MEG analysis of neural dynamics in Attention-Deficit/ Hyperactivity Disorder with Fuzzy Entropy

Jesús Monge[a], Carlos Gómez[a,*], Jesús Poza[a,b], Alberto Fernández[c,d], Javier Quintero[c,e] and Roberto Hornero[a,b]

[a] Biomedical Engineering Group, E.T.S. Ingenieros de Telecomunicación, Universidad de Valladolid, Campus Miguel Delibes, Paseo Belén 15, 47011 – Valladolid, Spain.

[b] IMUVA, Instituto de Investigación en Matemáticas, Universidad de Valladolid, Spain.

[c] Department of Psychiatry, Faculty of Medicine, Universidad Complutense de Madrid, Madrid, Spain.

[d] Laboratory of Cognitive and Computational Neuroscience, Center for Biomedical Technology, Universidad Complutense de Madrid, Madrid, Spain.

[e] Psychiatry Service, Hospital Infanta Leonor, Madrid, Spain.

* Corresponding author: **Carlos Gómez**

Biomedical Engineering Group, E.T.S. Ingenieros de Telecomunicación, Universidad de Valladolid, Campus Miguel Delibes, Paseo Belén 15, 47011 – Valladolid, Spain.

Tel. +34 983 423981

E-mail address: carlos.gomez@tel.uva.es

URL: www.gib.tel.uva.es

Abstract- The aim of this study was to analyze the neural dynamics in Attention-Deficit/Hyperactivity Disorder (ADHD). For this purpose, magnetoencephalographic (MEG) background activity was analyzed using fuzzy entropy (FuzzyEn), an entropy measure that quantifies signal irregularity, in 13 ADHD patients and 14 control children. Additionally, relative power (RP) was computed in conventional frequency bands (delta, theta, alpha, beta and gamma). FuzzyEn results showed that MEG activity was more regular in ADHD patients than in controls. Moreover, we found an increase of power in delta band and a decrease in the remaining frequency bands. Statistically significant differences (p-values < 0.05; nonparametric permutation test for multiple comparisons) were detected for FuzzyEn in the posterior and left temporal regions, and for RP in the posterior, anterior and left temporal regions. Our results support the hypothesis that ADHD involves widespread functional brain abnormalities, affecting more areas than fronto-striatal circuits, such as the left temporal and posterior regions.

Keywords- Attention-Deficit/Hyperactivity Disorder, fuzzy entropy, relative power, magnetoencephalography.

1. INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) is the psychiatric disorder most commonly diagnosed and treated in children. Its prevalence ranges between 8% and 12% children worldwide. Additionally, at least half of children with the disorder will continue suffering the symptoms in adulthood [1]. It is characterized by several behavioral disturbances, such as inattention, hyperactivity and impulsivity, which predispose the patients to academic and social dysfunctions, accidents or chaotic interpersonal relationships [2]. Pharmacotherapy helps children and adolescents with ADHD to concentrate and to be calmer, less hyperactive and more focused [3]. Methylphenidate is the most commonly used medicine in the management of ADHD, whereas atomoxetine is recommended when the former fails. However, medication should always be offered as part of a comprehensive treatment plan [3], [4].

Initially, it was believed that the etiology of the disease consisted on one simple cause. However, nowadays ADHD is considered a complex, multifactorial disorder caused by the confluence of many different types of risk factors (e.g., genes, biological predisposition and psychosocial adversity) [5]. This multifactorial view of ADHD is consistent with the heterogeneity in its pathophysiology and clinical expression [1]. The ADHD pathophysiology profile comprises dysfunction in the fronto-subcortical pathways and imbalances in the dopaminergic and noradrenergic systems [2]. Brain imaging studies fit well with this concept and also involve the cerebellum and corpus callosum in the pathophysiology of ADHD [6].

The complexity of the diagnosis cannot be ignored. Because there is no objective test or marker for ADHD, diagnosis relies entirely on clinical criteria [1]. Although there are well-defined criteria (Diagnostic and Statistical Manual of Mental Disorders,

DSM, and International Statistical Classification of Diseases, ICD), clinicians must deal with data from multiple informants (parents, teachers and friends) and must attend to developmental variations in symptom expression (comorbidity is a key clinical feature observed in ADHD patients). This complexity may explain the discrepancies among clinicians and among different studies of the disorder [5]. Hence, new approaches are needed to understand ADHD [7], [8]. With this aim, the analysis of brain activity can be a noteworthy alternative.

