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Entropy Analysis of MEG Background Activity in Attention-Deficit/Hyperactivity Disorder

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***Abstract*— The aim of this study was to analyze the magnetoencephalography (MEG) background activity in Attention-Deficit/Hyperactivity Disorder (ADHD) using fuzzy entropy (*FuzzyEn*), an entropy measure that quantifies signal irregularity. Five minutes of recording were acquired with a 148-channel whole-head magnetometer in 14 ADHD patients and 14 control children. Our results showed that MEG activity was more regular in ADHD patients than in controls. Additionally, there were statistically significant differences ($p < 0.01$, Student's *t*-test with Bonferroni's correction) in the five analyzed brain regions: anterior, central, posterior, left lateral, and right lateral. Using receiver operating characteristic (ROC) curves, the highest values of accuracy (82.14%) and area under the ROC curve (0.9005) were achieved in anterior area. Our results support the hypothesis that ADHD is characterized by a delay of cortical maturation in the prefrontal cortex.**

I. Introduction

Magnetoencephalography (MEG) is a non-invasive technique that uses an array of sensors positioned over the scalp. These sensors are extremely sensitive to very small changes in the electromagnetic brain activity [1]. MEG, as electroencephalography (EEG), allows recording neural activity with good temporal resolution. Both EEG and MEG signals are generated by synchronous activation of pyramidal neurons. However, the use of MEG technology has some advantages over EEG. Firstly, magnetic fields are less distorted by the resistive properties of the skull and the scalp. Secondly, EEG signals are strongly influenced by a wide variety of factors, such as distance between sensors, electrode location, reference point or conducting substance between skin and electrode. On the other hand, ambient magnetic fields are several orders of magnitude stronger than the weak magnetic signals generated by the brain. Superconducting quantum interference devices (SQUIDs), interference suppression systems and magnetic shielding are then mandatory [1]. As a consequence, MEG is characterized by limited availability and high equipment cost.

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Attention-Deficit Hyperactivity Disorder (ADHD) is the most common neurobehavioral disorder in children and adolescents [2]. Diagnostic guidelines identify the main symptoms of ADHD as inattentiveness, impulsivity, and hyperactivity. The symptoms persist during adulthood in a 50-60% of patients [3]. Guidelines also acknowledge that there is no objective test or marker for ADHD. Thus, diagnosis relies entirely on clinical criteria. In pediatric population, ADHD produces educational problems. Other problems are risk for alcohol and other substance abuse, marital disturbances, antisocial behaviors, car accidents, and earlier uncontrolled sexual relationships [4]. In spite of its clear medical, social and familial relevance, a neurobiological marker for ADHD has not been defined up to date. Nevertheless, neuropsychological, neuroimaging and neurophysiological studies offer evidence of brain and behavioral dysfunctions in ADHD. For instance, Shaw *et al.* [5] defined ADHD as a disorder characterized by a delay of cortical maturation, which affects in a higher degree the prefrontal cortex. Bush *et al.* [6] reviewed several functional neuroimaging studies and concluded that ADHD patients show a consistent pattern of frontal dysfunction in the brain. In agreement with these results, Fernández *et al.* [7] found a significant decrease of Lempel-Ziv complexity values in the MEG frontal activity of ADHD patients.

The electromagnetic brain activity (EEG and MEG) in ADHD has been researched in the last decades by means of signal processing techniques. Spectral analyses revealed that brain rhythms in ADHD show an increased activity in theta frequency band compared to control subjects, especially in frontal areas [8, 9]. However, the transfer characteristic of the neurons is essentially deterministic and inherently nonlinear. Additionally, several feedback loops are present in neural networks [10]. Consequently, nonlinear methods might be more suitable than traditionally linear techniques to analyze the brain activity. The use of nonlinear measures, as Lempel-Ziv complexity and approximate entropy (*ApEn*), revealed that the spontaneous activity is less complex and more regular in ADHD patients than in control subjects [7, 11].

In this study, we have examined the MEG background activity in ADHD using a nonlinear measure called fuzzy entropy (*FuzzyEn*). Entropy is a concept addressing randomness and predictability, with greater entropy often associated with more randomness and less system order [12]. Applied to time series, *FuzzyEn* quantifies the signal irregularity [13]. Our purpose was to test the hypothesis that entropy values of the magnetic brain activity would be different in both groups, hence indicating an abnormal type of neural dynamics associated with ADHD.

II. Materials and Methods

A. Subjects

MEG data were acquired from 28 subjects: 14 patients with ADHD and 14 control subjects. The clinical group comprised 14 children with ADHD (age = 9.64 ± 1.04 years; mean ± standard deviation, SD). Inclusion criteria included a full DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) diagnosis of ADHD combined type with associated impairment in at least two settings and a Conners' Parent Rating Scale (CPRS) hyperactivity rating greater than two SD above age- and sex-specific means [14]. The DSM-IV diagnosis of ADHD was based on the parent version of the Diagnostic Interview for Children and Adolescents [15]. ADHD patients were totally drug-naïve: they had never used any psychoactive drug or received any psychoactive therapy.

