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A Big-Data-Analytics Framework for Supporting Classification of ADHD and Healthy Children via Principal Component Analysis of EEG Sleep Spindles Power Spectra

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Abstract

Attention Deficit Hyperactivity Disorder (ADHD) diagnosis is essentially clinical and research of biomarkers represents a current great challenge. The interest in sleep spindle has been increased after the description of their role in cognitive functions and of their involvement in neurodevelopmental disorders. We aimed to investigate this peculiar aspect of sleep through EEG spectral analysis of three different spindle epochs (ante, spindle, post), in order to provide more and detailed information on sleep brain functioning in ADHD. These features can be analyzed via well-known big data analytics methods. In our case, they were evaluated by using classification methods to support ADHD diagnosis. We combined ADHD's related PSD features (i.e. theta, beta and sigma bands) with principal component analysis (PCA) for data dimensional reduction, and Linear Supported Vector Machine (Linear-SVM) as classification algorithm. In all bands and epochs, power values in Control group were higher than in ADHD children, although not statistically significant in all cases. Significant differences between ADHD and Control group were not detected for spindle epoch, while for ante and post epochs spectral power differed significantly in theta, beta and sigma bands. Results highlighted the possibility of using our new approach as a possible hallmark for ADHD. Indeed the analysis of PSD parameters combined with PCA and Linear-SVM classification resulted in a highly (94.1%) accurate discrimination between the two groups. The novelty of the approach is PSD analysis of different sleep spindles epochs combined with principal component analysis and Linear Supported Vector Machine classification. This study demonstrated the importance of analyzing sleep microstructures in ADHD. Encouraging results supports the potentiality of using EEG measures with specific methodologies we applied and should be confirmed in a large clinical study.

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1. Introduction

Attention-deficit hyperactivity disorder (ADHD), presenting an incidence of about 7% in children and 4% in adults [1], is a neurodevelopmental disorder which is characterized by attention deficit, as well as hyperactivity and impulsivity. This condition tends to persist to adulthood in 85% of cases, resulting in poor quality of life. ADHD in adults has been largely investigated, however, only a small percentage is adequately diagnosed and treated. Currently, ADHD diagnosis is made when nature, frequency and duration of patient's symptoms fulfill the diagnostic criteria according to current classification systems (DSM-V, ICD-10): by definition, symptoms are present in two or more contexts and there is clear evidence that they interfere with, or reduce quality of, social, school, or work functioning (DSM-5). In particular, these symptoms are measured through information questionnaires and interviews administered to parents and teachers to assess presence and severity level of this disorder. However, the diagnostic process remains clinical as to date no biological marker exist to support diagnosis in the routine clinical practice.

In the past, EEG spectral analysis was studied as possible marker for diagnosis in combination with clinical evaluation. Decreased relative beta activity, increased absolute and relative theta activity, or increased theta/beta ratio allowed to differentiate ADHD from controls [2-5]. In 2013, US Food and Drug Administration (FDA) approved the Neuropsychiatric EEG-Based ADHD Assessment Aid (NEBA) which suggests using EEG theta/beta power ratio, combined with a clinician's evaluation, to diagnose ADHD. However, recent studies discredited theta/beta ratio as diagnostically supportive parameter [6].

ADHD has also been correlated with sleep problems. Indeed, difficulties in fall asleep and maintaining sleep [7], are present in almost 70% of children with ADHD and these problems intensify existing impairments [8, 9]. Children with ADHD and sleep problems highlight more severe ADHD symptoms and poorer daily functioning [8]. A good sleep is fundamental for maintaining cognitive function and for restoring brain and body. Albeit association between sleep disorders and ADHD is well known, the correlation with specific aspects of sleep microstructure and of brain functioning modifications during sleep has not been fully understood. One of the aspects of sleep microstructure with growing research interest in neurodevelopmental disorders are sleep spindles.

Sleep spindles are characteristic bursts of oscillatory activity, representing physiological electroencephalographic hallmarks of non-REM sleep microstructure. Spindles are visually identified by the presence of 12-14 Hz rhythms (sigma band), lasting from 0.5 to 3 seconds, and a waxing-waning organized amplitude envelope [10]. This pattern was one of the first electroencephalographic waveforms identified by Hans Berger in his earliest recordings. Since 1969, several studies have been done with results of a more complete and detailed description of both spindles morphology and neurophysiological mechanism involved [11]. It has been discovered that patterns of the spindles within an individual are quite stable from night to night [12, 13]. Due to the intra-individual stability of spindles patterns, De Gennaro suggested that they could be used as a fingerprint of the subject [14]. However, what this fingerprint could identify remain to be determined.

