Complexity Analysis of Spontaneous Brain Activity in Attention-Deficit/Hyperactivity Disorder: Diagnostic Implications

Alberto Fernandez

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Alberto Fernandez, PhD[a,b]; Javier Quintero, MD, PhD[c;], Roberto Hornero MSc, PhD[d]; Pilar Zuluaga, PhD[e]; Marta Navas, MD[c], Carlos Gomez, MSc[d], Javier Escudero, MSc[d]; Natalia García-Campos, BA[f]; Joseph Biederman, MD[g]; Tomás Ortiz, MD, PhD[a,b]

a. Departamento de Psiquiatría, Universidad Complutense de Madrid, Spain
b. Centro de Magnetoencefalografía Dr. Perez-Modrego, Universidad Complutense de Madrid, Spain
c. Servicio de Psiquiatría, Hospital Infanta Leonor, Madrid, Spain
d. Grupo de Ingeniería Biomédica, Universidad de Valladolid, Spain
e. Departamento de Estadística e Investigación Operativa, Universidad Complutense de Madrid, Spain
f. Instituto Neuroconductual de Madrid, Spain
g. Pediatric Psychopharmacology Unit of the Psychiatry Department, Massachusetts General Hospital, Boston,MA, USA

Corresponding Author

Alberto Fernandez PhD
Centro de Magnetoencefalografía Dr. Perez-Modrego
Universidad Complutense de Madrid
Avda Complutense s/n 28040 Madrid, Spain
email: aferlucas@med.ucm.es
Telf/Fax: +34913942296/ +34913942294

Alberto Fernandez

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Alberto Fernandez

Abstract

Background: Attention-Deficit Hyperactivity Disorder (ADHD) is defined as the most common neurobehavioral disorder of childhood but an objective diagnostic test is not available yet up to date. Neuropsychological, neuroimaging and neuropsychological research offer ample evidence of brain and behavioral dysfunctions in ADHD but these findings have not been useful as a diagnostic test.

Method: Whole-head magnetoencephalographic recordings were obtained from 14 diagnosed ADHD patients and 14 healthy children during resting conditions. Lempel-Ziv complexity (LZC) values were obtained for each channel and child, and averaged in 5 sensor groups: anterior, central, left lateral, right lateral, and posterior.

Results: LZC scores were significantly higher in controls, with the maximum value in anterior region. Combining "age" and "anterior" complexity values allowed the correct classification of ADHDs and controls with a 93% sensitivity and 79% specificity. Controls showed an age-related monotonic increase of LZC scores in all sensor groups, while ADHDs exhibited a non-significant tendency towards decreased LZC scores. The age-related divergence resulted in a 100% specificity in children older than 9 years.

Conclusion: Results support the role of a frontal hypoactivity in the diagnosis of ADHD. Moreover, the age-related divergence of complexity scores between ADHDs and controls might reflect distinctive developmental trajectories. This interpretation of our results is in agreement with recent investigations reporting a delay of cortical maturation in the prefrontal cortex..

Alberto Fernandez

INTRODUCTION

Attention-Deficit Hyperactivity Disorder (ADHD) is the most common neurobehavioral disorder of childhood (1). Diagnostic guidelines identify the core symptoms of ADHD as "inattentiveness, impulsivity and hyperactivity". These guidelines also acknowledge that there is no objective test or marker for ADHD and therefore diagnosis relies entirely on clinical criteria. While neuropsychological (2), neuroimaging (3) and neurophysiological (4) research offer ample evidence of brain and behavioral dysfunctions in ADHD, these findings have not been useful as a diagnostic test.

Bush et al (5) reviewed functional neuroimaging studies of ADHD, ranging from PET, SPECT, fMRI to EEG. These authors found a consistent pattern of frontal dysfunction affecting closely-related areas, such as dorsolateral prefrontal cortex, anterior cingulate, ventrolateral prefrontal cortex, parietal cortex, striatal and cerebellar regions. Similarly to Bush et al, Willis and Weiler (6) focused on structural MRI and EEG studies of ADHD, concluding that frontal and caudate-nuclei volume reductions are the most frequently detected abnormalities. Earlier quantitative EEG (qEEG) studies revealed consistent group differences between control and ADHD children, including increased frontal theta activity, increased posterior delta, and decreased alpha and beta activity (6). More recent qEEG research, such as Monastra et al's study (7) used a classification model based on theta/beta power ratios and reported discrimination of ADHD from controls with 86% sensitivity and 98% specificity.

