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Regularity analysis of spontaneous MEG 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 a regularity measure: sample entropy (*SampEn*). Five minutes of recording were acquired with a 148-channel whole-head magnetometer in 14 ADHD patients and 14 control subjects. Our results showed that ADHD patients' MEGs were more regular than controls' recordings. Additionally, there were statistically significant differences (p < 0.01, Student's t-test with Bonferroni's correction) at the five analyzed brain areas: anterior, central, posterior, left lateral and right lateral. Using receiver operating characteristic (ROC) curves, the highest accuracy (82.14%) was achieved at posterior region, whereas the highest area under the ROC curves (0.8827) were reached at anterior and central brain regions. These results suggest the usefulness of *SampEn* to reveal an abnormal type of dynamics associated with ADHD.**

I. Introduction

MAGNETOENCEPHALOGRAPHY (MEG) is a non-invasive technique that allows recording the magnetic fields produced by brain activity. It provides an excellent temporal resolution, better than other methods for measuring cerebral activity, as magnetic resonance imaging, single-photon-emission computed tomography or positron-emission tomography [1]. A good spatial resolution can also be achieved due to the large number of sensors. Moreover, the activity in different parts of the brain can be monitored simultaneously with whole-head equipments [1]. On the other hand, the magnetic signals generated by the human brain are extremely weak. Thus, SQUID (Superconducting QUantum Interference Device) sensors are necessary to detect them. In addition, MEG signals must be recorded in a magnetically shielded room. Thus, MEG is characterized by limited availability and high equipment cost.

Attention-Deficit Hyperactivity Disorder (ADHD) is the most common neurobehavioral disorder of childhood [2]. Diagnostic guidelines identify the core symptoms of ADHD as inattentiveness, impulsivity, and hyperactivity. These guidelines also acknowledge that there is no objective test or marker for ADHD. Thus, diagnosis relies entirely on clinical criteria. In pediatric population, it produces scholar drop-out and social and familial disadaptation. The symptoms persist during adulthood in a 50-60% of patients, including impulsivity and antisocial behavior in 25% of cases [3]. 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 researches offer ample evidence of brain and behavioral dysfunctions in ADHD. Recently, Shaw *et al.* [4] defined ADHD as a disorder characterized by a delay of cortical maturation, which affects in a higher degree the prefrontal cortex. Bush *et al.* [5] reviewed several functional neuroimaging studies and found a consistent pattern of frontal dysfunction in ADHD patients. In agreement with these results, Fernández *et al.* [6] found a complexity decrease 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. Until the introduction of methods derived from nonlinear dynamics, ADHD brain recordings were analyzed with linear techniques based on coherence and spectral calculations [7, 8]. These analyses seem to discriminate ADHD patients from control subjects through an increased activity in theta frequency band, especially in frontal areas. However, the ability of human brain to perform sophisticated cognitive tasks supports the hypothesis that the EEG/MEG activity exhibits significant complex behavior with strong nonlinear and dynamical properties. Therefore, non-linear methods might be more suitable than traditionally linear techniques to analyze the EEG/MEG background activity. Previous studies suggest that the spontaneous activity is more regular and less complex in ADHD patients than in control subjects [6, 9].

In this study, we have examined the MEG background activity in ADHD using a regularity measure called sample entropy (*SampEn*). Entropy is a concept addressing randomness and predictability, with greater entropy often associated with more randomness and less system order [10]. Applied to time series, *SampEn* quantifies the signal regularity [11]. 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 dynamics associated with ADHD.

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II. MATERIALS AND METHODS

A. MEG recording

MEGs were recorded using a 148-channel whole-head magnetometer (MAGNES 2500 WH, 4D Neuroimaging) located in a magnetically shielded room. 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 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.

B. 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 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 [12]. The DSM-IV diagnosis of ADHD was based on the parent version of the Diagnostic Interview for Children and Adolescents [13]. ADHD patients were totally drug-naïve: they had never used any psychoactive drug or received any psychoactive therapy.

