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Research Report

EEG PHENOTYPES PREDICT TREATMENT OUTCOME TO STIMULANTS IN CHILDREN WITH ADHD

MARTIJN ARNS*

Brainclinics Diagnostics B.V./Brainclinics Treatment B.V.
Bijleveldsingel 34, 6524 AD Nijmegen, The Netherlands
martijn@brainclinics.com
www.brainclinics.com

JAY GUNKELMAN

Q-Pro Worldwide
Crockett, California, USA

MARINUS BRETELER

Radboud University Nijmegen/EEG Resource Institute
Nijmegen, The Netherlands

DESIRÉE SPRONK

Brainclinics Diagnostics B.V.
Nijmegen, The Netherlands

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This study demonstrates that the EEG phenotypes as described by Johnstone, Gunkelman & Lunt are identifiable EEG patterns with good inter-rater reliability. Furthermore, it was also demonstrated that these EEG phenotypes occurred in both ADHD subjects as well as healthy control subjects. The Frontal Slow and Slowed Alpha Peak Frequency and the Low Voltage EEG phenotype discriminated ADHD subjects best from controls (however the difference was not significant). The Frontal Slow group responded to a stimulant with a clinically relevant decreased number of false negative errors on the CPT. The Frontal Slow and Slowed Alpha Peak Frequency phenotypes have different etiologies as evidenced by the treatment response to stimulants. In previous research Slowed Alpha Peak Frequency has most likely erroneously shown up as a frontal theta sub-group. This implies that future research employing EEG measures in ADHD should avoid using traditional frequency bands, but dissociate Slowed Alpha Peak Frequency from frontal theta by taking the individual alpha peak frequency into account. Furthermore, the divergence from normal of the frequency bands pertaining to the various phenotypes is greater in the clinical group than in the controls. Investigating EEG phenotypes provides a promising new way to

*Corresponding author.

approach EEG data, explaining much of the variance in EEGs and thereby potentially leading to more specific prospective treatment outcomes.

Keywords: ADHD; EEG phenotypes; QEEG; medication response; personalized medicine; frontal slow; Slow Alpha Peak Frequency.

1. Introduction

Neurophysiological studies in ADHD based on group data have shown a consistent pattern for ADHD. Most of these studies have found increased slow (theta) [17, 23, 3, 5, 6, 21, 22] and decreased fast (beta) EEG activity in resting conditions [17, 6, 23, 21, 22]. Minor differences have been found in several studies between the DSM-IV TR (DSM) ADHD and ADD diagnosis, mainly showing a less severe pattern of deviation in the ADD group as compared to the ADHD group [3, 1].

Figure 1 shows an example from the Brain Resource International Database [BRID] based on 275 non-medicated ADHD patients. The averaged data shows increased theta and decreased beta with a frontocentral localization.

However, a more variable profile is evident in the individual dataset (see Fig. 2). Figure 2 shows the individual dataset of 36 ADHD patients from the BRID. This individual dataset constitutes the average data presented in Fig. 1. The quantitative EEG's (qEEGs) of these patients were compared to age and sex-matched controls from the BRID. These data show that while 47% of the ADHD patients showed increased EEG activity in the theta frequency band, only 6% showed a decrease in beta. In fact 22% showed increased beta. These data suggest a large variability in qEEG profiles within a "behaviorally homogenous population" of children with ADHD. This was also pointed out by Barry *et al.* [1] stating that "*. . .a limitation of most EEG studies is that they assume their clinical groups are homogenous. If this*

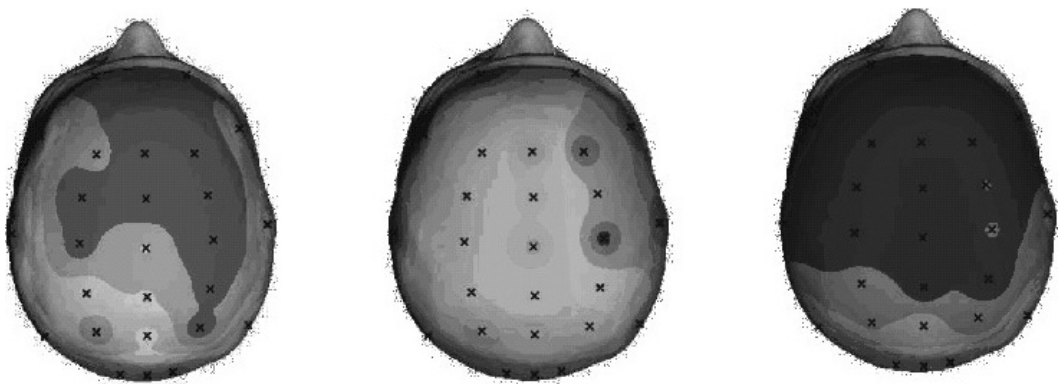

Fig. 1. The average EEG activity of 275 ADHD patients compared to a matched control group. The left figure shows the increased theta ($p < 0.0001$), the figure in the middle shows decreased absolute beta ($p < 0.0001$) while the right figure is the relative decrease in beta power ($p < 0.0001$). Note the frontocentral localization.

