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The variability of EEG functional connectivity of young ADHD subjects in different resting states

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HIGHLIGHTS

- Variability of connectivity reflects the ADHD status better than connectivity itself.
- Enhanced variability of nonlinear EEG connectivity characterizes ADHD at rest.
- Changes between states only occur in variability of theta band connectivity for ADHD.

ABSTRACT

Objective: To assess ADHD from global measures of EEG functional connectivity and their temporal variability in different resting states.
Methods: EEGs from sixteen cortical regions were recorded at rest during eyes-closed (EC) and eyes-open (EO) in 10 male combined-type ADHD subjects and 12 healthy male controls. The mean global connectivity (CM) of each region and its temporal variability (CV) were estimated from a number of EEG segments recorded in both states. Connectivity indices between regions were calculated using the magnitude squared coherence (Coh) in the delta(δ)/theta(θ)/alpha(α)/beta(β) frequency bands and the nonlinear index (L) of generalized synchronization.
Results: The CM did not present between-group differences in any region or state. However, the CV exhibited state-independent differences between both groups (ADHD > controls) mainly in frontal and parieto-occipital regions for all indices except Coh(α). Within group, only the CV-Coh(θ) of the centro-temporal region increased significantly for the ADHD subjects from EC to EO ($p < 0.001$) and was greater than controls in EO ($p < 0.001$).
Conclusions: The CV of index-L and of Coh(θ) seem to be the best state-independent and -dependent measurements, respectively, to discriminate ADHDs from control subjects using resting state EEG data.
Significance: The underlying neural dysfunctions producing the ADHD seem better reflected by the CV measurements.

1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a dysfunction characterized by difficulty in attentional maintenance and/or by excessive hyperactivity and impulsivity (APA, 2001). There are three subtypes of ADHD, which are distinguished according to their predominating symptoms (APA, 2001): predominantly inattentive (ADHD-I), predominantly hyperactive-impulsive (ADHD-HI) and combined (ADHD-C). The diagnostic evaluation of ADHD is mainly performed through clinical interviews and diagnostic scales based on the DSM-IV-TR (APA, 2001) and ICD-10 (Döpfner and Lehmkuhl, 2000).

Since around 1980, ADHD has been investigated using EEG techniques, assuming that the symptoms of the disorder are associated with alterations of either the individual or the coordinated

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activity (or both) of different brain areas and can therefore be assessed from their recorded neuroelectrical activity. According to the literature regarding functional magnetic resonance imaging (fMRI), ADHD subjects have impaired functional connectivity (FC) between different brain regions (Castellanos et al., 2008; Cocchi et al., 2012; Fair et al., 2010; Qiu et al., 2011). Likewise, EEG FC has been studied in ADHD patients by using different measures of interdependence between signals. The most widely used linear interdependence index is the magnitude of the coherence function, which measures the linear correlation between two signals at each frequency. Children with ADHD in resting state present impaired EEG coherence between certain cortical areas in different frequency bands (Barry et al., 2002, 2011; Clarke et al., 2005; Dupuy et al., 2010; González et al., 2013). Yet, the changes in the coherence of ADHD patients, as compared to healthy controls, depend on whether the pairwise or the average coherence is computed from intra or inter-hemispheric EEG channel pairs and whether the inter-channel distance is short, medium or long (Barry et al., 2002, 2011; Chabot and Serfontein, 1996; Clarke et al., 2005; Dupuy et al., 2010; Murias et al., 2007). Although coherence seems a good objective measure for the diagnosis of ADHD, some authors suggest that its results are age- and gender-dependent (Barry et al., 2004), which may affect their diagnostic efficacy in large groups of subjects. Ahmadlou and Adeli (2010) used instead a nonlinear FC measure and reported that the FC for the ADHD group was lower than that of the control group for posterior cortical areas at certain EEG bands. More recently, our group (González et al., 2013), has used a different nonlinear index (L) to assess FC between EEG electrodes in ADHD during resting state. We found that the FC of ADHD subjects was significantly higher than that of controls for certain cortical areas; additionally, differences were also found in certain pairwise interdependences involving central cortical areas. In short, the results found in the above mentioned studies of EEG FC from ADHD subjects suggest that they show abnormal connectivity between certain cortical areas and that these alterations in brain intercommunication are the neural correlates of the symptoms commonly found in the different types of ADHD.

An approach that has been seldom used in the context of quantitative EEG analysis of the ADHD is the study of the variability of EEG measures, even less so in the case of FC indices. Normally, any EEG measure is estimated during resting state by averaging its values in a certain number of EEG segments (usually 10–30 segments of 4–6 s duration), recorded/digitized at different times in the same experimental condition. In doing this procedure, one implicitly assumes that the resting state EEG remains stationary in the recording period. In healthy subjects, this hypothesis of stationarity could be true assuming that only random factors affect the measurements and cognitive/psychological and neurophysiological factors remain little altered during the recording period. Yet even in this case, recent evidence (see, e.g., Botcharova et al., 2014; Kitzbichler et al., 2009) clearly suggests that brain synchronization, as assessed from neurophysiological signals, is not constant, but it presents non-trivial time variability, which is disrupted in certain neuropathological conditions, such as epilepsy (Ramon and Holmes, 2013). It is therefore reasonable to think that such non-trivial variability may be captured by the FC measures of EEG, and that this variability may also change during the resting state of ADHD subjects. In fact, one of the characteristic symptoms of ADHD subjects is their inability to perform certain cognitive functions in a constant, reliable way, which is reflected in an increase in the standard deviation (SD) of the reaction time and attention in different psychological tests (Johnson et al., 2008; Kofler et al., 2013). It has also been reported that ADHD subjects can switch from hypo-arousal to hyper-arousal according to the time of day (Imeraj et al., 2012a,b), which is related to the state regulation deficit model (Sergeant, 2005; Van der Meere et al., 2005), a model that, together with the delay aversion one (Sonuga-Barke et al., 1992a,b), have been considered as "context-dependent dynamic processes in ADHD" (Sonuga-Barke et al., 2010).