In the last years, studies have been concentrated on the spindle function and empirical evidence indicates that they are associated with cognitive faculties and intelligence, with various disease conditions (e.g., schizophrenia, mental retardation, abnormal maturation) and with post stroke recovery processes, but recently they are considered to be significantly involved in sleep-dependent memory consolidation [15]. Brain oscillatory activity in terms of EEG power was poorly investigated in ADHD's as well as time variations before, during and after spindle event has not been studied.

Therefore we aimed to investigate EEG activity through well-known *big data analytics methods* (e.g., [24,25,26,27]). In our case, we propose to apply spectral analysis in order to provide more and detailed information on sleep brain functioning in ADHD and evaluate these features as novel ADHD biomarkers using classification

methods. This paper combines ADHD's related PSD features (i.e. theta, beta and sigma bands) with principal component analysis (PCA) for data dimensional reduction, and Linear Supported Vector Machine (Linear-SVM) as classification algorithm.

2. Materials and Methods

The study group included 8 consecutive ADHD subjects recruited from Children's Hospital "Burlo Garofolo" of Trieste. Inclusion criteria was the diagnosis of ADHD according to DSMV diagnostic criteria. Subjects under pharmacological treatment were excluded. Age matched control group (ADHD 8.75±0.46 years; Control 8.33±1.22 years; p-value=0.73) encompassed 9 healthy subjects without history of neurological disorders and not under medical drug treatment. Our research was conducted according to principles of the Declaration of Helsinki. Informed written consent for all children was obtained from their parents. Approval for the study had been obtained from local ethics committee.

40-minutes EEG recordings were performed during sleep in both groups. All subjects were deprived of sleep on the day of EEG acquisition to enhance deep sleep during recording. 19 channels EEG recordings were performed during sleep using amplifier SAM 32FO amplifier (Micromed S.p.A., Treviso, Italy) and Ag/AgCl electrodes arranged according to the international 10/20 system: Fp1, Fp2, F3, F4, F7, F8, Fz, C3, C4, Cz, T3, T4, P3, P4, Pz, T5, T6, O1 and O2. Monopolar derivations were used and referenced to the average of mastoid (A1 + A2)/2. Impedance <5 kOhm was controlled in each registration from impedance map EEG of the equipment. EEG signals were sampled at sample rate of 512 Hz.

Each EEG record was visually inspected by two experienced neurophysiologists (M.C. and C.Z.) who identified artefact free spindles and their start and end points. Center of spindle was estimated by calculating the maximum power peak in sigma band (11-15 Hz) of the Fz channel [6]. Spindle epoch was defined as interval of EEG recording 0.5 seconds before and after the sigma power peak. EEG signals processing was performed by using Matlab (Mathworks Inc., Natick, MA). Epochs before (ante) and after (post) spindle were obtained by calculating the time at which power value was below 95% of the maximum power peak before and after the spindle epoch, respectively. Using these two starting points, 1 second ante and post epochs were defined (Fig. 1). For each subject 8 different spindles were identified and subsequently for each of them ante, spindle and post epochs were extracted.