	theta	alpha	beta		theta	alpha	beta
2014	↑	↑		3824			
2193	↑		↑	3857	↑	↑	
2306		↑		4061			
2395		→		4151	↑		↑
2418		↑		4162	↑	↑	↑
2520		↑		4409	↑		
2553	↑	←		4397		→	↓
2575				4465			
2744	↑	←↓	↑	4476		↑	
2777	↑			4487	↑	→↑	↑
3149		↑		4926		↑	
3251	↑	↑		5163		→	↑
3330	↑	↑		5118	↑	↑	
3521				5208		↑	
3532				5400	↑	↑	
3576	↑	←↑		5411		↑	↑
3813		↑		5422	↑	←	↓
3846	↑	↑	↑	5332		←	

Fig. 2. Data from 36 individual patients with ADHD (4-digit ID codes) from the same dataset as Fig. 1. Arrows up and down indicate increased or decreased power of the frequency band involved; arrows to the left and right indicate low and high alpha peak frequency respectively. Some subjects showed increased theta (47%), however only 6% of these subjects showed decreased beta, while 22% showed increased beta. These demonstrate the variability of individual data that is not reflected in group averages.

is not so, the reported group differences may not accurately reflect the nature of EEG deviance in individual children with AD/HD".

Several studies have investigated EEG defined sub-types in ADHD. Chabot and Serfontein [3] identified a sub-group with increased beta in about 13%. Clarke *et al.* [6, 8, 7] also reported an EEG sub-group with increased beta in ADHD that showed a slightly different behavioral profile (e.g., increased rate of temper tantrums and moody behavior) that was present in about 20% of children. This seems in line with the above observation of increased beta in 22% of ADHD children. Furthermore, both Chabot and Serfontein [3] and Clarke *et al.* [9] report on different EEG clusters in ADHD where besides the excess beta sub-type, a "cortical-hypoarousal" sub-type and a "maturational-lag" sub-type could be further identified (for an overview see [1]).

The fact that Ritalin does not have a clinically significant effect in 20–40% of patients with ADHD [29, 14] could be related to the different EEG sub-types in

ADHD reported above (assuming that some sub-types respond better to medication than others). Several studies have shown that ADHD children with these EEG sub-types have a more favorable outcome when being prescribed stimulant drugs. For example, Ritalin responders are characterized by increased frontal slow activity (delta and theta [10, 26, 28]). However, the increased beta group described above were also found to respond favorably to stimulant medication [7] (this finding was also reported by Hermens *et al.* [18]). Chabot *et al.* [4] found that both alpha and beta excess were predictors of behavioral improvement, whereas excess theta was predictive of both positive and negative treatment responses, with the negative treatment responses characterized by more marked differences in theta. Suffin and Emory [28] assessed a group of attentionally disturbed patients. The authors found that stimulants were efficacious with the theta clusters (excess frontal theta), while antidepressants were efficacious with the alpha clusters (excess frontal alpha), regardless of whether the individuals were categorized as ADHD or depressed using DSM-IV. Similar findings were also published by Simeon *et al.* [27] who found that children with ADHD, who had increased alpha EEG power, responded well to the atypical antidepressant Buproprion.

Most of the studies mentioned above have investigated relative EEG power measures which can sometimes be misrepresentative. For example, when there is excess absolute theta, the relative power of other bands will be decreased. Furthermore, in all studies traditional EEG frequency bands, such as theta, alpha and beta, were investigated. Based on the work by Klimesch [20] on individual alpha frequency and the fact that the individual alpha peak frequency matures during development up to the age of ten years, it is conceivable that in some cases where studies referred to "excess theta" they might have been referring to "excess alpha" due to a slowing of the individual alpha peak frequency. This is especially true for ADHD/ADD studies where children in the range of 6 to 18 years are often studied. Furthermore, Clarke *et al.* [8] and Johnstone *et al.* [19] describe "beta spindles" which may be qualitatively different from a more generalized increase in beta [24].

In a paper recently published on EEG phenotypes Johnstone *et al.* [19] provide an interesting framework to perform individual classifications of EEG. The aim of this study is to further investigate the concept of EEG phenotypes and their predictive value for treatment outcome using stimulant medication in ADHD. In addition, we also investigated arousal measures such as heart rate (HR) and heart rate variability (HRV) and their relation to these EEG phenotypes. These measures were included as the action mechanism of stimulants is believed to be via increasing arousal.

2. Method

2.1. *Subjects*

Data from 49 males with ADHD (mean age = 11.33; range = 6–17 years) and 49 control children matched for age, gender and years of education (mean age =

11.92; range = 7–18 years) were obtained from the BRID [13, 15]. Exclusion criteria included a personal or family history of an Axis 1 psychiatric disorder (other than ADHD), physical brain injury, neurological disorder, genetic disorder or other serious medical condition and/or a personal history of drug or alcohol addiction. All subjects were asked to refrain from drinking caffeine and smoking cigarettes for two hours before the study session; and all subjects and/or their guardians provided written informed consent to participate in the study, in accordance with National Health and Medical Research Council guidelines.

All ADHD participants were medication free (for at least 48 hours) at the time of assessment. All ADHD participants were referred by paediatricians and diagnosis was confirmed using a semi-structured interview based on DSM-IV criteria for ADHD and Connors Parent Rating Scales (T-scores 1.0 SD above the norm in either Inattentive or Hyperactive/Impulsivity indices). The mean scores and SD's for the ADHD group on these subscales were: Inattentive: mean = 8.00; SD = 0.19; Hyperactive/Impulsive: mean = 5.28; SD = 0.43 and Impulsive: mean = 1.91; SD = 0.20. Twenty two subjects met DSM-IV criteria for the "combined" sub-type of ADHD, 22 met the criteria for ADHD of the predominantly "inattentive" sub-type and two individuals met the criteria for ADHD of the predominantly "hyperactive-impulsive" sub-type. Data were missing for three participants.

