psychosis (Immonen et al., 2017; Penttilä et al., 2014; Schimmelmann et al., 2008, 2007). Second, microstates have been proposed as endophenotype for schizophrenia (da Cruz et al., 2020). This would imply that psychosis-related microstate signatures are already present in early life, do not show evolution over age-groups nor differ between subjects at CHR and manifest psychosis. All of these aspects are supported by present data.

Aside from effects in microstate classes C and D, we also report group differences in classes A and B (Fig. 2). Overall, there is little knowledge about the relationship between classes A, B and psychosis. A recent study reported a decrease of class A in patients with schizophrenia (Murphy et al., 2020), but also an increase in FEP/CHR patients has been found (Andreou et al., 2014; de Bock et al., 2020), as well as absent differences between patients with schizophrenia or with increased risk for psychosis and controls (da Cruz et al., 2020; Tomescu et al., 2015, 2014). Similarly, mixed results in class B render it difficult what results can be expected in patients (Andreou et al., 2014; da Cruz et al., 2020; de Bock et al., 2020; Tomescu et al., 2015, 2014). Microstate findings in class A have been associated with transition to psychosis (Andreou et al., 2014) and findings in class B have been interpreted as compensatory signal in unaffected subjects with increased risk for psychosis (da Cruz et al., 2020) or as marker for illness progression within psychosis (de Bock et al., 2020). These conclusions are in contrast to present results, as in both classes we do not find differentiation between CHR and FEP patients. In sum, our data rather points to an unspecific role of classes A and B, possibly associated with general psychopathology. An increase of class B in CC compared to HC speaks in favor of this idea. However, for clarification of the roles of these two classes further research is needed and mixed results speak against applicability of these classes as reliable biomarker.

4.1. Strengths and limitations

Our study has several strengths and limitations. Among the strengths is the large sample size, in particular of the so far understudied CHR group, the age-range, as well as the inclusion of a clinical control group and of CHR patients meeting BS criteria. Yet, data was collected in two different centers with a clear sampling bias in respect to group assignment and a possible bias related to recording conditions (different EEG systems, number of electrodes and length of EEG recording, breaks with open eyes only in Bern). This bias might explain the slightly increased explained variance in CHR and FEP compared to HC. However, we did not find differences between groups in GFP and controlled for this potential confound in implementing separate microstate group means. Moreover, subjects were sampled in the same time period and geographical region, were age-matched and do not differ by sex distribution. Also, microstate analyses show overall good consistency across studies (Khanna et al., 2015; Michel and Koenig, 2018). The investigated groups differ in medication, adding a potential bias as microstates in the psychosis spectrum have been shown to be altered by antipsychotic medication (Kikuchi et al., 2007; Stevens et al., 1997). However, we controlled for antipsychotic dosage in our statistical model and also in further analysis no indication for an influence of medication on present data occurred. Moreover, a recent study comparing medicated and unmedicated FEP patients (Mackintosh et al., 2020) did not find differences in classes C and D (but in A/B). Another limitation is the cross-sectional design of our study that does not allow causal conclusions. Here, albeit longitudinal evolution of patients is challenging to study, further work is needed. In the discussion of our results, we assumed that all three investigated microstate parameters reflect comparable aspects of dynamics regarding one underlying neuronal generator (Khanna et al., 2015). This assumption is based on the fact that the three parameters are interdependent (Coverage = Occurrence * Duration), however further understanding of their specific qualities is needed.

5. Conclusions

This is the first study to directly investigate EEG microstate dynamics in a large sample of patients with high risk for and first-episode of psychosis in relation to age. Moreover, a clinical control group has been included. In patients compared to healthy and clinical controls, a psychosis-specific decrease of microstate parameters in class D was found, with no difference between CHR state and FEP. Importantly, findings were independent of age within the developmentally important age range from late childhood to young adulthood. Our findings strengthen the role of microstates as potential biomarker for psychosis, being of relevance as early as in adolescence and CHR state.

CRediT authorship contribution statement

Matthias Liebrand: Methodology, Software, Formal analysis, Data curation, Writing – original draft, Visualization, Project administration. **Angelos Katsarakis:** Data curation, Writing – review & editing. **Johannes Josi:** Methodology, Software, Formal analysis, Writing – review & editing. **Sarah Diezig:** Data curation, Writing – review & editing. **Chantal Michel:** Investigation, Resources, Writing – review & editing. **Frauke Schultze-Lutter:** Investigation, Resources, Writing – review & editing. **Vincent Rochas:** Investigation, Data curation, Writing – review & editing. **Valentina Mancini:** Investigation, Writing – review & editing. **Michael Kaess:** Resources, Writing – review & editing. **Daniela Hubl:** Resources, Writing – review & editing. **Thomas Koenig:** Conceptualization, Methodology, Software, Supervision, Writing – review & editing. **Jochen Kindler:** Conceptualization, Resources, Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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