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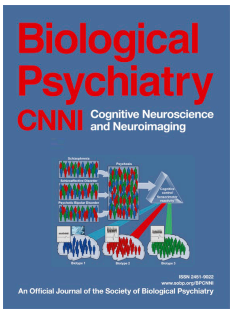

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EEG microstates as novel functional biomarkers for adult attention-deficit hyperactivity disorder

Victor Férat[1], Martijn Arns[2,3,4], Marie-Pierre Deiber[5,6], Roland Hasler[5,7], Nader Perroud[5,6], Christoph M. Michel[1,8], Tomas Ros[1,5,8]

[1] Functional Brain Mapping Laboratory, Department of Basic Neurosciences, Campus Biotech, University of Geneva, Geneva, Switzerland

[2] Research Institute Brainclinics, Brainclinics Foundation, Nijmegen, The Netherlands,

[3] Department of Psychiatry, Amsterdam UMC, University of Amsterdam, Location AMC, Amsterdam Neuroscience, The Netherlands,

[4] Department of Cognitive Neuroscience, Faculty of Psychology and Neuroscience, Maastricht University, Maastricht, The Netherlands

[5] Division of Psychiatric Specialties, Department of Psychiatry, University Hospitals of Geneva, Geneva, Switzerland

[6] Department of Psychiatry, Faculty of Medicine, University of Geneva, Geneva, Switzerland,

[7] Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia, Canada

[8] Centre for Biomedical Imaging (CIBM) Lausanne-Geneva, Geneva, Switzerland

Corresponding author:

Victor Férat
Victor.ferat@unige.ch
+41 22 379 54 57
Functional Brain Mapping Lab, Campus Biotech
Chemin des mines, 9 1202 Genève

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EEG microstates as biomarkers for adult ADHD

Keywords:

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- ADHD
- Attention
- Sleep disorders

Abstract

Background

Research on the electroencephalographic (EEG) signatures of attention-deficit hyperactivity disorder (ADHD) has historically concentrated on its frequency spectrum or event-related evoked potentials. In this work, we investigate EEG microstates, an alternative framework defined by the clustering of recurring topographical patterns, as a novel approach for examining large-scale cortical dynamics in ADHD.

Methods

Using kmeans clustering, we studied the spatio-temporal dynamics of ADHD during rest condition by comparing the microstate (MS) segmentations between adult ADHD patients and neurotypical controls, across 2 independent datasets: the first dataset consisted of 66 ADHD patients and 66 controls, while the second dataset comprised of 22 ADHD patients and 22 controls and was used for out-of-sample validation.

Results

Spatially, ADHD and control subjects displayed equivalent MS topographies (canonical maps), indicating preservation of prototypical EEG generators in ADHD. However, this concordance was accompanied by significant differences in temporal dynamics. At the group level, and across both datasets, ADHD diagnosis was associated with longer mean durations of a fronto-central topography (D), indicating its electrocortical generator(s) could be acting as pronounced “attractors” of global cortical dynamics. Lastly, in the first (larger) dataset, we also found evidence for decreased time coverage and mean duration of microstate A, which inversely correlated with ADHD scores, while microstate D metrics were correlated with sleep disturbance, the latter being known to have strong relation with ADHD.

Conclusions

Overall, our study underlines the value of EEG microstates as promising functional biomarkers for ADHD, offering an additional lens through which to examine its neurophysiological mechanisms.

Main Text

Introduction

Attention-deficit / hyperactivity disorder (ADHD) is characterized by developmentally inappropriate levels of inattention, hyperactivity, or impulsivity, and is one of the most common psychiatric disorders, with a prevalence of 1 out of every 20 adults (1,2). As a result, there is a pressing need to understand its neural underpinnings in the hope of devising better treatments.

Recent literature reviews point to abnormal resting (EEG) electroencephalogram activities in ADHD patients (3–6). This is exemplified by a significant cluster of ADHD patients with a high theta to beta power ratio (TBR) (5,7), a signature supportive of theories that ADHD may be caused by a delay of brain maturation (8), seeing that the theta/beta ratio is known to progressively attenuate during normal cortical development (9,10).

However more recent studies (11,12) have failed to replicate this finding of elevated TBR as a diagnostic feature in ADHD, which was also confirmed in a meta-analysis (13).

