Article Subject

Dynamical Nonstationarity of resting EEGs in Patients with Attention-Deficit/Hyperactivity Disorder (AD/HD)

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Abstract— This study applied dynamical nonstationarity analysis (DNA) to the resting EEGs of patients with Attention-Deficit/Hyperactivity Disorder (AD/HD). We aimed to assess and characterize AD/HD using features based on the local and global duration of dynamical microstate. We hypothesized that AD/HD patients would have difficulties in maintaining stable cognitive states (e.g., attention deficit and impulsivity) and that they would thus exhibit EEGs with temporal dynamics distinct from normal controls, i.e., rapidly and frequently changing dynamics. To test this hypothesis, we recorded EEGs from 12 adolescent subjects with AD/HD and 11 age-matched healthy subjects in the resting state with eyes closed and eyes open. We found that AD/HD patients exhibited significantly faster changes in dynamics than controls in the right temporal region during the eyes closed condition, but slower changes in dynamics in the frontal region during the eyes open condition. AD/HD patients exhibited a disruption in the rate of change of dynamics in the fronto-temporal region at rest, probably due to executive and attention processes. We suggest that the DNA using complementary local and global features based on the duration of dynamical microstates could be a useful tool for the clinical diagnosis of subjects with AD/HD.

Index Terms— ADHD, dynamical nonstationarity, dynamical microstate, EEG.

I. INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (AD/HD) is a common behavioral disorder characterized by inattention, hyperactivity, impulsivity and aggressiveness. AD/HD affects 4-7% of school children and 2-3% of adults worldwide, resulting in difficulties in school, family and social life [Froehlich et al. 2007, Polanczyk et al. 2007]. Studies have often highlighted the importance of developing a model of cognitive management function in this disorder (also known as the executive function that controls and manages other cognitive processes) [Arnsten and Li 2005, Willcutt et al. 2005].

Executive function involves working memory, response inhibition, planning and monitoring of actions [Arnsten and Li 2005], and it plays an important role in the selection of attention mechanisms [Barkley 1997, Willcutt et al. 2005]. Executive function also establishes communication between the prefrontal cortex (PFC) and subcortical regions such as the basal ganglia and some brainstem regions, along with catecholamine and serotonin modulatory centers. Therefore, disruptions in these communication processes (e.g., disruptions in executive function via PFC lesions or impairments in modulatory neurotransmitter regulation) often induce AD/HD symptoms [Bush et al. 2005]. Thus, the major objectives of our study are to quantify the resulting shifts in dynamical processes in AD/HD patients and demonstrate their applicability for clinical diagnosis.

AD/HD is a highly heterogeneous disorder, and while diagnosis of the disease primarily depends on questionnaires and psychological evaluations, no clear alternative clinical diagnostic tool is available. Tools have been proposed based on quantitative EEG studies on AD/HD patients, for example using Fourier transform analysis such as a discriminant function [Mann et al. 1992] and an absolute/relative power ratio analysis [Monastra et al. 2001], with classification accuracies for AD/HD ranging from 80-95%.

Recently, nonlinear dynamical methods have appeared as promising tools to investigate brain dynamics and as a complementary alternative to spectral analysis. The application of these methods to EEGs in patients with neurological and psychiatric disorders has proven to be an effective and reliable means of diagnosing various brain diseases and quantifying disease progress [Jeong 2004, Stam 2005]. More interestingly, the study of changes in dynamical parameters (using nonlinear models) over time and of changes that can be observed from a time series, also called dynamical nonstationarity analysis (DNA), has proven to be effective in detecting changes in mental state as shown in epilepsy detection [Dikanev et al. 2005] or sleep staging [Latchoumane and Jeong 2009]. We have shown that DNA is able to quantify higher levels of cognition based on microscopic changes in dynamics over time [Latchoumane and Jeong 2009]. Thus, DNA appears to be an appropriate method to understand the disruption in temporal dynamics that could regulate gating and switching functions such as attention control and executive function.