Another issue to take into account when analyzing EEG FC measurements in ADHD during resting state is the condition (eyes closed/eyes open) in which the measurement is taken. Different resting conditions present different arousal levels and widely different cognitive and sensorial relationships of the subjects with their environment. In fact, CNS arousal level – usually obtained by measuring subjects' skin conductance (SCL) – is greater with eyes open (EO) than with eyes closed (EC) (Barry et al., 2007; Hüfner et al., 2009). Furthermore, it has been reported that ADHD subjects have lower arousal levels than controls (Barry et al., 2009a,b; Clarke et al., 2013). It is noteworthy that this CNS hypo-arousal is one of the most widely reported theories for explaining the changes observed in the EEG power of ADHD subjects, although there is no agreement as to which EEG frequency bands are the most affected by this pathology (Barry et al., 2003; Barry et al., 2009a,b; Clarke et al., 2013; Hobbs et al., 2007; Lansbergen et al., 2011; Woltering et al., 2012). Although most of these studies have been carried out in the EC condition, decreased levels of alpha and theta band EEG power in resting state with EO have also been reported in ADHD (Buyck and Wiersema, 2014).

Barttfeld et al. (2014) reported that the FC of EEG in ADHD adults during resting state with EC presents increased temporal variability as compared to control subjects. These authors suggest that this increased variability in ADHD subjects is associated to executive function and memory deficits, i.e., deficits in cognitive performance. This finding, along with the results of the above mentioned studies, were the reasons for undertaking this research work, as they indicate that: (1) different resting conditions in ADHD subjects with different levels of arousal give rise to distinct alterations in EEG functional connectivity; (2) FC between two cortical areas depends on the distance between them and on the procedure used to compute it, i.e., whether it is calculated directly from the two channels/areas considered or from the partial or global average connectivity of one cortical area (averaging some or all intra- or inter hemispheric channel pairs connected with that area); (3) different linear and nonlinear connectivity measurements give rise to different results. In addition, to the best of our knowledge, the variability in connectivity i.e. the connectivity dynamics, has still not been studied in different resting conditions and may be of greater interest than the value of connectivity itself when analyzing the cognitive status of the subject in relation to its surroundings in each condition.

Therefore, in the present work, we study the average EEG FC and its temporal variability in a group of young ADHD subjects of mixed type and an age-matched healthy control group by using linear and nonlinear interdependence measurements. The aim of this work is to demonstrate that although EEG FC measurements do not discriminate ADHD from healthy controls, the temporal variability of the EEG FC measurements does. Furthermore, it will also be shown how the variability of some of these connectivity measurements is sensitive to changes in the resting state from EC to EO.

2. Material and methods

2.1. Subjects

We studied two group of subjects: one consisting of 10 boys diagnosed with combined type ADHD, aged between 10 and 15 years of age (mean: 11.9 ± SD: 2.0), who were selected from the patients of the Unit of Pediatric Psychiatry (University Hospital NS La Candelaria, Tenerife, Spain). Only those children who met diagnostic criteria for hyperkinetic disorder according to ICD-10 or the criteria for the diagnosis of ADHD combined type according to DSM-IV (APA, 2001) were included in the analysis. The ADHD subjects were evaluated by physical examinations, clinical interviews and lists of DSM-IV and ICD-10 (Döpfner and Lehmkuhl, 2000). The following were used as exclusion criteria: presence of developmental disorders or psychotic disorder, autism, disorders of mood, anxiety disorders, and disorders involving tics, substance abuse, and history of previous or recent epilepsy from EEG recordings indicative of epileptiform activity or another neurological problems. Boys with symptoms of comorbid conditions such as learning difficulties (dyslexia, dysgraphia, ...) or behavior strongly associated with hyperactivity/attention deficit mobility and behavioral disorders were also excluded. Subjects with combined type ADHD were chosen for the study for two main reasons: combined type ADHD is the most prevalent in our region (Tenerife, Spain); secondly, in our review of the literature on EEG functional connectivity measures in ADHD, we have found that, in the case of the coherence measures, combined type ADHD show higher statistical differences in the coherence (relative to controls) than inattentive type ADHD (Barry et al., 2002, 2005, 2006). The sample size has been limited by the availability of these patients in our hospital.

The control group (CONT) consisted of 12 boys of the same age range as ADHD group (mean: 12.3 ± SD: 1.8) who were selected from the children of the hospital staff who underwent a clinical check on their health in the Pediatric Department. The same exclusion criteria as those used for ADHD were applied.

The inclusion in any of the two groups was voluntary and informed written consent was obtained from the subjects' parents or tutors. The ethics committee of the University of La Laguna and the University Hospital of NS La Candelaria approved the protocol study, which was based on the Declaration of Helsinki.

2.2. Recordings

Each EEG recording session lasted approximately 20 min. Recordings were made in a soundproof room with controlled temperature and light; the room was magnetically and electrically isolated and was located in the Clinical Neurophysiology Service of the hospital. Six EEG epochs (of approximately 3–4 min each) were recorded alternately under EC and EO conditions.

The EEG was recorded using an analog–digital EEG machine Neurofax Nihon Kohden EEG-9200. Each subject used a cap with 16 electrodes/channels arranged according to the international 10/20 system: Fp1, Fp2, F3, F4, F7, F8, C3, C4, T3, T4, P3, P4, T5, T6, O1 and O2. Monopolar derivations were used and referenced to the average of the mastoid (A1 + A2)/2. Impedance was monitored in each subject from the impedance map EEG of the equipment before data collection and stayed within a similar range (3–5 kOhm) for all the electrodes. The parameters for EEG recordings were: 256 Hz sampling rate, online high and low pass filters of 0.05 Hz and to 80 Hz cutoff frequencies, respectively, and a notch filter of 50 Hz. Additionally, the electro-oculogram, the ECG and the abdominal breathing movements were also recorded to detect artifacts in the visual selection of EEG segments. Finally, a set of artifact-free, non-overlapping EEG segments of four seconds each were visually selected from each of the 3–4 min EEG epochs, and exported for further analysis.