Whereas other neuroimaging techniques, such as PET and SPECT, measure the brain activity in terms of vascular and metabolic changes, the EEG and magnetoencephalography (MEG) acquire the brain activity directly (8). This is due to the fact that both EEG and MEG record the electromagnetic oscillations produced by

the neurons. Moreover, MEG is a complementary signal to EEG and represents an entirely non-invasive procedure for brain analysis in children. MEG has been scarcely utilized in ADHD investigation (9-12) and, as far as we know, the diagnostic utility of this technique has never been tested in ADHD. It is important to notice that there are some major differences between EEG and MEG. First of all, MEG offers a better spatial resolution than EEG. Furthermore, MEG is sensitive to a broader frequencies spectrum compared to EEG as skull acts as a low-pass filter for electric, but not for magnetic fields (13,14).

Recently, non-linear analysis has been applied to MEG and EEG signals in an attempt to improve the traditional quantitative power-spectrum approach (15, 16). A branch of these non-linear estimates of brain activity is complexity analysis. Several complexity estimates have been applied to EEG and MEG: Correlation Dimension, First Lyapunov Component, Auto-mutual Information, Lempel-Ziv Complexity (LZC), etc. (17,18). Parameters of EEG-MEG complexity usually estimate the predictability of brain oscillations and/or the number of independent oscillators underlying the observed signals (19,20). Among those, LZC is a model-independent estimator of system complexity adequately suited for the analysis of biomedical signals (21). LZC is related to the number of bits of the shortest computer program which can generate the analysed time series (21). This complexity metric, which is based on counting the number of distinct substrings and their recurrence rate along the analysed signal, assigns higher values to more complex data (21). Only two simple operations are needed to compute LZC: sequence comparison and number accumulation. This metric has been successfully employed to quantify the relationship between brain activity patterns and depth of anaesthesia (22), to analyse neural discharges (23), to evaluate epileptic seizure

EEG time series data (24) and to analyse spontaneous MEG data in a population of Alzheimer's disease (AD) patients (25). This latter study is a precedent of our current investigation since AD patients exhibited a significantly reduced pattern of LZC, supporting Goldberger's theory of complexity loss in aging and disease (20). Moreover, recent studies have shown that LZC is related to the average information quantity in a signal as well as signal characteristics like spectral bandwidth and harmonic variability (26).

The main aim of this study was to further investigate the relationship between age, psychopathology, and MEG-derived complexity in a population of ADHDs and healthy controls. Based on the above-mentioned literature, we hypothesized there will be a pattern of reduced LZC values in ADHD, specially in anterior brain regions.

METHODS AND MATERIALS

SUBJECTS

The clinical group comprised 14 male (mean age, 9.64 ± 1.04 years; range 8-12) children with ADHD recruited from the community. Inclusion criteria included a full DSM-IV diagnosis of ADHD combined type with associated impairment in at least 2 settings and a Conners' Parents Hyperactivity rating greater than 2 SD above age- and sex-specific means. The D*SM-IV* diagnosis of ADHD was based on the Parent Diagnostic Interview for Children and adolescents. ADHD patients were totally drug-naïve, they had never used any psychoactive drug or were receiving any psychoactive therapy. Exclusion criteria were a full-scale IQ of less than 80, evidence of medical or neurological disorders, or any other axis I psychiatric disorder requiring treatment with medication (see Table 1). Thus, any potential comorbidity was eliminated from the study.

A clinical psychologist (N.G.C.) administered the Wechsler Intelligence Scale for Children (Revised) to 4 patients with ADHD and the WISC-IV to 10 patients. A total of 17 healthy children (mean age, 10.36 ± 1.48 years, range 8-13) matched for sex, handedness, and education were recruited from the community as well. Screening included an initial telephone interview, which consisted in the administration of the Conner Parent Rating Scale (CPRS). Once this preliminary evaluation was performed, an individual assessment including physical and neurological examinations (including handedness), and clinical history was obtained by a child and adolescent psychiatrist (M.N.). Three potential controls were excluded due to positive family psychiatric history and possible psychiatric diagnosis based on clinical examination. This study was conducted at an outpatient Child and Adolescent Psychiatry Unit between January 2007 and January 2008. The institutional review board approved this research protocol and written informed consent and assent to participate in the study were obtained from parents and children, respectively.

