Chapter 3

Assessment of ADHD Through Electroencephalographic Measures of Functional Connectivity

Julián J. González, Guzmán Alba, Soledad Mañas,
Almudena González and Ernesto Pereda

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Abstract

The main objective of the chapter is to review the types of electroencephalographic measures of functional connectivity that have been used so far in the study/diagnosis of ADHD. The review will include the methods and results so far reported in the literature as well as those conducted by our research group.

Keywords: ADHD, EEG Connectivity, Synchronization measures

1. Introduction

Quantitative EEG analysis techniques have been used since the beginning of 1990s to investigate the neural correlates of attention deficit hyperactive disorder (ADHD). Early works in this field analysed changes in univariate EEG linear measures, the main focus of these studies being the absolute or relative spectral power in different EEG frequency bands (see, e.g., [1-3]). Over the years, other univariate measures coming from the analysis of nonlinear systems have been incorporated into the study of ADHD. These measures are dedicated, among other factors, to assessing the complexity of EEG channels [4, 5]. Together with univariate measures, quantitative measures assess the linear or nonlinear interdependence between two EEG channels (bivariate measures) or a set of pairs of channels (multivariate measures) have been developed and used for the investigation of ADHD [4, 6-9]. These measures represent an estimate of the functional connectivity (FC, to be defined below) between the signals recorded from different electrodes of the subject under study and appear to offer a better perspective with regard to the clinical diagnosis of ADHD than univariate measures [4, 10]. This chapter is dedicated to describing and explaining the most commonly used multivariate EEG measures to date in the context of ADHD, as well as the most relevant results that have been derived from their implementation.

2. Functional connectivity from EEG

Functional connectivity (FC) refers to the existence of a statistical dependence between some of the features of two signals, be it their amplitudes, their phases or their reconstructed state spaces [11]. Among the linear methods most commonly used to assess the existence of such dependence, we can mention the cross correlation function and magnitude squared coherency (see description below), which analyses the relationship between signals in the time and frequency domains, respectively. At the end of the previous century and the beginning of the present one, different nonlinear methods stemming from the field of complex dynamical systems theory began to be used to characterize the existence of functional connectivity in EEG (see [12, 13] for reviews). Despite the usefulness of these methods and the potential interest of assessing the degree of interdependence between two EEG channels as a proxy of the relationship between two brain areas, its application in EEG studies is not straightforward [13]. On the one hand, the effect of volume conduction in extracranial EEG recordings, whereby the activity of one neural source is picked up by different electrodes, creates a spurious (i.e., not due to *true* interaction between two sources) FC between the electrodes [14]. Different strategies have been proposed to deal with this problem [14-18] but none of them are perfect.

On the other hand, the very nature of EEG, which includes a reference signal in the recordings, may also affect the FC estimators if the reference is active; this is a problem that has been well-documented in coherency studies [19, 20]. Current source density estimators may alleviate but not completely cure this flaw [21, 22]. Thus, in the case of EEG, interpretation of the results from FC analysis should be done very carefully and one should talk about a pattern of FC with a given reference and connectivity measure, rather than directly extrapolating the results to the existence of synchronization between the areas immediately below the electrodes. Such FC patterns are often further analysed by using the matrix of interdependence indices ξ_{ij} (where i, j = 1,..., n, are the number of recorded signals) as the adjacency matrix of a complex brain network, which can be characterized in terms of its different topological properties, which are known to be altered in different pathologies (see [13, 23] for recent reviews). Therefore, FC is still a useful tool for analysing EEG records, which provides insight into EEG changes associated with different pathologies such as ADHD.

3. Functional Connectivity in ADHD: A view from fMRI

FC between different brain regions can be studied with good spatial resolution using image analysis techniques such as positron emission tomography (PET), positron emission tomography simple (PETS) and functional magnetic resonance imaging (fMRI). Although this chapter covers EEG FC, for the sake of completeness, we will show some results of FC in ADHD obtained with analyses performed using fMRI, which has been the most widely used technique to study FC in different pathologies

This image technique provides excellent spatial resolution, as it perfectly identifies (up to 1-3 mm resolution) the most active brain areas, depending on oxygen levels in the blood. However, since some time is required to obtain the images (about 5-8 seconds), the activation sequence of cortical areas involved in the task can only be displayed at a low sampling rate. Therefore, fMRI provides a low temporal resolution for dynamic analysis of brain activity.

FC analysis of fMRI data assesses the existence of statistical dependence between voxel time series. fMRI studies on ADHD have been addressed using two different paradigms: resting state and task-based studies. In resting-state studies, the correlation of the activity of different brain regions is assessed at rest with the subjects having their eyes either open or (most often) closed. In the second case, researchers investigate the correlation of the activity of the brain regions that supposedly co-activate during the performance of a given task. In both cases, the fMRI is generally carried out by comparing an ADHD group with a healthy control group.

