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Archival Report

Electroencephalographic Microstates as Novel Functional Biomarkers for Adult Attention-Deficit/Hyperactivity Disorder

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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 (MSs), 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 k-means clustering, we studied the spatiotemporal dynamics of ADHD during the rest condition by comparing the MS segmentations between adult patients with ADHD and neurotypical control subjects across two independent datasets: the first dataset consisted of 66 patients with ADHD and 66 control subjects, and the second dataset comprised 22 patients with ADHD and 22 control subjects and was used for out-of-sample validation.

RESULTS: Spatially, patients with ADHD and control subjects displayed equivalent MS topographies (canonical maps), indicating the preservation of prototypical EEG generators in patients with 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 frontocentral topography (MS D), indicating that its electrocortical generator(s) could be acting as pronounced attractors of global cortical dynamics. In addition, its spatiotemporal metrics were correlated with sleep disturbance, the latter being known to have a strong relationship with ADHD. Finally, in the first (larger) dataset, we also found evidence of decreased time coverage and mean duration of a left-right diagonal topography (MS A), which inversely correlated with ADHD scores.

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

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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 in 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 electroencephalogram (EEG) activities in patients with ADHD (3–6). This is exemplified by a significant cluster of patients with ADHD 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), given that TBR 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 (5).

These divergent results suggest that the high TBR group, which is strongly associated with treatment response to methylphenidate (13) and neurofeedback (14,15), 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 (16–18), also display opposing pattern(s) comprising reduced alpha power (19,20) and/or excess higher-frequency beta power (21,22). Based on these findings, the emerging consensus is that ADHD is highly heterogeneous not only in terms of behavior (23) but also electrophysiologically (24).

Although previous research on ADHD has concentrated on examining its EEG frequency spectrum (24) and/or event-related potentials (25), in this work we propose resting-state EEG microstates (MSs) (26) as an alternative analytic framework. MS analyses in ADHD have so far been limited to event-related potential MSs (27,28); therefore, the spontaneous resting-state EEG still needs to be explored. By modeling spontaneous EEG as a sequence of recurring topographical patterns, MS analysis considers both spatial and temporal

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dynamics simultaneously. This could facilitate clearer spatiotemporal 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 identify the precise anatomical generators of the MSs 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 dynamic system (26). Previous work has identified significant links between MS dynamics and behavioral dimensions in clinical populations. For instance, the duration of a frontocentral topography often referred to in the literature as MS class D (MS D) has been found to correlate negatively with hallucinations in patients with schizophrenia (29). Interestingly, as MSs are estimated on a time point–by–time point 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 applied the below MS analysis to resting-state EEG recordings of 88 adult patients with ADHD, divided across two independent datasets. The first dataset, designated as the test sample, comprised 66 patients with ADHD and 66 neurotypical control subjects from the Netherlands. The second dataset, designated as the retest sample, comprised 22 patients with ADHD and 22 neurotypical control subjects from Switzerland.

METHODS AND MATERIALS

Datasets

Dataset 1: Participants. EEG recording of 66 patients with ADHD (31 female; mean age = 34.1, SD = 11.4 years) and 66 control subjects (41 female; mean age = 36.5, SD = 12.4 years) were obtained from participants enrolled by Research Institute Brainclinics and the neuroCare Group Nijmegen in the Netherlands between 2001 and May 2018 (30). Briefly, patients were screened for inclusion and included in case of an ADHD or attention-deficit disorder diagnosis (as confirmed by the Mini-International Neuropsychiatric Interview or by a qualified clinician), or when ADHD Rating Scale scores on either scale (attention deficit or hyperactivity/impulsivity) (31) was ≥5; for this study, only adults were included. Patients were also screened for sleep disorders through the Pittsburgh Sleep Quality Index (PSQI) (32). The sample comprised three ADHD subtypes, including 40 patients of mixed subtype (inattentive and hyperactive), 23 patients of inattentive subtype, and 3 patients of hyperactive subtype. All subjects signed an informed consent before treatment was initiated.