####Insert Table 1 about here####

DATA COLLECTION

MEGs were acquired with a 148-channel whole-head magnetometer (MAGNES 2500 WH®, 4D Neuroimaging, San Diego, CA) placed in a magnetically shielded room at "Centro de Magnetoencefalografía Dr. Pérez-Modrego" (Madrid, Spain). Subjects were in an awake but resting state with their eyes closed and under supervision during the recording. They were asked to avoid blinking and making movements. For each subject, five minutes of MEG signal were acquired at a sampling frequency of 678.17 Hz using a hardware band-pass filter of 0.1-200 Hz. Afterwards these recordings were down-sampled by a factor of 4 (169.549 Hz). Artefact-free epochs of 20 seconds were selected

off-line. Finally, these epochs were filtered between 1.5 and 40 Hz and copied to a computer as ASCII files for further complexity analysis.

LZC CALCULATION

LZC is a nonparametric measure for finite sequences related to the number of distinct substrings and the rate of their occurrence along the sequence, with larger values corresponding to more complexity in the data (22). *LZC* analysis is based on a coarse-graining of the measurements, so the MEG recording must be transformed into a finite symbol string. In this study, we used the simplest way: a binary sequence conversion (zeros and ones). By comparison with a threshold T_d, the original data are converted into a 0-1 sequence. We used the median as the threshold T_d due to its well-known robustness to outliers. The binary string obtained is scanned from left to right and a complexity counter $c(n)$ is increased by one unit every time a new subsequence of consecutive characters is encountered in the scanning process. The complete computational algorithm of $c(n)$ is described in Zhang et al (22).

In order to obtain a complexity measure which is independent of the sequence length n, $c(n)$ should be normalized. In general, $b(n)=n/log_2(n)$ is the upper bound of $c(n)$ for a binary sequence (21). Thus, $c(n)$ can be normalized via $b(n)$: $C(n)=c(n)/b(n)$. The normalized *LZC*, $C(n)$, reflects the arising rate of new patterns along with the sequence.

DATA REDUCTION AND ANALYSIS

A LZC-normalized score was obtained for each channel and participant. Thus, 148 LZC scores per subject were submitted to statistical analyses. Due to the relatively high number of dependent variables and the relatively reduced sample (14 + 14), a dimensionality problem might appear during data analysis. In order to prevent such

problem the initial 148 LZC scores were averaged into 5 regions: anterior, central left lateral, right lateral, and posterior, which are included as default sensor groups in the 4D-Neuroimaging source analysis software (see Figure 1). This approach has been broadly used when MEG data analysis is based on sensor-space and brain sources are not estimated (27-29).

####***Insert Figure 1 about here####***

Repeated-measures ANOVA and linear regression models were applied to explore potential regional effects and to analyse the relationship between LZC scores and age. A logistic regression model was applied in order to select those variables useful to correctly classify children into ADHD or Control groups. Our data come from an unmatched or separate sampling case-control study. The consequence of this fact is that inferences about the intercept parameter are not possible without knowledge of the sampling fractions τ_1 and τ_0, while the remaining parameters may be estimated using the methods developed for cohort data. We used, for the intercept parameter α, the estimator $\alpha^* = \alpha + \ln\left(\tau_1 / \tau_0\right)$, being α the intercept parameter estimator from cohort model (30).

RESULTS

REGIONAL EFFECTS

Means and standard deviations of LZC scores for ADHDs and Controls in the five regions are shown in Table 2. Controls means were greater than those of ADHD subjects in all regions. Moreover, the anterior LZC scores were higher in both groups

than the scores of the remaining four regions as measured through a repeated-measures ANOVA with two factors: Region (anterior, central, left lateral, right lateral, and posterior) and Group (ADHD versus Control). LZC scores were significantly modified by the main effects of Region ($F_{4,104}$ = 33,31; p< 0.01), Group ($F_{1,26}$ = 8.502; p< 0.01) and the interaction between both variables ($F_{4,104}$ = 2.53; p< 0.05). In order to identify Region x Group differences a post-hoc Bonferroni correction was applied. Post-hoc tests showed significant differences when anterior and central regions were compared with left lateral, right lateral and posterior regions (all p-values < 0.05). These effects indicated higher anterior and central LZC values and were valid for both ADHD and Control groups. In addition, anterior LZC scores were significantly higher than Central scores, but only within Control group (p=0.005).