2.3. Analysis methods

2.3.1. Preprocessing

The set of non-overlapping EEG segments selected above was then submitted to a second, more refined selection procedure to choose, from all the available ones, the 20 most stationary segments. For this purpose, we used an automatic selection method by applying the Kwiatkowski–Phillips–Schmidt–Shin (KPSS) test (at a critical level of 0.01) (Kwiatkowski et al., 1992), as implemented in the GCCA toolbox (Seth, 2010). The KPSS test was first used in econometrics (Kwiatkowski et al., 1992) and more recently also in MEG data analysis (Kipinski et al., 2011) for testing the null hypothesis that an observable time series is stationary around a deterministic trend. This test is based on the decomposition of the time series into the sum of a deterministic trend, a random walk and a stationary error component. The KPSS requires an estimate of the long-run variance, which is computed using a Bartlett (Newey–West) window.

The KPSS test output gives the H value [that correspond to the null hypothesis: if the signal is stationary $H = 1$ and the null hypothesis is accepted at the $p < 0.01$ level] and the k_s value, which corresponds to the KPSS test statistic value. By using the KPSS, each of the 16 segments/signals, whose mean and linear trend were previously removed, of each visually selected epoch was checked for stationarity ($H = 1$ in the test KPSS). The epochs in which any of the 16 segments did not verify $H = 1$ were discarded. The average stationarity (the mean of the values of k_s statistic) of the 16 segments of the corresponding channels was obtained from each of the remaining epochs. Twenty epochs of higher stationarity (lower average k_s) were chosen. Finally, for each channel, we checked the stationarity of all 20 segments previously selected by applying the KPSS test again to the signal resulting from the union of 20 segments. As the selected non-overlapping epochs were not consecutive, the 20 chosen ones were considered as an expression of EEG activity of the subjects during each of the two resting state conditions.

2.3.2. Interdependence indices

To estimate the degree of FC in each condition, we computed two bivariate indices of interdependence in each of such segments. Firstly, we calculated the magnitude square coherence (Coh), which is a measurement of linear correlation (amplitude and phase) between two signals as a function of the frequency. This is obtained from the (complex) function C_{xy} of coherence between two signals X and Y:

$$C_{xy}(f) = \frac{P_{xy}(f)}{\sqrt{P_{xx}(f)P_{yy}(f)}} \tag{1}$$

where $P_{xy}(f)$ is the cross-spectrum of both signals, $P_{xx}(f)$ and $P_{yy}(f)$ are the auto power spectra of each signal, and f is the discrete frequency.

Coh is simply the squared modulus of $C_{xy}(f)$:

$$\mathrm{Coh}(f) = |C_{xy}(f)|^2 \tag{2}$$

The Coh was calculated within the four most commonly used EEG frequency bands in clinical practice: delta band [0.5–4 Hz, Coh(δ)], theta band [4–8 Hz, Coh(θ)], alpha band [8–13 Hz, Coh (α)] and beta band [13–40 Hz, Coh(β)].

The average coherence in a certain frequency range is defined as:

$$\mathrm{Coh}(f_j) = \sum_{i}^{k} \frac{|C_{xy}(f_j)|^2}{N_f}; \tag{3}$$

where f_j ($j = i, ..., k$) are the discrete frequencies in the band $(k - j)$ and N_f is the total number of such frequencies.

Secondly, a nonlinear measure of the generalized synchronization between the reconstructed state spaces of two signals was also calculated. This methodology allows the investigation of the interaction between two nonlinear dynamical systems without any knowledge about their governing equations. To this end, the state

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space trajectory is reconstructed from each scalar time series $x(i)$ and $y(i)$ by using the time delay embedding method, as follows: for each discrete time i, a delay embedding vector X_i, corresponding to a point in the reconstructed state space of x, is constructed as:

$$X_i = (x(i), x(i-\tau), x(i-\hat{o}), \ldots, (x(i-(m-1)\hat{o}) \tag{4}$$

where m is the embedding dimension and $\hat{o}$ denotes the delay time. Similarly, the state space vectors of y (Y_i) can also be reconstructed. The values $m = 6$ and $\tau = 5$ were taken for both x and y, in agreement with previous studies (González et al., 2013).

Chicharro and Andrzejak (2009) developed an index (L) from these reconstructed state vectors, which provides a reliable estimate of the interdependence between two signals. Briefly, let $a_{i,j}$ (respectively, $b_{i,j}$) be the time indices of the k nearest neighbors of X_i (respectively, Y_i); moreover, for each X_i, let $g_{i,j}$ be the rank that the distance between X_i and Xj takes in a sorted ascending list of distances between X_i and all the other reconstructed vectors of X; the Y-conditioned mean rank is then

$$G_i^k(X|Y) = \frac{1}{k}\sum_{j=1}^{k} g_{i,b_{i,j}} \tag{5}$$

$L(X|Y)$ is calculated as:

$$L(X|Y) = \frac{1}{N}\sum_{i=1}^{N} \frac{G_i(X) - G_i^k(X|Y)}{G_i(X) - G_i^k(X)} \tag{6}$$

where $N = n(m-1)\tau$ is the total number of reconstructed vectors, and due to the normalization procedure, $G_i(X) = \frac{N}{2}$ and $G_i^k(X) = \frac{k+1}{2}$. $L(Y|X)$ is calculated analogously by exchanging the role of X and Y in the above definitions. Finally, the index L was obtained here by averaging $L(Y|X)$ and $L(Y|X)$. This ranges between 0 (independence) and 1 (strongest interdependence).

Thirdly, in order to check the reliability of the interdependence between two regions (X–Y) estimated via either Coh or L, the calculations were repeated after substituting one of the signals (X or Y) by different surrogate versions of it, which were independent of the other one by construction. In the case of Coh, surrogate signals were obtained by circularly and randomly shifting the start of one of the two original time series (e.g. Y) while leaving the other one unchanged (Pereda et al., 2001). The IAAFT algorithm (Schreiber and Schmitz, 2000) was used in the case of the L index. The original Coh or L indices were then compared with those obtained from the set of surrogate signals. If, as a result of the test, the value of the index was not significantly different from the distribution of surrogate ones, it was set to zero, otherwise it was left unchanged. The methodology for the bivariate surrogate test is detailed elsewhere (González et al., 2013). Finally, the Fisher's Z transform was applied to L and Coh to reduce intra-inter-subject variability.