One difficulty when establishing a profile of FC of ADHD in fMRI studies arises from the different methodology used for analysing the correlation of activity among brain regions; this has led to heterogeneous results in terms of the networks that are altered in ADHD. The primary brain areas that have been reported to exhibit altered FC in ADHD are the dorsal anterior cingulate cortex (dACC) [24-26], the frontostriatal circuit [27, 28], the default mode network (DMN) [25, 29-32] and the reward circuit [30, 33]. The increasing connectivity between the dACC and the thalamus, cerebellum, insula and pons bilateral in ADHD has been associated with abnormal autonomic activity [26], whereas reduced connectivity between the dACC and posterior components of the DMN is associated with symptoms of inattention and poor performance of working memory in ADHD [25]. This heterogeneity in results is due to methodological differences between studies and appears to be task-dependent, because when comparing resting-state with task-based fRMI studies, the dACC connectivity is enhanced in the first condition and reduced in the second [24]. Regarding the frontostriatal network, ADHD subjects presented reduced connectivity compared to controls, which has been linked to deficits in cognitive functions characteristic of this disorder, primarily the inhibitory control deficit [27, 28]. In the case of the DMN, the ADHD presented lower connectivity, which has been ascribed to the deficits in executive functions that are frequently observed in these subjects [25, 29, 30, 32, 34]. Finally, concerning the reward network, some studies [30, 33] suggest that it is highly connected in the case of ADHD, which is related to the symptoms of impulsivity and delay reward difficulty.

The results in this section demonstrate the existence of distinctive traits in the FC fMRI patterns of ADHD. Although these results cannot be directly extrapolated to EEG, which directly measures neural activity with high temporal but poor spatial resolution, it is clear that comparing brain activity in ADHD with that of healthy controls in terms of changes in FC and beyond the simple activation of individual areas/channels provides useful information about the neural correlates of this pathology.

4. Measures of interdependence between EEG signals for estimating functional connectivity in ADHD

4.1. Linear measures

The magnitude squared coherence is a measure of the linear correlation, both in amplitude and phase, between two signals at a given frequency. It is obtained from the (complex) coherency function between two signals x and y as follows:

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

where $S_{xy}(f)$ is the cross-spectrum between these signals, $S_{xx}(f)$ and $S_{yy}(f)$ are the respective auto-spectra and f is the discrete frequency.

The coherence is simply the squared modulus of $C_{xy}(f)$. For each f, coherence values range between 0 (no correlation) and 1 (full linear correlation). The mean value of the coherence for all the frequencies included in that band is normally taken for the coherence in a certain frequency band.

The argument of coherency provides an estimate of the phase delay between the signals:

$$\phi_{xy}(f) = \text{arctag}\frac{\text{Im}\left\{\text{C}_{xy}(f)\right\}}{\text{Re}\left\{\text{C}_{xy}(f)\right\}} \tag{2}$$

where *Im()* and *Re*() are the imaginary and the real part of $C_{xy}(f)$. Note that the imaginary part of coherency has been suggested as a robust index of interdependence between EEG data that is insensitive to volume conduction [14]; to the best of our knowledge, this idea has not yet been applied to ADHD research.

4.2. Non-linear measures

4.2.1. The concept of generalized synchronization

The first nonlinear indices of FC applied to EEG data were based on the concept of mutual or conditioned neighbours in the state spaces of two time series, which is a practical consequence of the existence of generalized synchronization (GS) between two dynamic systems [35]. Briefly, given a reference state space vector $\boldsymbol{x}_n$ in system X, their k mutual neighbours are those vectors in X that share the time indices of the nearest neighbours of y_n in system Y. Since GS manifests itself as the existence of a functional relationship between the state variables of X and Y, vectors close in X tend to also be close in Y. Thus, mutual neighbours are more similar to the reference vector than randomly selected vectors, which can be numerically quantified in a number of ways [36-38].

To date, two of these indices have been mainly applied to the EEG analysis of ADHD [4, 6]. The first [6] is a modified fuzzy version of the well-known synchronization likelihood (*SL*) method developed by [38]. The second [4] uses an advanced estimation of distances in the reconstructed state spaces, which is based on rank rather than on true Euclidean distance, as described in [37]. We will briefly describe each of these indices below, after describing how to reconstruct the state spaces from time series.

4.2.2. Reconstructing the state space from data

The first step needed to estimate FC from GS-based methods entails the reconstruction of the state spaces of the systems from the signals that they generate (in this case, the EEGs). Such a reconstruction is based on Takens' theorem [39], which ensures that under general conditions (see also [40]), the delayed vectors defined as:

$$X_i = \left(\mathrm{x}(\mathrm{i}), \mathrm{x}(\mathrm{i}\text{-}\tau), \mathrm{x}(\mathrm{i}\text{-}2\tau), \ldots, \mathrm{x}\left(\mathrm{i}\text{-}(\mathrm{m}\text{-}1)\tau\right)\right) \tag{3}$$

are equivalent to the original state vectors. In (3), m is the embedding dimension, which should be at least equal to the dimension of the system, and τ is the delay time, which has to ensure that two consecutive components of the vector are (almost) independent. Normally, m is obtained using a heuristic approach called "*false nearest neighbours*", whereas τ is estimated using the autocorrelation or the auto mutual information function of the data (see [41] for a review of practical considerations of state space reconstructions).