####***Insert Table 2 about here####***

AGE EFFECTS

Figure 2 displays scatter diagrams and regression lines representing the differential correlation among LZC scores and age. For ages greater or equal than 9 years, anterior scores were higher for Controls than for ADHDs, and this difference increased as a function of age (see Figure 2 top). Analogous results were obtained for the remaining regions (Figure 2). A positive slope-coefficient indicates that LZC scores increase with age in Control group (where all coefficients were significantly different from zero). On the other hand, for ADHD subjects all p-values were not significantly different from zero, but the slope coefficients were negative (except left lateral, though its value was

near zero 0.0001) indicating an opposite tendency to controls (see Table 3). Since these results suggested that age exerts a significant influence on LZC scores we included this variable in each logistic regression model.

####Insert Table 3 and Figure 2 about here####

LOGISTIC REGRESSION ANALYSES

Prior to undertaking a variable selection process, two types of predictor variables were considered: "age", which was included by default in all models (see above), and the LZC scores obtained for each region. The variable selection process began with an univariate analysis for each LZC variable. Following Hosmer & Lemeshow (31), we used a *p*-value of 0.25 for the likelihood ratio test (*LRT*) as a screening criterion to select candidate variables for every multivariate model. Three variables (p-anterior= 0.002, p-central= 0.037, and p-posterior= 0.032) demonstrated a significant predictive power in the univariate analysis($p<0.05$). In addition left lateral region matched Hosmer & Lemeshow's screening criterion for candidate variables to the multivariate model (p-left=0.178; $p<0.25$). Among those, a multivariate stepwise procedure selected anterior region as the only final candidate (see Figure 3). The logistic model including age and anterior variables was called Model 1 (see coefficients in Table 4). The model-building process continued by ascertaining the correct scale in the logit for age and anterior variables. This analysis showed evidence of linearity in both cases. Finally we searched for an age $\times$ anterior interaction. The interaction (p= 0.015) significantly improved Model 1. Based on these findings, a new model (Model 2) including age, anterior, and anterior x age variables was fitted (see Model 2 coefficients in Table 4). The Nagelkerke R^2 goodness-of-fit statistic for Model 2 was 0.645, which means that

about 64% of the "variation" in the dependent variable (ADHD vs. Control) is explained by the logistic model. The area under the receiver operating curve (ROC) was 0.898. Tables 5 and 6 show the percentages of correct classifications for Models 1 and 2, respectively, when a 0.5 cutoff point is set. Models 1 and 2 share the same specificity (78.6%), and the three incorrectly classified controls were identical in both cases. It is important to note that ages of incorrectly classified controls were not randomly distributed. The three misclassified children were ranked at the lowest values of controls age distribution (8 and 9 years). Model 1 sensitivity was 85.7%, while it was 92.9% in Model 2. Again, it is important to realize that the additional patient correctly classified by Model 2 was 8 years old, emphasizing the critical importance of age for the performance of the logistic models. Overall, the discriminant capability of the models tested was more accurate for older children, as it was previously demonstrated by the linear regression analyses (see Table 2). This Age influence is well addressed by the 100% specificity of Model 2 for children older than 9 years (see scatter diagram of Anterior region in Figure 2).

####Insert Tables 4, 5 and 6, and Figure 3 about here####

DISCUSSION

The implications of our results are twofold. First, a combination of "Age" and "Anterior" LZC variables allowed for correct classification of children with ADHD and controls with a high sensitivity (93%) and a relatively high specificity (78.6%). Second, and more relevantly, the age-related evolution of complexity scores showed a totally divergent tendency in ADHD and control subjects. While controls showed a significant steady increase of LZC scores, so that maximum values were obtained at the age of 12 years, ADHD subjects showed a non-significant tendency to decreased LZC scores as a

function of age. Such divergence was more pronounced in anterior brain regions and exerted a dramatic influence on the discriminant capability of the statistical model, since all controls older than 9 years are correctly classified, thus attaining a 100% specificity. These results were obtained using an entirely non-invasive technique, suitable for children evaluation, and all patients and controls were able to undergo the MEG evaluation.