Dataset 1: Recordings. Two-minute eyes-open EEG recordings were performed using a standardized reliable and consistent procedure (33,34) developed by Brain Resource Ltd. (35,36). Signals were recorded continuously using Quickcap, a 26-electrode cap, with a sampling rate of 500 Hz, placed according to the 10–20 international system. The ground electrode was placed on the scalp at AFz, and data were 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. Electrooculography correction based on Gratton *et al.* (37) was applied to the data.

Dataset 2: Participants. Resting-state EEG recordings of 22 adults patients with ADHD (12 female; mean age = 32.3, SD = 9.2 years) and 22 healthy control subjects (14 female; mean age = 31.1, SD = 7.3 years) were obtained from (19). Patients with ADHD were recruited through the Adult ADHD Unit at Geneva University Hospitals. After giving written informed consent, patients and control subjects answered four clinical questionnaires including the Adult ADHD Self-Report Scale (ASRS) version 1.1, which evaluates current ADHD symptoms in adolescents and adults in 18 questions (38).

The clinician's diagnosis 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 (39)], and the French version of the Diagnostic Interview for Genetic Studies (mood disorder parts only) (40) [see (19) for extended description]. The sample was comprised three ADHD subtypes: the mixed one comprising 16 patients of mixed subtype, the inattentive subtype comprising 5 patients, and the hyperactive subtype comprising the last patient.

This study was approved by the Research Ethic Committee of the Republic and Canton of Geneva (Project No. 2017-01029).

Dataset 2: Recordings. Here, the 3-minute duration of the eyes-open rest was recorded continuously using a 64 Ag/AgCl electrode cap (ANT Waveguard), placed according to the 10–20 international system, at 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), and all electrode impedances were kept below 5 kΩ.

Preprocessing

Both datasets underwent the same preprocessing pipeline: data were processed in MATLAB version 2018b with EEGLAB (The MathWorks, Inc.) (41), using the default settings of the Harvard Automated Processing Pipeline for Electroencephalography (42). Concisely, this involved first filtering between 1 and 100 Hz, removing line noise with a notch filter (between 48 and 52 Hz), rejection of bad channels (SD cutoff of $z = 3$), and removal of noncerebral artifacts such as eye blinks and muscle activity using independent component analysis [via the MARA plug-in (43)]. Finally, the rejection of bad 1-s EEG segments was carried out using amplitude-based and joint-probability artifact detection (SD cutoff of $z = 3$).

Fitting

The deartifacted data (from datasets 1 and 2) were bandpass filtered between 1 and 30 Hz and re-referenced to common

average reference. MS topographies were estimated separately for each dataset (datasets 1 and 2) and for ADHD and control groups. We used the Koenig Microstate toolbox for EEGLAB (available at https://www.thomaskoenig.ch/index.php/software/microstates-in-eeglab). For each subject's resting-state recording, 2000 global field power peaks were selected randomly and submitted to modified (i.e., polarity-independent) k-means clustering with 100 repetitions. For each cluster number from k = 4 to k = 7, MS maps (i.e., cluster centroids) were estimated, first at the subject level and then optimally reordered between subjects by minimizing the average spatial correlation across maps. Finally, the 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.

Backfitting

The k = 5 global dominant topographies of both datasets were then fitted back to the original EEGs using Cartool (44). During this procedure, time points were assigned to cluster labels (i.e., MS topography) by spatial correlation analysis: each time point was assigned to the topography 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 labeled as nonassigned. A smoothing window of seven samples (56.0 ms) was used to ensure temporal continuity of the signal by adjusting the correlation of the central time point with a smoothing factor of 10. Identical label sequences that 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. At the end of this procedure, nonassigned time points were removed, and participants with $z \geq 3$ for unlabeled time points were excluded from further analysis. A label sequence was derived for each individual recording and used to compute three metrics. First, global explained variance (GEV), which is the sum of variances weighted by the global field power of all time points assigned to a label. This metric is expressed in percentage (%). Second, time coverage, which is the proportion of time during which a label is present in the recording. This metric is expressed in percentage (%). Third, mean duration, which is the mean temporal duration during which a label is present without interruption. This metric is expressed in milliseconds.

