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Linear and non-linear EEG analysis of adolescents with attention-deficit/hyperactivity disorder during a cognitive task

Hansem Sohn [a,1], Inhye Kim [b,1], Wonhye Lee [a], Bradley S. Peterson [c], Hyunju Hong [d], Jeong-Ho Chae [e], Sayong Hong [b], Jaeseung Jeong [a,c,*]

[a] Department of Bio and Brain Engineering, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 305-701, South Korea
[b] Department of Physics, Kongju National University, Kongju 314-701, South Korea
[c] Department of Psychiatry, Columbia College of Physicians and Surgeons, New York, NY 10032, USA
[d] Department of Psychiatry, College of Medicine, Hallym University, Seoul, South Korea
[e] Department of Psychiatry, College of Medicine, The Catholic University of Korea, Seoul, South Korea

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ABSTRACT

Objective: We aimed to investigate whether electroencephalograph (EEG) dynamics differ in adolescents with attention-deficit/hyperactivity disorder (ADHD) compared with healthy subjects during the performance of a cognitive task.
Methods: We recorded EEGs from 19 scalp electrodes in 11 adolescent boys with ADHD and 12 age-matched healthy boys while the subjects were at rest and during a continuous performance test (CPT). The approximate entropy (ApEn), a non-linear information-theoretic measure, was calculated to quantify the complexity of the EEGs.
Results: The mean ApEn of the ADHD patients was significantly lower than the healthy subjects over the right frontal regions (Fp2 and F8) during the performance of the cognitive task, but not at rest. The spectral analysis showed significant differences between the two groups in the P3 and T4 regions at rest and the Fp2 and F8 regions during task performance.
Conclusions: The differences in EEG complexity between the two groups suggest that cortical information processing is altered in ADHD adolescents, and thus their levels of cortical activation may be insufficient to meet the cognitive requirements of attention-demanding tasks.
Significance: This study suggests that a non-linear measure such as ApEn is useful for investigating neural dysfunctions in adolescents with ADHD.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent childhood behavioural disorders, affecting 5–10% of all children. It persists into adulthood (Wilens et al., 2002) in approximately 4% (Biederman, 2005). The symptoms of ADHD include inattention, hyperactivity and impulsivity (American Psychiatric Association, 2000), and many patients with ADHD have lower academic or occupational performance and display a co-occurring affective illness, substance abuse or oppositional behaviour (Biederman et al., 1997; Lambert and Hartsough, 1998).

Previous electrophysiological studies of ADHD reported a relative increase in the power of the theta frequency and a relative decrease in the power of the alpha and beta frequencies in resting subjects, regardless of whether their eyes were open or closed (Clarke et al., 1998, 2001a,b; Lazzaro et al., 1998; Bresnahan et al., 1999; Barry et al., 2003; Hermens et al., 2005; Snyder and Hall, 2006). Although several electrophysiological studies of ADHD have been conducted during the performance of cognitive tasks, these studies have yielded inconsistent results owing (in part) to the different tasks employed (such as reading and drawing) (Mann et al., 1992; Janzen et al., 1995; DeFrance et al., 1996; Monastra et al., 1999; El-Sayed et al., 2002; Swartwood et al., 2003; Hermens et al., 2005; Plessen et al., 2006). In contrast, cognitive tasks such as the Stroop, go/no-go and stop-signal tasks have been used widely in functional imaging studies; the results of these studies have emphasised the importance of fronto-striatal pathways in supporting attentional processes and their contribution to the pathophysiology of ADHD (DeFrance et al., 1996; Bush et al., 1999; Rubia et al., 1999; Pliszka et al., 2006). Anatomical imaging studies have reported reduced volumes of the striatum and frontal lobe in ADHD

* Corresponding author at: Department of Bio and Brain Engineering, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 305-701, South Korea. Tel.: +82 42 350 4319; fax: +82 42 350 4310.
E-mail address: jsjeong@kaist.ac.kr (J. Jeong).
[1] Both authors equally contributed.

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patients, particularly in prefrontal cortices (Teicher et al., 2000; Castellanos et al., 2002; Sowell et al., 2003; Durston et al., 2004), as well as enlargement of the hippocampus (Plessen et al., 2006).

The inherently complex, time-evolving behaviour of neural processes in the brain can be studied using non-linear dynamics, which investigates the complex emergent phenomena underlying dynamical chaotic systems. Many non-linear measures have been successfully employed in electroencephalograph (EEG) time-series analyses, extracting meaningful information about neurophysiological processes in the brain that could not otherwise be obtained using linear analysis (Babloyantz et al., 1985; Theiler and Rapp, 1996; Stam, 2005). For example, the correlation dimension (D2) (which estimates the degree of freedom of neural processes) and the largest Lyapunov exponent (which quantifies the sensitivity of the time series to initial conditions) have been used in the analysis of EEG time-series data to identify differences in neural processing in psychiatric patients and healthy subjects (Jeong, 2004). When used to analyse EEG data, these methods can improve our understanding of the pathophysiology of ADHD (Heinrich et al., 1999, 2001). Among many possible non-linear dynamics measures, the approximate entropy (ApEn) is particularly useful for short, noisy time series because it is capable of providing a robust, model-independent, information-theoretic estimation of dynamical complexity (Pincus, 1991, 1995). Prior studies have shown that EEG-based ApEn can be a sensitive discriminator of various neurophysiological states or conditions such as sleep, anaesthesia, epilepsy, depression and Alzheimer's disease (Radhakrishnan and Gangadhar, 1998; Hornero et al., 1999; Bruhn et al., 2000; Levy et al., 2003; Abasolo et al., 2005; Burioka et al., 2005a,b). According to previous studies, the ApEn measures the complexity of the EEG and may indicate the degree of arousal (Stam, 2005). To our knowledge, no previous studies have used the ApEn to study the dynamic complexity of EEGs in ADHD patients. We believe this novel approach to EEG analysis may provide an integrative understanding of ADHD.