The aim of this study was to examine the speed of change in dynamics (dynamical nonstationarity) of EEGs in AD/HD patients during the resting state with eyes closed and eyes open. We hypothesized that because AD/HD patients have difficulties paying attention to one event for a long period of time, they should exhibit more frequent or different structures of dynamical changes in their EEGs than normal controls. This finding would indicate more instability in the temporal processing in the brains of AD/HD patients. We propose that DNA could be a real-time, fast and reliable diagnostic tool to differentiate AD/HD and that it could be

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particularly suitable for the characterization of individual symptoms in clinical uses.

II. SUBJECTS AND EEG RECORDINGS

We selected 11 adolescent subjects from among South Korean high school students diagnosed as AD/HD (mean age 16.54±0.52; range 16-17 years old) and 12 age-matched healthy subjects (mean age 16.77±0.43 years; range 16-17 years). The diagnosis of AD/HD was performed through a semi-structured interview based on DSM-IV criteria, the Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Korean version (K-SADS-PL), the Brown Attention Deficit Disorder Scale, the omission/commission error levels on audio (CPT-A) and visual Continuous Performance Tasks (CPT-V), a Train Making Test, IQ tests, parents' and teachers' AD/HD ratings-VI and a diagnosis by a psychiatrist. The AD/HD group was actually a heterogeneous group with one patient diagnosed as AD/HDhyp (dominant hyperactive), three diagnosed as AD/HDin (dominant inattention) and seven patients diagnosed as AD/HDcom (combined inattention and hyperactivity).

The subjects were given Conner's continuous performance test (CPT) for visual and auditory cues for 9 minutes per subject and task. A total of 685 questions were administered, including 135 target stimuli (20%). Each stimulus was presented for 200 msec, with an 800 msec interval between each stimulus presentation. Table 1 shows the clinical description and performance (CPT-A, CPT-V and rating scales) of the AD/HD and control groups. The academic performance was defined as the participant's percentile ranking among other students in the same grade.

EEGs were recorded from 19 channels (gold-cup scalp electrodes) placed using the international 10-20 system against reference and ground earlobe electrodes. The recordings were sampled and digitized at 250 Hz using a 32-channel amplifier-AD converter (Neuroscan SynAmps). A zero-phase quadratic filter was used to reduce low-frequency movement artifact and noise. An independent component analysis (ICA) guided by component kurtosis, spatial weight, frequency analysis and artifact wave form was used to extract EMG and eye movement contamination as well as spatially spread noise. A final visual inspection was used to discard subjects whose EEGs did not contain at least 2 min of noise-free recordings, resulting in the discarding of two AD/HD patients and four control subjects for the resting eyes closed condition and three ADHD patients and four controls for the resting eyes open condition.

Table 1. Clinical information for the AD/HD and control groups. CPT-A and CPT-V denote auditory and visual continuous performance tasks, respectively. Significant differences between the two groups are marked with * ($p < 0.05$) and ** ($p < 0.01$). Academic performance is the percentile ranking among students of the same grade.

	ADHD patients (n=11)	healthy subjects (n=12)
Age	16.55±0.52	16.77±0.44
IQ	105.55±16.84	117.38±14.30
Academic performance (%)*	85.14±21.44	25.86±26.30
CPT-A performance		
Correct response**	126.40±2.95	131.67±2.31
Omission error**	8.60±2.95	3.33±2.31
Commission error*	4.70±4.06	1.33±1.61
Reaction time (seconds)	0.552±0.032	0.550±0.049
CPT-V performance		
Correct response	131.1±3.4	132.1±2.8
Omission error	3.8±3.4	2.9±2.8
Commission error	1.4±1.9	0.5±0.7
Reaction time (seconds)	0.405±0.036	0.409±0.041
ADHD-IV Rating Scale scores		
Parents**	36.73±5.20	5.58±5.90
Teachers**	44.73±6.90	4.83±9.03

III. DYNAMICAL NONSTATIONARITY ANALYSIS

Dynamical nonstationarity analysis (DNA) characterizes and segments a time series according to changes in the dynamical properties found in that time series. These changes in dynamics can be assessed using a phase space dissimilarity measure (PSDM) [Hively et al. 2000] and comparing moving segments of the time series to reference segments of the same time series, forming a map of dynamical change also called a dynamical dissimilarity map (DDM). Because the DDM contains information about the microstructural changes in temporal dynamics, it can be used to identify a given macrostate using an entropy measure [Latchoumane and Jeong 2009] or using an index quantifying the speed of change in dynamics.