The above procedure was applied to each of the 120 different pairs of channels and each of the 20 EEGs selected in each subject and condition. The mean and standard deviation of the set of 20 indices (Coh or L) of each electrode pair, subject and condition were then computed. The mean value for an x_i series is defined as:

$$\bar{x} = \frac{1}{N}\sum_{i=1}^{N} x_i \tag{7}$$

where $\bar{x}$ is the global mean connectivity CM and N (=15 in our case) is the number of channel pairs per electrode. Thus, e.g., CM for the coherence of C3 channel in the beta band [CM(C3, beta)], would be obtained by averaging the 15 values of the set which are: [Coh(C3-Fp1, beta), Coh(C3-F3, beta),………, Coh(C3-Fp2, beta), ……, Coh (C3-O2, beta)].

In turn, the variability of the connectivity CV is the standard deviation σ of the distribution of interdependence values:

$$\sigma = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N}(x_i - \bar{x})^2} \tag{8}$$

The symbols are as in the mean.

Once the connectivity matrices (16 × 16) for Coh and L were obtained, the global FC of each cortical area (CM) and its variability (CV) were estimated by averaging the values of M and SD corresponding to the set of pairs associated with that cortical area as shown in Fig. 1 for the case of C3. It is noteworthy that, when FC was estimated by the Coh function, there were actually four connectivity values, one for each frequency band. Therefore, the following five values for the CM and the CV were obtained for each cortical area: Coh(δ), Coh(θ), Coh(α), Coh(β) and L index.

2.4. Statistical analyzes

The existence of between-groups differences in CM and CV (factor GG: ADHD versus CONT) was checked in each of the 16 cortical areas considered (factor CC: Fp1, …, O2) and in the 2 conditions studied (factor EE: EC and EO) using a MANOVA test for repeated measurements. Firstly, the MANOVA test was performed considering two factors of repeated measurements for the values of CM (respectively CV): topology, with 16 areas (CC) and the two conditions (EE). The MANOVA test provides, among others, the following results for each index: (a) the contrast between groups (GG) considering the average across all the means in both conditions; (b) the EE * GG contrast indicating whether GG differences are influenced by the condition EE independently of the area considered; (c) the CC * GG contrast indicates whether GG differences depend on the region factor CC regardless of condition, and finally (d) the EE * CC * GG contrast examines whether the GG differences depend on the condition and on the cortical area. The MANOVA steps (b), (c) and (d) were performed by a multivariate test including Wilk's, Pillai's, Hotelling's and Roy's test. The Mauchly's test of sphericity was considered when the within effects table showed significant differences for any of these ($p < 0.05$ or lower). If the condition of sphericity did not hold, the Greenhouse–Geisser and Huynh–Feldt estimate of the F statistic was used. Finally, when an effect was statistically significant, post hoc Bonferroni test was applied to compare GG differences between conditions or between cortical areas and conditions.

Furthermore, a MANOVA test was then repeated as before but now taking the channels associated to one of the three following cortical regions of interest as the CC factor: (1) frontal F–F for the

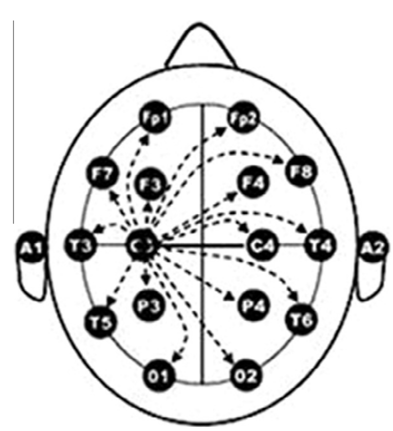

Fig. 1. EEG channel placement. Discontinuous arrows indicate the way one channel (here C3) is connected to the rest of the channels to compute its overall cortical connectivity by averaging the connectivity of all the channels pairs associated with it.

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six F channels, (2) centro-temporal C–T for the six C/T channels and (3) parieto-occipital for the four P/O channels (see Fig. 1 for channel placement). The aim of using this test was to analyze which of the three selected regions, if any, presents the greatest GG differences in any condition.

Finally, and to get information on the topography of the differences in the previous case, a *t*-test for independent measurements was applied to compare group differences separately for each cortical region and condition.

All the signal processing steps were performed in custom-made Matlab code, including a modified version of the script to calculate the *L* index as provided in the Supplementary material of Chicharro and Andrezejak (2009). In turn, the MANOVA tests for repeated measurements and the *t*-test were performed using the STATISTICA (Statsoft Inc, v. 8.0.550) software package.

3. Results

For the sake of clarity, henceforth we only show the *F* values of those factors and interactions in which statistically significant differences were found.

Table 1 shows the *p* values of the MANOVA test for repeated measurements corresponding to the CM and the CV for the two interdependence indices computed. Here the group (CONT vs. ADHD) is the independent (or between-group) factor (GG), whereas the within-subjects factors (repeated measures) are the 16 EEG channels (CC) and the 2 conditions (EO, EC) analyzed (EE). GG differences were only found for CV regardless of CC and EE factors for the following CV indices: the CV of the index *L* (F (1, 20) = 28.399) and the CV of the Coh(δ) (F (1, 20) = 10.049), Coh(θ) (F (1, 20) = 12.076) and Coh(β) (F (1, 20) = 4.732). Fig. 2 shows the mean values of CV for both groups ADHD and CONT for each of the CV indices. Furthermore, as shown in the Table 1, this result is valid regardless of the EE condition (interaction EE*GG), except for the CV of Coh(θ) which shows that the EE condition (F (1, 20) = 5.345) affects the GG differences. In this case, it was found that the Coh(θ) of ADHD was only greater than that of CONT during EO. GG differences did not show either interactions with the cortical area factor (CC * GG) or joint interaction EE * CC * GG (*p* values of these latter effects are not shown in the Table 1). These two aforementioned results were to be expected because the large number of comparisons to be introduced in the statistical calculus when the number of channels (16) and the two conditions have to be considered and the sample size (number of subjects) is relatively small.

The results for CM for those interactions in which CV showed significant results are also shown in Table 1 for comparative purposes.