2.2. *Procedure*

ADHD subjects were assessed on two separate occasions. In the first session all subjects were medication free (at least 48 hours). Of the 49 ADHD children, 30 subjects were medication naïve. In the second session (post-medication) all participants in the ADHD group had been taking a prescribed course of medication (38 Methylphenidate, 7 Dexamphetamine and 4 Strattera) for a period of at least four weeks. Participants were required to take their typical dose 60 minutes before the testing session commenced. During each session they were seated in a sound and light attenuated room, controlled at an ambient temperature of 24°C. Electroencephalographic and neuropsychological assessments were completed in the following order: EEG EO and EC, followed by the CPT task. Further details from these procedures can be obtained from our publications [13–15].

2.3. *Psychophysiological data acquisition*

EEG data were acquired from 26 channels: Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4, T3, C3, Cz, C4, T4, CP3, CPz, CP4, T5, P3, Pz, P4, T6, O1, Oz and O2 (Quickcap; NuAmps; 10–20 electrode international system). Data were referenced to averaged mastoids with a ground at Fpz. Horizontal eye-movements were recorded with electrodes placed 1.5 cm lateral to the outer canthus of each eye. Vertical eye movements were recorded with electrodes placed 3 mm above the middle of the left eyebrow and 1.5 cm below the middle of the left bottom eyelid. Skin resistance was

< 5 K Ohms and above 1 K Ohm for all electrodes. A continuous acquisition system was employed and EEG data were EOG corrected offline [16]. An additional ECG lead was placed on the arm. The sampling rate of all channels was 500 Hz. A low pass filter with attenuation of 40 dB per decade above 100 Hz was employed prior to digitization.

2.4. *Eyes open (EO) and eyes closed (EC) resting conditions*

Subjects were asked to rest quietly with their eyes open for the duration of the recording. They were informed that the task would last for 3 minutes. Following this, subjects were asked to rest quietly with their eyes closed for the duration of the task.

2.5. *Continuous performance test (CPT)*

Performance on the Continuous Performance Test was used as a measure of treatment effect and was assessed for the ADHD group both pre- and post-medication. Subjects were presented with a series of letters (B, C, D and G) on the computer screen for 20 msec, with an interstimulus interval of 2.5 sec. They were instructed to simultaneously press two buttons with each index finger, when the same letter appeared twice in a row. Speed and accuracy of response were equally stressed in the task instructions. There were 125 stimuli in total: 85 background letters and 20 pseudo-randomly presented target letters (i.e., repetitions of the previous letter). In addition to the letters, 20 distracter stimuli (black and white 1×1 cm checkerboards) were randomly interwoven with the letter stimuli. Subjects were instructed to ignore the "checkerboards". Subjects were told the task would take 8 minutes and were given a brief practice session to clarify the task instructions. Reliability and validity data for these tasks are reported elsewhere [5, 25, 31].

2.6. *Psychophysiological variables*

Average EEG power spectra were computed for 28 epochs during the eyes open and closed conditions. Each two minute epoch was divided into adjacent intervals of four seconds. Power spectral analysis was performed on each four second interval by first applying a Welch window to the data, and then performing a Fast Fourier Transform (FFT) on each epoch which was then averaged. Epochs were rejected if the signal at three or more sites exceeded 100 μV for that particular epoch. A low pass filter at 100 Hz was used. The Heart Rate (HR: beats per minute) and Heart Rate Variability (HRV: Standard Deviation of the HR) were obtained from an ECG lead at the wrist during EO and EC conditions.

2.7. *EEG phenotype rating*

For each of the 98 subjects, a full individual report was obtained with the EOG corrected [16] raw EEG for EO and EC condition. Furthermore, a Brain Resource

"Neurofeedback" report containing individual data compared to matched normative controls in the International Database was obtained. Data were first rated by the first author and subsequently by the second author. Rating was not blind with respect to diagnosis, so raters were aware of the subject's diagnosis, though both raters were blind to medication response. Subjects could be rated to have one or more of the EEG phenotypes. See Johnstone *et al.* [19] for an outline of all EEG phenotypes. A brief description of the EEG phenotypes and the exact definitions used in this study is provided below:

(1) "Normal EEG": the EEG could not be classified into any of the other EEG phenotypes. Therefore, this type is a normal EEG type showing neither abnormalities nor the presence of EEG phenotypes.
(2) Frontal Slow: Required a visual inspection of the raw EEG and the finding of slow activity, which could not be considered as either frontal alpha or a Slowed Alpha Peak Frequency as per Niedermeyer and Lopes da Silva [24]. This EEG phenotype is also often called frontal theta (excess 4–8 Hz activity) and in the Johnstone *et al.* [19] paper this phenotype is linked to frontal lobe disturbances.
(3) Low Alpha Peak Frequency (Low APF): alpha peak frequency findings were interpreted dependent on age in agreement with Niedermeyer and Lopes da Silva [24]. An alpha peak frequency of lower than 9 Hz was considered a slow alpha peak frequency. For ages below nine years of age this data was interpreted with caution and an APF needed to be lower than 8.5 Hz. Location was Pz.
(4) Frontal Beta Spindles: at least 1–2 occurrences of frontal beta spindles exceeding amplitude of 20 μV (as per definition of Niedermeyer and Lopes da Silva [24]) and center frequency higher than 14 Hz.
(5) Low Voltage: This phenotype was classified when the EEG power in all frequency bands was reduced as evidenced by a significant decrease in most frequency bands (delta, theta, alpha and beta) according to the subject's individual report. In the Johnstone *et al.* paper [19] this sub-type is called Generally Low Magnitudes.
(6) Frontal Alpha: This phenotype was classified when there was a clear presence of frontal alpha, further evidenced by a significant increase in the alpha content (8–12 Hz or lower frequency range for younger ages) at frontal regions according to the subject's individual report. A distinction was made between frontal alpha and frontal slow, by taking the individuals IAF (individual alpha frequency) into account as per Klimesch [20].
(7) Persistent Alpha EO: This phenotype was classified when there was a less than 50% decrease in alpha power during EO as compared to EC, with Pz as the primary site analyzed.
(8) Temporal Alpha: Clear presence of alpha at one of the temporal sites (T3, T4, T5 or T6) in the raw EEG, where the presence of alpha occurred in the temporal sites is independent from occipital or parietal alpha.