Fourteen healthy children (age = 10.36 ± 1.48 years, range 8–13) were recruited from the community as well. ADHD patients and control subjects did not differ statistically in terms of age and years of education (6.82 ± 1.22 in ADHD patients and 7.28 ± 1.38 in controls), and all were strictly right-handed. The Institutional Review Board approved this research protocol and written informed consent and assent to participate in the study were obtained from parents and children, respectively.

C. Sample entropy (SampEn)

SampEn is an embedding entropy that quantifies the regularity of a signal [11]. *SampEn* 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 *SampEn*, two input parameters must be specified: a run length m and a tolerance window r. *SampEn* is the negative natural logarithm of the conditional probability that two sequences similar for m points remain similar at the next point, where self-matches are not included in calculating the probability [11]. Pincus has suggested parameter values of m = 1 or m = 2, and with r a fixed value between 0.1 to 0.25 times the SD of the original time series [14]. In our study, we have chosen m = 2 and r = 0.2 times the SD of the original time series.

SampEn has already been used to study some biological signals. Kim *et al.* [15] investigated the non-linear characteristics of heart rate variability for different recumbent positions using *SampEn*. In a recent study, this measure has been applied to MEG signals from Alzheimer's disease patients [16].

Given a time series $X = x(1), x(2),... x(N)$, the algorithm to compute the *SampEn* is the following [11]:

1) Form $N - m + 1$ vectors $X_m(i)$ defined by: $X_m(i) = X_m(i + k)$ with $0 \le k \le m - 1$.
2) The distance between two of this vectors is the maximum difference of their corresponding scalar components:
$$d[X_m(i), X_m(j)] = \max(|x(i+k) - x(j+k)|) \quad (1)$$
for $0 \le k \le m - 1$.
3) Define $B_i^m(r)$ as $1/(N - m - 1)$ times the number of vectors $X_m(j)$ within r of $X_m(i)$, where $1 \le j \le N - m$ ($j \ne i$). Then, set $B_m(r)$ as:
$$B_m(r) = \frac{1}{N-m}\sum_{i=1}^{N-m} B_i^m(r) \quad (2)$$
4) Similarly, calculate $A_i^m(r)$ as $1/(N - m - 1)$ times the number of j ($1 \le j \le N - m$; $j \ne i$), such the distance between $X_{m+1}(j)$ and $X_{m+1}(i)$ is less than or equal to r. Set $A_m(r)$ as:
$$A_m(r) = \frac{1}{N-m}\sum_{i=1}^{N-m} A_i^m(r) \quad (3)$$
5) Finally, we define:
$$SampEn(m,r) = \lim_{N\to\infty}\left[-\ln\frac{A_m(r)}{B_m(r)}\right] \quad (4)$$
which is estimated by the statistic
$$SampEn(m,r,N) = -\ln\frac{A_m(r)}{B_m(r)} \quad (5)$$

III. RESULTS

SampEn algorithm was applied to the 148 MEG channels with m = 2 and r = 0.2 times the SD of the original time series. The average *SampEn* value for the control group was 0.88 ± 0.08 (mean ± SD), whereas it reached 0.67 ± 0.10 for the ADHD patients. Fig. 1 summarizes the average *SampEn* values estimated for the ADHD patients and the control subjects, for all the MEG channels. This figure shows that entropy values were higher in the control group than in the ADHD group for all channels, which suggests that this disorder is accompanied by a MEG irregularity decrease. To simplify the analyses, we grouped the 148 channels in five brain areas: anterior, central, posterior, left lateral, and right lateral. Differences between patients and controls were statistically significant in the five brain regions (Student's t-test with Bonferroni's correction), with the lowest value achieved at frontal area: p-value = 0.0012 at anterior region, p-value = 0.0021 at central area, p-value = 0.0037 at