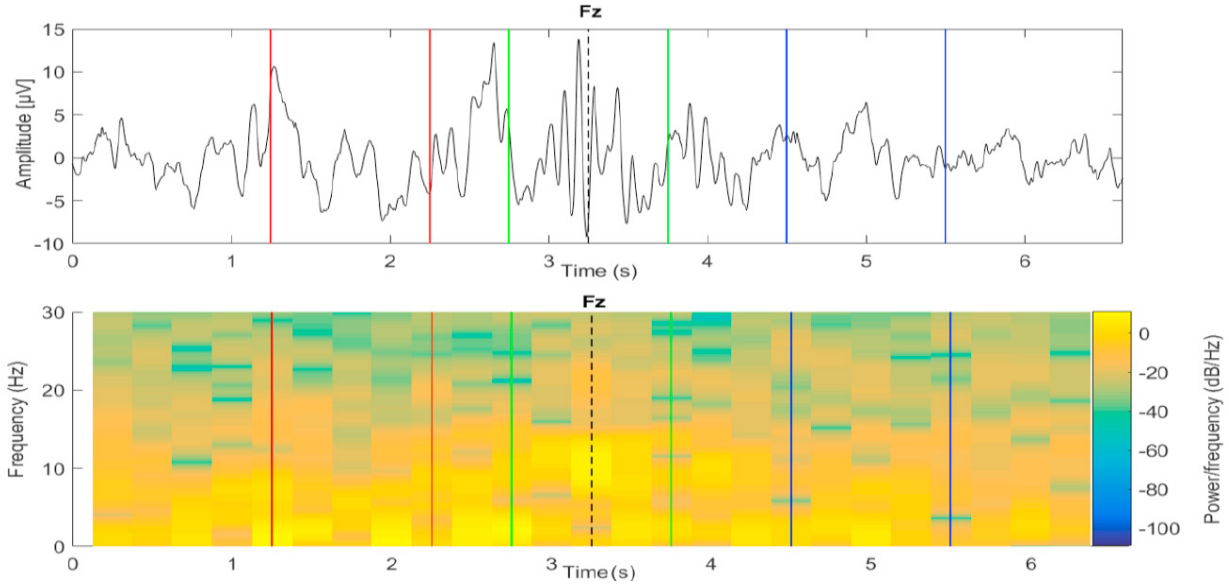

Figure 1. Example of epochs division based on Fz channel. Red lines represent the ante epoch, green lines represent the spindle epoch and blue lines the post epoch. Black dotted line represent the maximum power peak of the sigma band.

EEG signals in identified epochs were band-pass filtered (0. 5 – 45 Hz; Butterworth second order filter). For each channel power spectral density was obtained by the periodogram of a single entire epoch and spectral power in theta (4-8 Hz), beta (13-30Hz) and sigma bands (11-15 Hz) were calculated. Spectral power of all channels were averaged for each epoch and spectral band.

Statistical analysis was performed by using Matlab (Mathworks Inc., Natick, MA) Wilcoxon test for independent samples, on all bands and epochs in order to evaluate the presence of significant differences between the two groups. P-value less than 0.05 was considered statistically significant.

Finally, in order to evaluate these EEG features as novel ADHD hallmarks, PCA and Linear SVM for classification has been performed. Before applying SVM we summarized data by applying principal component analysis (PCA) [16] on epochs and bands that resulted statistically different. This method allows to reduce dimensionality of data, while preserving as much of the variance in input data as possible. First principal components that accounted for at least 95% of the variance were considered.

SVM classification algorithm based the classification on find a hyperplane that optimally separates data into two classes returning as output the accuracy of division [17].

3. Results

Mean ± 1SD power values of theta, beta e sigma bands for each of three epochs (spindle, ante and post) and both ADHD and Control groups are reported in Table 1. In all bands and epochs, power values in Control group were higher than those of ADHD children, although not statistically significant in all cases. Significant differences between ADHD and Control group were not detected for spindle epoch, while for ante and post epochs spectral power differed significantly in theta, beta and sigma bands.

Table 1. Mean ± 1SD power values of theta, beta and sigma band of all the three epochs spindle, ante and post in both groups. Differences between the two groups are represented by the p-value. Significant p-values <0.05 are marked with *.

	ADHD	Controls	p-value
THETA			
Spindle	2.411 ± 0.604	3.511 ± 1.356	0.108
Ante	1.301 ± 0.357	1.880 ± 0.528	0.018*
Post	1.206 ± 0.364	2.529 ± 0.902	0.001*
BETA			
Spindle	1.149 ± 0.429	1.984 ± 1.014	0.070
Ante	0.247 ± 0.052	0.304 ± 0.061	0.049*
Post	0.252 ± 0.040	0.369 ± 0.105	0.018*
SIGMA			
Spindle	1.332 ± 0.455	2.295 ± 1.128	0.055
Ante	0.315 ± 0.087	0.406 ± 0.075	0.043*
Post	0.308 ± 0.057	0.515 ± 0.145	0.002*

PCA and subsequently Linear SVM were applied on spectral parameters of ante and post epoch which resulted statistically different between two groups. Finally, linear SVM used 3 PCA components for classification that explained more than 95% of the variance.

Figure 2 shows the division between distribution of the subjects of two group in the PCA component space, with almost clear difference between ADHD and the control group. Indeed, by applying linear SVM resulted in a classification accuracy of 94.1%. Confusion matrix is reported in table 2, highlighting high sensitivity (100%) and specificity (88.9%).

Table 2. Confusion matrix resulted from the linear SVM classification.