MEGs were also obtained from 14 healthy children (age = 10.36 ± 1.48 years, range 8–13) without past or present neurological disorders. ADHD patients and control subjects did not differ statistically in terms of age and years of education (6.82 ± 1.22 years in ADHD patients and 7.28 ± 1.38 years in controls; mean ± SD), and all were strictly right-handed. The Institutional Review Board approved this research protocol. Written informed consent and assent to participate in the study were obtained from parents and children, respectively.

B. MEG recording

MEG signals were acquired with a 148-channel whole-head magnetometer (MAGNES 2500 WH, 4D Neuroimaging) located in a magnetically shielded room at the MEG Center Dr. Pérez-Modrego (Spain). The subjects lay comfortably on a patient bed, in a relaxed state and with their eyes closed. They were asked to stay awake and to avoid eye and head movements. For each subject, five minutes of MEG recording were acquired at a sampling frequency of 678.17 Hz. These recordings were down-sampled by a factor of four, obtaining a sampling rate of 169.55 Hz. Data were digitally filtered between 0.5 and 40 Hz. Finally, artifact-free epochs of 5 seconds (848 samples) were selected by visual inspection.

C. Fuzzy entropy (FuzzyEn)

FuzzyEn is an embedding entropy that quantifies the irregularity of a signal [13]. Embedding entropies provide information about how a signal fluctuates with time by comparing the time series with a delayed version of itself [16]. *ApEn* is an embedding entropy proposed for the analysis of short and noisy data sets [17]. For this reason, it has been widely used to study the irregularity of several kinds of biomedical signals. Nevertheless, *ApEn* overestimates the similarity and is thus biased. To solve this, sample entropy (*SampEn*) algorithm was proposed [18]. *SampEn* is largely independent of the signal length and displays relative consistency under circumstances where *ApEn* does not [18]. Moreover, *SampEn* algorithm is simpler than the used to compute *ApEn*. Nevertheless, the similarity definition of vectors is based on Heaviside function in both *ApEn* and *SampEn*. Due to inherent imperfections of Heaviside function, some problems exist in the validity of these entropies definitions [19]. To overcome these drawbacks, *FuzzyEn* measure was proposed. Previous results showed that it is a more accurate irregularity measure [19].

FuzzyEn assigns a non-negative number to a sequence, with larger values corresponding to greater apparent process randomness or serial irregularity, and smaller values corresponding to more instances of recognizable features or patterns in the data. To compute *FuzzyEn*, three input parameters must be specified: the width (r) and the gradient (n) of the boundary of the exponential function, and a run length m [13]. In our study, we have chosen $r = 0.2$ times the SD of the original time series, $n = 2$, and $m = 2$ [13, 17].

Given a time series $X = u(1), u(2),...,u(N)$, the algorithm to compute the *FuzzyEn* is the following [13]:

1) Form $N - m + 1$ vectors X_i^m defined by:

$$X_i^m = \{u(i), u(i+1), \ldots, u(i+m-1)\} - u_0(i), \quad (1)$$

where $u_0(i)$ is given by:

$$u_0(i) = \frac{1}{m}\sum_{j=0}^{m-1} u(i+j). \quad (2)$$

2) Compute the distance between two of this vectors X_i^m y X_j^m, d_{ij}^m, as the maximum difference of their corresponding scalar components:

$$d_{ij}^m = \max_{k\in(0\,m-1)} \left|\left(u(i+k) - u_0(i)\right) - \left(u(j+k) - u_0(j)\right)\right|. \quad (3)$$

3) Calculate the similarity degree, D_{ij}^m, of X_j^m to X_i^m through a fuzzy function $\mu\left(d_{ij}^m, n, r\right)$. In our study, the exponential function was used:

$$D_{ij}^m(n,r) = \mu\left(d_{ij}^m, n, r\right) = \exp\left(-\left(d_{ij}^m\right)^n / r\right). \quad (4)$$

4) Define the function ϕ^m as follows:

$$\phi^m(n,r) = \frac{1}{N-m}\sum_{i=1}^{N-m}\left(\frac{1}{N-m-1}\sum_{j=1,j\neq i}^{N-m} D_{ij}^m\right). \quad (5)$$

5) Increase the dimension to $m + 1$, form the vector set $\{X_i^{m+1}\}$ and get the function ϕ^{m+1}:

$$\phi^{m+1}(n,r) = \frac{1}{N-m}\sum_{i=1}^{N-m}\left(\frac{1}{N-m-1}\sum_{j=1,j\neq i}^{N-m} D_{ij}^{m+1}\right). \quad (6)$$