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

Power Spectrum Analysis

Absolute power spectral density was computed using the Welch method for frequencies ranging from 2 to 30 Hz. The window had an effective size of 2.048 s 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 (2–30 Hz). The obtained values were then added up within each studied frequency band for further analysis: delta (2–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), low-beta (12–20 Hz), and high-beta (20–30 Hz).

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 (36), 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 Rating Scale contains two subscales for symptoms of inattention and hyperactivity.

For dataset 2, this was the Adult ADHD Self-Report Scale version 1.1, which comprises 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 (43). The ADHD Self-Report Scale contains two subscales that assess the dimensions of hyperactivity and inattention.

Statistics

Group comparisons were made based on the three spatio-temporal parameters obtained from the unpaired permutation test for equality of means. Owing to the absence of a pre-established hypothesis, the two-sided test was used for the first dataset. Results derived from this first analysis were used to establish the working hypotheses for the second dataset, leading to the use of one-sided tests. p Values were estimated by simulated random sampling with 10,000 replications. Cohen's d was used to report the effect size as the standardized difference of means. When applicable, statistical results were corrected for multiple comparisons using the Bonferroni method.

Correlations between MS parameters and clinical scores were computed using the two-sided permutation test (10,000 permutations) on the Pearson correlation coefficient.

RESULTS

Dataset 1

MS Topographies. In the first dataset, we examined the 2-minute resting-state EEG data of 66 patients with ADHD and 66 control subjects. Neither mean age ($p = .25$) nor sex (Fisher's exact test, $p = .08$) differed significantly between groups.

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

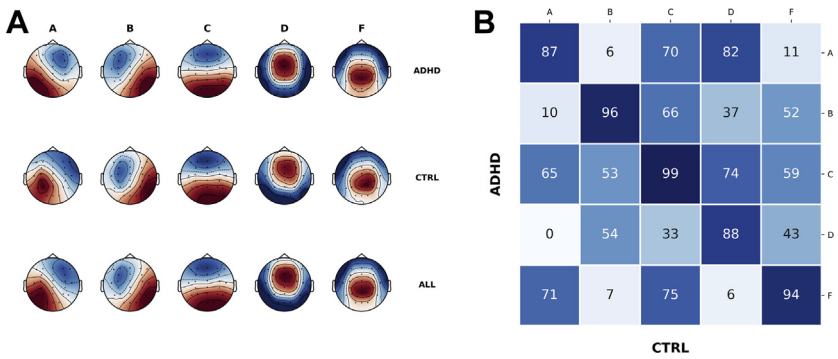

Figure 1. Dataset 1. Electroencephalographic microstate topographies in adults with attention-deficit/hyperactivity disorder (ADHD) (n = 66) vs. control subjects (CTRL) (n = 66). **(A)** The five electroencephalographic resting-state topographies for the three conditions: ADHD, CTRL, and ALL (ADHD+CTRL). **(B)** Spatial correlation coefficients of the five resting-state topographies between ADHD and CTRL.

Consequently, we concatenated the EEGs of both ADHD and control groups into a single-pooled k-means analysis, to obtain a set of common topographies for both groups. These latter maps were used for backfitting all individual participant data.

MS Segmentation

As can be seen in Figure 2, we first observed a reduced temporal prevalence of MS A in the ADHD group compared to the control group: in other words, the relative amount of time subjects spent in this configuration was significantly reduced