The neurobiological basis of ADHD has been widely studied using neuroimaging techniques (for a review, see [9] and/or [10]). Initially, single photon emission computed tomography (SPECT) and positron emission tomography (PET) were used to study the involvement of basal ganglia [11], blood flow measurement [12] and cerebral glucose metabolism [13], among other parts and characteristics of the brain. However, these early studies showed some methodological concerns (poor subject matching, absence of control group, etc.). Hence, it is difficult to assess their results and make cross-comparisons. Later, other neuroimaging techniques, like functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI), enabled functional and structural connectivity studies, respectively [14]. Their main results suggest that the core symptoms of ADHD might derive from dysregulated modulation of cortical plasticity in the developing brain, which leads to altered patterns of corticocortical connectivity [14]. Structural connectivity studies involve alterations in the white matter frontostriatal and in the superior longitudinal fasciculus. Alternatively, functional connectivity studies put forward that functional disconnections within frontostriatal and mesocortico-limbic circuits play a fundamental role in the generation of ADHD symptoms. On the other hand, neurophysiological measures can provide complementary information to neuroimaging techniques about this issue [14].

Electroencephalography (EEG) and magnetoencephalography (MEG) measure the electric and magnetic fields generated by the neurons, respectively [15]. Both EEG and MEG have higher temporal resolution than PET and fMRI. Likewise, they record the neural activity directly, without the need to interpret it in terms of proxy measures, such as glucose consumption [15], [16]. MEG offers some advantages over EEG, since magnetic fields are reference-free and less affected by distortions produced by the resistive properties of the skull and the scalp [15]. On the other hand, MEG equipment is distinguished by limited availability and high costs in comparison to EEG devices [17], [18]. Previous researches have proven that the analysis of EEG/MEG activity can be useful to characterize the brain activity in ADHD [19].

The neurophysiology of ADHD has been mainly examined by means of quantitative EEG/MEG analyses and event-related potentials (ERPs). For resting EEG, a slowing of brain oscillatory activity in comparison to normal children was found. In this sense, an increase in relative theta power and a reduction in relative alpha and beta power, along with increased theta/alpha and theta/beta ratios, are the most reliably findings associated with ADHD [20], [21]. In the case of ERPs, a complex range of deficits has been associated with the disorder, for example, in the preparatory responses or auditory modality [22]. Studies using nonlinear measures have found a decrease of complexity in the MEG frontal activity of ADHD patients [23]. Kovatchev *et al.* [24] employed a consistency index, derived from a specific mathematical representation of EEG data, to validate the idea that ADHD interferes with transitions from one task to another. The differences were especially significant in male children, which reported good values of ADHD/control classification. Recent studies suggested that irregularity analyses based on entropy measures can provide valuable information to understand brain dynamics in ADHD. These studies found that MEG activity in ADHD patients

was less irregular than in controls [25] – [27]. In summary, nonlinear metrics and spectral analyses have been useful to explore the neurophysiological substrate of neural dysfunction in ADHD so far. Nevertheless, further research is indeed required to describe the neural dynamics associated with this disorder.

In this study, we analyzed the neural dynamics of ADHD by means of fuzzy entropy (FuzzyEn) and spectral analysis. FuzzyEn quantifies the signal irregularity and exhibits a more flexible behavior than other previous entropy metrics, due to the exponential function it uses as a classifier [28]. In addition, relative power (RP) in five frequency bands (delta, theta, alpha, beta and gamma) was calculated in order to explore the spectral content of MEG recordings. In the current research, we attempt to address the following questions: (i) Can FuzzyEn provide further insights into the underlying brain dynamics associated with ADHD?; (ii) Can spectral analysis provide complementary results to FuzzyEn?; (iii) Can FuzzyEn and RP results reflect the regional abnormalities of ADHD?

2. MATERIAL AND METHODS

A. Subjects

In this study, MEG recordings were acquired from 27 subjects. Thirteen children were included in the ADHD group (age = 9.5 ± 1.3 years, mean ± standard deviation, SD; range 8-12 years). They fulfilled the criteria of 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 [29]. The DSM-IV used the parent version of the Diagnostic Interview for Children and Adolescents [30]. The patients had never taken any psychoactive drug or received any psychoactive therapy. The control group was formed by 14 children

(10.4 ± 1.5 years, mean ± SD; range 8-13 years) without past or present neurological disorders.

Both groups, patients and control subjects, had similar age and years of education (6.8 ± 1.2 years in ADHD patients and 7.3 ± 1.4 years in controls; mean ± SD). All of them were strictly right-handed. Children and parents gave their written informed consent and assent to participate in the study. The Institutional Review Board approved the research protocol.

B. MEG recording

MEG signals were recorded from each participant using a 148-channel whole-head magnetometer (MAGNES 2500 WH, 4D Neuroimaging) placed in a magnetically shielded room at MEG Center "Dr. Pérez-Modrego" (Spain). Before the recording process, subjects were asked to remain in a relaxed state, lying in a bed, with their eyes closed and awake, in order to reduce the presence of artifacts in the recordings.