(9) High Alpha Peak Frequency (High APF): An alpha Peak Frequency of 11 or greater at site Pz was considered a fast alpha peak frequency.

2.8. *Treatment*

All ADHD subjects were treated with a stimulant (Dexamphetamine or Methylphenidate) or a non-stimulant (Strattera). The four individuals treated with Strattera were excluded from the analysis, in order to focus the treatment outcome results specifically on stimulant medication. The remaining 45 subjects were treated with a stimulant, either Methylphenidate ($n = 38$) or Dexamphetamine ($n = 7$). No control subjects received medication.

2.9. *Statistical analyses*

The inter-rater reliability at classification for all 98 subjects' phenotypes was calculated using Cohen's Kappa. The subjects were first classified into EEG phenotype groupings, with the additional label of ADHD or control. Chi-square tests were used to test significant differences in the occurrence of EEG phenotypes between the ADHD group and the control group (e.g., percentage of Frontal Slow in controls versus the percentage of Frontal Slow in ADHD). One-way ANOVA's were used to test differences in age between the "Normal EEG" group and the different EEG phenotypes.

Repeated measures ANOVA was used to test the medication effect with pre-medication and post-medication as the repeated measure and CPT performance as the dependent variable. Univariate tests were performed using as the fixed factor, both Group (ADHD vs. control) and EEG phenotype (present versus not present) and as the dependent variable, autonomic measures (HR or HRV).

3. Results

3.1. *Inter-rater reliability*

The inter-rater reliability between the two raters (first and second author) were generally high, suggesting that these EEG phenotypes can be reliably identified by two raters, with Kappa values around 0.90 or better. The persistent EO alpha and frontal alpha phenotypes showed the lowest inter-rater reliability scores. Table 1 shows the number of subjects per EEG phenotype sub-group, together with the Kappa values. Note that for this study, phenotype classification was used only when both raters agreed on the EEG phenotype classification.

3.2. *Prevalence of EEG phenotypes*

Figure 3 shows the prevalence of the different EEG phenotypes in ADHD and matched controls. There were no significant age differences between the EEG phenotype groups. The ADHD group tended to show a higher occurrence of "Frontal

Table 1. The number of subjects in the different EEG phenotype groups and corresponding inter-rater reliabilities.

	N ADHD	N Controls	Inter-Rater Reliability
"Normal EEG"	5	11	Kappa: 0.90; $p < 0.0001$
Frontal Slow	13	9	Kappa: 0.94; $p < 0.0001$
Low APF	13	5	Kappa: 0.90; $p < 0.0001$
Frontal Beta Spindles	8	10	Kappa: 0.97; $p < 0.0001$
Low Voltage	6	1	Kappa: 0.93; $p < 0.0001$
Frontal Alpha	8	4	Kappa: 0.47; $p < 0.0001$
Persistent Alpha EO	7	5	Kappa: 0.64; $p < 0.0001$
Temporal Alpha	5	6	Kappa: 0.89; $p < 0.0001$
High APF	3	5	Kappa: 0.94; $p < 0.0001$

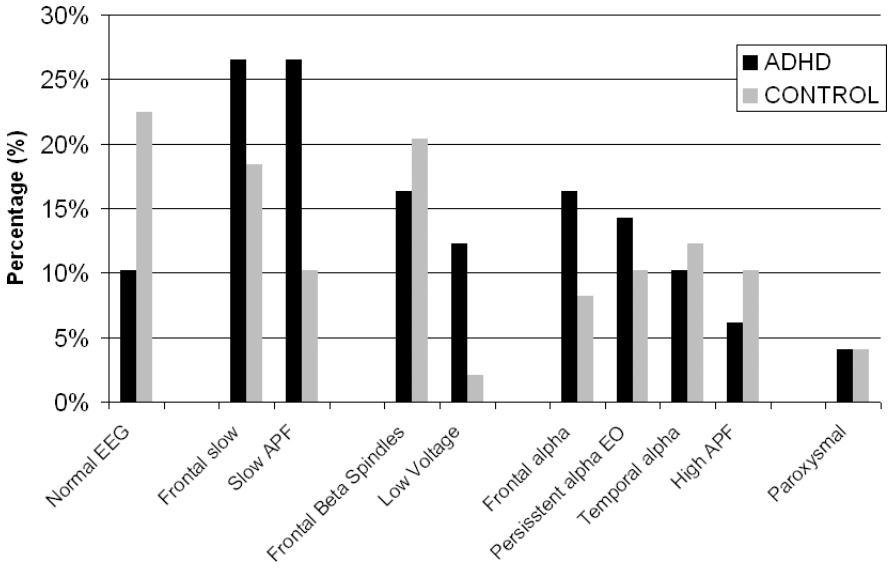

Fig. 3. The occurrence of the different EEG phenotypes for both ADHD and control groups. Note the higher occurrence of Frontal Slow, Slow Alpha Peak Frequency and Low Voltage EEG in the ADHD group. Also note that the control group had occurrences of several EEG phenotypes. Only 25% displayed a "normal" EEG.