4.2.3. Fuzzy synchronization likelihood

Many of the originally derived indices of GS in the state spaces are asymmetric [42] and thus potentially able to provide information on the directionality of the interaction (i.e., which system acts as driver). However, the initial enthusiasm about the abilities of these indices cooled after some studies [43, 44] showed that differences in their values in X and Y may be simply due to differences in the complexity of the individual systems. In light of these results, [38] defined the synchronization likelihood (*SL*) index as a measure of GS in the reconstructed state spaces, which sacrifices the (possibly misleading) information about directionality in the interaction in return for obtaining an unbiased, symmetric quantitative estimation of the interdependence between two signals. Although intrinsically multivariate in nature (it measures the degree of similitude among M>2 signals), *SL* is almost invariably used to estimate the FC between two time series and is arguably one of the most widely used indices of FC in EEG studies (see [10, 38, 45] for technical details on the estimation of *SL* in both broad and narrow band signals, respectively).

In the framework of EEG studies of ADHD, [6, 46, 47] have proposed a modified version of the *SL* algorithm, termed fuzzy synchronization likelihood *(FSL)*. Briefly, given a reconstructed reference vector in signal x_k such as (3), a window $W_{w_2}^{w_1}(k, i)$ around this vector contains all the $2(\mathrm{w}_2 - \mathrm{w}_1)$ state vectors$\boldsymbol{X}_{i,m}$ whose indices satisfy the condition $\mathrm{w}_1 < |\mathrm{i}–\mathrm{m}| < \mathrm{w}_2$, where w_1 is the

Theiler correction [48] and w_2 determines the temporal resolution of the window. The *fuzzy* in the *FSL* comes from the fact that, in this window, a Gaussian membership (a Gaussian kernel) with a centre at $X_{k,i}$ and a standard deviation of $\varepsilon_{k,i}$ is used [6]:

$$\mu_{\mathrm{k,i}}\left(X_{k,m}\right) = \exp\left(-\left(\left|X_{k,m} - X_{k,i}\right| 2 / \varepsilon_{\mathrm{k,i}}\right)\right) \tag{4}$$

where $\mu_{\mathrm{k,i}}(X_{k.m})$ is the membership of $X_{k.m}$ in the window and $|X_{\mathrm{k.m}} - X_{\mathrm{k,n}}|$ is the Euclidean distance. Then, the probability that $X_{k,m}$ is closer to $X_{k,i}$ than $\varepsilon_{\mathrm{k,i}}$ is computed:

$$P_{k,i}^{\varepsilon_{k,i}} = \frac{1}{2(\mathrm{w}_2 - \mathrm{w}_1)} \sum_m \mu_{k,i}(X_{k,m}) \tag{5}$$

Finally, the *FSL* between X_A and X_B for time index i is computed as follows:

$$FSL_{A-B,i} = \frac{1}{2P_{ref}(\mathrm{w}_2 - \mathrm{w}_1)} \sum_m \frac{\mu_{A,i}(X_{A,m})}{\mu_{B,i}(X_{B,m})} \tag{6}$$

where $P_{ref} << 1$ is a reference probability. Sliding the window along the time series, the *FSL* is computed in each shifted window and is finally averaged for all shifted windows, which leads to the *FSL* between X_A and X_B.

4.2.4. FC estimation based on rank of distances

In the above section, we described a modified version of the *SL* index, the *FSL*, which in the same way as the original *SL*, sacrifices directional information in return for being unbiased. Instead of *SL* or *FSL*, it is possible to compute a robust estimator of directionality based on the GS concept using rank distances [37], the so-called *L* index. In order to compute $L(X_A | X_B)$, delayed state vectors $X_{A,i}$ and $X_{B,i}$ are reconstructed from X_A and X_B as in (3). Then, let $a_{i,j}$ (respectively, $b_{i,j}$) be the time indices of the *k* nearest neighbours of $X_{A,i}$ (resp. $X_{B,i}$); for each $X_{A,i}$, let $g_{i,j}$ be the rank that the distance between $X_{A,i}$ and $X_{A,j}$ takes in the sorted ascending list of distances of each vector to $X_{A,i}$; the $X_{B,,i}$ -conditioned mean rank is then $G_i^k (X_A | X_B) = \frac{1}{k}\sum_{j=1}^{k} g_{i,b_{i,j}}$ and the measurement *L* is defined as:

$$L(X_A | X_B) = \frac{1}{N} \sum_{i=1}^{N} \frac{G_i(X_A) - G_i^k(X_A | X_B)}{G_i(X_A) - G_i^k(X_A)} \tag{7}$$

Dummy Text where $N = n - (m-1)\tau$, $G_i(X_A) = \frac{N}{2}$ and $G_i^k(X_A) = \frac{k+1}{2}$. $L(X_B | X_A)$ can be calculated analogously. Finally, the index *L* of interdependence between the two signals is obtained by averaging both estimations. *L* ranges between 0 (independence) and 1 (identical signals interdependence).