The results of the MANOVA test for repeated-measurements for CM and CV for the three regions of interest considered are shown in Table 2: 1) frontal F–F (CC: Fp1, Fp2, F3, F4, F7, F8), 2) centro-temporal C–T (CC: C3, T3, T5, C4, T4, T6) and 3) parieto-occipital P–O (CC: P3, O1, P4, O2). Significant differences were only found for the CV (GG factor and EE*GG interaction). Only those factors or interactions where statistical significant results were found are shown in the table. For comparative purposes, the results for CM for those interactions in which CV showed significant results are also shown.

GG significant differences for CV in the F–F region-independently of EE and CC factors – were found for the index *L* (F (1, 20) = 13.882) and the Coh(δ) (F (1, 20) = 7.841), Coh(θ) (F (1, 20) = 5.313) and Coh(β) (F (1, 20) = 4.489) indices. This result was found in the C–T region for the index *L* (F (1, 20) = 20.939) and the Coh(δ) (F (1, 20) = 6.117) and Coh(θ) (F (1, 20) = 14.132). In addition, GG differences in this region for the CV of Coh(θ) were influenced by the EE factor (F (1, 20) = 8.028) as happened when the 16 channels were considered together but now with greater significance. This result is shown in detail in Fig. 3, which shows that during EO, the ADHD group have greater CV-Coh(θ) than CONT ($p < 0.001$) and that ADHD group have greater CV-Coh(θ) ($p < 0.001$) during EO than during EC (results from Bonferroni post hoc test and after Bonferroni alpha adjustments). GG differences in the P–O region were observed again for the index *L* (F (1, 20) = 47.502) and the Coh(δ) (F (1, 20) = 18.030), Coh(θ) (F (1, 20) = 15.454) *y* Coh(β) (F (1, 20) = 6.143) indices. It can be observed that the *p* values for the significant results found for CV were lower for the P–O region than for the two others.

In short, the results obtained for each of the CV indices in the three selected regions show: (a) that the index *L* had a great GG differences in the C–T region and this was even greater in the P–O region; (b) the Coh(δ) exhibited the greater GG differences in the P–O region; (c) the Coh(θ) exhibited greater GG differences in the F–F and P–O regions with the C–T region presenting dependency on EE condition (Fig. 3); (d) finally the Coh(β) exhibited greater GG differences in the P–O region too.

Once more in the MANOVA results GG differences did not show interactions either with the cortical area factor (CC * GG) or joint interaction EE * CC * GG (these are not shown in Table 2). The large number of comparisons needed to be made for such an interaction and the relatively small sample size used (number of subjects) are probable causes of this result.

Although the above MANOVA results show an overall picture of the cortical regions of ADHD with a higher CV, a *t*-test for independent measurements was applied separately to each area in each condition to get a finer view of GG differences for each cortical area. In this case, it is only possible to get a general view of the GG differences in each cortical area and condition but comparisons between cortical areas and/or condition cannot be made unless Bonferroni or any other correction for multiple comparisons is applied.

Fig. 4 shows a topographic map of the *p* values of the differences (CONT vs ADHD) in the CV obtained from the t-test for independent measurements individually applied to each of the 16 EEG channels and each EE condition. The results show a good agreement with those obtained from MANOVA test (Tables 1 and 2 and Figs. 2 and 3). In fact, all indexes, except for alpha coherence, had statistically significant GG differences for certain cortical areas, in which (as shown in Fig. 1) the CV of ADHD was greater than CONT. However, these maps show that the significance level of GG differences is neither the same for all cortical areas nor in both EO and EC conditions. Thus, the maps show that the GG differences for the CV-index *L* during EC condition are maintained for all cortical areas and that this does not occur for the EO situation; one can see in the maps that there are no GG differences in the F–F area and the left C–T region. However, there were clear GG differences in the P–O area in both EO and EC conditions, which agrees with the results of the MANOVA.

Table 1
Between-group differences for CM and CV of both *L* and Coh for the four frequency bands.

	Factors	Index L	Coh(δ)	Coh(θ)	Coh(α)	Coh(β)
CM	GG	0.207	0.235	0.738	0.402	0.533
	EE*GG	0.853	0.069	0.463	0.096	0.920
CV	GG	**0.000*****	**0.005****	**0.002****	0.114	**0.042***
	EE*GG	0.933	0.278	**0.032***	0.649	0.597

p values for the repeated-measurements MANOVAs of the connectivity CM and its variability CV (first column) corresponding to the five calculated indices of functional connectivity: Index *L*, delta coherence Coh(δ), theta coherence Coh(θ), alpha coherence Coh(α) and beta coherence Coh(β). The grouping factor GG (ADHD/CONT) and the GG*EE interactions (EE conditions EC/EO) appear in the second column. Statistical significance appear expressed as: ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$.

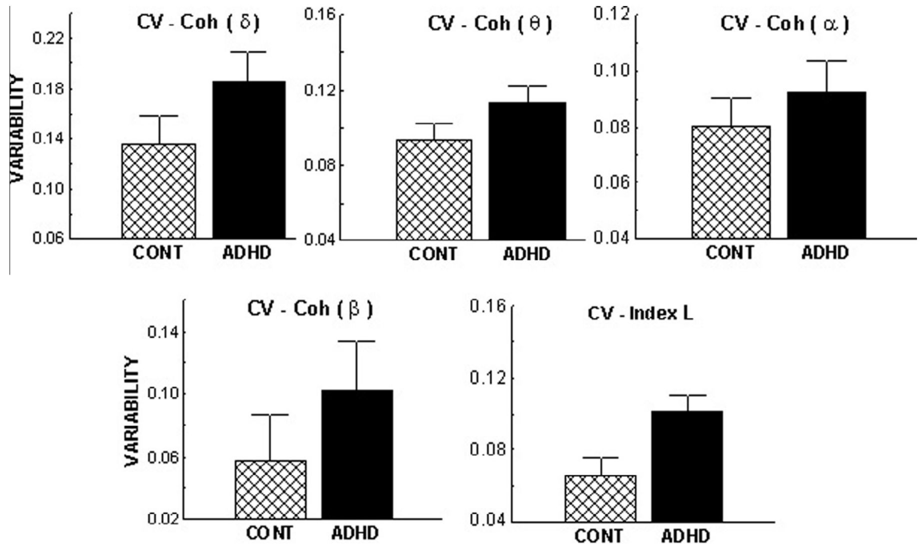

Fig. 2. Mean values (±95% of confidence interval) of the connectivity variability CV of each EEG connectivity index estimated for CONT and ADHD groups. Titles at the top are the indices: the nonlinear synchronization index (L), the delta Coh(δ), theta Coh(θ), alpha Coh(α) and beta Coh(β) coherences. Statistical significance of differences between CONT and ADHD is shown in Table 1.