Slow", "Slow Alpha Peak Frequency" and "Low Voltage EEG" as compared to the control group. However, the Chi-square tests failed to show any significant differences between the groups. Only the differences for low voltage EEG ($p = 0.050$) and Slow Alpha Peak Frequency ($p = 0.074$) tended towards significance. This lack of effect is probably due to the low subject numbers per sub-group.

Figure 4 shows the Eyes Open spectral plots for three different EEG phenotypes. This figure illustrates that although these EEG phenotypes also occur in healthy controls, that EEG phenotypes are more expressed in the clinical group. In the Frontal Slow phenotype, the ADHD group has more Frontal Slow EEG power when

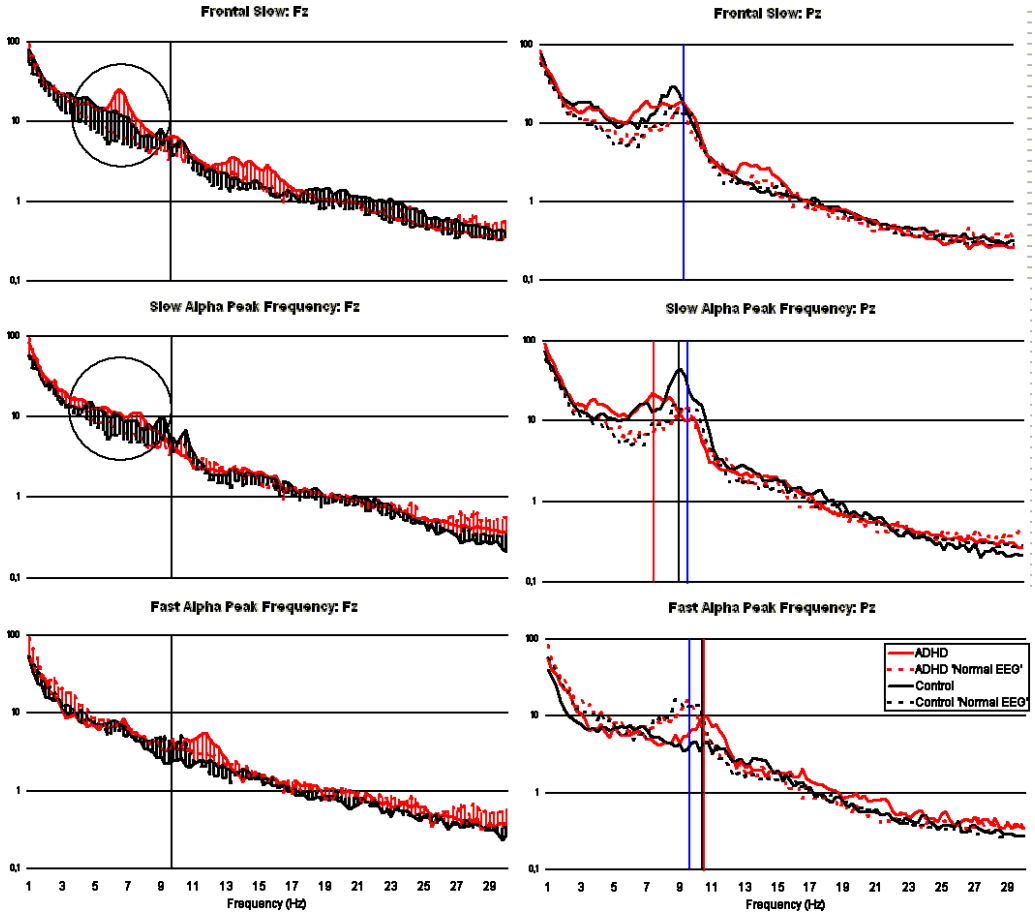

Fig. 4. Average FFT's for Eyes Open for the Frontal Slow phenotype (Top), The Slowed Alpha Peak Frequency phenotype (Middle) and the Fast Alpha Peak Frequency EEG phenotype (Bottom). Red depicts the ADHD group and Black the control group, dashed lines represent the "Normal EEG" sub-group averages. Left pictures are Fz and right pictures are Pz. The vertical lines in the right graphs (Pz) indicate the alpha Peak Frequency for the ADHD (red), control (black) and "Normal EEG" (blue) groups. Note the similarity of the power in the "theta frequency band" (4–7.5 Hz) for both the Frontal Slow and the Slow Alpha Peak Frequency group. Also note how similar the "Normal EEG" sub-groups are for both ADHD and controls, indicating that most of the variance are explained by the EEG phenotype. Finally, note the exaggeration for the respective EEG phenotypes in the ADHD group as compared to the controls (as demonstrated by the shadowed black or red area in the left graphs showing the difference between the "Normal EEG group" versus the respective "phenotype" group).

compared to the control group. Additionally, the Slow Alpha Peak Frequency for the ADHD group (red vertical line) is slower compared to the control group's peak alpha frequency (black vertical line).