We used ApEn to study EEG complexity in adolescent boys with ADHD and in age- and sex-matched healthy subjects while the subjects were at rest and during a continuous performance test (CPT). Recent studies have proposed a conceptual framework that links reduced EEG complexity to an increased degree of dysfunction (Stam, 2005; Pincus, 2006). Therefore, we hypothesised that the complexity of the EEG time series in ADHD adolescents would be altered over frontal regions relative to healthy subjects. In addition, we expected these changes to become more pronounced during the performance of the CPT because it assesses attentional control and executive functions that are not required in the resting condition. We thus compared ApEn values between the ADHD and healthy groups in each condition and used surrogate data to determine whether the complexity of the EEGs is generated by a non-linear dynamical process. Finally, we analysed the power spectra of the EEGs in both groups because previous studies have reported abnormal profiles of EEG power spectra in ADHD patients (Abasolo et al., 2005; Pincus, 2006; Papadelis et al., 2007). Whether or not the ApEn and power spectra reveal similar (or complementary) features in the EEGs of ADHD patients is a critical issue because the association between ApEn and other general time-series characteristics is currently unknown (Abasolo et al., 2005; Pincus, 2006; Papadelis et al., 2007).

2. Methods

2.1. Subjects

The subject group was composed of 11 ADHD adolescents between 16 and 17 years of age (mean age = 16.55 ± 0.52 years) and 12 age- and sex-matched healthy subjects (16.75 ± 0.45 years). All participants were first-year students at Hwahong High School in Suwon City, a mid-sized city located in the southern part of Seoul, South Korea. We explained the purpose of the study to all 298 first-grade male students at the school and distributed the Brown Attention-Deficit Disorder Scale (BADDS) (Brown, 1996). Subjects in the ADHD group scored in the highest 10th percentile (>75) on BADDS (30 students met this criterion), and control subjects scored in the lowest 30th percentile on BADDS (30 subjects). Subjects were excluded if their history included a neurological disorder, a brain injury, a major medical illness, mental retardation, a learning disability, psychiatric treatment, substance abuse or the use of psychotropic medication, including stimulants. A clinical diagnostic evaluation was performed on those who agreed to participate. To establish an ADHD diagnosis, the ADHD supplement section of the Kiddie-schedule for affective disorders and schizophrenia-present and lifetime version-Korean version (K-SADS-PL) was administered in person to participants and via telephone to their parents (Kim et al., 2004). The 11 ADHD patients included three with the predominantly inattentive subtype, one with the predominantly hyperactive-impulsive subtype and seven with combined-type ADHD. None of the 12 controls fulfilled the diagnostic criteria for ADHD. The parents of all children provided written informed consent for their child to participate in the study and the children too provided written assent. The study was approved by the Institutional Review Board of the Catholic University of Korea, St. Mary's Hospital.

The Korean version of the ADHD rating scale (K-ARS) for parents and teachers was used to rate the severity of ADHD symptoms (So et al., 2002). It indicates 18 symptoms of ADHD based on the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, third revision (DSM-IV-TR) diagnostic criteria; nine questions measure attentional problems and nine more measure hyperactive-impulsive problems (full range of the scale = 0–54) (DuPual et al., 1998). Intelligence quotient (IQ) was also estimated using the Korean intelligence test-primary (KIT-P), an assessment of IQ that has been standardised using a large sample of Korean high school students (Korean Institute for Research in the Behavioral Sciences, 1996). Finally, academic performance was defined as the participant's percentile ranking among other students in the same grade.

2.2. EEG recording

The EEG data from ADHD and healthy subjects were recorded with a sampling frequency of 250 Hz; subjects were in an eyes-open, resting condition and performed an auditory version of the CPT-A. This task assesses attention and motor inhibitory control, requiring the subject to respond to only 1 of 10 possible stimuli (single digits ranging from 0 to 9). The task measures omission and commission errors as well as correct responses. EEG recording was performed for nine min immediately following the administration of the CPT-A. The sequence in which target and non-target stimuli were presented was determined randomly. The inter-stimulus interval was 800 ms, and the stimulus duration was 200 ms. There were 135 target stimuli and 540 non-target stimuli.

EEG recordings were collected for at least 2 min in each condition. EEG data were obtained from 19 gold-cup scalp electrodes placed according to the international 10–20 system (Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz and Pz). A Neuroscan SynAmps 32-channel amplifier was used for data acquisition. EEG segments containing noise from swallowing, sweating, eye movements (detected with electrooculography) or body movements (detected using electromyography) were excluded from the analysis. All EEG data were processed using a digital Butterworth IIR band-pass filter with cut-off frequencies of 1 and 50 Hz for the eyes-open resting condition; the cut-off frequencies for the CPT-A condition were 3 and 50 Hz to reduce movement artefacts

that only occurred during the CPT-A condition. We selected 20 s (5000 data points) of noise-free recording through a visual inspection of the EEGs from all channels.