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5. Estimating the reliability of the interdependence measures

As mentioned above, estimating FC from extracranial EEG data is a complicated issue, due to, e.g., volume conduction and reference effects. There is, however, another more general problem associated with the estimation of interdependence measures from finite, noisy experimental data. Due to these two features (shortage and noise), any interdependence index (whether coherence, FSL, *L* or any other one) may be greater than 0 even for two completely independent signals. In order to tackle this issue, it is possible to use the bivariate surrogate data test [12, 49, 50]. This method tests the reliability of an interdependence measure (IM) between two EEGs X_A and X_B, by repeating the calculation of IM after replacing one of the signals (e.g., X_A) with *s* modified (surrogate) versions of it ($X^s{}_A$), which share most of its features (amplitude distribution, spectrum and even its nonlinear properties, if any) with X_A but are independent from X_B by construction (see [49] for details on how to construct different types of surrogate data). The IM (e.g., the *L* index) from the original signals is then compared with the distribution of surrogate L indices obtained from the *s* surrogates, which can be done either parametrically or non-parametrically. Parametrically, the following Z-score index (σ) is calculated:

$$\sigma = \frac{| IM_{orig} - IM_{surr} |}{SD_{surr}} \tag{8}$$

where IM_{orig} is the value of IM for the original data and IM_{surr} and SD_{surr} are the mean and the standard deviation of the distribution of the values for the *s* surrogates, respectively. If this distribution is Gaussian, σ follows a student's t-test distribution with *p* degrees of freedom. We need $s = (1/\alpha)-1$ surrogate data for a statistical level of significance of $100*(1-\alpha)\%$ and it is sufficient to take s=19 for testing the difference at the 95% level of statistical significance ($p<0.05$). We must have $\sigma > 2.1$ to reject the null hypothesis of independence in the original EEG signals for this statistical level. Lack of significance ($\sigma \leq 2.1$) is taken into account by setting the corresponding index to zero. If, however, the distribution is non-Gaussian, then the p-value for the rejection of the null hypothesis of independence is estimated as the ratio

$$p = \frac{1 + Ns}{1 + s} \tag{9}$$

where N_s is the number of surrogate data for which the value of the IM is greater than that of the original data, $IM_{orig.}$ Note that, in either case (parametric or nonparametric method), we are only testing the hypothesis that the original data present some type of interdependence, yet the effect of both volume conduction and the active reference cannot be examined with this approach.

6. Results

The results of the main works in the literature of EEG connectivity as applied to ADHD research are summarized in Table 1 below.

First Auth.	Subjects	Method	Conditions	Main results and trends
Montague (1975)	10 Hyperkinetic 10 CONT	Coherence profile	Resting	Interhemispheric Coh ↓↓ . Intrahemispheric Coh ↑↑ .
Chabot (1996 a, b)	407 ADHD 310 CONT	Coherence in δ, θ, α and β bands	Resting EC	Coh in ADHD ↑↑ or ↓↓ depend on brain regions paired.
Lubar (1999)	23 ADHD	Coherence in δ, θ, α and β bands.	Resting EO	MPH ↓↓ Coh alterations.
Barry (2002)	40 ADHDcom 40 ADHDinat 40 CONT	Coherences in δ, θ, α and β bands.	Resting EC	Coh in ADHD ↑↑ or ↓↓ depend on inter-channels distances.
Barry (2005)	40 ADHDcom 40 ADHDinat 40 CONT	Coherences in δ, θ, α and β bands.	Resting EC	ADHD boys display coherence anomalies age-dependent & differing between subtypes.
Clarke (2005)	20 ADHDcom 20 CONT	Coherences in δ, θ, α and β bands.	Resting EC	MPH does not affect Coh.
Barry (2006)	40 ADHDcom 40 ADHDin 40 CONT	Coherences in δ, θ, α and β bands.	Resting EC	ADHD Coh is age and gender-dependent. ADHD girls no differences between subtypes.
Barry (2007)	40 ADHD+ODD 40 ADHD-ODD 40 CONT	Coherences in δ, θ, α and β bands.	Resting EC	Coh intrahemisph in ADHD + ODD ↓↓ versus ADHD-ODD
Clarke (2007)	30 ADHD 30 ADHD + ↑↑ β	Coherences in δ, θ, α and β bands.	Resting EC	There are differences between ADHD and ADHD + ↑↑ β.
Murias (2007)	42 ADHD 21 CONT	Coherence in frequencies of 2-12 Hz.	ERP word processing task	Deficient connectivity in ADHD and a stimulus-induced state frontal overconnectivity.
Dupuy (2008)	20 ADHD 20 CONT	Coherences in δ, θ, α and β bands.	Resting EC	Medication ↑↑ Coh.
Barry (2009)	20 ADHD+RD 20 ADHD-RD 20 CONT	Coherences in δ, θ, α and β bands.	Resting EC	ADHD+RD ↓↓ Coh δ and α.
Dupuy (2010)	18 ADHDg 17 ADHDp	Coherences in δ, θ, α and β bands.	Resting EC	ADHDg ↑↑ Coh β.