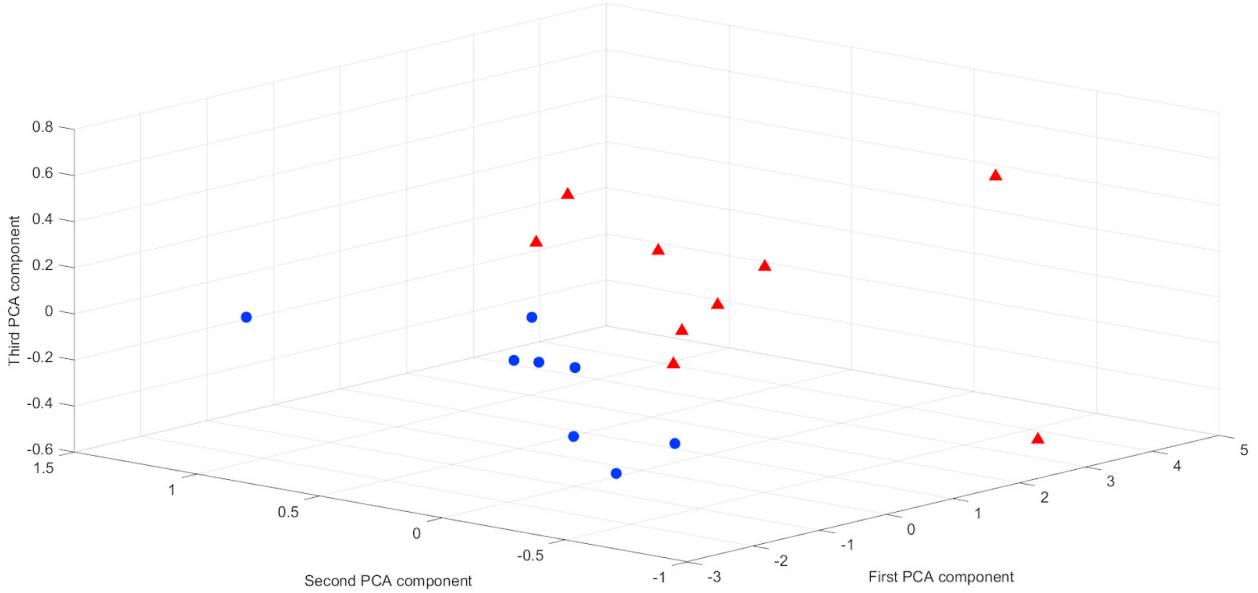

Figure 2. X, Y and Z axes represent respectively the first, second and third Principal Component, blue circles are the ADHD children, red triangle are the Controls

Confusion Matrix	Predicted: Control	Predicted: ADHD
Actual: Control	8	1
Actual: ADHD	0	8

4. Discussion

Despite its longstanding shared neurobiological pathogenesis, diagnosis of ADHD is essentially clinical and research of biological markers represents a current great challenge as neurobiological pathogenesis. Objective measures of brain oscillatory activity alterations could support neuropsychiatrists in the diagnosis. Spindles are considered brain oscillatory activity that could affect the steady state of brain during sleep, and even if the role of sleep spindle in childhood is still not fully understood, it is well known that their abnormality can be related to certain neurodevelopmental pathologies, strokes and mental disorders [18, 19].

Main finding of this study is the possibility to discriminating the two groups (ADHD and healthy children) by spectral analysis of only theta, beta and sigma bands in ante and post epochs of sleep spindle, and the subsequent application of PCA and linear SVM classification.

In the past, differences between ADHD and healthy children have been analyzed by using classical spindles parameters: number of spindles per sleep stages, spindle density, amplitude, and frequency peak [20]. However, none of studies highlighted significant differences between the two groups and there still a lack in individuation of physiological biomarker [21, 22]. There is only one study concerning spectral power values changes in spindle related time epochs, but it was conducted only on adult subjects [23]. Important novelty described in this study consists in the analysis of different time periods, chosen after power spectra analysis of the EEG signal, in order to evaluate temporal and dynamic changes of spindles activity.

In our study lower power values in ADHD children compared to healthy group were found for theta, beta and sigma bands. This could be explained by a lower power of spindle activity in cognitive functions in ADHD. Moreover, since spindles are also considered important for sleep maintenance, these lower power values compared to Controls especially in ante and post epochs could be related with their sleep problems.

Finally, the spectral power features extraction, combined with PCA for data dimensionality reduction and Linear-SVM for classification allowed to differentiate ADHD and Control groups with high specificity and sensitivity.

The explorative nature of the study determined some limitations. Results of this study should be interpreted bearing in mind the reduced study population. High classification accuracy has not to be considered evidence of an effective discriminatory rule discovery but has rather to be interpreted as a good possibility to discriminate between the two groups by using selected features. In particular, separation of ADHD and Controls is encouraging and unveils the potential of using EEG measures with specific methodologies we applied.

5. Conclusions

Results of this study showed that the proposed EEG based approach could be useful for discriminating ADHD and healthy children. Novelty of the approach is PSD analysis of different spindles epochs combined with principal component analysis and Linear Supported Vector Machine classification. This study demonstrated the importance of analyzing sleep microstructures in ADHD. Encouraging results supports the potentiality of using EEG measures with the specific methodologies we applied and should be confirmed in a large clinical study.

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