Although it is impossible to ascertain with certainty whether the percentage of magnetic activity measured in anterior sensors derived from frontal and prefrontal cortices, due to the distinctive technical characteristics of MEG (for an entire review of this issue see (32)) it was possible to assume that most of the anterior sensors activity originated on anterior brain regions. Keeping this limitation in mind our results support the evidence of frontal hypoactivation in drug-naïve ADHD subjects. Furthermore, including only drug-naïve ADHD subjects in our study adds extra value to our results since psychotropic medication might have biased the study ability to attribute group differences to the underlying psychopathology and not to its treatment (33).

A similar conclusion was put forward by Loo and Barkley (34) in another EEG investigation of children with ADHD. These investigators claim that most of EEG differences between ADHD and control subjects can be described in terms of increased anterior and central theta activity; with a higher theta/beta ratio which is accepted as the most robust EEG finding. Increased frontal theta is interpreted as a sign of cortical hypoarousal in children and adolescents with ADHD and might represent a delayed process of cortical maturation. Classic qEEG studies have been enhanced by the application of innovative analysis techniques. Murias et al (35) evaluated the functional connectivity of the frontal cortex in controls and ADHD subjects using EEG coherence.

Their results showed elevated coherence in the lower alpha band (8Hz) and reduced coherence in the upper alpha band. This finding is important to understand our own results as increased coherence or synchronization in certain frequency bands exert a clear influence on the estimates of EEG-MEG complexity. A key-point here is that the meaning of complexity estimates exceeds conventional frequency and power spectrum analyses. According to Lutzenberger et al (36), complexity values obtained through Correlation Dimension in a system (i.e. the brain) made of multiple oscillators increase monotonically with the number of oscillators. In line with this idea, Aboy and coworkers (26) tried to uncover the interpretation of LZC scores in the field of biomedical signals. These researchers focused on how certain factors such as frequency content, noise, number of harmonics, etc., affect LZC values. They concluded that LZC quantifies primarily the signal bandwidth and the bandwidth of the signal harmonics. Namely, LZC represent an estimate of the number of different frequency components that actually compose the brain signals. As a consequence highly coherent or synchronized signals over relatively long periods of time (i.e. epileptic seizures) yield low complexity scores (24) and brain signals derived from patients who suffer from a disease that impairs the "normal" patterns of brain connectivity (i.e. Alzheimer's disease) produce low LZC scores as well (25). Furthermore, the complexity of brain activity measured using EEG-MEG signals has been considered intimately associated with the integrity of brain connectivity (37). This interpretation is also well supported by our own data and studies of EEG complexity during brain development (19,38,39). Such studies reveal that complexity increases monotonically from early childhood to adulthood in all regions (39). More importantly, the evolution of EEG-MEG complexity seems to parallel white-matter maturation (40,41).

Alberto Fernandez

Our findings suggest that the development of ADHD patients' complexity diverges from that of healthy controls. Such divergence might imply an altered or delayed process of cortical maturation which specially affects anterior brain regions. These findings are consistent with Rapoport et al (42) suggestion that childhood psychiatric disorders reflect abnormalities of brain development. As these authors stated, the association between developmental anomalies and pediatric cognitive disorders is clearer when such disorders produce disturbances of the central nervous system, but remains controversial when brain disturbances are subtler. In fact, Castellanos et al (43) reported parallel developmental trajectories for all brain structures, except caudate, when children and adolescents with ADHD were compared to controls. Considering this investigation and similar studies (44) it was thought that ADHD brain abnormalities are fixed rather than an ongoing (i.e. developmental) process. This point of view has been re-examined after the recent publication of Shaw et al's (45) study on ADHD cortical maturation. Shaw et al obtained MRI scans from ADHDs and controls in a combined longitudinal and cross-sectional study employing sophisticated methods of analysis to estimate trajectories of brain growth and cortical thickness. ADHDs' and controls' patterns of brain development were similar specially in primary motor and sensory areas but had marked differences in timing. Shaw et al inferred that ADHD is characterized by a delay rather than by a deviance of cortical maturation which is more prominent in the prefrontal cortex, a cortical region involved in a family of cognitive functions that have all been implicated in the pathogenesis the disease.