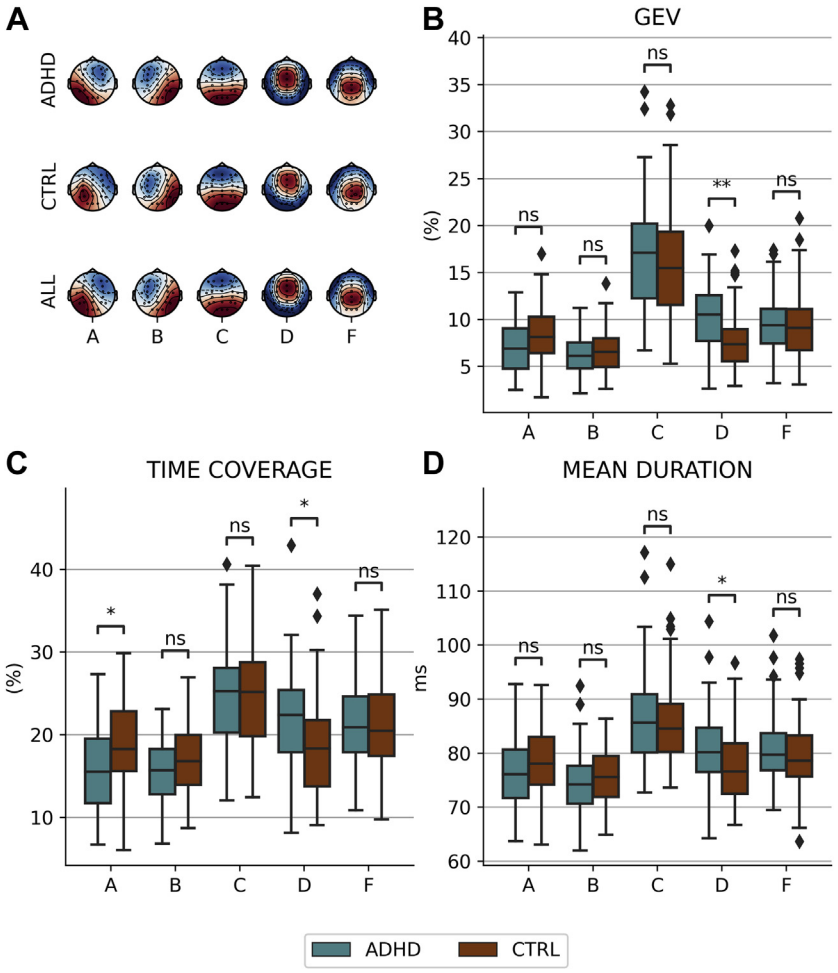

Figure 2. Dataset 1. Measures of electroencephalographic microstate (MS) dynamics in adults with attention-deficit/hyperactivity disorder (ADHD) (n = 66) vs. control subjects (CTRL) (n = 64). **(A)** The five electroencephalographic MSs for the three conditions: ADHD, CTRL, and ALL (ADHD+CTRL). **(B)** Global explained variance (GEV) of each MS. **(C)** Time coverage of each MS. **(D)** Mean duration of each MS. $^{**}p \leq .001$, $^{*}p \leq .05$, Bonferroni corrected for 15 comparisons. Boxplots consist of median (Q2), first quartile (Q1), third quartile (Q3), maximum (Q3 + 1.5 × [Q3 − Q1]), and minimum (Q1 − 1.5 × [Q3 − Q1]). ns, not significant.

($p \leq .05$, $d = -0.43$) in the ADHD group compared to the control group. In addition, although nonsignificant (n.s.), state durations of MS A were, on average, lower for the ADHD group (n.s., $d = -0.59$), and the amount of global variance explained by MS A was also reduced on average (n.s., $d = -0.32$).

Interestingly, opposite effects were found for MS D, which exhibited a relative increase in prevalence in the ADHD group: the frontocentral topography of MS D explained on average more global variance (GEV, $p \leq .01$, $d = 0.71$), dominated an increased temporal proportion (time coverage, $p \leq .05$, $d = 0.59$) and had longer state durations (mean duration, $p \leq .05$, $d = 0.53$) in the ADHD population. No significant results were found for other topographies.