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First Auth.	Subjects	Method	Conditions	Main results and trends
	18 CONT			
Ahmadlou (2010)	47 ADHD 7 CONT	SL Radial Basis Function (RBF)	Resting EC	ADHD ↓ ↓ SL.
Ahmadlou (2011)	12 ADHD 12 CONT	FSL Graph Theory	Resting EC	Deficient connection of posterior and anterior areas in ADHD.
Ahmadlou (2011b)	47 ADHD 7 CONT	FSL and conventional SL in δ, θ, gamma, α and β bands.	Resting EC	ADHD had anomalies in δ and θ SLs. FSL better than conventional SL.
Barry (2011)	40 ADHD 40 CONT	Coherences in δ, θ, α and β bands.	Resting EC	Coh in ADHD ↑ ↑ or ↓ ↓ depend on inter-channels distances.
Ahmadlou (2012a)	15 ADHDg 15 ADHDp	FSL Graph Theory	Resting EC	ADHDg ↓ ↓ FSL in β band after treatment.
Ahmadlou (2012b)	12 ADHD 12 CONT	FSL Small-world network	Resting EC	ADHD FSL ↑ ↑ C and ↓ ↓ L in δ band.
González (2013)	22 ADHD 21 CONT	Coherence Index L	Resting EC and EO	ADHD ↑ ↑ Coh and index L in certain brain regions.
Liu (2014)	13 ADHD 13 CONT	SL in δ, θ, α and β bands	Resting	ADHD ↑ ↑ SL in α and β bands

Vertical arrows ↑ ↑ / ↓ ↓ indicate increasing or decreasing trends; Coh for coherence; ODD for comorbid Oppositional Defiant Disorder, RD for Reading Disabilities; SL for synchronization likelihood; FSL for fuzzy synchronization likelihood; EC closed eyes, EO open eyes; index L for the nonlinear index of GS; Greek letters δ, θ, α and β for EEG delta, theta, alpha and beta frequency bands, respectively. ERP – event related potential.

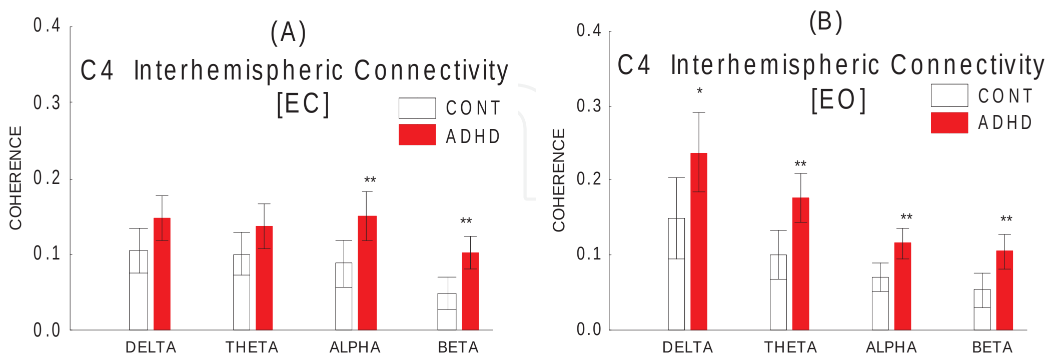
Table 1. Review of the literature on EEG functional connectivity in ADHD.

6.1. Results from coherence

The first study where the profile of EEG coherence is analysed in the context of ADHD was conducted 40 years ago [51]. By using a group of behavioural and physiological measures, the author found that EEG coherence was the measure that best differentiated between a group of hyperkinetic children and a control group. Specifically, he reported that the hyperkinetic group had greater intrahemispheric coherence than controls in the low frequency band (up to 8 Hz). Later, [1, 52] analysed patients already diagnosed with ADHD and reported altered values of coherence in almost every frequency band (delta, theta, alpha and beta) in subjects with ADHD compared to subjects with normal development. Coherence in ADHD can be enhanced or reduced depending on the brain regions that are paired for calculating this index.

Over the past 15 years, the study of EEG FC in ADHD using coherence has been carried out primarily by researchers of the Brain & Behaviour Research Institute and Department of Psychology at the University of Wollongong in Australia, who have studied coherence, both intra- and interhemispheric, by planned contrast and by considering short, medium and long distances between electrodes. They have reported that ADHD subjects, compared to healthy controls, present higher intrahemispheric coherences in short/medium distances in delta, theta and beta frequency bands [7-9, 53-55], reduced laterality in the theta band [8, 53, 55, 56] and increased frontal interhemispheric values in the delta and theta bands [8, 9, 53-55]. Coherence results found from our group [4] indicate, in agreement with previous results, that for certain pairs of channels at short (e.g., C3-C4, O1-O2) and medium (e.g., C3-T4, T3-C4, O1-C4) interhemispheric distances, FC was clearly greater for the ADHD group than for controls, whereas for large interhemispheric distances (e.g., Fp1-O2), the reverse was true during both EC and EO.

When the focus was not on pairwise FC but on seed-based connectivity (that of one channel with a certain set of channels or cortical areas (intra or inter-hemispheric)) the results differed, because of the inherent averaging involved. Thus, for example, the intrahemispheric FC of the C3 channel was estimated by averaging coherence from the electrode pairs C3-T3, C3-F3 and C3-P3; interhemispheric coherence of C3, in turn, required averaging the values of C3-C4, C3-F4 and C3-P4. Figure 1 (A) and (B) show the seed-based interhemispheric coherence for the C4 electrode (average of C4-C3, C4-T3, C4-Fp1 and C4-O1) for the delta, theta, alpha and beta bands during EC and EO, respectively, for the same groups of subjects analysed in our former study [4]. This interhemispheric coherence for ADHD was greater than the control during EC in the higher frequency bands; this was also true for the low frequency bands during EO. Therefore, an increase in interhemispheric EEG coherence for ADHD subjects – in this example for the C4 electrode – is associated with higher frequency bands, regardless of the resting condition (EC, EO) and with low frequency bands only for the EO condition. Figure 2 shows a topographic map of the seed-based interhemispheric connectivity of each channel or cortical area for a standard configuration of 16 EEG channels. Once more, the connectivity of ADHD were greater than for controls for certain areas, resting conditions and connectivity indices.