A. Local vs. Global Dynamical Analysis

DNA relies on the analysis of the phase space, a multidimensional space in which a system's consecutive states can be represented using its dynamical parameters. The phase space is thus a geometrical representation of a system's dynamical states along its degrees of freedom. The limit set formed by the state trajectories in the phase space is called an attractor and characterizes the nonlinear invariant of a system's dynamics.

In this manuscript, the phase space was obtained using a time-delay reconstruction method [Takens 1981] applied to each EEG channel individually (local dynamics) and using a combination of channels [Dvorak 1990, Lachaux et al. 1997] associated with brain regions for global dynamics.

For the local dynamical analysis, we estimated the reconstruction parameters using the differential entropy ratio method [Gautama et al. 2003], and we found that 5 and 15 were suitable values for the embedding dimension d and the time delay τ, respectively. For the global dynamical analysis, we grouped the electrodes into five regions constituted by five electrodes each, i.e., $K = d = 5$: frontal (Fp1, Fp2, F3, F4 and Fz), left temporal (F7, C3, P3, T3 and T5), central (Fz, C3, Cz, C4 and Pz), right temporal (F8, C4, P4, T4 and T6) and posterior (P3, Pz, P4, O1 and O2). The phase space trajectory was obtained for the five regions based on the time series of their electrodes. Note that the regional grouping allows for a spatial standardization of DNA analysis that is compatible with any EEG setup. The grouping also proposes a simpler function-related approach for statistical validation and localization of the region of interest that is particularly useful for classification, clinical screening and interpretation.

B. Dynamical Dissimilarity Map (DDM)

For each electrode or region, we defined a set of test segments taken over the entire recording (i.e., a moving window) of duration *W* data points and an overlapping of OV data points. We defined the set of reference segments as the contiguous segments of duration *W* data points (i.e., non-overlapping) taken over the entire recording. The dynamical dissimilarity map (DDM) is the matrix that contains the dynamical dissimilarity calculated using the PSDM between each reference segment and the test segments. The DDM is then a matrix of dissimilarity values with Nref rows and Ntest columns, where $N_{ref} \sim N/W$, $N_{test} \sim N/(W-OV)$ and *N* is the total number of data points in the time series. This map contains information about changes in dynamics for a given electrode or region. For all calculations, we used the values *W* = 2000 (8 sec), *OV = 1950* (i.e. windows center to center distance = W-OV = 50 or 200 msec) and *S* = 5 for the DNA. The values *W*, *OV* and *S* were chosen to satisfy the trade-off between the number of points required to estimate the occupation frequency distributions, the goal of minimizing computational cost and the resolution of observable dynamical changes. The parameter estimation was derived from our previous study and was confirmed on the dataset used in this study. Similar results were found for *W* ranging from 2000 to 4000 data points, *OV* ranging from 1250 to 1950 and *S* ranging from 5 to 15.

C. Phase Space Dissimilarity Measure (PSDM)

The phase space dissimilarity measure assesses how the occupation frequency distributions of two phase spaces differ from each other.