Five minutes of MEG data were acquired from each subject at a sampling frequency of 678.17 Hz. A process of down-sampling by a factor of four was carried out, resulting a sampling rate of 169.55 Hz. Data were digitally filtered using a 1-65 Hz band-pass filter and a 50 Hz notch filter. Both visual inspection and independent component analysis (ICA) were performed to minimize the presence of oculographic, cardiographic and myographic artifacts. A mean of 23.2 ± 14.1 artifact-free epochs of 5 s (848 data points) per channel and subject were selected for further analyses. Figure 1 shows examples of MEG epochs (channel A1, placed at central region) from an ADHD patient and a control.

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C. Fuzzy entropy (FuzzyEn)

FuzzyEn is a measure of time series irregularity. Similar to other embedding entropies, as approximate entropy (ApEn) or sample entropy (SampEn), it provides information about how a signal fluctuates with time by comparing the time series with a delayed version of itself [31]. It is defined as the negative natural logarithm of the conditional probability that two similar vectors remain similar when the dimension changes from m to $m + 1$ [28]. To compute FuzzyEn, three parameters must be fixed. The first parameter, m, is the length of the vectors to be compared, like in ApEn and SampEn. The other two ones, r and n, are the width and the gradient of the boundary of the exponential function, respectively. Similar to ApEn and SampEn, FuzzyEn can be applied to noisy physiological signals with relatively short datasets [28]. However, FuzzyEn provides some advantages over ApEn and SampEn. Firstly, using the concept of fuzzy set, FuzzyEn measures the similarity of two vectors by means of an exponential function rather than the Heaviside function, used by ApEn and SampEn. The latter function is a two-state classifier with a rigid boundary, unsuitable in the real physical world because of the ambiguity in the boundaries between different classes [28]. Due to the soft and continuous boundaries of fuzzy functions, FuzzyEn offers more flexibility in the selection of the parameters than ApEn and SampEn [32]. Likewise, it ensures to be well-defined even at small values of such parameters. Secondly, FuzzyEn excludes self-matching (i.e., vectors are not compared to themselves) and considers only the first $N – m$ vectors of length m, being N the length of the original time series. Therefore, all the compared vectors exist, even when their lengths change from m to $m + 1$. Finally, FuzzyEn removes the baseline in the construction of m-dimensional vectors. Thereby, vectors similarity depends on their shapes rather than their absolute coordinates. These features provide to FuzzyEn

stronger relative consistency and less dependence of data length than ApEn and SampEn algorithms [28], [32].

Given a time series $X = x(1), x(2), \ldots, x(N)$ the FuzzyEn algorithm reads as follows [28]:

1) Compose $N–m+1$ vectors of length m such that:

$$X_i^m = \{x(i), x(i+1), \ldots, x(i+m-1)\} - x_0(i) \quad (1)$$

where $x_0(i)$ is given by:

$$x_0(i) = \frac{1}{m}\sum_{j=0}^{m-1} x(i+j) \quad (2)$$

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

$$d_{ij}^m = d(X_i^m, X_j^m) = \max_{k\in(0,m-1)}\left[\left(x(i+k) - x_0(i)\right) - \left(x(j+k) - x_0(j)\right)\right] \quad (3)$$

3) Given n and r, calculate the similarity degree, D_{ij}^m, between X_i^m and X_j^m through a fuzzy function $\mu(d_{ij}^m, n, r)$:

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

4) Define the function ϕ^m as:

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

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

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

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

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

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

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

D. Spectral Analysis

Spectral analysis is a classic approach to characterize electromagnetic brain recordings. It offers a complementary view of the neural dynamics in comparison to non-linear analysis. In this study, the power spectral density (PSD) for each MEG signal was estimated as the Fourier transform of the autocorrelation function, according to the Wiener-Khinchin-Einstein theorem [33]:

$$PSD_x(k) = \frac{1}{N}\cdot\sum_{i=0}^{2N-1} R_{xx}(i)\cdot e^{-j\frac{2\pi ki}{2N-1}}, k = 0,1,\ldots,2N-1, \tag{9}$$

where $R_{xx}(i)$ denotes the discrete-time autocorrelation function of time series $X = x(1), x(2),\ldots,x(N)$.

The PSD was then averaged for each channel and participant. Likewise, only positive frequencies were selected to obtain the one-sided PSD. Finally, the one-sided PSD was normalized to a scale from 0 to 1, leading to the normalized PSD (PSD_n):

$$PSD_n(m) = \frac{PSD_x(m)}{\sum_{m=m_1}^{m_2} PSD_x(m)}, m = 0,1,\ldots,N-1, \tag{10}$$

where m_1 and m_2 denote the discrete cut-off frequencies. They can be replaced by the continuous frequencies $f_1 = f_s \cdot m_1/N$ and $f_2 = f_s \cdot m_2/N$, where f_s represents the sampling frequency, whereas f_1 = 1 Hz and f_2 = 65 Hz are the cut-off frequencies of the digital band-pass filter.