2.3. Approximate entropy

ApEn is an index that quantifies the irregularity or complexity of a dynamical system. It is particularly effective with short and noisy time-series data. ApEn measures the logarithm of the frequency with which neighbourhoods of temporal patterns of length m within a certain distance r in phase space (see ahead) remain close together ($<r$) for patterns that are augmented by one time point (i.e., for patterns of length $m+1$). Thus, smaller values of ApEn imply stronger regularity or persistence in a time series. Conversely, larger values of ApEn signify greater fluctuation or irregularity in a time series.

ApEn is computed from the correlation integral $C_i^m(r)$, which represents the number of points within a distance r from the ith point of the time series when the signal is embedded in an m-dimensional space, that is, when embedded in a phase space with embedding dimension m:

$$C_i^m(r) = (N-(m-1)\tau)^{-1}\sum_{j=1}^{N-(m-1)\tau}\Theta(r-|X_i-X_j|), \quad (1)$$

where $\Theta(t)$ is the Heaviside function (if $t \geqslant 0$, $\Theta(t)$; if $t<0$, $\Theta(t)=0$) and X_i and X_j are vectors constructed from the time series $[x(1),x(2),\ldots,x(N)]$ as

$$\begin{aligned} X_i &= \{x(i), x(i+\tau), \ldots, x(i+(m-1)\tau)\} \\ X_j &= \{x(j), x(j+\tau), \ldots, x(j+(m-1)\tau)\}, \\ & \quad i,j = 1,2,\ldots,N-(m-1)\tau, \end{aligned} \quad (2)$$

where τ is the time lag at which the temporal correlation between consecutive samples becomes negligible. These two vectors represent size-m vectors (or temporal patterns) of x values at regular intervals, beginning with the ith and jth points, respectively. ApEn is defined as

$$\mathrm{ApEn}(m,r) = \Phi^m(r) - \Phi^{m+1}(r), \quad (3)$$

where $\Phi^m(r) = (N-(m-1)\tau)^{-1}\sum_{i=1}^{N-(m-1)\tau}\ln C_i^m(r)$.

The time delay τ is usually estimated as the first local minimum of the average mutual information, a construct that measures the linear and non-linear dependence between two variables, which in this case are the measurements $x(t)$ and $x(t+T)$.

Two input variables, m and r, should be fixed to compute ApEn; m is the relative length of the runs, and r can be effectively considered a filter. Here, we selected $m=3$ and $r=20\%$ of the standard deviation (SD) of the EEGs as suitable values; these values are based on a previous study showing their validity for estimating ApEn (Abasolo et al., 2005).

2.4. Surrogate data analysis

The purpose of surrogate data analysis is to test for the presence of non-linear deterministic dynamics in the original time series. Surrogate data are a randomly shuffled sequence of the original data such that they have the same histogram and an identical power spectrum as the original data; however, any non-linear deterministic structure present in the original data is destroyed. Indices of non-linear dynamics, including ApEn, are computed for several surrogate data series and their values are compared with the value computed for the original data. The absence of a significant difference between the values for the original and the surrogate data is interpreted as evidence that the original series derives from a linear or stochastic process. On the other hand, a significant difference between the values for the original and the surrogate data is evidence for the presence of non-linear deterministic dynamics in the original signal (Hegger et al., 1999; Schreiber and Schmitz, 2000).

To generate surrogate data, we randomly shuffled data using the TISEAN package method; 20 surrogate data sets were generated to match the original signal for each electrode recording. Let ApEn(D) be the ApEn of the original data, and let ApEn(S) and SD(ApEn(S)) be the mean and SD values of the ApEn values for the 20 surrogate data, respectively. A measure of statistical significance σ was computed as follows:

$$\sigma = |\mathrm{ApEn}(D) - \mathrm{ApEn}(S)|\mathrm{SD}(\mathrm{ApEn}(S)). \quad (4)$$

This statistic represents the distance (in number of SDs (σ)) of ApEn(D) from the mean of SD(ApEn(S)). It follows a Student's t-test distribution with 19 degrees of freedom. At the 0.95 level of significance, the critical value of t is 2.093. Accordingly, when σ is larger than 2.093, the null hypothesis is rejected at the 5% probability level, and the original data are considered to contain non-linear dynamical features.

2.5. Spectral analysis

The power spectral density of the EEGs was estimated using a fast Fourier transform implemented using MATLAB® (MathWorks, Natick, MA, USA). The powers were integrated in the following frequency bands from which the relative power spectra were calculated: theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz) and gamma (30–45 Hz).

2.6. Statistical analysis

For demographic data, a two-sample t-test was used after Levene's test for equality of variances. Corrections for the inequality of variances were performed whenever necessary. To test our *a priori* hypothesis, a mixed-design, two-way analysis of variance (ANOVA) for repeated measures was used at each channel with diagnosis and condition as the between-subjects and the within-subjects factors, respectively. Because there were only two within-subjects levels, the sphericity was always met. Thus, we compared the results of multivariate ANOVA to a multiple univariate ANOVA for six measures including ApEn, σ and four relative powers. As there was no difference between the analyses, we adopted the multiple univariate ANOVA.