Table 2
Between-group differences for CM (top) and CV (bottom) of both L and Coh for the four frequency bands in three different cortical regions.

	Factors	Index L	Coh(δ)	Coh(θ)	Coh(α)	Coh(β)
Connectivity mean (CM)						
Area F–F	GG	0.602	0.721	0.695	0.671	0.533
	EE*GG	0.809	0.083	0.496	0.225	0.920
Area C–T	GG	0.252	0.309	0.827	0.493	0.438
	EE*GG	0.694	0.062	0.351	0.125	0.786
Area P–O	GG	0.060	0.054	0.178	0.150	0.483
	EE*GG	0.824	0.135	0.722	0.050	0.566
	Factors	Index L	Coh(δ)	Coh(θ)	Coh(α)	Coh(β)
Connectivity variability (CV)						
Area F–F	GG	**0.001*****	**0.011***	**0.032***	0.223	**0.047***
	EE*GG	0.766	0.538	0.093	0.613	0.880
Area C–T	GG	**0.000*****	**0.022***	**0.001****	0.120	0.059
	EE*GG	0.729	0.729	**0.010****	0.810	0.559
Area P–O	GG	**0.000*****	**0.000*****	**0.000*****	0.059	**0.022***
	EE*GG	0.805	0.105	0.166	0.762	0.616

p values for repeated-measurement MANOVAs for the connectivity mean (CM) and the connectivity variability (CV) corresponding to the five calculated indices of functional connectivity: Index L, delta coherence Coh(δ), theta coherence Coh(θ), alpha coherence Coh(α) and beta coherence Coh(β). The three considered cortical regions, frontal (F–F), centro-temporal (C–T) and parieto-occipital (P–O) appear in the first column and the grouping factor GG and its interactions (repeated variables) with EE (the two conditions EO, EC) EE*GG appear in the second column. Statistical significance is expressed as: $^{***}p < 0.001$; $^{**}P < 0.01$; $^{*}P < 0.05$.

The CV-Coh(delta) does not show GG differences in frontal and temporal regions in either EO or EC situations, however, GG differences exist in the P–O area in both EO and EC conditions which agrees with the results of the MANOVA. As regards the CV-Coh (theta), the C–T area (mainly the central and left temporal) is the only area in EO showing GG differences that not are observed during EC; this result partly agrees with the MANOVA table, but the GG differences shown in this table are independent of EE in the P–O region and this effect is not clear in the topographic map. As for the CV-Coh(beta), the central anteroposterior area shows GG differences during EC and EO that are not in good agreement with the MANOVA results.

Regarding the differences between the results of the MANOVA test and the individual contrast topography from t-test observed in the 16 cortical areas in the two conditions, the MANOVA test allows the contrast of the existence of GG differences and whether they differ for various channels and for the two conditions tested. At the same time, the topographic results provide information as to whether a given cortical area in a certain condition presents GG differences. Although we cannot draw any conclusions from the visual topographic comparisons between different areas in different conditions, topographic visualization GG individual differences in each cortical region in each condition allows an analysis of the results of MANOVA in a more graphical and detailed way.

4. Discussion

Previous studies have reported results of EEG functional connectivity measurements in ADHD subjects (Ahmadlou and Adeli, 2010; Barry et al., 2011; González et al., 2013). The connectivity is usually estimated through linear or nonlinear measurements of interdependence between all possible pairs of registered EEG channels (connectivity matrix). The functional connectivity results

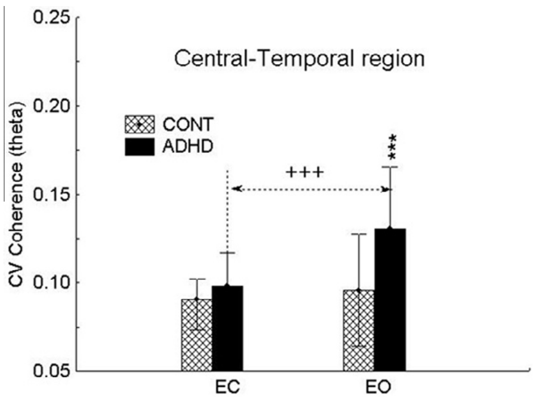

Fig. 3. Average value of the CV (±95% of confidence interval) of theta coherence in the central-temporal region in both CONT and ADHD groups and both EC and EO experimental conditions. The statistical significance of differences between groups (∗∗∗ and +++p < 0.001) come from post hoc Bonferroni test applied to the EE*GG interaction of the MANOVA for repeated-measurements.

depend on the two individual channels selected (e.g. the connectivity between C3–T3 could be different to that of C3–F3) or on the set of channel pairs selected when calculating the connectivity (average) of a determinate cortical area, e.g., the connectivity of C3 area obtained from the average of C3–Fp1, C3–F3, C3–F7 will probably be different to that obtained from the average of C3–T3, C3–T5, C3–P3. The works carried out so far show that some of these connectivities in ADHDs are different to those of healthy subjects: which may be higher or lower depending on, among others, the distance between cortical areas considered, on the EEG frequency band for the coherence measurements or on the set of channels considered to assess the net cortical connectivity of a particular cortical area (Ahmadlou and Adeli, 2010; Barry et al., 2002, 2005, 2006, 2011; Clarke et al., 2005, 2007, 2008; Dupuy et al., 2008, 2010; González et al., 2013).