For a segment of time series of the i^{th} channel $x_i(t)$, we obtained a discrete or binned time series $s_i(t)$ taking *S* values, as shown in Eq. 1:

$$s_i(t) = INT\left[(S-1)(x_i(t) - x_{i,\min})/(x_{i,\max} - x_{i,\min})\right], \quad (1)$$

where INT is a function that returns the next lower integer of its input and $x_{i,min}$ and $x_{i,max}$ are the minimum and maximum of the entire time series $x_i(t)$, respectively. An upfront low-bit analog/digital conversion could also reduce the computational cost of data acquisition and processing. In the following, we obtained the single channel reconstruction using the time-delay embedding theorem, as shown in Eq. 2:

$$P^i_{\text{single}}(t) = \left[s_i(t), s_i(t+\tau), ..., s_i(t+(d-1)\tau)\right], \quad (2)$$

where *d* is the embedding dimension and τ is the time delay. The multichannel reconstruction of the phase space was obtained using *K* specified channels for a given region Reg. A point at time t in the phase space is then expressed as in Eq. 3:

$$P^{Reg}_{\text{multi}}(t) = \left[s_1(t), ..., s_r(t), ..., s_K(t)\right], \quad (3)$$

where $s_r(t)$ is the value of the r^{th} channel of the region Reg at time t, with $r = 1, \ldots, K$ (i.e., *K* channels used for each region). Because every time series $s_i(t)$ has only *S* values, the reconstructed phase space is subdivided into S^d hypercubes (single channel reconstruction) or S^K hypercubes (multichannel reconstruction). Considering the segment of time series of duration *W* data points, the occupation frequency distribution *DP* is simply obtained by counting the number of points present (i.e., frequency) in each hypercube of the phase space.

We finally obtained the dynamical dissimilarity between two time segments Seg_1 and Seg_2 of duration *W* data points for the same times series (single channel) or the same region (multichannel) by comparing their occupation frequency distribution DP_1 and DP_2 using a normalized chi-square difference:

$$\chi_{1,2} = \frac{1}{W}\sum_j \frac{(DP_1(j) - DP_2(j))^2}{DP_1(j) + DP_2(j)}, \quad (4)$$

where *j* represents all non-empty hypercubes. The PSDM will take on values close to 0 for similar dynamics and values close to 1 for dissimilar dynamics.

D. Dissimilarity Rate

This study uses a simple index that estimates the speed of change in dynamics from the DDM of each subject's electrode/region: the dissimilarity rate. The index is estimated as follows: (1) the minimum value of DDM is computed over all reference segments (rows) for each test segment (column); (2) the area under the curve (AUC) of the resulting time series is divided by the number of reference segments; and (3) the average AUC is then normalized to the duration of a reference segment $W_{ref} = W/(W-OV)$. The minimum of DDM takes on 0 at the center of each reference segment, i.e., the test segment is identical to the reference segment. From the center of the reference segment, the minimum dissimilarity increases at a slow (similar dynamics) or fast (changing dynamics) rate, and this rate summarizes the temporal structure of the dynamics. The dissimilarity rate represents the average change in the speed of dynamics from reference segment to reference segment.

IV. RESULTS

A. Resting Condition with Eyes Closed and Eyes Open

We compared the dissimilarity rate between control subjects and AD/HD patients using a two-sample Student's t-test available in the Matlab® (the MathWorks, Inc.) statistical toolbox. During the eyes closed condition (Fig. 1-a), we found that AD/HD adolescents had a significantly higher dissimilarity rate for leads F4 (df = 15, t = -2.17; p = 0.047) and C3 (df = 15; t = -2.42; p = 0.029). Using global features, we found that AD/HD adolescents had a significantly higher dissimilarity rate in the right temporal region (df = 15; t = -2.30; p = 0.036, Fig. 1-b). This result indicates that AD/HD patients exhibit dynamics of shorter duration, which is particularly visible in the right temporal region.

As shown in Fig.2-a, in the resting eyes open condition, AD/HD patients had a significantly lower dissimilarity rate than controls for leads Fp1 (df = 14; t = 3.07; p = 0.0082), Fp2 (df = 14; t = 3.47; p = 0.0037), F3 (df = 14; t = 3.41; p = 0.0042), Fz (df = 14; t = 3.04; p = 0.0087) and F8 (df = 14; t = 4.42; p = 0.0006). A significantly lower dissimilarity rate was observed in the frontal region (df = 14; t = 3.22; p = 0.0061, Fig. 2-b), indicating a longer duration of dynamics as compared to the controls.