As a *post hoc* analysis, we compared the mean ApEn of the ADHD patients with that of the healthy subjects in each condition; we did not perform this comparison between the conditions because EEG data were pre-processed differently in each condition. The analysis consisted of a Levene's test for equality of variances followed by a two-sample t-test. The same statistical test was applied to compare the means of σ from the surrogate data analysis with the relative power of the frequency bands between groups in each condition.

For all statistical tests except *post hoc* analyses, the alpha value was set at 0.05. For *post hoc* analyses, the alpha value was set at 0.01 because a strict Bonferroni correction for multiple comparisons would overestimate the number of independent statistical tests and increase the probability of type II (false-negative) errors. The 0.01 value was intended to balance type I and type II errors (for details, see the Supplementary Material). All statistical tests were two-sided and performed using the Statistical Package for the Social Sciences (SPSS 13.0). A more detailed explanation of the correction for multiple tests is provided in the Supplementary Material.

3. Results

3.1. Subjects

The mean (±SD) IQ of the ADHD subjects was 105.55 (±16.84) and the mean of the healthy subjects was 118.00 (±14.76). There were no significant differences between the two groups in age or IQ. The academic performance rankings were significantly higher for the healthy subjects (25.86 ± 26.30) than ADHD ones (85.14 ± 21.44) ($p < 0.01$). During the CPT-A, the ADHD subjects had significantly more commission errors (4.70 ± 4.06 vs. 1.33 ± 1.61; $p < 0.05$), omission errors (8.60 ± 2.95 vs. 3.33 ± 2.31; $p < 0.01$) and fewer correct answers (126.40 ± 2.95 vs. 131.67 ± 2.31; $p < 0.01$) than the healthy subjects. In addition, the ADHD subjects had significantly higher K-ARS scores from parents (36.73 ± 5.20 vs. 5.58 ± 5.89; $p < 0.01$) and teachers (44.73 ± 6.90 vs. 2.25 ± 1.71; $p < 0.01$) than the healthy subjects (Table 1).

3.2. Analysis of approximate entropy

The mixed-measures ANOVA revealed a significant between-subjects main effect of the factor 'diagnosis' at F8 ($F(1,21) = 4.44$, $p = 0.047$) as well as a significant within-subjects main effect of 'condition' at all channels. The p values were smaller than 0.01 for all channels except F4, C3, P3 and T4. A significant interaction between diagnosis and condition was found at 10 channels including Fp1 ($F(1,21) = 4.37$, $p = 0.049$), Fp2 ($F(1,21) = 7.87$, $p = 0.011$), C4 ($F(1,21) = 6.30$, $p = 0.020$), O2 ($F(1,21) = 5.30$, $p = 0.032$), F7 ($F(1,21) = 6.15$, $p = 0.022$), F8 ($F(1,21) = 6.32$, $p = 0.020$), T5 ($F(1,21) = 5.70$, $p = 0.026$), T6 ($F(1,21) = 4.44$, $p = 0.047$), Cz ($F(1,21) = 6.46$, $p = 0.019$) and Pz ($F(1,21) = 4.47$, $p = 0.047$).

In *post hoc* analyses, the mean ApEn values did not significantly differ between groups for any EEG channel when subjects were at rest with their eyes-open, indicating that the EEGs of the ADHD subjects were as complex as healthy subjects in the resting condition. While performing the CPT-A, however, the mean ApEn values of the ADHD subjects were lower than the controls over all 19 EEG channels, reaching statistical significance at channels Fp2 ($t(13.98) = -3.33$, $p = 0.005$) and F8 ($t(21) = -3.16$, $p = 0.005$). Thus, the EEG complexity of both groups increased during CPT-A, but this increase was much smaller in the ADHD subjects, particularly over the right frontal regions (Fig. 1 and Supplementary Table S1).

3.3. Surrogate data analysis

While performing the CPT-A and at rest, the values of σ in both groups for all EEG channels were larger than the critical value of the two-sided t-test (2.09352), indicating that the ApEn of the EEGs was likely derived from non-linear deterministic sources within the brain. In the related ANOVA, there was no significant between-subjects, within-subjects or interaction effect. Moreover, the values of σ for both the ADHD patients and controls did not significantly differ in any channel in either condition.