* p<0.05 and ** p<0.01.

Figure 1. (A) Seed-based interhemispheric coherence (C4 area) during EC estimated by averaging the coherence between channel pairs C4-Fp1, C4-C3, C4-T3 and C4-O1. (B) The same results as in (A) but during EO. Results are for coherence in DELTA, THETA, ALPHA and BETA frequency bands. Asterisks indicate the statistical significance of a paired t-test between ADHD and controls (CONT).

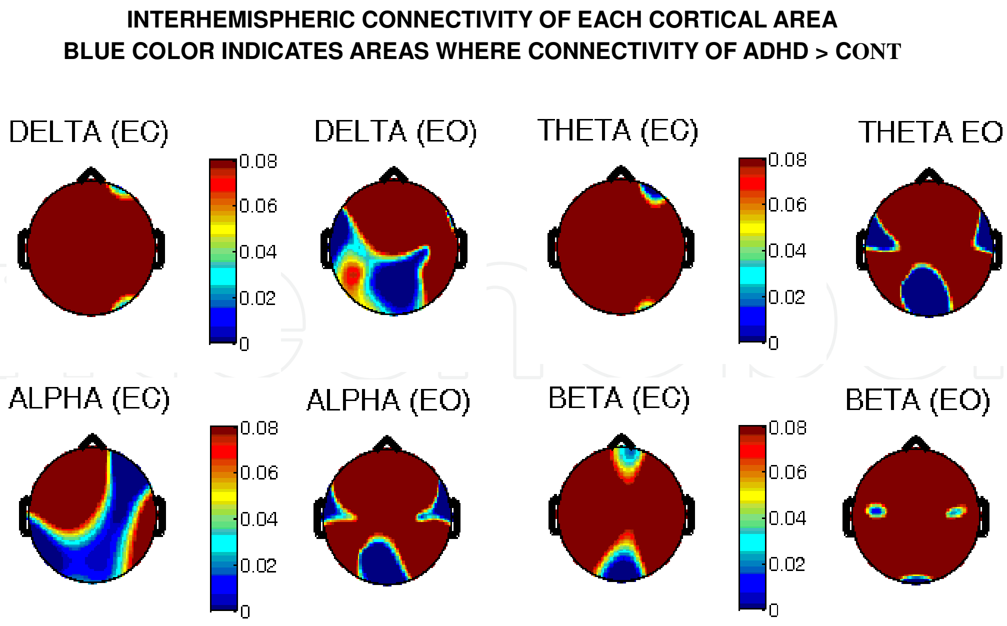


Figure 2. Topographic maps of the seed-based interhemispheric coherence of each cortical area (16 EEG channel configuration) in the DELTA, THETA, ALPHA and BETA EEG frequency bands during EC and EO. Color bar indicates *p* values obtained by comparing ADHD and CONT using a t-test, applied to each cortical area separately, and corrected for multiple comparisons. Blue color indicates areas where connectivity of ADHD was greater than CONT.

The analysis of EEG coherence in subjects with ADHD has also been used to study the effects on the cortical connectivity of factors such as gender, age and comorbid disorders, as well as to understand the influence of certain pharmacological treatments used in ADHD therapy. Thus, a study on the effect of age on EEG coherence [57] analysed three groups of boys, one with ADHD of a combined type, another with ADHD of an inattentive type and a third consisting of control subjects; within each group, the authors studied four subgroups by age (range 8-12 years). They found that there were age-dependent differences in EEG coherence among the three groups. The same authors carried out a similar study involving girls to analyse gender differences [58] and found differences in EEG coherence between ADHD groups and the control group, but not between the ADHD subtypes. Furthermore, this study revealed that such differences were also age-dependent in girls, but not in the same way as they were in boys, in both healthy and ADHD children. The authors concluded from these results that changes in EEG coherence associated with ADHD are different for both genders.

Regarding comorbid disorders, boys with ADHD and oppositional defiant disorder (ODD) presented lower intrahemispheric coherences in shorter distances than ADHD without reading disabilities in delta, theta and beta bands [9]. Furthermore, children with ADHD and reading disabilities had lower intrahemispheric coherences in shorter distances than ADHD without ODD in delta bands [7].

Regarding pharmacological treatments of ADHD, the most commonly used drug to treat the disorder is methylphenidate (MPH), a CNS stimulant that reduces ADHD symptoms. Although its action mechanism is not entirely clear, MPH is known to increase the levels of norepinephrine and dopamine in the frontal cortex and subcortical regions associated with motivation and reward [59]. The results of the effect of MPH on the profile of coherence in ADHD are contradictory. In fact, [60] have found that it reduces the alterations found in EEG coherence profiles in children with ADHD; in contrast, other authors have found neither that MPH ingestion produces changes in the EEG coherence of ADHD, nor that the coherence profile comes closer to that of the controls after treatment [53]. In another study, [56] reported a change in the profile of EEG coherence after MPH ingestion in girls with ADHD and specifically an increase in the delta band between intrahemispheric cortical areas at short distances, resulting in a reduction of the differences between the ADHD and control groups. In [55], the authors reported that ADHD boys showing good response to MPH differed from those unresponsive to the drug, in that MPH produced greater intrahemispheric coherence (shorter and medium distances) in the delta band of the ADHD good response group.