A set of global connectivity measurements for 16 cortical areas were calculated in this study. This was performed by taking various EEG segments recorded at different times in the same resting condition and calculating the average EEG functional connectivity (CM) of each cortical area with the rest of areas and its temporal variability (CV) from linear and nonlinear interdependence indices. When analyzing the GG differences for all the channels and conditions, it was found that the CM connectivity showed no between groups differences for any of the connectivity indices: neither when the overall connectivity of all the 16 cortical areas nor when the overall connectivity for the three separately cortical areas: F–F, C–T and P–O was considered. We based our selection of regions on a purely topographical differentiation, as suggested by previous studies (Barry et al., 2002, 2005, 2006; Clarke et al., 2005, 2007; Dupuy et al., 2010). Therefore, EEG connectivity measurements are effective when they are estimated between certain pairs of specific channels, mainly inter hemispheric channels (Ahmadlou and Adeli, 2010; Barry et al., 2011; González et al., 2013); but when the connectivity of a cortical area is obtained from the average of connectivities of all pairs that are associated with it, as is the case in this study, the connectivity measurements lose their effectiveness in discriminating differences between groups, i.e., by averaging EEG connectivities between channel pairs decreases their discriminatory capacity. Instead, CV for all channels taken together clearly shows between groups differences and this happens for all connectivity indexes except for the alpha band coherence, with the CV of ADHD being in all cases greater than that of CONT. This result is also true for the three cortical areas analyzed separately (frontal, centro-temporal and parieto-occipital). The analysis of the results obtained in the three areas considered showed that the between group differences for CV had an anterior to posterior cortical gradient, and the P–O region was the region where a greater discrimination between groups was observed. Furthermore, the CV from index L was the CV measurement which had a greater between group discrimination. Index L is a measurement of the nonlinear generalized synchronization between two chaotic systems. Thus, the complex or perhaps chaotic dynamics of functional connectivity among cortical regions may be responsible for this result.

In short, the variability of the global connectivity of different cortical areas is the connectivity feature which is higher in subjects with ADHD compared to CONT but not the connectivity itself. In the only work we have found in the literature about variability in the EEG connections in ADHD (Barttfeld et al., 2014) reported that the variability in the functional EEG connectivity -measured through synchronization likelihood method (SL)- is enhanced in ADHD adults (at rest with EC) versus CONT. They found this result for many single EEG channel pairs of many different cortical areas of both hemispheres. This result is fairly consistent with our results, mainly for those concerning the CV of index L. In fact, SL index is also a measurement of generalized synchronization between two systems. Moreover, Barttfeld et al. (2014) reported that the ADHD variability in the connectivity is associated with executive function and memory deficits, i.e., deficits in cognitive performance. This association cannot be confirmed from our results. But if the magnitude of the global functional connectivity of a particular cortical area X at a given time and in a certain resting condition depends on the amount or number of cortical areas co-activated with X at that moment and condition, then, the existence of a temporal variability in the X global connectivity means that this number is not constant over time but fluctuates in that condition. Therefore, if the change in resting status (e. g., passing from EC to EO) also produces a further change in the variability of the X global connectivity this would mean that the number of co-activated cortical areas in this new condition changes over time (fluctuates) in greater proportion. The latter is what we think happens in ADHD subjects (in contrast to the controls) when passing from EC to EO and when connectivity is estimated from theta coherence. This effect could produce a deficit in the cognitive performance in ADHD subjects when compared with healthy subjects which agrees with previously reported results. As for the variability of cognitive functions, we have found some works in clinical psychology in which the performance of the ADHD subjects in certain cognitive tests is analyzed and where it is reported that the standard deviation (SD) of certain functions, such as time reaction or attention, is pathologically higher in ADHD (Kofler et al., 2013; Johnson et al., 2008). This result could be related to the increased variability in the connectivity of ADHD subjects reported here. Thus, the instability in cognitive performance would have its neurophysiological correlate in the anomalous fluctuations of the functional connectivity of certain ADHD brain regions.

On the other hand, it is worth mentioning that the P–O region was the one where the greater between-group differences were found for CV. This brain region performs, among other functions, control of selective and focused visual attention (Baluch and Itti, 2011; Bisley and Goldberg, 2010; Gottlieb and Balan, 2010). Therefore, we think that the high connectivity fluctuations that occur in this region for ADHD subjects are related to attention deficit features of this disorder. Although our focus was on analyzing the topographical changes of CV between ADHD and controls, we emphasize the cognitive importance of the P–O region because it could be of interest in future psycho-physiological studies.

When the between-groups differences during EO and EC conditions are compared for CM and CV, the results indicate that only the CV, estimated by the coherence in the theta band, and mainly in the C–T region, showed significant between-groups differences during EO but not in EC. Specifically, it was found that ADHD

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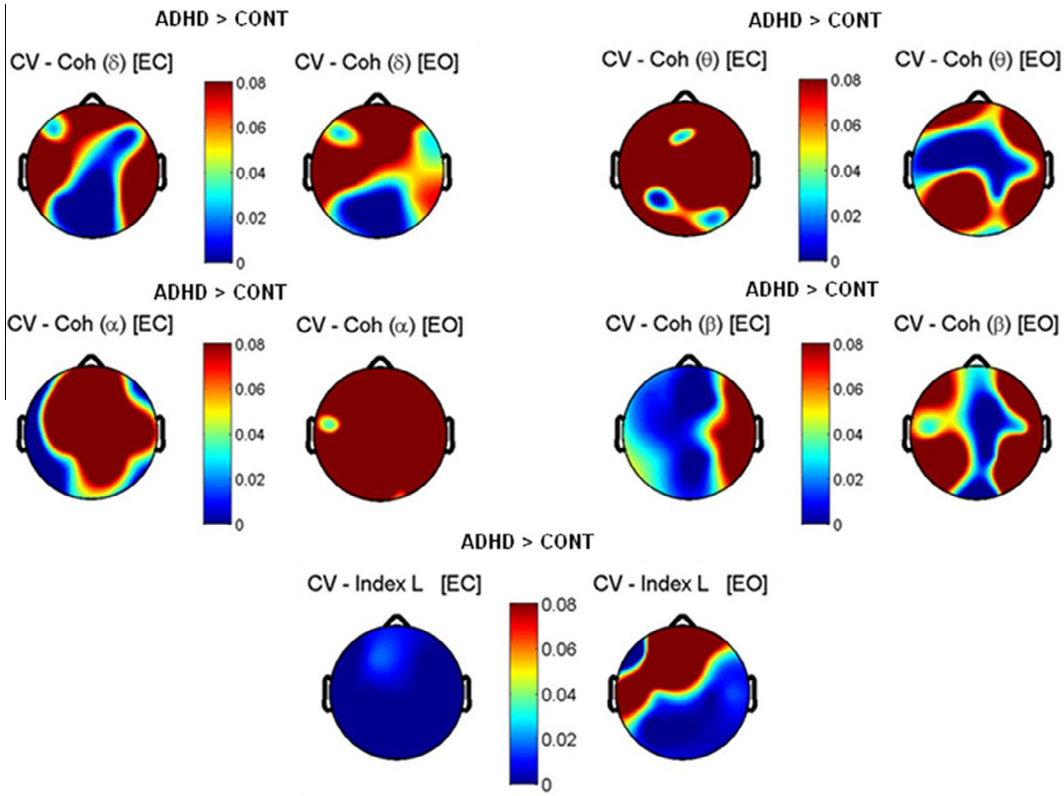