3.4. Spectral analysis

According to the ANOVA, there were significant between-subjects main effects (diagnosis) at C3 ($F(1,21) = 5.40$, $p = 0.030$), P3 ($F(1,21) = 4.49$, $p = 0.046$), F7 ($F(1,21) = 4.44$, $p = 0.047$), F8 ($F(1,21) = 11.17$, $p = 0.003$) and Fz ($F(1,21) = 6.62$, $p = 0.018$) for the theta band. All channels showed significant within-subjects effects (condition) but no significant interaction effect. For the alpha band, significant between-subjects effects were observed at F3 ($F(1,21) = 5.26$, $p = 0.032$), F4 ($F(1,21) = 8.06$, $p = 0.010$), C3 ($F(1,21) = 5.73$, $p = 0.025$), C4 ($F(1,21) = 6.29$, $p = 0.020$), P3 ($F(1,21) = 5.94$, $p = 0.024$), P4 ($F(1,21) = 5.27$, $p = 0.032$), F8 ($F(1,21) = 11.88$, $p = 0.002$), T4 ($F(1,21) = 12.07$, $p = 0.002$), Fz ($F(1,21) = 7.48$, $p = 0.012$), Cz ($F(1,21) = 5.10$, $p = 0.035$) and Pz ($F(1,21)$=4.56, $p = 0.045$). Tests of within-subjects factors revealed significant effects at all channels except O2, T4 and T5. There were significant interaction effects at Fp1 ($F(1,21) = 5.83$, $p = 0.025$), Fp2 ($F(1,21) = 5.14$, $p = 0.034$) or F8 ($F(1,21) = 4.35$, $p = 0.049$). In the case of the beta band, O1 ($F(1,21) = 5.89$, $p = 0.024$), T4 ($F(1,21) = 5.62$, $p = 0.027$) and T5 ($F(1,21) = 4.62$, $p = 0.043$) exhibited significant within-subjects effects and both F3 ($F(1,21) = 4.37$, $p = 0.049$) and C3 ($F(1,21) = 4.37$, $p = 0.049$) showed significant interaction effects. There were no significant between-subjects effects. For the gamma band, significant within-subjects effects were observed at six channels including Fp1 ($F(1,21) = 8.55$, $p = 0.008$), Fp2 ($F(1,21) = 5.76$, $p = 0.026$), O1 ($F(1,21) = 14.38$, $p = 0.001$), O2 ($F(1,21) = 12.46$, $p = 0.002$), T4 ($F(1,21) = 7.78$, $p = 0.011$) and T5 ($F(1,21) = 5.97$,$p = 0.024$). No significant between-subjects effect or interaction effect was found.

Post hoc analysis revealed that, in the eyes-open resting condition, ADHD subjects had more power in the theta band and less power in the alpha band of their EEG recordings; there were significant differences between groups in theta power at P3 ($t(14.62) = 3.112$, $p = 0.007$) and in alpha power at T4 ($t(20.353) = -3.118$, $p = 0.005$). The groups did not differ significantly in the power of their beta or gamma bands. While performing the CPT-A, theta-band power was significantly greater in ADHD subjects at F8 ($t(20.69) = 3.562$, $p = 0.002$) and alpha power was significantly reduced at Fp2 ($t(21) = -2.42$, $p = 0.007$) and F8 ($t(21) = -3.76$, $p = 0.001$). The groups did not differ significantly in beta or gamma power (Fig. 2). Thus, the regions that showed significant slowing changed from P3 and T4 to Fp2 and F8. Detailed

Table 1
Demographics of the ADHD patients and the healthy subjects.

Characteristic	ADHD patients ($N = 11$)		Healthy subjects ($N = 12$)		Statistical analysis		
	Mean	SD	Mean	SD	T	df	p
Age (years)	16.55	0.52	16.75	0.45	−1.01	21.00	0.33
IQ	105.55	16.84	118	14.76	−1.89	21.00	0.07
Academic performance (%)	85.14	21.44	20.62	19.47	7.57	21.00	<0.001
CPT-A performance[a]							
Correct responses	126.4	2.95	131.64	2.42	−4.46	19.00	<0.001
Omission errors	8.6	2.95	3.36	2.42	4.46	19.00	<0.001
Commission errors	4.7	4.06	1.27	1.68	2.58	19.00	<0.02
K-ARS scores							
Parents	36.73	5.2	5.58	5.89	13.40	21.00	<0.001
Teachers	44.73	6.9	2.25	1.71	19.86[b]	11.13	<0.001

[a] Data are missing for two ADHD patients.
[b] Equal variances are not assumed.

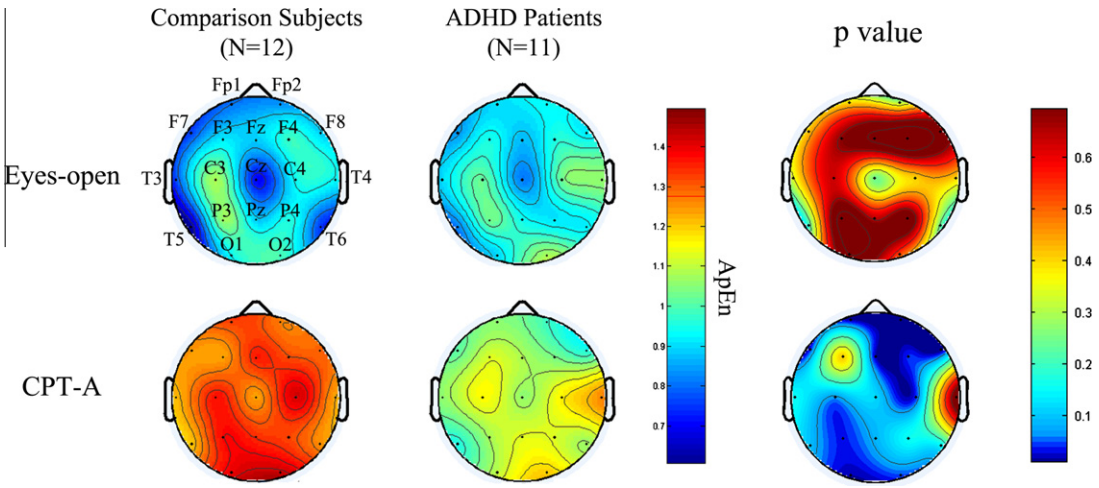

Fig. 1. Topographic comparisons of ADHD subjects and healthy subjects using the ApEn calculated from EEGs recorded during an eyes-open resting condition and during an auditory attentional task.