These divergent results suggest that the high TBR group, which is strongly associated with treatment response to methylphenidate (14) and neurofeedback (15,16), is only a subgroup within a wider spectrum of abnormal electrocortical activities. These different subtypes can also be found with the EEG signatures derived from adults with ADHD: which besides excess power of lower-frequency rhythms (17–19), also display opposing pattern(s) comprising of reduced alpha power (20,21) and/or excess higher-frequency beta power (22,23).Based on

these findings, the emerging consensus is that ADHD is not only highly heterogeneous in terms of behavior (24), but also electrophysiologically (25).

Although previous research on ADHD has concentrated on examining its EEG frequency spectrum (25), and/or event-related potentials (ERPs) (26) in this work we propose resting state EEG microstates (27) as an alternative analytical framework. Microstate analyses in ADHD have so far been limited to ERP microstates (28) (29), hence the spontaneous resting-state EEG still needs to be explored. By modelling the spontaneous EEG as a sequence of recurring topographical patterns, microstate (MS) analysis considers both spatial and temporal dynamics *simultaneously*. This could facilitate clearer spatio-temporal dissociations to be made in ADHD, as any uncovered deviations in MS dynamics would imply abnormal temporal activations of spatially distinct cortical generators. Although it is difficult to the identify microstates' precise anatomical generators through mere clustering of scalp EEG data, their abnormal temporal signatures nevertheless point to significant departures from typical cortical dynamics. This may be a valuable framework when considering the brain as a large-scale dynamical system (27) . Previous work has identified significant links between microstate map dynamics and behavioral dimensions in clinical populations. For instance, the duration of microstate class D has been found to correlate negatively with hallucinations in patients with schizophrenia (30). Interestingly, as MS topographies are estimated on a timepoint-by-timepoint basis (i.e. instantaneously) using a broadband (e.g. 1-30 Hz) signal, MS measures may be able to capture cortical dynamics that are either independent or common across EEG frequencies.

To validate these hypotheses, we apply below MS analysis to resting-state EEG recordings of 88 adults with ADHD, divided across two independent datasets. The first dataset, designated as the "test" sample, comprised of 66 ADHD patients and 66 neurotypical controls from the Netherlands. The second dataset, designated as the "retest" sample, comprised of 22 ADHD patients and 22 neurotypical controls from Switzerland.

Methods

I. Datasets

i. Dataset 1

Participants

EEG recording of 66 ADHD Patients (31 female, mean age: 34.1, SD: 11.4) and 66 controls (41 female, mean age: 36.5, SD: 12.4) were obtained from participants enrolled by Research Institute Brainclinics and the neuroCare Group Nijmegen in the Netherlands between 2001 and May 2018. (31). Briefly patients were screened for inclusion and included in case of an ADHD or ADD diagnosis (as confirmed by the MINI Diagnostic Interview or by a qualified clinician), or when ADHD-RS scores on either scale (ATT or HI) (32) was equal to or higher than 5, for this study only adults were included. Patients were also screened for sleep disorders trough the Pittsburgh Sleep Quality Index (PSQI) (33). Sample was composed of 3 ADHD subtypes including 40 patients of mixed subtype (inattentive and hyperactive), the "inattentive" subtype composed of 23 patients, and the "hyperactive" subtype composed of 3 patients. All subjects signed an informed consent before treatment was initiated.

Recordings

2-minute Eyes Open (EO) EEG recordings were performed thanks to a standardized reliable and consistent (34,35) developed by Brain Resource Ltd (36,37). Signals were recorded continuously using "Quickcap" a 26-electrode cap placed according to the 10–20 international system, with a sampling rate of 500 Hz. The ground electrode was placed on the scalp at AFz, and data was referenced to averaged mastoids. All electrode impedances were kept below 5 kΩ. In addition to that, a low pass filter above 100 Hz was applied prior to digitization and Horizontal and vertical eye movements were controlled for. EOG-correction based on Gratton et al. (38) was applied to the data.

ii. Dataset 2

Participants

Resting state EEG recordings of 22 ADHD (12 female, mean age: 32.3, SD: 9.2) adult patients and 22 healthy controls (14 female, mean age: 31.1, SD: 7.3) were obtained from (20). ADHD Patients were recruited through the Adult ADHD Unit at Geneva University Hospitals. After giving the written informed consent patient and controls underwent four clinical questionnaires including the Adult ADHD Self-Report Scale (ASRS v1.1) evaluates in 18 questions current ADHD symptoms in adolescents and adults (39).