6) Finally, *FuzzyEn*(m,n,r) is defined as the negative natural logarithm of the deviation of ϕ^m from ϕ^{m+1}:

$$FuzzyEn(m,n,r) = \lim_{N\to\infty}\left[\ln\phi^m(n,r) - \ln\phi^{m+1}(n,r)\right], \quad (7)$$

which, for finite datasets, is estimated by the statistic:

$$FuzzyEn(m,n,r,N) = \ln\phi^m(n,r) - \ln\phi^{m+1}(n,r). \quad (8)$$

III. Results

FuzzyEn measure was applied to the 148 MEG channels with parameter values of $r = 0.2$ times the SD of the original

time series, n = 2, and m = 2. Figure 1 summarizes the average *FuzzyEn* values estimated over all the MEG channels for both ADHD and control gruops. This figure shows that entropy values were lower in the ADHD group than in the control group for all channels, which suggests that this disorder is accompanied by a MEG regularity increase. In order to simplify the statistical analyses, we grouped the 148 channels into five brain areas (anterior, central, posterior, left lateral, and right lateral) and *FuzzyEn* values were averaged over these areas. Differences between patients and controls were statistically significant in the five brain regions (Student's *t*-test with Bonferroni's correction): *p*-value = 0.0021 in anterior brain area, *p*-value = 0.0030 in central region, *p*-value = 0.0031 in posterior area, *p*-value = 0.0031 in left lateral, and finally *p*-value = 0.0111 in right lateral.

Furthermore, we evaluated the ability of *FuzzyEn* to discriminate ADHD patients from control children using receiver operating characteristic (ROC) curves. A ROC curve is a graphical representation of the trade-offs between sensitivity and specificity. We define sensitivity as the rate of ADHD patients who test positive, whereas specificity represents the fraction of controls correctly recognized. Accuracy quantifies the total number of subjects appropriately classified. The area under the ROC curve (AROC) is a single number summarizing the performance. AROC indicates the probability that a randomly selected ADHD patient has a *FuzzyEn* value lower than a randomly chosen control. In order to calculate these values, a leave-one-out cross-validation procedure was used. In the leave-one-out method, the data from one subject are excluded from the training set one at a time and then classified on the basis of the threshold calculated from the data of all other subjects. The leave-one-out cross-validation procedure provides a nearly unbiased estimate of the true error rate of the classification procedure. The highest accuracy was obtained at anterior and right lateral brain areas (82.14%), whereas the highest AROC value was reached at anterior region: 0.9005. Table 1 shows the sensitivity, specificity, accuracy, and AROC values.

TABLE I. SENSITIVITY, SPECIFICITY, ACCURACY AND AROC VALUES OBTAINED WITH *FUZZYEN* IN EACH BRAIN AREA

	Sensitivity	Specificity	Acurracy	AROC	*p*-value
Anterior	92.86%	71.43%	82.14%	0.9005	0.0021
Central	85.71%	71.43%	78.57%	0.8903	0.0030
Posterior	64.29%	85.71%	75.00%	0.8724	0.0031
Left lateral	64.29%	71.43%	67.86%	0.8469	0.0031
Right lateral	100.00%	64.29%	82.14%	0.8571	0.0111