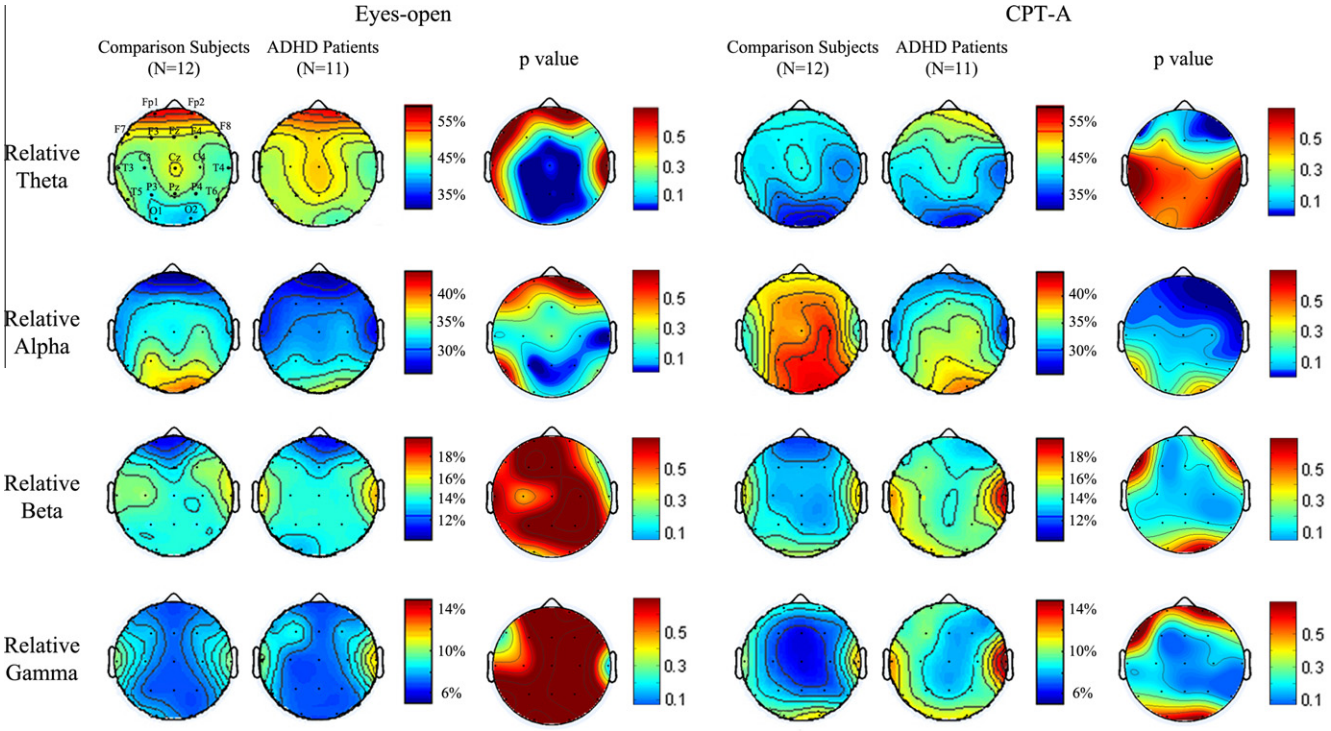

Fig. 2. Topographic comparisons of ADHD patients and healthy subjects for relative theta, alpha, beta, and gamma of EEGs recorded during an eyes-open resting condition and during an auditory attentional task.

information about the spectral analysis of the EEG is provided in the Supplementary Material (Supplementary Tables S2–S5).

Linear regression analysis was performed to investigate whether the EEG abnormalities in ADHD patients were associated with cognitive performance. In ADHD patients, we found no correlation between linear (spectral band power) or non-linear (ApEn) EEG measures and CPT cognitive performance measures, including correct responses and omission/commission errors.

4. Discussion

This study aimed to provide neurophysiological evidence for associations between abnormalities in the complexity of cortical activation patterns, frontal dysfunctions and impaired executive functions and attention. We looked for differences in power spectrum and complexity between EEGs obtained from healthy subjects and those obtained from adolescents with ADHD, both while they were at rest and during performance of a cognitive task. The mean ApEn of the ADHD patients was significantly lower than the healthy subjects over the right frontal region during the performance of the cognitive task but not at rest. Surrogate data analysis revealed that the complex EEG patterns largely arose from non-linear dynamical processes. In addition, the spectral analysis indicated that, in ADHD patients at rest, the brain regions that exhibited relatively slow rhythms were the parieto-temporal regions (P3 and T4); however, these rhythms were found in the frontal regions (Fp2 and F8) while performing the task. Taken together, these findings suggest that the reduced cognitive performance on the CPT in ADHD adolescents is associated with impaired cortical

information processing, as indicated by the lower complexity of the EEG. This is the first investigation to analyse EEG recordings from medication-naive ADHD subjects and healthy subjects using a non-linear measure of brain activity.