Clinician's diagnostic was based on three structured questionnaires: the ADHD Child Evaluation for Adults (ACE+), https://www.psychology-services.uk.com/adhd.htm), the

French version of the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II,(40)) and the French version of the Diagnostic Interview for Genetic Studies (DIGS, mood disorder parts only, (41)(see (20) for extend description). Sample was composed of 3 ADHD subtypes: the "mixed" one composed of 16 patients of mixed subtype the "inattentive" subtype composed of 5 patients, and the "hyperactive" subtype composed of the last patient.

This study was approved by the Research Ethic Committee of the Republic and Canton of Geneva [project number 2017-01029].

Recordings

Here, 3 min of EO rest was recorded continuously using a 64 Ag/AgCl electrode cap (ANT Waveguard, Netherlands) placed according to the 10–20 international system, with a sampling rate of 500 Hz. The ground electrode was placed on the scalp at a site equidistant between Fpz and Fz, and the reference electrode at CPz. Electrical signals were amplified using the eego mylab system (ANT Neuro, Netherlands), and all electrode impedances were kept below 5 kΩ.

II. Preprocessing

Both datasets underwent the same preprocessing pipeline: data was processed in Matlab with EEGLAB (42), using the default settings of the Harvard Automated Processing Pipeline for Electroencephalography (HAPPE) (43). Concisely, this involved first filtering between 1-100 Hz, removing line noise with a notch filter (between 48-52 Hz), rejection of bad channels (standard deviation cutoff of z=3), removal of non-cerebral artifacts such as eye-blinks and

muscle activity using independent component analysis (via the MARA plug-in (44)). Lastly, rejection of "bad" 1-second EEG segments was carried out using amplitude-based and joint probability artifact detection (standard deviation cutoff of z=3).

III. Fitting

The de-artifacted data (from Datasets 1 and 2) was band-passed filtered between 1-30 Hz and re-referenced to common average reference. Microstate maps were estimated separately for each dataset (Dataset 1 and 2) and group (ADHD and CTRL). Here, we used Koenig's Microstate toolbox for EEGLAB (available at https://www.thomaskoenig.ch/index.php/software/microstates-in-eeglab). For each subject's resting-state recording, 2000 GFP (Global Field Power) peaks were selected randomly and submitted to modified (i.e. polarity-independent) kmeans clustering with 100 repetitions. For each cluster number k=4 to k=7, microstate (MS) maps (i.e. cluster centroids) were estimated firstly at the subject level, and then optimally re-ordered between subjects by minimizing the average spatial correlation across maps. Finally, respective MS maps were averaged across all subjects (within each dataset/group) to give the aggregate map for each cluster. We found that k=5 provided the highest map reliability across subjects and datasets, which was estimated as the mean spatial correlation of each subject's map with the group's aggregate.

IV. Backfitting

The k=5 global dominant maps of both datasets were then fitted back to the original EEGs using Cartool (45). During this procedure, each time point was assigned to a cluster label (i.e. microstate map) by spatial correlation analysis: each time point was assigned to the map with which it shared the highest absolute spatial correlation. If the spatial correlation was below the r=0.5 correlation threshold, the time point was labelled as "non-assigned". A smoothing window of 7 samples (56.0 ms) was used to ensure temporal continuity of the signal by adjusting correlation of the central time point with a smoothing factor of 10. Identical label sequences which did not reach a duration of 3 samples (24.0 ms) were split into two parts, each sharing the highest spatial correlation with its neighboring segment and relabeled accordingly to the latest. At the end of this procedure, non-assigned timepoints were removed and participants with z >= 3 of unlabeled timepoints were excluded of further analysis. A label sequence was derived for each individual recording, which was used to compute 3 metrics:

Global explain variance (Gev): the sum of variances weighted by the global field power of all time points assigned to a label. This metric is expressed in percentage (%).

Time coverage (TimeCov): the proportion of time during which a label is present in the recording. This metric is expressed in percentage (%).

Mean duration (MeanDur): mean temporal duration during which a label is present without interruption. This metric is expressed in milliseconds (ms).

After backfitting, outlier detection based on a high number of unlabeled timepoints (z score >3, dataset 1 = 13% | dataset 2 = 18%) identified two control subjects from dataset 1 and one control subject from dataset 2. These subjects were excluded from further analysis.