Regression Analysis Between MS Parameters and Clinical Measures. By focusing on the significant results of the groupwise analyses, we hypothesized that MS A and D dynamics might be related to differences in ADHD severity. We evaluated the relationship between the parameters of these two MSs and individual scores on the ADHD Rating Scale in patients with ADHD. As shown in Figure 3, correlation analyses revealed a negative correlation between MS A parameters and clinical ADHD scores: significant negative correlations were found between MS A time coverage and the ADHD_total score ($p \leq .05$ $F(x) = -0.2x + 15$, $R^2 = 7.7\%$), as well as ADHD_Hyperactivity ($p \leq .05$ $F(x) = -0.1x + 7$, $R^2 = 7.4\%$). Similar results were found between MS A GEV and the ADHD_total score ($p \leq .05$ $F(x) = -0.3x + 14$, $R^2 = 7.7\%$) and ADHD_Hyperactivity ($p \leq .05$ $F(x) = -0.2x + 7$, $R^2 = 7.1\%$). The mean duration of MS A was also correlated to the ADHD_total score ($p \leq .05$ $F(x) = -0.1x + 22$, $R^2 = 9.3\%$) and ADHD_Inattention ($p \leq .05$ $F(x) = -0.06x + 11$, $R^2 = 5.8\%$). In this dataset, no significant correlations were found between clinical measures and MS D parameters.

MS D dynamics were also associated with PSQI (Figure 4) in the ADHD group, where higher PSQI scores indicate greater sleep disturbance. Here, positive correlations were found between the PSQI total score and MS D GEV ($p \leq .05$ $F(x) = 0.3x + 5.8$, $R^2 = 7.8\%$) and time coverage ($p \leq .05$ $F(x) = 0.2x + 4.8$, $R^2 = 8.4\%$).

Dataset 2

MS Topographies. In this second replication dataset, we applied the same MS analysis pipeline to the 3-minute resting-state EEG data of 22 adult patients with ADHD and 22 adult control subjects. Neither mean age ($p = .66$) nor sex (Fisher's exact test, $p = .8$) differed significantly between groups.

We observed remarkably similar MS topographies to dataset 1 (Figure 5), with a minimal interdataset spatial correlation of 0.89 (Figure S1). Both the ADHD and control groups exhibited the five classical MS topographies A, B, C, D, and F. Spatial correlation analysis revealed minor difference between ADHD and control 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, we used the group-concatenated MS topographies for backfitting to dataset 1 and estimation of MS dynamics at the level of individual subjects.

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

We replicated the deviations for MS D, in terms of both effect size and statistical significance: time points assigned to MS D were significantly longer ($p = .05$, $d = 0.77$) in the ADHD population, while noticeable (but nonsignificant) increases of GEV (n.s., $d = 0.49$) and time coverage (n.s., $d = 0.57$) were also present. No significant differences were found for MS A, and hence ADHD deviations in this MS were not replicated (n.s., GEV: $d = -0.14$ | time coverage: $d = -0.07$ | mean duration: $d = 0.42$) in terms of statistical significance.

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

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

Spectral Power Analysis

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

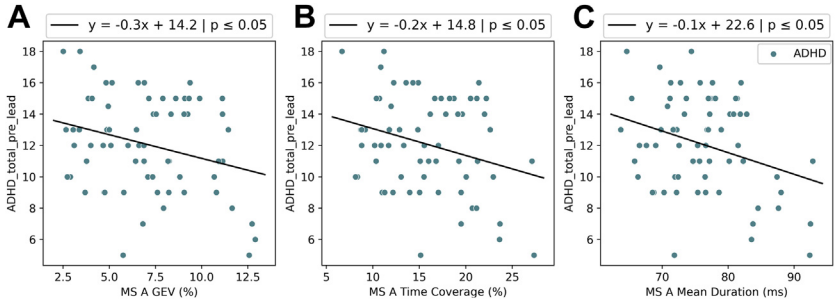

Figure 3. Dataset 1. Correlation between electroencephalographic microstate (MS) parameters and attention-deficit/hyperactivity disorder (ADHD) clinical scores (patients with ADHD only, $n = 66$). Scatterplots between **(A)** ADHD clinical score (ADHD_total) and MS A global explained variance (GEV) (%), **(B)** ADHD clinical score (ADHD_total) and MS A time coverage (%), and **(C)** ADHD clinical score (ADHD_total) and MS A mean duration (ms). Patients with ADHD only ($n = 66$); all univariate regressions are significant.