Finally, research on EEG evoked related potentials (ERP) studied the differences in the coherence between ADHD subjects and healthy controls (coherence between different cortical areas for certain frequency bands) during a word-processing task [60]. The ADHD group presented greater differences during the stimulus interval, a deficient connectivity during both intervals and an increase in frontal connectivity within and between hemispheres during a stimulus interval. The intake of medication in this study improved the connectivity pattern of the ADHD group.

6.2. Results from the nonlinear analysis and complex network methods

With regard to the nonlinear indices of FC, these are being increasingly used in the study of EEG of subjects with ADHD. Thus, *SL* was the first nonlinear index used to study the EEG connectivity of ADHD patients [10]. These authors found that, by using filtered EEG (by wavelet decomposition techniques), the SL of the ADHD group was lower than that of the control group for posterior cortical areas at certain EEG bands. In another work by the same authors [6], they applied the FSL index described above and found that ADHD subjects had a lower FC than controls on the centreline of the brain, which could affect the communication between anterior and posterior lobes. In a parallel study [46], these authors compared the SL with the FSL and found that FSL discriminated ADHD from controls better than the non-fuzzy version. Later, the same research group [47, 62] conducted two further studies; in the first [47], they calculated the matrix of FSL values for all possible pairs of channels and then used it to estimate the characteristics of the FC network using graph theoretic-measures. They found that network segregation, as assessed by the clustering index C, was higher in ADHD in the delta band, while network integration, as assessed by the average shortest path length (L) was lower in the same band, thereby suggesting that the small-world character [63] of the FC brain network of ADHD subjects is enhanced in this band, compared to control subjects. Interestingly, increased small-worldness in low frequency bands is a trademark of different neurological pathologies [23]. In the second work [62], the researchers assessed the differences in FSL before and after neurofeedback treatment in a group of ADHD subjects with positive response to treatment and in another group of subjects without response; they found that the former group presented a greater reduction in beta band synchronization compared to that of the group without changes.

Results from our group [4] using the L index described in section 4.2.3 indicated that, as already indicated by coherence, the nonlinear FC of the ADHD subjects was greater than that of controls for short (C3-C4, O1-O2) and medium range (C3-T4, T3-C4, O1-C4) connections during EC. When considering intra- or interhemispheric seed-based FC between one channel and the remaining ones of the same or opposite hemisphere, respectively, we found in the 8 EEG channels configuration that the interhemispheric FC of C3, C4 and O1 was greater in ADHD than in control subjects during EC (see Figure 3 for C4). Figure 4 shows a topographic map of the interhemispheric FC of each channel or cortical area for a standard configuration of 16 EEG channels. As for the corresponding coherence figure (Figure 2), values were obtained by averaging the L indices of the eight pairs that each channel has with the eight channels of the opposite hemisphere. Once more, connectivity in ADHD was only greater than controls for certain areas and resting conditions (EC, EO).

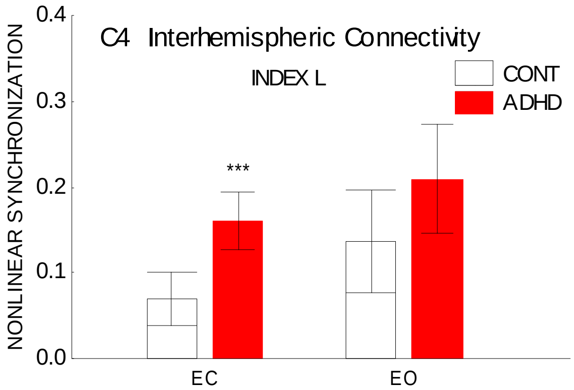


Figure 3. Interhemispheric connectivity of C4 area during EC and EO estimated by averaging the nonlinear synchronization index L between the channel pairs C4-Fp1, C4-C3, C4-T3, C4-O1. Asterisks are for the statistical significance from t-test between ADHD and control (CONT) groups (*** p<0.001).

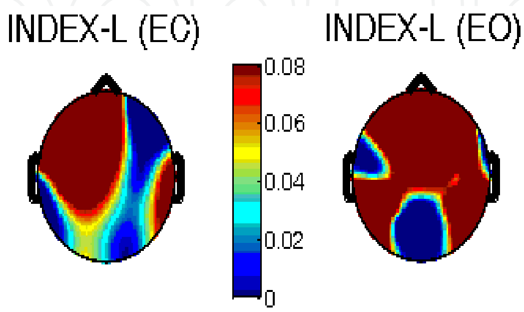


Figure 4. Topographic maps of the interhemispheric connectivity of each cortical area (16 EEG channels configuration). Here connectivities were estimated from the nonlinear synchronization index L. Color bar indicates p values obtained by comparing ADHD and CONT through a t-test applied to each cortical area separately. Blues colors indicate cortical areas where connectivity of ADHD was greater than CONT.