However, this study had several limitations, including a small sample size and reduced statistical power. The small sample size also precluded an investigation of the complexity of the EEGs among different ADHD subtypes. Furthermore, co-morbidities with other psychiatric disorders such as anxiety disorders, depression and tic-borne illnesses were not taken into account in our study. The relatively high alpha level produced by our statistical analysis also suggests that further investigation with a larger number of subjects is required. However, it is likely that the significant differences in our results are not associated with type I errors because the differences in both the ApEn and the power spectra between the two groups were considerably clustered (for details, see the Supplementary Material). In addition, this study included only boys to reduce the heterogeneity of the sample. Because we examined only boys, we were unable to study sex differences and this prevented us from drawing a general conclusion. Finally, the use of gold electrodes with our designated band-pass filter may have lead to distortions in the EEG patterns, a problem exacerbated by the altered properties of high-pass filtering (Tallgren et al., 2005).

The application of non-linear dynamical analysis to EEG recordings has provided valuable information about cortical dysfunctions in neuropsychiatric disorders that cannot be assessed by linear analysis. Neural processes, from single neurons to neural circuits and neural brain systems, are inherently non-linear (Babloyantz et al., 1985; Jeong, 2004; Stam, 2005). While power spectral analysis of EEGs simply assumes the stationarity of the underlying system, non-linear dynamical analysis assumes that statistical non-stationarity may be an inherent property of neural signals. Thus, non-linear analyses can detect subtle changes in brain dynamics and provide novel interpretations of complex neural dynamics that cannot be detected by linear analyses (Pincus, 2006).

Non-linear dynamical analysis of EEGs quantifies the complexity of EEG recordings using the D2, the ApEn and the first positive Lyapunov exponent. The ApEn measure is particularly relevant to the present study because it estimates the complexity of a time series based on the unpredictability of the trajectories in the phase space; this unpredictability reflects the complexity of the cortical dynamics underlying EEG recordings. ApEn displays good reproducibility in short, noisy recordings with a small number of data points in the time series and can demarcate subtle changes in complicated activation patterns in the EEG (Pincus, 1991, 1995; Abasolo et al., 2005; Papadelis et al., 2007). This capability probably derives from the relative loosening of a constant set of frequencies that occurs when assessing the degree of recurrent pattern matching (Pincus and Singer, 1996; Pincus, 2006). When compared with other non-linear measures such as the D2 or largest Lyapunov exponent, ApEn has the advantage of not relying on a hypothetical model such as a deterministic dynamical system, a pure stochastic system or a composite system.

Spectral entropy and wavelet entropy measure the complexity of a time series and they are frequently harnessed to quantify the degree of disorder or uncertainty (i.e., the amount of information provided according to information theory (Powell and Percival, 1979; Quiroga et al., 2001; Rosso et al., 2001). In EEG applications, it has been proposed that these measures could reveal the level of EEG desynchronisation or the interactive dependencies among multiple frequency components (Yordanova et al., 2002, 2003). Furthermore, higher values of entropy are implicated in neuronal coupling and enhanced connectivity during cognitive processing (Inouye et al., 1991, 1993). Although all entropy measures are based on information theory, ApEn analyses the complexity and irregularity in the phase space rather than the time–frequency domain. In other words, ApEn is distinct from other measures because it is a gradient of the correlation integrals based on an increase in the embedding dimension by one rather than a simple correlation integral at a specific embedding dimension (see Eq. (4)). Hence, a direct investigation of the relation between traditional entropy and ApEn is necessary to shed light on the fundamental characteristics of signals that produce an increase or decrease in complexity measures.

Within-subjects ANOVA revealed that transitioning from the resting condition to the CPT-A was statistically significant in most channels for ApEn, theta and alpha power. Although the groups had similar ApEn values in all electrodes while at rest, the ADHD group had significantly lower values than the controls over the right frontal regions during the performance of the attention-demanding task. This finding suggests that the reduced dynamical complexity found in ADHD patients during the CPT-A reflects a relative inability to deal with the cognitive demands of flexible information processing, a theory that has been proposed in a previous study (DeFrance et al., 1996). Previous studies have associated the conceptual paradigm of reduced EEG complexity with elevated dysfunction (Nandrino et al., 1994; Bruhn et al., 2000; Levy et al., 2003; Abasolo et al., 2005; Burioka et al., 2005a; Papadelis et al., 2007). However, reduced ApEn values (i.e., low complexity) may not be directly associated with simple hypoactivation of the underlying system, but instead may reveal easily recognisable features of serial patterns within the system. The complexity of cortical dynamics arises from integrating the activities of functionally segregated neuronal groups and also incoming stimuli with ongoing activity. Therefore, the decoupling and isolation of the underlying system from external influences may be a source of the lower ApEn values, a theory validated by representational mathematical models (Pincus, 2006; Papadelis et al., 2007) and consistent with previous studies (Inouye et al., 1991, 1993).