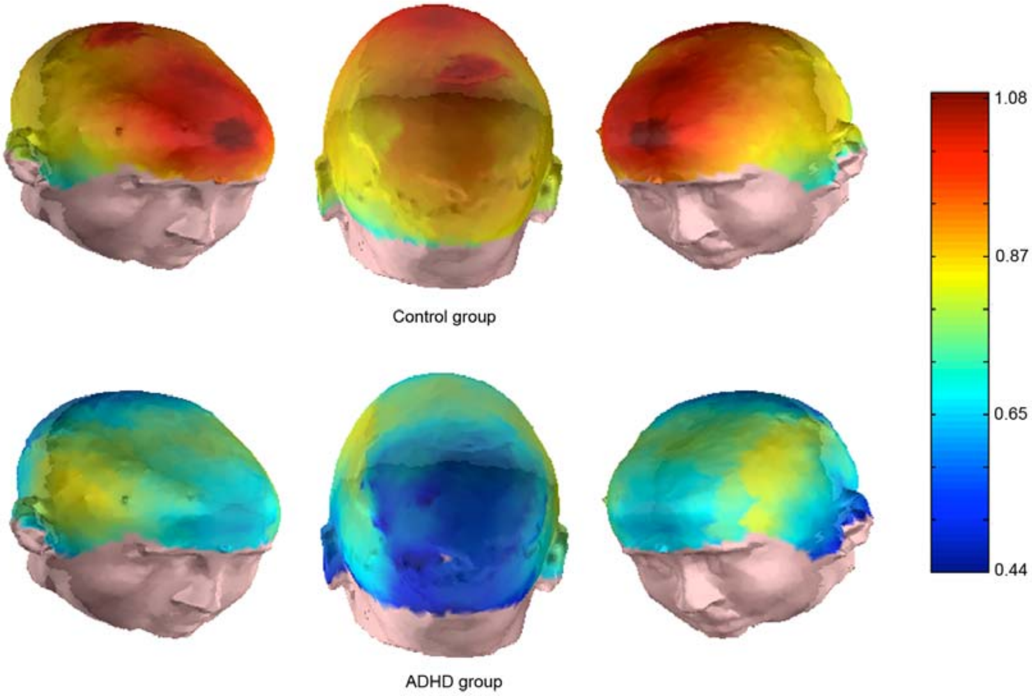

Fig. 1. Average *SampEn* values in ADHD patients and control subjects for all channels.

posterior brain area, p-value = 0.0016 at left lateral, and p-value = 0.0055 at right lateral.

Furthermore, we evaluated the ability of *SampEn* to discriminate ADHD patients from elderly control subjects by means of 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 precisely 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 *SampEn* value lower than a randomly chosen control subject. 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. Fig. 2 represents the ROC curves obtained at each brain area, whereas Table 1 shows the sensitivity, specificity, accuracy, and AROC values.

IV. Discussion and conclusions

We analyzed the MEG background activity from 14 ADHD patients and 14 control subjects by means of a *SampEn*. Our purpose was to check the hypothesis that MEG background activity was different in both groups. *SampEn* has proven to be effective in discriminating ADHD patients from controls at the five analyzed brain areas. Our results revealed that ADHD patients are associated with lower *SampEn* values, indicating an increase of the MEG regularity. These findings are in agreement with previous research works that have applied other embedding entropies, as approximate entropy, to estimate the regularity of brain recordings from ADHD patients [9]. Other methods have been used to study the EEG/MEG activity in ADHD. For instance, Murias *et al.* [8] evaluated the functional connectivity of the frontal cortex using EEG coherence. A recent MEG study has suggested a complexity decrease in ADHD by means of Lempel-Ziv complexity [6].

TABLE II
Sensitivity, Specificity, Accuracy and AROC Values Obtained with *SampEn* at each Brain Area

	Sensitivity	Specificity	Acurracy	AROC
Anterior	85.71%	64.29%	75.00%	0.8827
Central	64.29%	78.57%	71.43%	0.8827
Posterior	71.43%	92.86%	82.14%	0.8418
Left lateral	78.57%	78.57%	78.57%	0.8776
Right lateral	85.71%	64.29%	75.00%	0.8571

ROC curves were used to assess the ability of *SampEn* to classify ADHD patients and control subjects. The highest accuracy (82.14%) was achieved at posterior region, whereas the highest AROC values (0.8827) were reached at anterior and central areas. Nevertheless, these values should be taken with caution due to the small sample size.