V. Power Spectrum Analysis

Absolute power spectral density (PSD) was computed using Welch's method for frequencies ranging from 2 to 30Hz. The window had an effective size of 2.048 seconds and no overlap. To obtain a relative metric that could be used for between subject comparisons, all values were divided by the sum of the full spectrum (2 - 30Hz). Obtained values were then added up within each studied frequency band: delta (2 - 4Hz), theta (4 - 8 Hz), alpha (8 - 12 Hz), low-beta (12 - 20 Hz) and high-beta (20 - 30 Hz) for further analysis.

VI. Clinical measures of inattention and hyperactivity

For each dataset, we selected the standardized clinical questionnaires that best reflected current (i.e. adult) symptoms of ADHD.

For dataset 1, this was the ADHD Rating Scale (ADHD-RS, (37), which contained 23 questions regarding the presence of symptoms on a 4-point scale (0 =rarely or never, 1 =sometimes, 2 =often, 3 =very often). The ADHD-RS contains two subscales for symptoms of inattention and hyperactivity.

For dataset 2, this was the Adult ADHD Self-Report Scale (ASRS v1.1) which uses 18 questions on a 5-point scale (0 =never, 1=rarely, 2=sometimes, 3=often, 4=very often) to

evaluate current ADHD symptoms in adolescents and adults (44). The ASRS contains two subscales that assess the dimensions of hyperactivity and inattention.

VI. Statistics

Group comparisons were conducted on the 3 spatiotemporal parameters thanks to unpaired permutation test for equality of means. Due to the absence of pre-established hypothesis, two-sided test was used for the first dataset. Results derived from this first analysis were used to establish working hypotheses for the second dataset leading to the use of one-sided tests. P-values were estimated by simulated random sampling with 10000 replications. Cohen's d (d) was used to report effect sizes as standardized difference of means. When applicable, statistical results were corrected for multiple comparisons using Bonferroni method.

Correlations between microstates parameters and Clinical scores were computed using two-sided permutation test (10000 permutations) on Pearson correlation coefficient.

Results

I. Dataset 1

i. Microstate topographies

In the first dataset, we examined two minutes resting-state EEG data of 66 patients with ADHD and 66 controls. Neither mean age ($p = 0.25$) nor gender (fisher exact test, $p=0.08$) between groups differed significantly.

We applied microstate (MS) segmentation to both groups independently to identify potential topographies that might be specific to one population. We identified 5 equivalent maps across both ADHD and CTRL groups (Figure 1), corresponding to traditional MS topographies previously reported in the literature: a left-right diagonal orientation (A), a right-left diagonal orientation (B), a fronto-posterior orientation (C), fronto-central maximum (D) and a parieto-central maximum (F). Spatial correlation analysis revealed negligible differences between group MS maps, with a minimum absolute correlation of 87% for matched topographies.

Consequently, we concatenated the EEGs of both ADHD and CTRL groups into a single 'pooled' kmeans analysis, to obtain a set of common maps for both groups. These latter maps were used in the backfitting of all individual participant data.

ii. Microstate Segmentation

As seen in Figure 2, we firstly observed a reduced temporal prevalence of map A in the ADHD group compared to CTRL: in other words, the relative amount of time subjects spend in this configuration was significantly reduced ($p \leq 0.05$, d= -0.43) in the ADHD group compared to CTRL. Additionally, although non-significant, state durations of map A were on average lower for the ADHD group (n.s., d= -0.-59) and the amount of global variance explained by map A was also reduced on average (n.s., d= -0.32).

Interestingly, opposite effects were found for map D, which exhibited a relative increase in prevalence in the ADHD group: the fronto central topography of map D explained on average

more global variance (GEV, $p \leq 0.01$, $d = 0.71$), dominated an increased temporal proportion (Time Coverage, $p \leq 0.05$, $d = 0.59$) and had longer state durations (Mean Duration, $p \leq 0.05$, $d = 0.53$) in the ADHD population.