B. Correlation Analysis

We observed a significant positive Pearson's correlation between the right temporal region and parents' (R = 0.484, p = 0.048) and teachers' (R = 0.550, p = 0.022) ratings for the resting eyes closed condition. In the eyes open condition, a highly significant, negative correlation was observed between the frontal region and parents' and teachers' ratings (R = 0.665, p = 0.005). This result indicates that the dissimilarity rate could relate to the degree of severity of the disease, particularly considering the global features. We also found a

positive correlation between the frontal dissimilarity rate and the theta/beta ratio, a commonly used index for AD/HD differentiation [Shi et al. 2012], for the eyes open condition (R = 0.7014, p = 0.0025). No correlation was found for the temporal region in the eyes closed condition (R = 0.3994, p = 0.1122) between the dissimilarity rate and the theta/beta ratio.

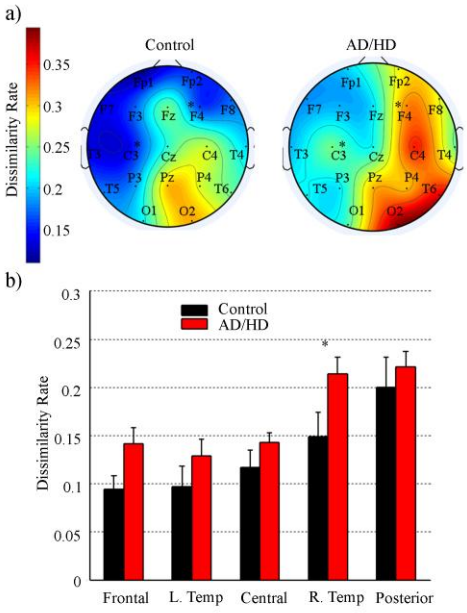

Fig.1: Dissimilarity rate for control and AD/HD subjects in the resting eyes closed condition. (a) Topological headplot of the local features; (b) global features; significant differences ($p < 0.05$) are marked with *.

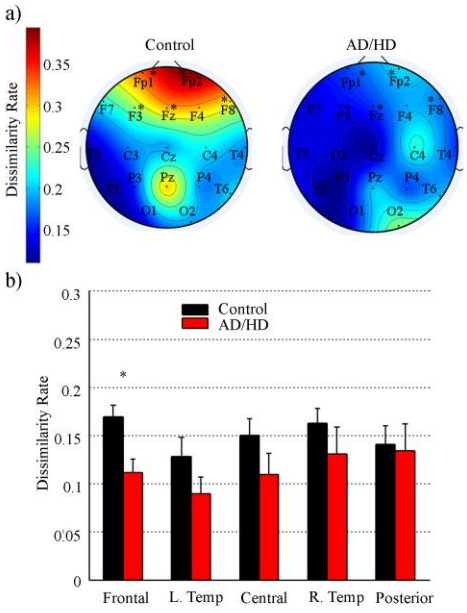

Fig.2: Dissimilarity rate for control and AD/HD subjects in the resting eyes open condition. (a) Topological headplot of the local features; (b) global features; significant differences ($p < 0.05$) are marked with *.

V. DISCUSSION AND CONCLUSION

The shift in temporal dynamics observed in AD/HD patients confirmed our hypothesis about the disruption of temporal information processing in this disorder. In the resting state, AD/HD patients showed a decrease in the characteristic duration of dynamics in the eyes closed condition and ,surprisingly, an increase in the duration of dynamics in the eyes open condition, which indicates that frontal or fronto-temporal mechanisms might be involved at rest in AD/HD and could result in unstable states with characteristics of impulsivity, hyperactivity and a lack of focus [Arnsten and Li 2005]. Our results also showed a strong correlation between the dissimilarity rate and the Theta/Beta ratio for the frontal region in the eyes open condition, demonstrating that nonlinear analysis of EEGs can complement spectral analysis to identify the region of interest from one condition to another (eyes closed to eyes open). The correlation between these measures and the clinical information available on the AD/HD patients, particularly rating scales, indicated that the dissimilarity rate and DNA could be useful as a clinical index for future AD/HD diagnosis.

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