Our results indicate that entropy measures could be useful in ADHD diagnosis. Nevertheless, some limitations of our study merit consideration. Firstly, the sample size is small to prove the usefulness of these measures as diagnostic tools. Moreover, the detected decrease in irregularity is not

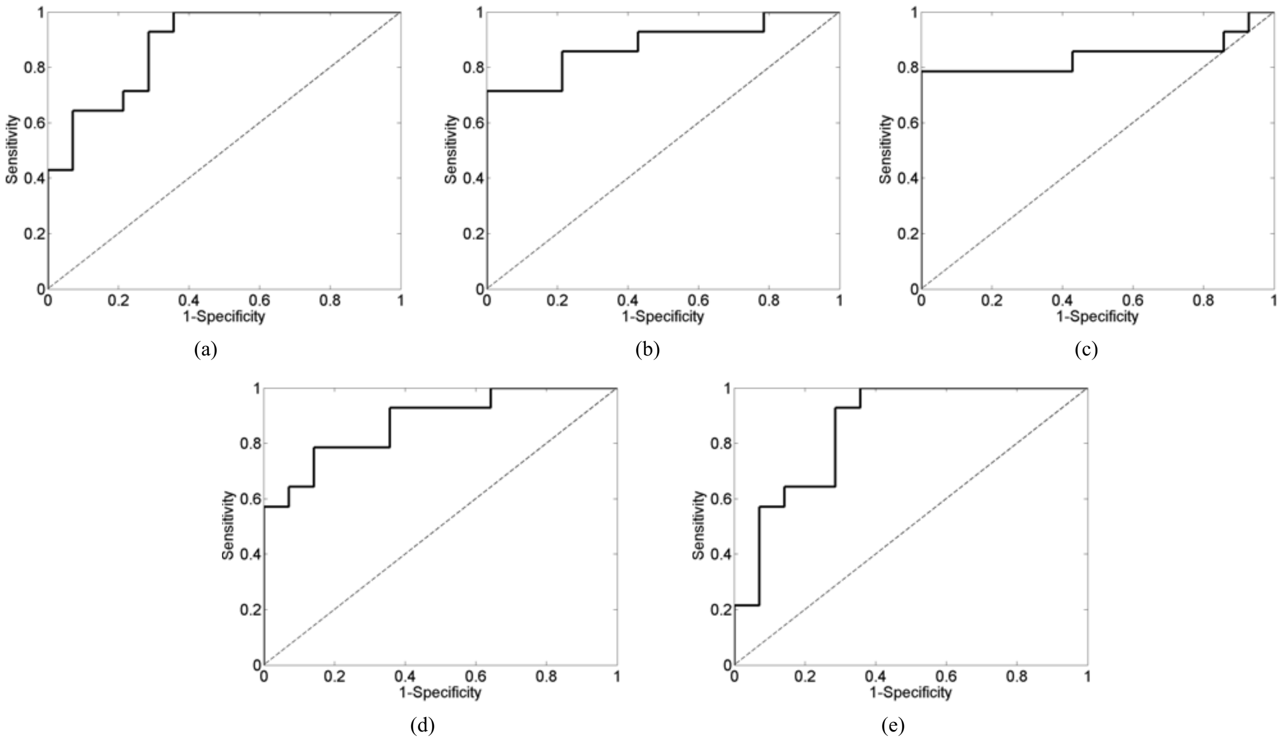

Fig. 2. ROC curves showing the discrimination between ADHD patients and control subjects with *SampEn* at the following brain areas: (a) anterior, (b) central, (c) posterior, (d) left lateral, and (e) right lateral.

specific to ADHD, appearing in other brain disorders. Additionally, the results were averaged to simplify the analyses, loosing the spatial information of MEG signals. Therefore, future efforts will be focussed to combine the *SampEn* results across the five brain regions to yield a single more robust classifier. Finally, a larger MEG database is needed to confirm the performance of our method.

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 *SampEn* showed significant differences between ADHD patients and controls, indicating an abnormal type of dynamics associated with ADHD.

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