The definition of RP was obtained summing the contribution of the spectral components in the conventional frequency bands: delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz) and gamma (30-65 Hz):

$$RP^{m_b} = \sum_{m \in m_b} PSD_n(m), m_b = \{\text{delta}, \text{theta}, \text{alpha}, \text{beta}, \text{gamma}\}, \quad (11)$$

where m_b denotes the discrete frequency range corresponding to each conventional frequency band.

E. Statistical Analysis

Initially, an exploratory analysis was carried out to study the data distribution. In order to evaluate the normality and the homoscedasticity of FuzzyEn and RP values, the Lilliefors' test and the Bartlett's test were used, respectively. FuzzyEn and RP values did not meet the parametric test assumptions. Hence, grand-averaged FuzzyEn and RP values were compared between ADHD patients and control subjects by means of Mann-Whitney *U*-tests ($\alpha < 0.05$).

Statistical analyses at the sensor level for FuzzyEn and RP were carried out using a multiple comparisons nonparametric permutation test [34]. This test is useful to achieve a strong control over type I error in situations in which the multiplicity of testing must be taken into account (e.g., 148 sensors). In permutation test, the distributional assumption is weak. Typically, it is assumed that each distribution has the same shape, though possibly different means. The null hypothesis asserts that the distributions have equal means, and hence they are the same. Consequently, the

246 permutation of the distributions within the available observations leads to an equally
247 likely statistic. Therefore, the goal is to compute the permutation distribution for the
248 maximal statistic F^{max} (i.e., the maximum of the sensor statistics for each permutation).
249 Multiple comparisons were then corrected by selecting a critical threshold at the c+1
250 largest member of the permutation distribution for F^{max}, where $c = \lfloor \alpha N \rfloor$, αN rounded
251 down (α represents the significance level, typically 0.05, and N is the number of
252 permutations, 5000). Sensors with F statistics exceeding this threshold exhibit evidence
253 against the corresponding sensor hypothesis at level α. The corrected p-value for each
254 sensor is estimated according to the proportion of the permutation distribution for F^{max}
255 that exceeds the observed sensor statistic [34].

256 # 3. RESULTS

257 *A. Optimization of FuzzyEn parameters*

258 FuzzyEn is more flexible than other entropy algorithms to select the value of its
259 parameters. Chen *et al.* [28] recommended choosing m such as $N \in (10^m - 30^m)$.
260 Regarding the fuzzy similarity boundary determined by the other two parameters, r and
261 n, choosing narrow ones will enlarge the influence of the noise, whereas a broad
262 boundary may cause an information loss. Thus, FuzzyEn was calculated for the 148
263 MEG channels for all the combinations among the following parameter values: m = 1,
264 2; r = 0.1, 0.15, 0.20, 0.25 times the SD of the original time series; and n = 1, 2, 3. The
265 lowest p-value according to the Mann-Whitney U-test was achieved for the parameter
266 combination: FuzzyEn (2,0.2·SD,3). As shown in Figure 2, the shape of the exponential
267 function makes possible the maximal exploitation of its properties: continuity (there is
268 no abrupt change like in Heaviside function) and convexity (its maximum correspond to
269 the self-similarity case).

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B. Global analysis

FuzzyEn results were grand-averaged based on all the artifact-free 5 s epochs. Mean values (± SD) for control and ADHD groups were 0.4811 ± 0.0376 and 0.4415 ± 0.0960, respectively. Consequently, we can infer that the brain abnormalities and dysfunctions, which underlay ADHD, can be associated with a decrease in irregularity of MEG activity. Figure 3 summarizes the boxplots of averaged results for each group. Even though non-significant differences were observed, the results showed a trend toward significance (p-value = 0.0680; Mann-Whitney U-test).

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Additionally, RP in delta, theta, alpha, beta and gamma frequency bands was calculated to complement FuzzyEn results. Figure 4 shows the normalized PSD for control and ADHD groups. The spectral analysis showed a significant increase of RP in delta band for ADHD patients (p-value = 0.0061; Mann-Whitney U-test). The results in theta band showed that ADHD patients obtained lower RP values than controls. Even though non-significant differences were found, a trend toward significance was observed (p-value = 0.0688; Mann-Whitney U-test). In the remaining bands (alpha, beta, gamma), control subjects exhibited higher values of RP than ADHD patients, although differences were not statistically significant. RP mean values and the corresponding p-values are shown in Table 1.

PLEASE, INSERT TABLE 1 AND FIGURE 4 AROUND HERE

C. Sensor-level analysis

In addition to global analysis, we explored the spatial patterns of FuzzyEn and RP values. The averaging process performed for global analysis may oversimplify ADHD related effects on MEG activity. For this reason, further analyses are needed to accurately characterize the neural activity in ADHD. Figure 5 depicts the brain maps showing the spatial distribution of the averaged FuzzyEn for each group and the corresponding statistical analyses (multiple comparisons nonparametric permutation test). The major differences can be appreciated in the posterior region, though some differences can also be observed in the left temporal and anterior regions. Significant differences did not appear in the global analyses due to the aforementioned averaging process.