Several previous studies have suggested that the symptoms of ADHD derive from dysfunction in the neural systems associated with sustained attention and motor inhibition (Barry et al., 2003; Biederman, 2005; di Michele et al., 2005). Many cognitive tasks, such as the CPT, Stroop, go/no-go and stop-signal tasks, place demands on these neural systems and reveal group differences in experimental settings. We have provided evidence of a deficit in the allocation of neural resources in the frontal cortices, an allocation required to move from a resting state to one requiring sustained attention and motor control. Candidate neural substrates for this deficiency in the complexity and coordinated activation of neural activity include the cortico-striatal–thalamo-cortical and septal–hippocampal circuits (di Michele et al., 2005; Plessen et al., 2006). In particular, the hypoactivity of prefrontal cortices may derive from reduced dopaminergic transmission from the midbrain, disturbances in the functioning of the basal ganglia or other subcortical nuclei or anatomical and functional disturbances located primarily within the frontal cortices, as suggested by numerous neuroimaging studies (DeFrance et al., 1996; Bush et al., 1999; Rubia et al., 1999; Teicher et al., 2000; Rubia et al., 2005; Silk et al., 2005; Vaidya et al., 2005; Pliszka et al., 2006). The interconnected frontal network that encompasses the anterior cingulate cortex and the dorsolateral prefrontal cortex is implicated in the detection of error and the inhibitory control of irrelevant stimuli. Hence, the low ApEn values at Fp2 and F8 in ADHD patients during the CPT-A suggest that the decoupling and segregation of the dorsolateral prefrontal cortex and the anterior cingulate cortex from related brain regions is involved in anomalous self-regulation, and consequently in compromised cognitive performance as well. Considering the interconnectivity of the neural components in the fronto-striatal network, this finding raises the possibility that the lack of integration with external feedback in the prefrontal cortex results in ADHD-related behavioural dysfunc-

tions (Casey and Durston, 2006; Plessen et al., 2006). However, because the relation between ApEn and the dynamical time-series properties that produce certain ApEn values is currently unknown, any mechanistic interpretation of the altered ApEn values in terms of their neurophysiological underpinnings is limited.

In addition, the surrogate data analyses suggested that the ApEn values were largely derived from non-linear deterministic processes and not simply linear or stochastic processes; however, caution is required when generalising these findings to other time series. Furthermore, the σ values of groups did not significantly differ. This similarity suggests that the degree of non-linear determinism, which is measured by σ values, is indistinguishable between ADHD patients and healthy subjects.

Analyses of EEG power spectra may complement ApEn complexity analyses because they isolate different aspects of physiological processes or localised information within frequency bands (Pincus, 2006). Methodologically, it is rare to compare ApEn and power spectra directly. Based on a few previous studies, a reduction in the ApEn of ADHD patients during a CPT-A may be compatible with a slowing EEG (Abasolo et al., 2005; Papadelis et al., 2007). In our study, ADHD subjects were unable to generate a decrease in theta or an increase in alpha power over their frontal cortices during this attentional task, behaviours that were exhibited by the controls; this finding is consistent with previous electrophysiological studies (Mann et al., 1992; DeFrance et al., 1996). These results suggest that patients with ADHD have an impaired capacity to generate the requisite neural resources for top-down attentional processing, particularly within the frontal cortices. The reduced alpha power at P3 and T4 at rest may reflect ADHD-related structural and/or metabolic abnormalities (Teicher et al., 2000; Sowell et al., 2003). However, recent studies have reported that the temporo-parietal regions that are impaired in ADHD exhibited diminished activation during the performance of the switch task, Simon task and Stroop task (DeFrance et al., 1996; Tamm et al., 2006). This discrepancy may result from the CPT used in the present study which does not test cognitive interference inhibition, set shifting or cognitive flexibility. Furthermore, the regions that were significantly slowed in the ADHD patients changed from the right temporal and left parietal regions during the eyes-open resting condition to the right prefrontal and frontal regions during performance of the CPT-A; this switch demonstrates that the abnormalities in cortical functioning dynamics are task-dependent (Swartwood et al., 2003; Murias et al., 2006).

It has been proposed that there is a one-to-one relationship between the specific neural network (possibly the cortico-striatal–thalamo-cortical and/or septal-hippocampal circuits) and the alpha- or theta-band generator (di Michele et al., 2005). However, the results from spectral analysis in our study suggest that complex dynamical interactions between network components in each state produce the specific frequency component variation, rather than one-to-one associations between the alpha- or theta-band generator and specific anatomical structures.

Many previous studies of ADHD have revealed that both environmental factors and genetic factors play important roles in the onset of the disease (Faraone et al., 2005). These factors produce complex effects such that ADHD exhibits both phenotypic heterogeneity and co-morbidity. Therefore, it is still difficult to reach definitive conclusions about the pathophysiology, diagnosis or treatment of ADHD. Rather than the current strategy of diagnosing the disorder, selecting treatment and closely monitoring the effects of medication – effects that are behaviourally determined and thus often ambiguous – the development of more objective strategies using quantitative EEGs would greatly enhance the validity and reliability of all aspects of diagnosis and treatment (Clarke et al., 2002; Chabot et al., 2005). As ADHD likely results from a central nervous system (CNS) dysfunction and EEG provides a direct measure of cortical function, EEG analysis may be a useful tool for assessing this disorder. A number of researchers have investigated the use of EEG in the clinical treatment of ADHD and reported that it may be useful because it diagnoses ADHD patients with a high degree of accuracy (Chabot and Serfontein, 1996; Monastra et al., 1999, 2001; Chabot et al., 2005).

Furthermore, it is possible that EEG analysis can reveal specific aspects of abnormal cognitive information processing in ADHD. As brain dysfunction is more pronounced during cognitive tasks such as the CPT-A, EEGs recorded during cognitive tasks may help to significantly improve the sensitivity and specificity of diagnosis, treatment selection and/or the monitoring of medication. The task-dependent effects revealed in this study suggest that further assessments of neural dynamics are required, for example, measurements recorded during the administration of a more diverse set of cognitive tasks such as the go/no-go, stop-signal or N-back tasks. Therefore, we suggest that ApEn and other non-linear measures may increase our ability to diagnose ADHD.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.clinph.2010.04.007.

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