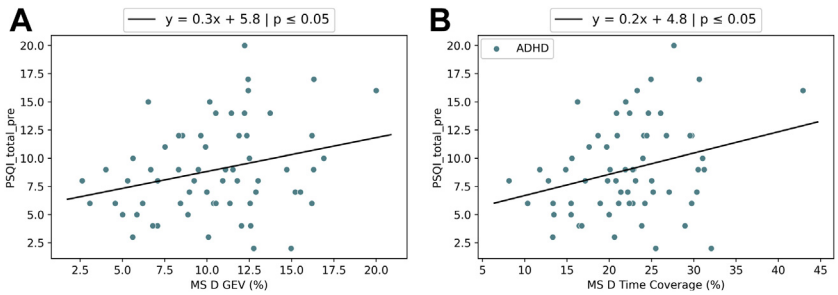

Figure 4. Dataset 1. Correlation between electroencephalographic microstate (MS) parameters and attention-deficit/hyperactivity disorder (ADHD) sleep quality (patients with ADHD only, n = 66). Scatterplots between **(A)** ADHD Pittsburgh Sleep Quality Index (PSQI) total score (PQSI_total_pre) and MS D global explained variance (GEV) (%) and **(B)** ADHD PSQI total score (PQSI_total_pre) and MS D time coverage (%). Patients with ADHD only (n = 66); all univariate regressions are significant.

DISCUSSION

This study aimed to investigate EEG MSs as potentially novel functional biomarkers of ADHD. By applying this method to adult patients with ADHD, we uncovered new electrophysiological characteristics of this disorder. To this end, we applied spatial k-means clustering to two independent datasets, each comprising adults with ADHD and a neurotypical control group. We first observed a close correspondence between the ADHD topographies and classical MS topographies (A, B, C, D, and 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, while testing for any statistical differences between the ADHD and control samples. We identified a longer mean temporal duration of the frontocentral topography (MS 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). Second, in the first (larger) dataset, we found additional evidence for decreased time coverage (d = −0.59) and mean duration (d = −0.43) of MS A, which inversely correlated with ADHD inattention scores.

Microstate D

Interestingly, MS D has been reported to be more expressed during attentional tasks, such as mental arithmetic (45,46); hence, it is intriguing (and perhaps counterintuitive) that it is also observed to be more prevalent in ADHD. However, a stronger temporal prevalence of specifically MS D has also been found to accompany periods of unresponsiveness to stimuli during transitions to drowsiness (47). In contradistinction, a recent study reported that MS D duration was positively correlated with vigilance level (48). MS D prevalence has also been observed to be altered during hypnosis (49), hallucinations (29), and sleep (45,50) and in patients with schizophrenia (51). In view of the larger prevalence and duration of MS D in both of our datasets, this balance seems to be tipped toward the upper end of the distribution in adult ADHD. As a result, we hypothesize that the electrocortical generator(s) of MS D may be acting as persistent attractors of cortical dynamics, thereby reducing their global variability and/or complexity. This interpretation is also compatible with a recent review suggesting that MS D may be responsible for aspects of reflexive attention such as reorientation and switching of attentional focus (26,52,53).

Anatomically, the frontocentral topography of MS D has previously been associated with activation of the right inferior parietal lobe, right middle and superior frontal gyri, and right insula (45,54,55). These brain regions are known to be a part of the dorsal attention network (56,57). Hence our findings tentatively point to abnormal dynamics within this network and are supported by functional magnetic resonance imaging studies (58).

Relationship With Sleep Disturbance

Interestingly, we observed a significant correlation between MS D prevalence and poorer sleep quality in patients with ADHD. Several relationships have previously been established between sleep disorders and attentional deficits [see (59) for a review)]. This result is even more intriguing considering a recent study by Ke *et al.* (60), who reported increases in MS D