3.3. *Treatment effect on CPT performance*

Figure 5 shows the treatment effects on the CPT for EEG phenotypes. The Fast Alpha Peak Frequency, Temporal Alpha, Low Voltage and Persistent Alpha EO

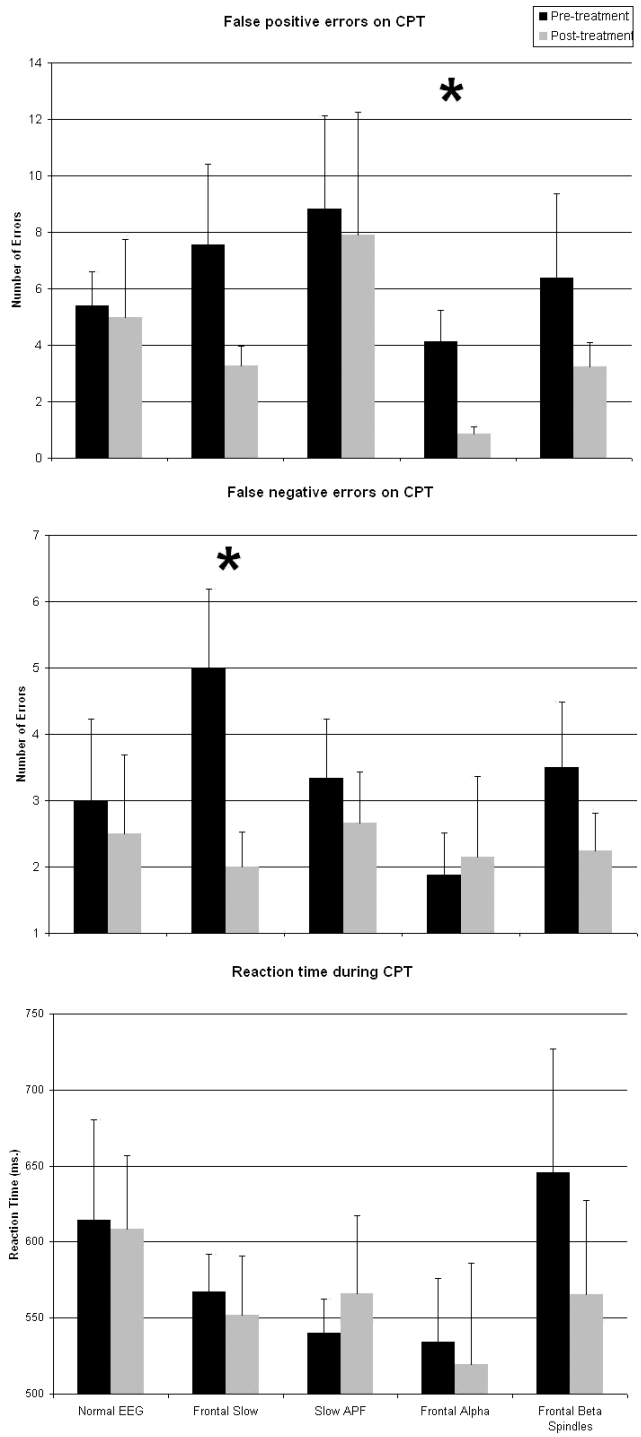

Fig. 5. Pre-treatment and post-treatment performance for the ADHD group on different CPT measures (false positive errors, false negative errors and reaction time) for EEG phenotypes ($n = 45$). Note that the Frontal Slow and Slow Alpha Peak Frequency groups made more errors as compared to the other groups, and that only the Frontal Slow group responds to treatment with a stimulant ($^*p < 0.05$). There were no treatment effects on reaction times.

Table 2. Percentages of ADHD sub-types for the different EEG phenotypes. As can be seen here there is no clear relationship between the different EEG phenotypes and ADHD sub-types, showing that the behavioral sub-types do not correlate very highly with the EEG phenotypes.

	"Normal"	Frontal Slow	Slow APF	Frontal Alpha	Frontal Beta Spindles
Inattentive	50%	55%	73%	86%	50%
Combined	50%	45%	27%	14%	37%
Hyperactive/ Impulsive	0%	0%	0%	0%	13%

groups have been omitted due to small sample sizes ($n < 8$). For the false positive errors, there was a significant treatment effect for the Frontal Alpha group ($F = 10.454$; $df = 1, 6$; $p = 0.018$). The number of false positive errors was significantly larger in the pre-treatment (mean = 4.125; SEM = 1.125) as compared to the post-treatment assessment (mean = 0.857; SEM = 0.26) assessment.

Patients with the Frontal Slow phenotype demonstrated a significantly improved performance on the CPT task. They demonstrated a significant treatment effect for the false negative errors ($F = 6.972$; $df = 1, 10$; $p = 0.025$) The Frontal Slow phenotype group therefore made more false negative errors pre-treatment (mean = 5; SEM = 1.19) as compared to post-treatment (mean = 2; SEM = 0.52).

Notably, as can be seen in Fig. 5 the Frontal Slow and Slow Alpha Peak Frequency phenotypes both made many errors as compared to the other groups, but *only* the Frontal Slow group responded to treatment with a stimulant. There were no significant medication effects on reaction times in the CPT.