No significant results were found for other topographies

iii. Regression analysis between microstates parameters and clinical measures

By focusing on the significant results of the group-wise analysis, we hypothesized that microstate A and D dynamics might be related to differences in ADHD severity. We evaluated the relationship between the parameters of these two microstates and individual scores on the ADHD Rating Scale in ADHD patients. As show in in Figure 3, correlation analyses revealed a negative correlation between the microstate A parameters and clinical ADHD scores: significant negative correlations were found between map A Time coverage and ADHD_total score ($p \leq 0.05$ ($F(x) = -0.2x + 15, R^2 = 7.7\%$), as well as ADHD_Hyperactivity ($p \leq 0.05$ $F(x) = -0.1x + 7, R^2 = 7.4\%$). Similar results were found between map A global explained variance (Gev) and ADHD_total score ($p \leq 0.05$ $F(x) = -0.3x + 14, R^2 = 7.7\%$) and ADHD_Hyperactivity ($p \leq 0.05$ $F(x) = -0.2x + 7, R^2 = 7.1\%$). Mean duration of map A was also correlated to ADHD_total score ($p \leq 0.05$ $F(x) = -0.1x + 22, R^2 = 9.3\%$) and ADHD_Inattention ($p \leq 0.05$ $F(x) = -0.06x + 11, R^2 = 5.8\%$). In this dataset, no significant correlations were found between clinical measures and map D parameters.

Microstate D dynamics were also associated with Pittsburgh Sleep Quality Index (PSQI) (Figure 4) in the ADHD group, where higher PSQI scores indicate greater sleep disturbance. Here, positive correlations were found between PSQI total score and microstate D global explained variance ($p \leq 0.05$ $F(x) = 0.3x + 5.8$, $R^2 = 7.8\%$) and time coverage ($p \leq 0.05$ $F(x) = 0.2x + 4.8$, $R^2 = 8.4\%$).

II. Dataset 2

i. Microstate topographies

In this second 'replication' dataset, we applied the same MS analysis pipeline to 3 min resting-state EEG data of 22 adult ADHD patients and 22 adult controls. Neither mean age ($p = 0.66$) nor gender (fisher exact test, $p=0.8$) between groups differed significantly.

. We observed remarkably similar MS topographies to dataset 1 (Figure 5), with a minimal inter-dataset spatial correlation of 0.89 (Figure S1). Both ADHD and CTRL groups exhibited the 5 classical microstate topographies ABCDF. Spatial correlation analysis revealed minor difference between ADHD and CTRL group topographies (Figure 4a), with a minimum absolute correlation of 91% on the diagonal. Topographies were unchanged after concatenation of the ADHD and CTRL data. Similarly, to dataset 1, we used the group concatenated MS maps for backfitting and estimation of MS dynamics at the level of individual subjects.

ii. Microstate Segmentation

Based on the independent, group-wise differences found in the first dataset, we hypothesized that microstate D parameters would be elevated in the ADHD population while those of map A would be reduced. To test this, we performed directional (i.e. one-sided) permutation tests for equality of means on microstate A and D parameters only (Figure 6). Hence, in this section, statistical results were corrected for 6 comparisons.

We replicated the deviations for map D both in terms of effect size and statistical significance: timepoints assigned to map D were significantly longer ($p = 0.05$, $d = 0.77$) in the ADHD population, while noticeable (but non-significant) increases of global explained variance (n.s., $d = 0.49$) and time coverage (n.s., $d = 0.57$) were also present. No significant differences were found for map A, hence ADHD deviations in this microstate were not replicated (n.s., GEV: $d = -0.14$ | time coverage: $d = -0.07$ | mean duration: $d = 0.42$) in terms of statistical significance.

iii. Clinical correlations

Based on group analyses led on both datasets, we tested the assumption that only microstate A and D would have a significant relationship with clinical scores.

Analysis of ADHD patients alone did not reveal any significant correlations between ADHD clinical scores and those MS parameters.

Spectral power analysis

None of the EEG bands demonstrated significant differences between ADHD and CTRL groups after Bonferroni correction, either for the first or second dataset (Fig 7).

Discussion

The aim of this study was to investigate EEG microstates (MS) as potentially novel functional biomarkers for attention deficit and hyperactivity disorder (ADHD). By applying this method to adult ADHD patients, we uncovered new electrophysiological characteristics of this disorder. To this end, we applied spatial kmeans-clustering to two independent datasets, each composed of adults with ADHD and a neurotypical control group. We firstly observed a close correspondence between ADHD topographies (i.e. map clusters) and classical MS maps (A, B, C, D, F) typical of the normal population, suggesting no major deviations in the spatial organization of electrocortical generators. This equivalence enabled us to estimate each MS map underlying temporal dynamics, while testing for any statistical differences between ADHD and control samples. Here, we identified a longer mean temporal duration of a fronto-central topography (microstate D), which was statistically significant and had a medium-to-large effect size in both the first and second datasets (d=0.59 and d=0.77, respectively). Secondly, in the first (larger) dataset, we found additional evidence for decreased time coverage (d = -0.59) and mean duration (d = -0.43) of microstate A, which inversely correlated with ADHD inattention scores.