Fig. 4. Cortical topographic maps drawn from p values corresponding to the GG differences (ADHD > CONT) expressed in the central bar according to the t-test. The CV of the EEG functional connectivity of each cortical area with the others is shown in EC and EO conditions. The CV connectivity measurements considered were the nonlinear synchronization index (CV-Index L) and the coherence in the different frequency bands: delta CV-Coh(δ), theta CV-Coh(θ), alpha CV-Coh(α) and beta CV-Coh(β).

subjects had higher CV-Coh(theta) during EO than during EC; this result was not present in the CONT. We did not find any previous studies in the literature investigating the CV in ADHD at different resting conditions, we only know that the EEG local connectivity between different cortical areas estimated through coherence in theta band are higher in ADHD vs. CONT and that this increase occurs during EC as well as during EO (Barry et al., 2011; Clarke et al., 2007; González et al., 2013). On the contrary, our results indicate that the CV of Coh(θ) in ADHD is greater than in CONT but only during EO. This result could be attributed to a different arousal level during EO than during EC. In fact, in normal children, EO is associated with an increased level of arousal and a parallel decrease in EEG power for all frequency bands (Barry et al., 2004, 2007). These authors suggest that the decrease in delta and theta power may be a marker of activation while only the alpha band would be associated with the level of arousal. Assuming that it is true that arousal level in healthy subjects is higher during EO than EC, our results indicate that the CV of Coh(θ) does not appear to be associated with the level of arousal since the CV of Coh(θ) of our healthy CONT group had the same value during EC as EO and it only changes for the ADHD group.

The answer to the question of why only the CV associated with theta waves is the only type of CV that depends on the resting state may lie in the origin and meaning of these waves. Theta oscillations have long been associated with spatial navigation in rats (O'Keefe and Recce, 1993); and these oscillations occur more frequently in humans in more complex mazes (Kahana et al., 1999). Bearing in mind that problems related to visual navigation or resolutions of mazes do not occur during EC in CONT and ADHD subjects: both groups did not need to keep track of their location within the environment. Thus, neural networks involved in navigation do not need to be activated in this EC resting condition. Therefore, if we hypothetically consider the variability of Coh(θ) connectivity as an expression of the dynamic of neural networks associated with spatial navigation, then such variability should not differ during EC in both groups as has been found by us. On the other hand, O'Keefe and Burgess (1996) reported that spatial navigation is modulated by visual inputs. Healthy subjects at rest during EO keep track of their environment without having to make any special effort of spatial navigation and as happens during EC, and therefore their CV of Coh(θ) does not alter. However, we found that the CV of Coh(θ) of ADHD subjects was higher during EO than EC. This result could be attributed to a dysfunction of the neural mechanism governing spatial navigation in the ADHDs, although the cortical area where changes in this CV (C3 and C4 or somatosensory cortex) were observed does not completely correspond to the anatomical regions that have been related with spatial navigation (Kahana et al., 1999; O'Keefe and Recce, 1993; O'Keefe and Burgess, 1996). It is well-known that the hippocampus is the region primarily responsible for spatial navigation (O'Keefe and Recce, 1993; Kahana et al., 1999; O'Keefe and Burgess, 1996). Although the somatosensory cortex (whose activity is mainly recorded by electrodes C3, C4 in our setup) has significant functional connections (through slow delta, or theta waves) with the hippocampus in rodents (Sirota et al., 2003, 2008; Xie et al., 2013), the functional explanation of this neuronal network is still unresolved. Two somatosensory functions may be associated with spatial navigation: proprioception and tactile sense (Gener et al., 2013). And indeed, proprioception has been reported to be impaired in ADHD (Goulardins et al., 2013; Poet and Rosa-Neto, 2007; Iwanaga et al., 2006). Therefore, the increased variability of Coh(theta) in ADHD as compared to healthy subjects could be attributed to the fact that the corporal schema (related with proprioception) of healthy subjects is adapted to the spatial environment and the change from EC to EO does not imply a change in that variability. Instead, in ADHD subjects, the body schema could be somewhat impaired and, in consequence, they need to adapt to the new situation. This explanatory argument for the change in the variability of Coh (theta) from EC to EO in the ADHD but not in controls is, in our opinion, a reasonable hypothesis. Furthermore, the arguments put forward here could support the state regulation deficit model (Van der Meere et al., 2005) which has been contemplated as a context-dependent dynamic dysfunction in ADHD (Sonuga-Barke et al., 2010).

In conclusion, the present study shows that although the global connectivity of each cortical area compared to the other regions in resting ADHD of mixed type is no different to that of healthy subjects, the variability of such connectivity is higher in ADHD than in CONT. This result holds for the different measurements of connectivity analyzed in this work except for coherence in the alpha band. We believe that this effect may be related to temporal irregularities in the associations among neural networks in ADHD and could explain the deficits in cognitive performance of these subjects. The index L of generalized nonlinear synchronization in the P–O region during either EC or EO is the best connectivity index to highlight the CV between-group differences (ADHD > CONT). Moreover, the CV estimated from the coherence in theta band was the only connectivity feature showing state-dependent differences, but this was only the case for ADHD and not for CONT. This effect may be attributable to an anomaly in the neural mechanism associated with keeping track of the environment as occurs in ADHD during EO. The above findings have the disadvantages that have been obtained from a relatively small sample, yet, despite it, we found highly significant differences here, for some of the effects reported.

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