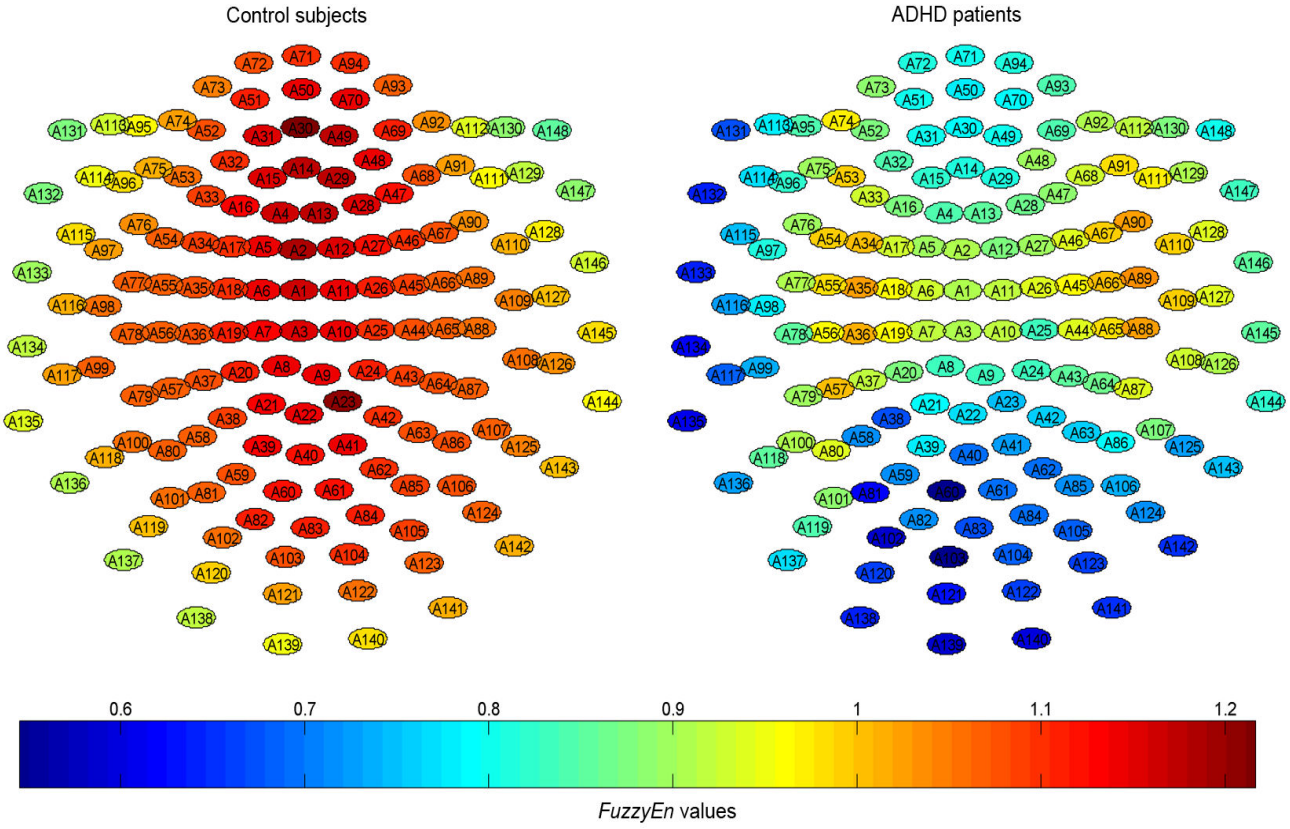

Figure 1. Average *FuzzyEn* values in ADHD patients and control subjects for all MEG channels.

IV. Discussion and conclusions

In this study, MEG activity in ADHD was analyzed using *FuzzyEn*, an entropy measure that quantifies time series irregularity. Our purpose was to check the hypothesis that MEG recordings reflect the alterations in patients' brain. *FuzzyEn* has proven to be effective in discriminating ADHD patients from controls in the five analyzed brain areas. Our results revealed that ADHD patients are associated with lower *FuzzyEn* values compared to controls, indicating a decrease of the MEG irregularity. These findings are in agreement with previous research that applied other embedding entropies, like *ApEn* and *SampEn*, to estimate the irregularity of brain recordings from ADHD patients [11, 20]. Other methods have also been applied to analyze the EEG/MEG activity in ADHD. For instance, coherence was applied to EEG signals to evaluate the functional connectivity of the frontal cortex [9]. Fernández *et al.* [7] concluded that ADHD is characterized by a MEG complexity decrease using Lempel-Ziv complexity. In summary, all these studies support the hypothesis that ADHD is characterized by a delay of cortical maturation in the prefrontal cortex.

ROC curves were used to assess the ability of *FuzzyEn* to classify ADHD patients and control subjects. The highest values of accuracy and AROC were reached in anterior region (82.14% and 0.9005, respectively). These values are similar to those achieved in our previous work, when *SampEn* was computed over the same database [20]. However, in our previous study, the best results were obtained in posterior, anterior and central areas. Therefore, *FuzzyEn* may reflect more accurately the frontal dysfunction in ADHD. Nevertheless, these values should be taken with caution due to the small sample size.

Our results suggest that *FuzzyEn* could be useful to help physicians in ADHD diagnosis. Nevertheless, some limitations of our study merit consideration. Firstly, the sample size is small. Moreover, the detected decrease in irregularity is not specific to ADHD, appearing in other brain disorders. Additionally, entropy values were averaged to simplify the interpretation of the results and to reduce the type I error in the statistical analysis, loosing the spatial information of MEG signals. Future efforts will be focussed on increase our database to confirm the performance of our method. Furthermore, in order to yield a more robust classifier, we will try to combine *FuzzyEn* results over the five brain regions. Finally, it may be useful to apply *FuzzyEn* algorithm and/or other types of entropy-based approaches to MEG activity in different frequency bands, since some of them (i.e. theta) may be more affected by ADHD [8, 9].

In sum, our study leads us to conclude that MEG background activity in ADHD patients is more regular than in control subjects. The results obtained with *FuzzyEn* showed significant differences between ADHD patients and controls, indicating an abnormal type of dynamics associated with ADHD, especially in frontal brain region.

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