Microstate D

Interestingly, microstate D has been reported to be more expressed during attentional tasks, such mental arithmetic (46,47), so it is intriguing (and perhaps counterintuitive) that it is also observed to be more prevalent in ADHD. However, a stronger temporal prevalence of specifically microstate D has also been found to accompany periods of unresponsiveness to stimuli during transitions to drowsiness (48). In contradistinction, a recent study reported that microstate D duration was positively correlated with vigilance level (49). Microstate D prevalence has also been observed to be altered during hypnosis (50), hallucinations (30), sleep (46,51) and in patients with schizophrenia (52)In view of the larger prevalence and duration of microstate D in both our datasets, this balance seems to be tipped towards the upper end of the distribution in adult ADHD. As a result, we hypothesize that the electrocortical generator(s) of map D may be acting as persistent "attractors" of cortical dynamics, thereby reducing their global variability and/or complexity. This interpretation would also be compatible with a recent review suggesting that microstate D may be responsible for aspects of reflexive attention such as reorientation and switching of attentional focus (27,53,54).

Anatomically, the fronto-central topography of map D has previously been associated with activation of the right inferior parietal lobe, the right middle and superior frontal gyri, and the right insula (46,55,56). These brain regions are known to be part of the Dorsal Attention Network (57,58). Hence, our findings tentatively point to abnormal dynamics within this network and are supported by functional MRI studies (59).

Relationship with sleep disturbance

Interestingly, we observed a significant correlation between microstate D prevalence and poorer sleep quality in ADHD patients. Several relationships have previously been established between sleep disorders and attentional deficits (see (60) for a review). This result is even more intriguing considering a recent study by Ke and colleagues (61), who reported increases in microstate D coverage (and a reduction in microstate A) in sleep deprived individuals. These results, which overlap with those observed in the present study, support pre-existing hypotheses of a trinity between sleep, hyperactivity disorder and abnormal EEG signatures (62,63).

Microstate A

In the larger dataset,, we additionally observed significantly decreased time coverage of microstate A, which was inversely correlated with clinical inattention scores in the ADHD sample. A recent study has shown that states of increased vigilance/alertness were associated with relatively less prevalence of microstate A (and longer durations of microstate D) (49). Thus, the combined signature of lower microstate A coverage and increased microstate D duration in our study would imply that ADHD could be characterized as a condition of "hyper-vigilance", consistent with its behavioral symptoms of physical and emotional hyperactivity (65,66).

Spectral Power differences

Classical EEG spectral power analyses have frequently revealed slow-wave (e.g. theta) abnormalities with a fronto-central topography in clinical cohorts with ADHD (e.g. (67,68)). A plethora of studies have investigated spectral power differences in childhood and adult ADHD (5,69), but ultimately systematic reviews report an absence of consistent resting EEG abnormalities that could be characteristic of ADHD (6). This is in line with the data presented here, for which no significant differences in relative spectral power were found between ADHD and CTRL groups. Specifically, in the first dataset we observed relatively decreased low-beta power in ADHD patients compared to controls, while the second dataset appeared to have the opposite pattern. One may notice significance of this result different from the original article (20) using dataset 2. In our view, the difference may be explained by first a loss of statistical power owing to a smaller sample size necessary for balancing the dataset during MS analysis, and second a change in filter settings, since in the study broadband was defined as 1 - 30 Hz while original work used 0.5 - 40 Hz.

Consequently, it is possible that microstate measures, in particular microstate D, may prove to be more generalizable auxiliary biomarkers for the diagnosis and/or prognosis of ADHD.

Conclusion

In conclusion, and to the best of our knowledge, we present the first study resting-state microstate dynamics in adult with ADHD. We have confirmed across two datasets that microstates D and/or A may be promising functional biomarkers of ADHD (or at least one subtype of it). To date, although no biological markers have been successfully used to clearly diagnose or guide ADHD treatment, the potential application of microstate analysis in this

population could prove to be an additional asset, to better understand its neurophysiological mechanisms.