Table 2 shows the percentages of ADHD sub-types (Inattentive, Combined and Hyperactive/Impulsive) for the different EEG phenotypes. It can be seen that there is no clear relationship between the EEG phenotypes and the ADHD sub-types based on behavior, although there is a trend that the Inattentive sub-type is more associated with the Slow APF and Frontal Alpha EEG sub-types.

3.4. *Autonomic arousal*

Only the Frontal Slow EEG phenotype showed a significant increase in HR during EO ($F = 6.627$, $df = 1$; $p = 0.015$) and EC ($F = 4.351$, $df = 1$; $p = 0.045$) conditions as compared to the "Normal EEG" group for both ADHD and the control group (EEG phenotype effect). The overall group effects were also significant indicating that ADHD individuals in the "Normal EEG" and "Frontal Slow" sub-groups have a significant decrease in HR during EO ($F = 12.158$; $df = 1$; $p = 0.001$) and EC ($F = 6.156$; $df = 1$; $p = 0.018$) as compared to the control group. There were no other significant relationships between EEG phenotypes and HR or HRV in EO or EC conditions.

4. Discussion

This study used the EEG phenotype classification proposed by Johnstone, Gunkelman and Lunt [19] in a group of 49 children with ADHD and 49 matched controls. The identification of these EEG phenotypes by two raters was reproducible in individual data, with high Kappa values mostly exceeding 0.90. The inter-rater reliability scores were lower for Persistent Alpha and Frontal Alpha. The lower agreement for those EEG phenotypes, may be due to the lower occurrence of these EEG phenotypes ($< 10\%$). The phenotype raters were not blind to diagnosis which could have affected the ratings. However, given the small differences between the ADHD and control group in prevalence of EEG phenotypes, this is unlikely to have had a large effect.

As mentioned in the introduction, a large qualitative heterogeneity existed in EEG phenotypes in both the ADHD group and controls. From Table 2 it is clear that the differences in EEG phenotypes could not be explained completely by behaviorally diagnostic differences such as ADD or ADHD diagnosis. A greater number of subjects from the control group exhibited a "normal EEG" as compared to the ADHD group (25%). ADHD subjects more often showed a frontal slow — "frontal theta" — EEG phenotype. However, the Slow Alpha Peak Frequency tended to discriminate between both groups even better.

To the best of our knowledge this is the first study assessing individually scored Alpha Peak Frequency as a sub-group in ADHD. Previous studies e.g., Chabot and Serfontein [3] did assess the alpha mean frequency, however this is different from assessing the individual APF. The alpha mean frequency is the mean frequency between 8–12 Hz, whereas the individual APF is the peak frequency which can be 7 Hz or lower or sometimes higher than 12 Hz [20]. The average APF of the Slow APF group was 8.2 Hz and when using the traditional theta frequency band (4–7.5 Hz), it becomes clear that this group will show up as "increased theta EEG power". This is also demonstrated in Fig. 4 where for the slow APF groups there is an increase in power in the frontal "theta band". For this reason we speculate that the subjects from our Slowed APF group in previous studies have shown up as a frontal slow EEG. However these two patterns have completely different etiologies as described in the IFCN report on the basic mechanisms of EEG rhythmicity [30]. This is also further evidenced by the results from this study where the Frontal Slow group responded well to stimulants with a substantial decrease in the number of false negative errors on the CPT and the lack of a treatment response in the slowed APF group.

This could partly explain the contradictory findings with some studies finding good medication response in excess frontal slow EEG sub-types [10, 26, 28] and other studies finding good medication response in excess alpha EEG sub-types [4]. For future studies it is therefore important to clearly dissociate Frontal Slow from slowed APF by taking the individual APF into account.

We also found that the Frontal Alpha sub-group responded to stimulant medication, although on a different measure: false positive errors. The Frontal Alpha sub-group already performed better than most other EEG phenotypes, hence this effect could reflect a nonspecific floor-effect. The Frontal Slow and Slow APF groups both performed poorly on most CPT measures, implicating that the effect for the Frontal Slow group is clinically most relevant. False positive errors can be regarded as a measure of impulsivity (commission errors), whereas false negative errors can also be regarded as inattention (omission errors). In this context, it may be argued that ADHD children with frontal slowing are specifically those with the inattentive component, which also responds very well to stimulant medication. However, Table 2 does not confirm this, since the occurrence of inattentive was 55% and combined 45% for the Frontal Slow group. Furthermore, ADHD children with a frontal alpha could be considered the least impulsive (see Fig. 6) since they already make the