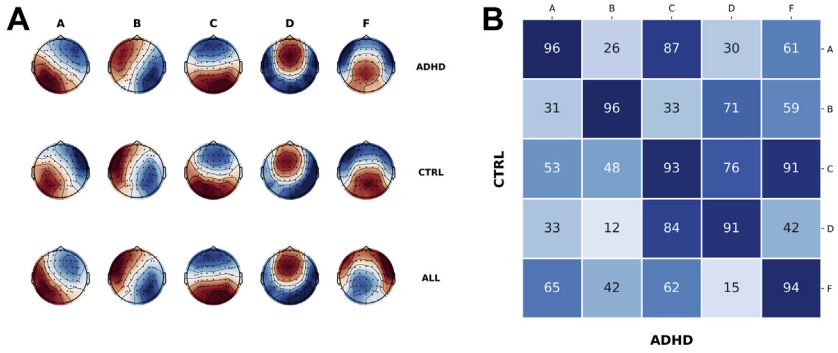

Figure 5. Dataset 2. Electroencephalographic topographies in adults with attention-deficit/hyperactivity disorder (ADHD) (n = 22) vs. control subjects (CTRL) (n = 22). **(A)** The five electroencephalographic resting-state topographies for the three conditions: ADHD, CTRL, and ALL (ADHD+CTRL). **(B)** Spatial correlation coefficients of the five resting-state topographies between ADHD and CTRL.

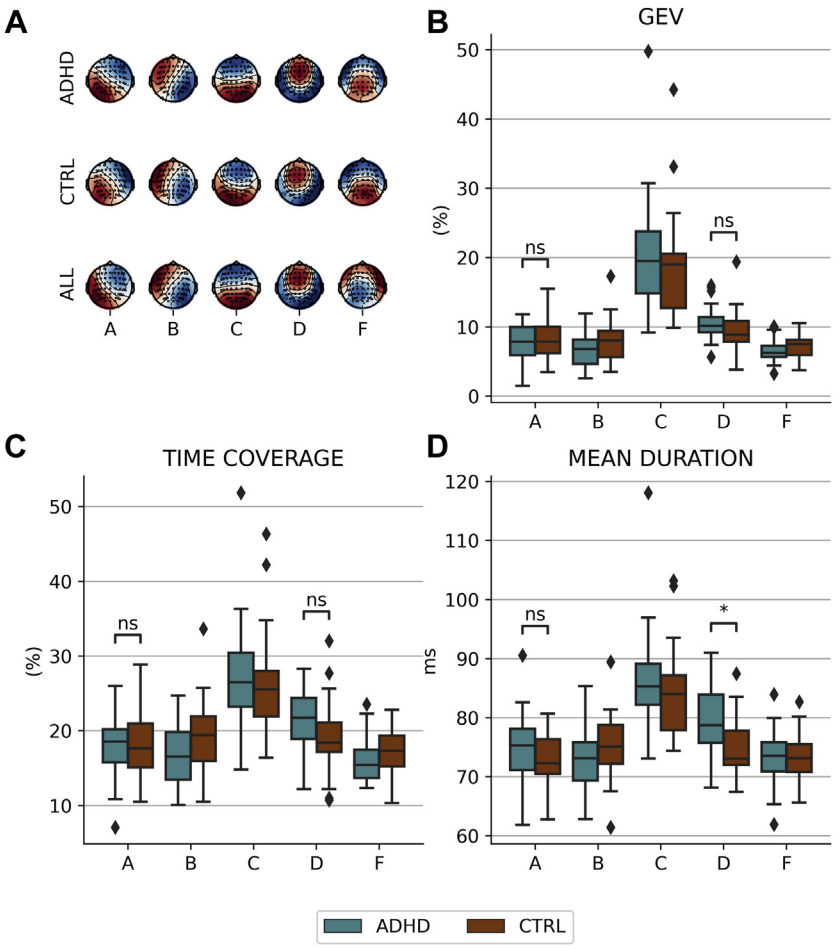

Figure 6. Dataset 2. Electroencephalographic microstates (MSs) in adults with attention-deficit/hyperactivity disorder (ADHD) (n = 22) vs. control subjects (CTRL) (n = 21). **(A)** The five electroencephalographic MSs for the three conditions: ADHD, CTRL, and ALL (ADHD+CTRL). **(B)** Global explained variance (GEV) of each MS. **(C)** Time coverage of each MS. **(D)** Mean duration of each MS (*$p \leq .05$, Bonferroni corrected for six a priori comparisons). Boxplots consist of median (Q2), first quartile (Q1), third quartile (Q3), maximum (Q3 + 1.5 × [Q3 − Q1]), and minimum (Q1 − 1.5 × [Q3 − Q1]). ns, not significant.