Limitations

Given the case-cohort design as well as correlational analyses of this cross-sectional study, there was no way of being certain whether the observed MS differences were actually a cause or a consequence of ADHD. It is important to note that the process of diagnosing ADHD may have differed between and within our two datasets, given the involvement of different clinicians and psychiatric scales, and that those diagnostic methods may differ for current standard (70,71) especially for the second dataset which has not considered symptom history (71). Hence, it is possible that the microstate biomarkers uncovered are not specific to ADHD as a diagnosis per se but some of its behavioral subcomponent; for example, sleep disturbance (72).

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Disclosures

MA is unpaid chairman of the non-profit Brainclinics Foundation, a minority shareholder in neuroCare Group (Munich, Germany), and a co-inventor on 4 patent applications related to EEG, neuromodulation and psychophysiology, but receives no royalties related to these patents. The other authors report no biomedical financial interests or potential conflicts of interest.

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Legends for tables and figures

Figure 1

Dataset 1: EEG microstate topographies in ADHD adults (n=66) vs. controls (CTRL, n=66). A) *The five EEG resting-state topographies for the 3 conditions: ADHD, CTRL and ALL (ADHD + CTRL).* ***B)*** *Spatial correlation coefficients of the 5 resting-state topographies between ADHD and CTRL.*

Figure 2

Dataset 1: Measures of EEG microstate dynamics in ADHD adults (n=66) vs. controls (CTRL, n=64). A) *The five EEG microstates for the 3 conditions: ADHD, CTRL and ALL (ADHD + CTRL).* ***B)*** *global explained variance (GEV) of each microstate.* ***C)*** *time coverage of each microstate.* ***D)*** *mean duration of each microstate. (**p ≤ 0.001, *p ≤ 0.05, Bonferroni corrected for 15 comparisons). Boxplots consist of median (Q2), first quartile (Q1), third quartile (Q3), maximum (Q3 + 1.5*(Q3 - Q1)), minimum (Q1 -1.5*((Q3 - Q1).*

Figure 3

Dataset 1: Correlation between EEG microstate parameters and ADHD clinical scores (ADHD patients only, n=66). *Scatterplots:* ***A)*** *between ADHD clinical score (ADHD_total) and microstate A global explained variance (Gev, %).* ***B)*** *between ADHD clinical score (ADHD_total) and microstate A Time Coverage (%).* ***C)*** *between ADHD clinical score (ADHD_total) and microstate A Mean Duration (ms). ADHD patients only (n= 66), all univariate regressions are significant.*

Figure 4

Dataset 1: Correlation between EEG microstate parameters and ADHD sleep quality (ADHD patients only, n=66). *Scatterplots:* ***A)*** *between ADHD PSQI total score (PQSI_total_pre) and microstate D global explained variance (Gev, %).* ***B)*** *between ADHD PSQI total score (PQSI_total_pre) and microstate D Time Coverage (%). ADHD patients only (n= 66), all univariate regressions are significant.*

Figure 5

Dataset 2: EEG topographies in ADHD adults (n=22) vs. controls (CTRL, n=22). A) *The five EEG resting-state topographies for the 3 conditions: ADHD, CTRL and ALL (ADHD + CTRL).* ***B)*** *Spatial correlation coefficients of the 5 resting-state topographies between ADHD and CTRL.*

Figure 6

Dataset 2: EEG microstates in ADHD adults (n=22) vs. controls (CTRL, n=21). A) *The five EEG microstates for the 3 conditions: ADHD, CTRL and ALL (ADHD + CTRL).* ***B)*** *global explained variance (GEV) of each microstate.* ***C)*** *time coverage of each microstate.* ***D)*** *mean duration of each microstate(*p ≤ 0.05, Bonferroni corrected for 6 a priori comparisons). Boxplots consist of median (Q2), first quartile (Q1), third quartile (Q3), maximum (Q3 + 1.5*(Q3 - Q1)), minimum (Q1 -1.5*((Q3 - Q1).*

Figure 7

EEG relative power spectrum differences between ADHD and CTRL groups*. For dataset 1 (left panel, ADHD=66, CTRL=66) and dataset 2 (right panel, ADHD=22, CTRL=22): relative band-power values over all electrodes. Solid lines represent mean value across subjects; shaded areas represent 95% confidence intervals. Traditional frequency bands: delta (orange, 2 - 4Hz), theta (green, 4 - 8 Hz), alpha (blue, 8 - 12 Hz), low-beta (red, 12 - 20 Hz) and high-beta (purple, 15 - 30 Hz) are highlighted on the x-axis.*