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Finally, Figure 5 summarizes the spatial distribution of mean RP values for each frequency band and the corresponding statistical analyses. Delta band exhibits significant differences in the posterior, left temporal and anterior regions, whereas theta band shows only significant differences in the posterior and left temporal areas. Regarding alpha band, significant differences can be found in the posterior region. Beta band displays significant differences in anterior and posterior regions. Lastly, significant differences were found in the posterior area for gamma band.

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4. DISCUSSION

In this paper, we have analyzed MEG background activity from 14 control subjects and 13 ADHD patients by means of FuzzyEn, a measure of time series irregularity. In addition, RP has been computed to complement the FuzzyEn results.

A. FuzzyEn and the neural activity of ADHD

Regarding the first research question, we put forth the idea of whether FuzzyEn could be useful to provide further insights into the underlying brain dynamics of ADHD. Our findings support the notion that FuzzyEn provides an original description of ADHD neural dynamics. We found that ADHD patients show significantly lower FuzzyEn values than control subjects, especially in the posterior region. Hence, neural dynamics in ADHD are characterized by a less irregular neurophysiological behavior in this region. Moreover, these results agree with the hypothesis of a loss of physiological complexity due to diseases [35]. However, the dysfunctional implications of this decrease in MEG irregularity are not clear [9]. Initially, it was hypothesized that the neurobiological basis of ADHD involves structural and functional brain abnormalities in fronto-striatal circuits. This hypothesis has been widely supported by neuroimaging studies [10], [14]. However, a second hypothesis stresses that the abnormalities are more widespread and affect other cortical regions as posterior parietal cortex and the cerebellum [9]. Despite the fact that MEG signals are thought to reflect the cerebral cortex activity, previous work suggests that they can be also useful to study the activity of the cerebellum [36]. Several MRI studies detected a decreased size of the posterior inferior lobe of the cerebellum (lobules VIII-X) in ADHD patients in comparison with controls [37] – [41]. This reduction of the volume may explain the decrease in irregularity that was found in the posterior region. Consequently, the present results

would support the second hypothesis from a different perspective of neuroimaging techniques.

B. Spectral analysis to complement non-linear measures

The second research question addresses the issue of whether RP results could complement FuzzyEn results. Our findings indicate that they complement each other. All frequency bands show to some extent significant differences in the posterior region. Moreover, left temporal and anterior regions also exhibit significant differences in several frequency bands. Thereby, the spectral analysis involves at least the two cerebral regions in which the neurobiological substratum of the ADHD lies according to the second previous hypothesis (anterior region: prefrontal cortex; posterior region: cerebellum). In that way, we can suggest that, while the first hypothesis is necessary for explaining ADHD pathophysiology, it is not sufficient.

Although significant differences were found in the left temporal region for both FuzzyEn and RP (delta and theta bands), the pathophysiological explanation is uncertain. Only few neuroimaging cerebral studies reported significant differences in this area. For instance, Castellanos *et al.* [6] detected significantly reduced temporal lobe volumes. Sowell *et al.* [42] described abnormal morphology with reduced regional brain size in inferior portions of dorsal prefrontal cortices and in anterior temporal cortices, bilaterally. Again, these changes in size are believed to produce an irregularity reduction and a slowing in MEG background activity [9].

C. Widespread abnormalities as core of ADHD pathophysiology

We raised the third research question about whether there is a relationship between our results and the ADHD regional abnormalities. Taking into account that ADHD is considered as a multifactorial, heterogeneous and complex disorder [5], it seems more logic to think that its pathophysiology is caused by impaired interactions

among different parts of the brain, and not only by abnormalities or dysfunctions in a particular element. In sum, the second approach is more consistent with the etiological theory of the disorder and our results support it. In this sense, it should be investigated further to discover how genetic disorder, biological predisposition and social adversities modify brain development, leading to a heterogeneous neurobiological profile. Additionally, it should be noted that the prefrontal cortex is one of the brain areas more developed in the human beings and is among the latest cerebral regions that complete their development. Hence, the functions that prefrontal cortex controls or carries out may be more sensitive and, therefore, more easily detectable [43]. This may partially explain why originally several neuroimaging studies have postulated the prefrontal cortex and its connections with other cortical regions (fronto-striatal circuits) as the main pathophysiological basis of ADHD.