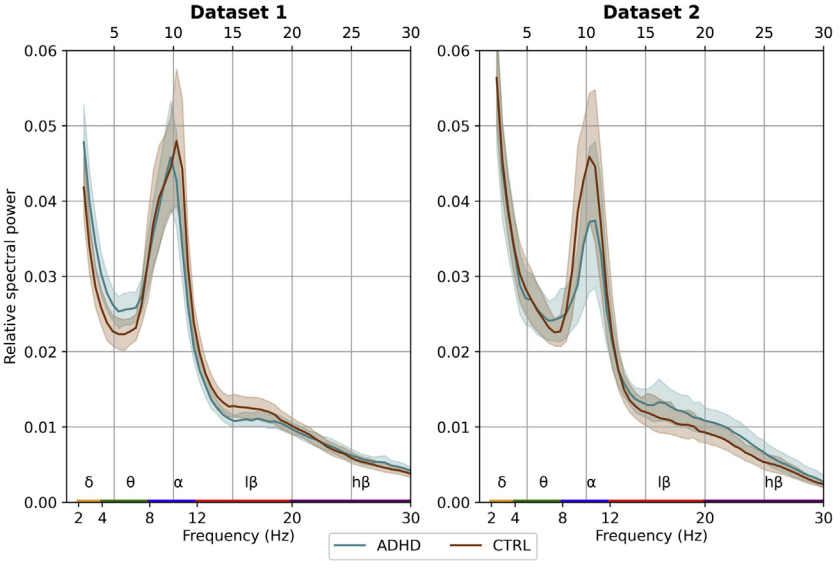

Figure 7. Electroencephalographic relative power spectrum differences between attention-deficit/hyperactivity disorder (ADHD) and control (CTRL) groups. For dataset 1 (left panel: ADHD n = 66, CTRL n = 66) and dataset 2 (right panel: ADHD n = 22, CTRL n = 22): relative band-power values over all electrodes. Solid lines represent mean value across subjects; shaded areas represent 95% confidence intervals. Traditional frequency bands: delta (orange, 2–4 Hz), 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.

coverage (and a reduction in MS A) in sleep-deprived individuals. These results, which overlap those observed in the present study, support preexisting hypotheses of a trinity of sleep, hyperactivity disorder, and abnormal EEG signatures (61,62).

Microstate A

In the larger dataset, we additionally observed significantly decreased time coverage of MS 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 MS A (and longer durations of MS D) (48). Thus, the combined signature of lower MS A coverage and increased MS D duration in our study implies that ADHD could be characterized as a condition of hypervigilance, consistent with its behavioral symptoms of physical and emotional hyperactivity (63,64).

Spectral Power Differences

Classical EEG spectral power analyses have frequently revealed slow-wave (e.g., theta) abnormalities with a frontocentral topography in clinical cohorts with ADHD (65,66). A plethora of studies have investigated spectral power differences in childhood and adult ADHD (5,67), 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 the ADHD and control groups. Specifically, in the first dataset, we observed relatively decreased low-beta power in patients with ADHD compared with control subjects, while the second dataset appeared to have the opposite pattern. One may notice the significance of this result, different from that of the original article (19), 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, as in our study, broadband was defined as 1–30 Hz while the original work used 0.5–40 Hz.

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

Conclusions

In conclusion, and to our knowledge, we present the first study on resting-state MS dynamics in adults with ADHD. We have confirmed across two datasets that MS 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 MS 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 the current standard (68,69), especially for the second dataset which did not consider symptom history (69). Hence, it is possible that the MS biomarkers uncovered are not specific to ADHD as diagnosis per se but to some of its behavioral subcomponents; for example, sleep disturbance (59).

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