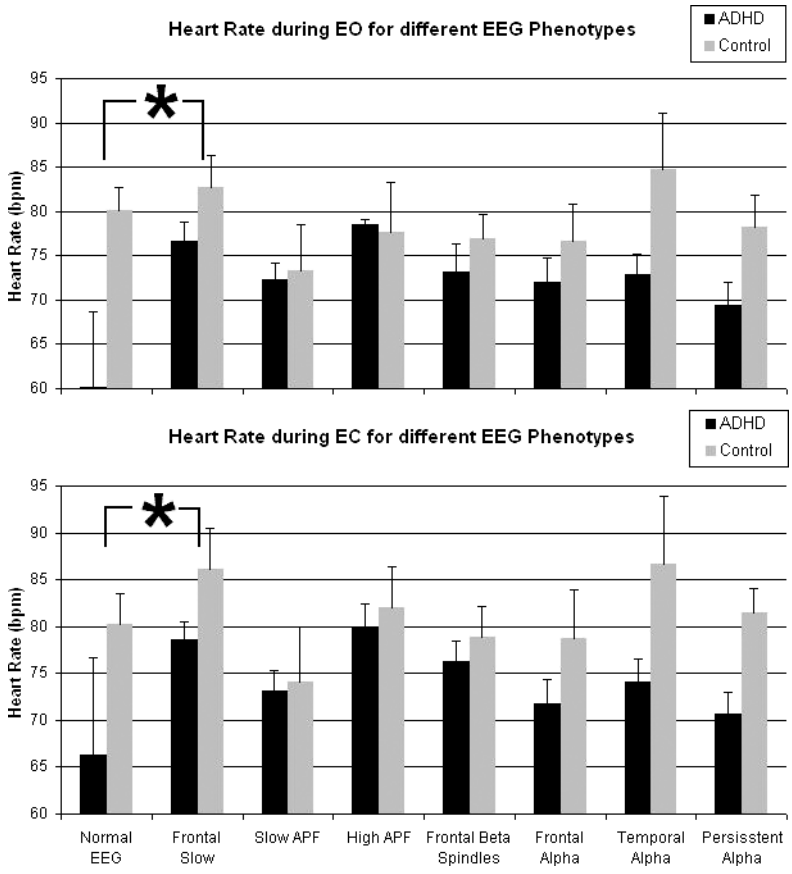

Fig. 6. The interrelationships between Heart Rate (HR) during Eyes Open and Eyes Closed conditions and the different EEG phenotypes. The Frontal Slow EEG phenotype (for both ADHD and control group) showed an increased HR during resting conditions. Furthermore, ADHD children in general seem to have a decreased HR in comparison to controls.

fewest false positive errors, and with a stimulant they make even fewer false positive errors. This is confirmed from Table 2 showing that in the Frontal Alpha group 86% had a diagnosis inattentive, without the impulsive component.

It is a surprising finding that the prevalence of the different EEG phenotypes is comparable between the ADHD and control group. However, in Fig. 4 it can be seen that the expression of a given EEG phenotype is more excessive for the ADHD group as compared to the control group. It is of note that both groups contained two subjects who displayed paroxysmal EEG activity (neither of these subjects had a diagnosis of epilepsy).

4.1. *Autonomic interrelations*

In general, subjects with ADHD showed decreased heart rate at rest as compared to the control group. The frontal slow EEG phenotype was specifically associated with an increase in resting heart rate during EO and EC conditions as compared to the "normal EEG" groups for both children with ADHD and controls, suggesting a lower vagal nerve tone associated with a frontal slow EEG (irrespective of group). This relationship was found for only the Frontal Slow phenotype and not for the Slow Alpha Peak Frequency, showing another functional dissociation between these two EEG phenotypes which are the most common patterns in ADHD. This finding is especially interesting to note since most studies report that stimulants such as Methylphenidate have been found to "normalize" excess theta [32, 12] and cause a task-related increase in heart rate in healthy volunteers [2, 11]. The Frontal Slow (or frontal theta) phenotype already exhibited increased heart rate as compared to the other EEG phenotypes for both the ADHD and control group. Therefore, the increased heart rate caused by drugs such as methylphenidate could be considered an unwanted effect for subjects in the Frontal Slow EEG phenotype, whereas clinically they respond the best (also see Fig. 6; the ADHD children with the Frontal Slow phenotype seem to have a heart rate comparable to the control group for other phenotypes).

4.2. *Limitations of this study*

While Kappa reliability values were high, raters were not blind to group status. Thus the apparently increased severity of the phenotypes in the ADHD group may be due to a rater's bias. Therefore, this result must be considered preliminary until this finding is replicated by other groups using blinded ratings.

Another limitation lies in the small number of subjects involved, also due to the sub-grouping. On the one hand this means that the results may be biased due to selection of subjects. On the other hand the small number of subjects may cause a lack of explanatory power, thus precluding conclusion with regard to smaller effects. Finally, no Connors or other outcome measures were available at follow-up. Thus, the clinical relevance of the findings needs further elaboration.

This study demonstrated that the EEG phenotypes as described by Johnstone, Gunkelman and Lunt [19] are clearly identifiable EEG patterns which can be classified reliably by two raters. Furthermore, it was also demonstrated that these EEG phenotypes occurred in both ADHD subjects as well as healthy control subjects. The Frontal Slow, the Slow Alpha Peak Frequency and the Low Voltage EEG phenotype discriminated ADHD subjects best from the control group (albeit not significantly). Only the Frontal Slow EEG phenotype showed a clinically relevant treatment response to stimulant medication, whereas the Slowed Alpha Peak Frequency group did not respond to stimulant medication as measured by the performance on a CPT.

The data suggest that the two most prevalent EEG phenotypes: Frontal Slow and Slowed Alpha Peak Frequency may have shown up in previous studies most likely as a Frontal theta group, whereas these two EEG phenotypes have very different etiologies as evidenced by the treatment response to stimulants. Future research employing EEG measures in ADHD should avoid using traditional frequency bands only, but clearly dissociate frontal slow from slowed APF by taking the individual APF into account. Furthermore, the severity of the phenotype divergence from normal is greater in the clinical group than in the controls. This is an area of potentially high yield for a subsequent study, since it will be interesting to investigate the "severity" of a given EEG phenotype and its relation to behavior rather than the presence or absence of an EEG phenotype.

Investigating EEG phenotypes provides a promising way to approach EEG data, explaining much of the variance, and thereby potentially leading to more specific prospective treatment outcomes.

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