According to our results and other neuroimaging studies, an element that may be involved is the cerebellum. The cerebellum is associated with the coordination and the motor motion. It also plays a role in executive functions, such as timing of events, cognitive planning or affective processes, and has connections with the frontal brain [44]. The left temporal region also showed significant differences. This region contains areas relevant to the auditory-linguistic function. Consequently, both may be of interest in ADHD. Additionally, the dopamine transporter may play a crucial role. It is thought that a deficit or an excess of noradrenaline or dopamine receptor stimulation impairs neural and subsequent cognitive functions (working memory, executive functions, etc.), known to be deficient in ADHD [45]. Besides, projections from the ventral tegmental area, where is the origin of the dopaminergic cell bodies of the mesocorticolimbic dopamine system, to the striatum and the prefrontal cortex are fundamental in motor control and attention [46]. Finally, high levels of catecholamine released during severe

stress may disrupt cognitive functions of the prefrontal cortex [45]. Similarly, alterations in the superior longitudinal fasciculus [14], a pair of long bi-directional bundles of neurons connecting the front and the back of the cerebrum, emphasize the idea of that ADHD cerebral alterations and dysfunction are widespread.

D. Limitations and future research lines

There are some concerns that merit consideration. First of all, the size of the sample is small. This shortcoming causes that our findings must be taken as preliminary results. Hence, this approach should be extended on a much larger patient population, especially to assess the usefulness of FuzzyEn and/or RP as diagnostic tools, as well as to analyze the changes induced in the brain activity by pharmacological and non-pharmacological therapies. Secondly, one cannot forget the comorbidity of mental disorders. The detected decrease of MEG irregularity is not specific of ADHD. It appears in other physiological and pathological states in children, such as sleep [47] or epilepsy [48]. Regarding the spectral analysis, the same observation can be made. For instance, Onoe and Nishigaki [49] also perceived an increase of the delta power in febrile delirium children patients. Finally, we would like to indicate that brain imaging techniques are not absent from debate either [50]. The multitude of analytic techniques and measurements employed in different studies make difficult replication and cross-study comparisons [14].

5. CONCLUSION

In summary, FuzzyEn and spectral analyses of MEG activity exhibited significant differences mainly in the posterior and left temporal regions. The results support the hypothesis that the pathophysiology of ADHD is not only focused on a particular area, such as fronto-striatal circuits, but it is more widespread and it affects other parts of the brain, like the cerebellum. Along with the possible cerebral abnormalities, other factors

411 involved in the ADHD pathophysiology may also explain the differences (e.g., the
412 dopamine transporter, projections from the ventral tegmental area to the striatum and
413 the prefrontal cortex, high levels of catecholamine released during severe stress or
414 alterations in the superior longitudinal fasciculus). The previous ideas are consistent
415 with its multiple etiology pathways and agree with the results provided by
416 neuroimaging studies.

417

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CONFLICT OF INTEREST

There are no conflicts of interest that could inappropriately influence this research work.

ETHICAL APPROVAL

Psychiatry service of Hospital Clinico San Carlos with number: 12/106-E.

AUTHORSHIP RESPONSIBILITY

- The material in this manuscript is original and contains no matter libelous or otherwise unlawful.

- The manuscript represents valid work and that neither this manuscript nor any other with substantially similar content under my authorship has been published or is being considered for publication elsewhere.

- I have participated sufficiently in the work to take public responsibility for all its content.

REFERENCES

[1] Bierderman J, Faraone SV. Attention-deficit hyperactivity disorder. Lancet 2005; 366(9481):237–48.

[2] Bierderman J. Attention-deficit/hyperactivity disorder: a selective overview. Biol Psychiatry 2005;57(11):1215–20.

[3] Parker, C. Pharmacological treatments for ADHD. Prog Neurol Psychiatry 2013; 17(4):11–20.

[4] Parr JR, Ward A, Inman S. Current practice in the management of Attention Deficit Disorder with Hyperactivity (ADHD). Child Care Health Dev 2003;29(3): 215–8.

[5] Faraone SV, Biederman J. Neurobiology of Attention-deficit hyperactivity disorder. Biol Psychiatry 1998;44(10):951–8.

[6] Castellanos FX, Lee PP, Sharp W, Jeffries NO, Greenstein DK, Clasen LS, *et al.* Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. JAMA 2002;288(14): 1740–8.

[7] Wolraich ML, Wibbelsman CJ, Brown TE, Evans SW, Gotlieb EM, Knight JR, *et al*. Attention-deficit/hyperactivity disorder among adolescents: a review of the diagnosis, treatment, and clinical implications. Pediatrics 2005;115(6):1734–46.

[8] Wigal SB, Wigal TL. Special considerations in diagnosing and treating attention-deficit/hyperactivity disorder. CNS Spectr 2007;12(6 Suppl 9):1–14.

[9] Seidman LJ, Valera EM, Makris N. Structural brain imaging of attention-deficit/hyperactivity disorder. Biol Psychiatry 2005;57(11):1263–72.