Findings presented in this work are limited by the small sample size, and further larger studies should be carried out to confirm the predictive diagnostic power of MEG-LZC scores in ADHD children. Additionally, the sensitivity of the model should be tested in

other subtypes of ADHD (predominantly inattentive or hyperactive/impulsive). In a subsequent step, the sensitivity and specificity of the model should be tested in neurobehavioral disorders which share some common features with ADHD (negativistic-oppositional disorder, for example). Notwithstanding, our results suggest that MEG methodology may have diagnostic utility as an objective, non-invasive diagnostic test in children with ADHD.

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Alberto Fernandez

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Alberto Fernandez

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Alberto Fernandez

FOOTNOTES

Table 1. Age, education and IQ information of ADHD patients. Abbreviations, **YOE**: years of education; **TIQ**: total IQ; **VIQ**: verbal IQ; **PIQ**: performance IQ; **VC**: verbal comprehension; **PR**: perceptual reasoning; **WM**: working memory; **PS**: processing speed. "*" symbols indicate patients evaluated using WISC-R, while "†" symbols indicate patients evaluated using WISC-IV.

Table 2. Means and standard deviations of the five LZC variables in ADHD and Control groups

Table 3. Slopes coefficients of the five regions regression lines, their p-values and correlation coefficients (r).

Table 4. Logistic Regression coefficients for Model 1 and Model 2 (being ADHD the reference category)

Table 5. Classification Table for Model 1 with a cutoff of 0.5. The off-diagonal entries of the table display the number of incorrectly classified patients.

Table 6. Classification Table for Model 2 with a cutoff of 0.5. The off-diagonal entries of the table display the number of incorrectly classified patients

Figure 1. Sensor-space representation of the five regions submitted to statistical analyses.

Figure 2. Scatter diagrams and regressions lines of LZC scores versus age, plotted for the 5 regions. Black crosses and solid lines correspond to Control group, while open circles and dotted-lines correspond to ADHDs. "X" axis represents age values of patients and controls. Sample size, ADHD= 14, Controls = 14.

Figure 3. Average LZC values in ADHD patients and control subjects for all channels, from A1 to A148, displayed in a colour scale. A significant reduction of anterior scores can be observed. Sample size, ADHD= 14, Controls = 14.

Alberto Fernandez

Table 1

Patient	Age	YOE	TIQ	VIQ	PIQ	VC	PR	WM	PS
1*	9	5	127	115	134				
2†	9	4	93			107	81	97	102
3†	10	5	114			107	109	105	124
4†	12	7	100			114	95	105	4
5†	9	4	126			132	131	93	112
6†	9	4	110			122	100	125	110
7*	9	4	132	135	125				
8*	10	5	91	88	97				
9†	9	4	112			103	132	105	93
10†	11	6	106			110	89	110	113
11†	10	5	112			116	123	82	110
12†	9	4	95			113	91	93	88
13*	8	4	107	97	115				
14†	11	6	109			114	114	102	97
Mean	9,6	4,34	110						

Table 2

		Anterior	Central	Left Lateral	Right Lateral	Posterior
ADHD	Mean	0.5898	0.5752	0.5396	0.5511	0.5095
	SD	0,0308	0,0354	0,0249	0,0208	0,0839
Control	Mean	0.6257	0.6049	0.5604	0.5670	0.5650
	SD	0,0249	0,0246	0,0285	0,0295	0,0277

Table 3

	Anterior	Central	Left	Right	Posterior
ADHD	-0.0081 p=0.2594 r=-03233	-0.0074 p=0.3728 r=-0.2581	0.0001 p=0.9781 r=0.0080	-0.0029 p=0.5554 r=-0.1725	-0.0001 p=9957 r=-0.0015
Control	0.0087 p=0.042 r=0.5272	0.0119 p=0.0035 r=0.7231	0.0141 p=0.0022 r=0.7431	0.0120 p=0.0199 r=0.6123	0.0100 p=0.0444 r=0.5437

Alberto Fernandez

Table 4

	Model 1	Model 2
Age	-0.435	30.599
Anterior	- 47.338	418.363
Age×Anterior		-51.180
Intercept	32.991	-249.222

Table 5

Predicted Diagnosis

Observed Diagnosis	***ADHD***	***Control***	***Percent Correct***
ADHD	**12**	**2**	**85.7%**
Control	**3**	**11**	**78.6%**

Table 6

Predicted Diagnosis

Observed Diagnosis	***ADHD***	***Control***	***Percent Correct***
ADHD	**13**	**1**	**92.9%**
Control	**3**	**11**	**78.6%**

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