A recent work [64] studied the strength of the connections and the variability of SL, as well as the organization of functional brain networks as described by this index. The researchers found that the strength of connections was greater in the ADHD group in the fronto-occipital networks and that this group also presented a higher SL variability. Other research [65] studied SL in delta, theta, alpha and beta bands and found that this index was greater in the ADHD group for alpha and beta bands.

The results of cortical FC estimated from different nonlinear indices are dependent on the index considered to estimate connectivity and the method used to compute the connectivity of each cortical area with other zones, i.e., whether individual channel pairs or averaging intra- and/or interhemispheric channels pairs are considered. Although the results initially appeared to be heterogeneous, they show some consensus in indicating that the EEG of ADHD subjects are hypersynchronized when compared to that of healthy controls. This is also confirmed by applying graph theory methods to the connectivity matrix of FC patterns.

6.3. Results from diagnostic procedures based on connectivity measures

The section above reviewed the current state of the literature on nonlinear FC indices as applied to the EEG of ADHD subjects. In all cases, the analysis strategy was similar: a set of statistical comparisons was used to study the existence of differences between one (or more) group of ADHD subjects and age- or gender-matched healthy controls. An alternative approach, which has become very popular in recent years, consists of regarding the matrices of FC indices as connectivity patterns that can be used as training vectors for a machine learning classification algorithm [4, 10, 46]. This approach not only allows for determination, of which FC features are the most discriminative for deciding whether a subject's EEG presents any ADHD traits, but also renders unnecessary any discussion on the true relationship between FC of two EEG channels and the existence of synchronization between the underlying cortical networks.

In this framework, the studies cited above [4, 10, 46] have shown that the nonlinear measures of EEG FC present a high degree of accuracy and sensitivity. Thus, [10, 46] combined the radial basis function neural network as classification algorithm and the leave one out cross validation method (see, e.g., [66] for details on the methodologies) to learn from SL and FSL patterns of EEG FC. The researchers found that SL reached an accuracy of 95.6% for diagnosis of ADHD with a variance of 0.7%, whereas the FSL index reached an accuracy of 87.50%.

As for the diagnostic usefulness of the L index, in a recent work, [4] combined the well-known receiver operating characteristic curves and the binomial logistic regression classification technique to verify the diagnostic utility of the EEG FC measures. These results showed that ADHD children are best discriminated from age-matched healthy controls by using inter-hemispheric interdependence measures computed from a few single EEG channel pairs, rather than by using the corresponding inter-hemispheric averages. In fact, the coherence in the beta band between inter-occipital regions and between left/occipital-right/central regions provided an overall accuracy classification rate of 74.4%, but even greater accuracy (86.7%) was obtained by using the *L* index between left/occipital-right/central regions and left/central-right/temporal regions during resting state with EC.

7. Conclusions and future perspectives

The results presented here clearly suggest that the EEG FC of ADHD subjects presents a complex pattern of significant alterations when compared to that of healthy controls across different frequency bands. For instance, depending on the distance between the paired brain regions, the EEG FC in the ADHD group can be greater or smaller than that of the healthy control group. Additionally, the coherence in resting state is influenced by/for age, sex, comorbid disorders and medication. In ERP analysis, the scarcity of results to date indicates that ADHD differences in coherence are more discriminative in the stimulus interval than in the alert interval.

As for the nonlinear FC measures, the results are also heterogeneous; however, when the different nonlinear methodologies are compared, it can be concluded that: the *FSL* is a better discriminator than *SL* and that the use of graph theoretic measures increases the sensibility of these measures for distinguishing between the EEG of ADHD and that of healthy controls. Furthermore, the index *L* seems to present a good perspective that can be applied to distinguishing between ADHD and controls.

Bearing in mind all these results and the usefulness of EEG patterns of FC for classification, it is somewhat surprising that other popular nonlinear FC methods such as those based on the concept of phase synchronization [67] have been applied less often in this field. Moreover, new and improved methods for the study of GS from time series [36, 68], which allow for the estimation of causal interdependence from multivariate data, has recently been successfully applied to EEG data [69]. In addition, recent results (e.g., [70]) have demonstrated that FC indices can be successfully combined with graph theoretic methods and advanced machine learning algorithms such as support vector machines, which can handle high dimensional feature vectors, in order to diagnose neurological pathologies using multivariate neurophysiological data. In fact, another interesting (yet relatively unexplored possibility) entails the combination of data from different modalities such as EEG, MRI and neurophysiological testing [64] to describe the effects of the pathology on different data. This would be very helpful both at applied and basic levels. Taken together, all these old and new results pave the way for further studies regarding the patterns of EEG FC, which can provide further insight into the EEG correlates of ADHD.

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Author details

Julián J. González[1*], Guzmán Alba[1], Soledad Mañas[2], Almudena González[1] and Ernesto Pereda[3]

*Address all correspondence to: jugonzal@ull.edu.es

1 Physiology Unit, Health Sciences Faculty. La Laguna University, Spain

2 Clinical Neurophysiology Unit, University Hospital La Candelaria, Tenerife, Spain

3 Department of Industrial Engineering, School of Engineering and Technology, University of La Laguna, Tenerife, Spain

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