[10] Bush G, Valera EM, Seidman LF. Functional neuroimaging of attention-deficit/hyperactivity disorder: a review and suggested future directions. Biol Psychiatry 2005;57(11):1273–84.

[11] Lou HC, Henriksen L, Bruhn P, Borner H, Nielsen JB. Striatal dysfunction in attention deficit and hyperkinetic disorder. Arch Neurol 1989;46(1):48–52.

[12] Kim BN, Lee JS, Cho SC, Lee DS. Methylphenidate increased regional cerebral blood flow in subjects with attention deficit/hyperactivity disorder. Yonsei Med J 2001;42(1):19–29.

[13] Zametkin AJ, Nordahl TE, Gross M, King AC, Semple WE, Rumsey J, *et al.* Cerebral glucose metabolism in adults with hyperactivity of childhood onset. N Engl J Med 1990;323(20):1361–6.

[14] Liston C, Cohen MM, Teslovich T, Levenson D, Casey BJ. Atypical prefrontal connectivity in attention-deficit/hyperactivity disorder: pathways to disease or pathological end point? Biol Psychiatry 2011;69(12):1168–77.

[15] Rossini PM, Rossi S, Babiloni C, Polich J. Clinical neurophysiology of aging brain: from normal aging to neurodegeneration. Prog Neurobiol 2007;83(6):375–400.

[16] Hinkley LBN, Owen JP, Fisher M, Findlay AM, Vinogradov S, Nagarajan SS. Cognitive impairments in schizophrenia as assessed through activation and connectivity measures of magnetoencephalography (MEG) data. Front Hum Neurosci 2010;3:73.

[17] Hasen PC, Kringelbach ML, Salmelin R. MEG: an introduction to methods. New York: Oxford University Press; 2010.

[18] Hari R; Magnetoencephalography in clinical neurophysiological assessment of human cortical functions. In: Niedermeyer E, Lopes Da Silva F. Electroencephalography: Basic principles, clinical applications, and related fields, Philadelphia: Lippincott Williams & Wilkins; 2005, pp. 1165–97.

[19] Stam CJ. Nonlinear dynamical analysis of EEG and MEG: review of an emerging field. Clin Neurophysiol 2005;116(10):2266–301.

[20] Barry RJ, Clarke AR, Johnstone SJ. A review of electrophysiology in attention-deficit/hyperactivity disorder I. Qualitative and quantitative electroencephalography. Clin Neurophysiol 2003;114(2):171–83.

[21] Monastra V, Lubar J, Linden M, VanDeusen P, Green G, Wing W, *et al*. Assessing attention deficit hyperactivity disorder via quantitative electroencephalography: an initial validation study. Neuropsychology 1999;13(3):424–33.

[22] Barry RJ, Johnstone SJ, Clarke AR. A review of electrophysiology in attention-deficit/hyperactivity disorder: II. Event-related potentials. Clin Neurophysiol 2003; 114(2):184–98.

[23] Fernández A, Quintero J, Hornero R, Zuluaga P, Navas M, Gómez C, *et al*. Complexity analysis of spontaneous brain activity in attention-deficit/hyperactivity disorder: diagnostic implications. Biol Psychiatry 2009;65(7):571–7.

[24] Kovatchev B, Cox D, Hill R, Reeve R, Robeva R, Loboschefski T. A psychophysiological marker of attention deficit/hyperactivity disorder (ADHD) – defining the EEG consistency index. Appl Psychophysiol Biofeedback 2001; 26(2):127–40.

[25] Gómez C, Poza J, García M, Fernández A, Hornero R. Regularity analysis of spontaneous MEG activity in attention-deficit/hyperactivity disorder. Conf Proc IEEE Eng Med Biol Soc 2011;1765–8.

[26] Gómez C, Poza J, Fernández A, Bachiller A, Gómez J, Hornero R. Entropy analysis of MEG background activity in attention-deficit/hyperactivity disorder. Conf Proc IEEE Eng Med Biol Soc 2013:5057–60.

[27] Shon H, Lee W, Kim I, Jeong J. Approximate entropy (ApEn) analysis of EEG in attention-deficit/hyperactivity disorder (ADHD) during cognitive tasks. World Congr Proc Med Phys Biomed Eng 2006;14:1083–6.

[28] Chen W, Wang Z, Xie H, Yu W. Characterization of surface EMG signal based on fuzzy entropy. IEEE Trans Neural Syst Rehabil Eng 2007;15(2):266–72.

[29] Conners CK. Spanish Conners' parent rating scales-revised. Multi-Health Systems, Norh Tonawanda, New York: Systems Inc; 2000.

[30] Reich W, Welner Z. Revised version of the diagnostic interview for children and adolescents (DICA-R). Washington University, School of Medicine: Department of Psychiatry. St. Louis: 1998.

[31] Sleigh JW, Steyn-Ross DA, Steyn-Ross ML, Grant C, Ludbrook G. Cortical entropy changes with general anesthesia: theory and experiment. Physiol Meas 2004;25(4):921–34.

[32] Chen W, Zhuang J, Wangxin Y, Wang Z. Measuring complexity using FuzzyEn, ApEn, and SampEn. Med Eng Phys 2009;31(1):61–8.

[33] Haykin S. Communication systems. New York: John Wiley & Sons; 2001.

[34] Nichols TE and Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. Hum Brain Mapp 2002;15(1):1–25.

[35] Goldberger AL, Peng CK, Lipsitz LA. What is physiologic complexity and how does it change with aging and disease? Neurobiol Aging 2002;23(1):23–6.

[36] Tesche CD, Moses SN, Houck JM, Martin T, Hanlon FM, Jackson E, *et al*. Dynamics of frontal and cerebellar activation during aversive conditioning: a MEG study. Int Congr Ser 2007;1300:437–40.

[37] Krain AL, Castellanos FX. Brain development and ADHD. Clin Psychol Rev 2006;26(4):433–44.

[38] Hill DE, Yeo RA, Campbell RA, Hart B, Vigil J, Brooks W. Magnetic resonance imaging correlates attention-deficit/hyperactivity disorder in children. Neuropsychology 2003;17(3):496–506.

[39] Mostofsky SH, Reiss AL, Lockhart P, Denckla MB. Evaluation of cerebellar size in attention-deficit hyperactivity disorder. J Child Neurol 1998;13(9):434–9.

[40] Berquin PC, Giedd JN, Jacobsen LK. Cerebellum in attention-deficit hyperactivity disorder: a morphometric MRI study. Neurology 1998;50(4):1087–93.

[41] Bussing R, Grudnik J, Mason D, Wasiak M, Leonard C. ADHD and conduct disorder: an MRI study in a community sample. World J Biol Psychiatry 2002; 3(4):216–20.

[42] Sowell ER, Thompson PM, Welcome SE, Henkenius AL, Toga AW, Peteron BS. Cortical abnormalities in children and adolescents with attention-deficit hyperactivity disorder. Lancet 2003;362(9397):1699–707.

553 [43] Capilla-González A, Fernández-González S, Campo P, Maestú F, Fernández-
554 Lucas A, Mulas F, *et al*. Magnetoencephalography in cognitive disorders involving
555 frontal lobes. Rev Neurol 2004;39(2):183–8.

556 [44] Gordon N. The cerebellum and cognition. Eur J Paediatr Neurol 2007;11(4):232–
557 4.

558 [45] Biederman J, Spencer T. Attention-deficit/hyperactivity disorder (ADHD) as a
559 noradrenergic disorder. Biol Psychiatry 1999;46(9):1234–42.

560 [46] Krause K-H, Dresel SH, Drause J, la Fougere C, Ackenheil M. The dopamine
561 transporter and neuroimaging in attention deficit hyperactivity disorder. Neurosci
562 Biobehav Rev 2003;27(7):605–13.

563 [47] Scraggs TL. EEG maturation: viability through adolescence. Neurodiagn J. 2012;
564 52(2):176–203.

565 [48] Rosso OA, Hyslop W, Gerlach R, Smith RLL, Rostas JAP, Hunter M. Quantitative
566 EEG analysis of the maturational changes associated with childhood absence
567 epilepsy. Phys. A: Statistical Mechanics and its Applications 2005;356(1):184–9.

568 [49] Onoe S, Nishigaki T. EEG spectral analysis in children with febrile delirium. Brain
569 Dev 2004;26(8):513–8.

570 [50] Baumeister AA, Hawkins MF. Incoherence of neuroimaging studies of attention
571 deficit/hyperactivity disorder. Clin Neuropharmacol 2001;24(1):2–10.

572

TABLE CAPTIONS

Table 1. RP values (mean ± SD) in the delta, theta, alpha, beta and gamma frequency bands for ADHD patients and control subjects, together with the corresponding statistical analyses (Mann-Whitney *U*-test).

FIGURE LEGENDS

Figure 1. Example of MEG time series from (a) an ADHD patient and (b) a control subject.

Figure 2. Exponential function used in vector similarity measurement of FuzzyEn for the combination: $m = 2$, $r = 0.2 \cdot \mathrm{SD}$ and $n = 3$.

Figure 3. Boxplots of the grand-averaged FuzzyEn results.

Figure 4. Grand-averaged normalized PSD for control subjects and ADHD patients.

Figure 5. Topographic brain maps of averaged FuzzyEn values for each group and the corresponding statistical analyses (nonparametric permutation test corrected for multiple comparisons).

Figure 6. Topographic brain maps of the averaged RP for each group and the corresponding statistical analyses (nonparametric permutation test corrected for multiple comparisons) at (a) delta, (b) theta, (c) alpha, (d) beta and (e) gamma frequency bands.