EEG Phenotypes predict treatment outcome to stimulants in children with ADHD.

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Abstract: This study demonstrates that the EEG Phenotypes as described by Johnstone, Gunkelman & Lunt [19] are clearly 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, the Slow Alpha Peak Frequency and the Low Voltage EEG Phenotype seemed to discriminate ADHD subjects best from the control group, however not significantly. 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 very different etiologies as evidenced by the treatment response to stimulants. In previous research the 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 clearly 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 seems to be a promising new way to approach EEG data, explaining much of the variance in EEG’s, 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 quite consistent picture for ADHD. Most of these studies have found increased slow (theta) EEG activity [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 based on 275 non-medicated ADHD patients. This averaged data shows increased theta and decreased beta with a frontocentral localisation.

![Figure 1: The average Brain activity of 275 ADHD patients compared to a matched control group. The figure left shows the increased theta (p<.0001), the figure in the middle shows the decreased absolute beta (p<.0001) and right the relative decreased beta power (p<.0001). Note the frontocentral localisation.](image)

However, a different picture emerges when looking at the individual data (see figure 2). Figure 2 shows the individual data from 36 ADHD patients from this exact same dataset from the Brain Resource International Database, showing the individual data underlying the average data shown above in figure 1. The quantitative EEG’s (qEEGs) of these patients – were compared to a normative database consisting of more than 5000 healthy controls, allowing an individual comparison. These data show that indeed 47% of these ADHD patients showed increased EEG activity in the theta frequency band. However, only 5.6% showed decreased beta whereas 22% showed increased beta. These data suggest a large variability in QEEG profiles within a ‘behaviourally 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 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 on such an EEG sub-group with increased beta in ADHD with a slightly different behavioural profile (increased rate of temper tantrums and moody behaviours) present in about 20% of children with ADHD. 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] reported on different EEG clusters in ADHD where besides the excess beta subtype, a ‘cortical-hypoarousal’ subtype and a ‘maturational-lag’ subtype could be identified (see for an overview [1]).

The fact that Ritalin does not have a clinically significant effect in 20-40% of patients with ADHD [29, 14] could well be related to the above reported EEG-Subtypes in ADHD, assuming that some sub-types respond better to medication than others. Several studies have shown that these EEG subtypes are indeed related to favourable outcome of stimulant drugs. For example Ritalin responders are characterized by increased frontal slow (Delta and Theta [10, 26, 28]). However, for the excess beta group described above it was found that they too respond favourably to stimulant medication [7] which was also found by Hermens et al [18]. Chabot et al. [4] found that both alpha and beta excess were

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Figure 2: Data of 36 patients with ADHD (4-digit ID codes) from the exact same dataset as in figure 1. However, here the individual data are depicted. 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. Indeed some subjects showed increased theta (47%), however only 5.6% of these subjects showed a decreased beta and even 22% showed increased beta. This demonstrates the contrast between group-average data vs. individual data.
predictors of behavioural improvement, whereas excess theta was predictive of both positive and negative treatment responses, with the negative treatment responses characterized by a more severe excess theta. In a study by Suffin and Emory [28] a group of attentionally disturbed clients were studied, where they showed that stimulants were efficacious with the theta clusters (excess frontal theta), but antidepressants were efficacious with the alpha clusters (excess frontal alpha), regardless whether they were categorized as ADHD or depressed using DSM standards. 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 Bupropion.

Most of the above mentioned studies have investigated relative EEG power measures which can sometimes give a misrepresentation (i.e. when there is excess absolute theta, the relative power of other bands will be decreased due to this theta excess). Furthermore, in all studies the traditional EEG frequency bands (like theta, alpha and beta) were investigated. Based on the work by Klimesch [20] on the individual alpha frequency and the fact that the individual alpha peak frequency matures during development up to the age of 10 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 slower 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. Also, Clarke et al. [8] and Johnstone et al. [19] make mention of ‘Beta Spindles’ which might be qualitatively different from general increased beta [24]. The recently published paper by Johnstone et al. [19] on EEG Phenotypes provides an interesting framework to perform individual classifications of EEG, taking the above issues in mind. Therefore, in this study we aim 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, since the main effects of stimulants are considered to be through increasing arousal.

2.0 Method

2.1 Subjects

Data from 49 children with ADHD (all male, average age = 11.33; range 6 – 17) and 49 control children (matched on age, gender and education; average age = 11.92; range 7 – 18) were drawn from the Brain Resource International Brain Database [13, 15]. All subjects were medication free (at least 48 hours) at the time of assessment. The 49 children with ADHD were recruited from the Sydney metropolitan region. All ADHD subjects were referred by two paediatricians and a 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 average 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 subtype of ADHD, 22 met the criteria for ADHD of the predominantly inattentive subtype and 2 individuals met the criteria for ADHD of the predominantly hyperactive-impulsive subtype. For 3 subjects these data were missing.
Exclusion criteria included a personal or family history of 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.

2.2 Procedure

ADHD subjects were tested on two separate occasions. The first occasion was pre-medication. All subjects were medication free (at least 48 hours) at the first occasion and 30 subjects of these were medication naïve. For the second occasion (post-medication) all ADHD subjects were taking their prescribed course of stimulant medication (38 Methylphenidate, 7 dexamphetamine and 4 Strattera) for a period of at least four weeks and were required to take their typical dose 60 minutes before the testing session commenced.

Subjects were seated in a sound and light attenuated room, controlled at an ambient temperature of 24°C. Electroencephalographic and neuropsychological assessments were completed in order (first the EEG for Eyes Open and Eyes Closed was taken followed by the CPT test). Details of these procedures have been published elsewhere [13, 14, 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 1.5cm lateral to the outer canthus of each eye. Vertical eye movements were recorded with electrodes placed 3mm above the middle of the left eyebrow and 1.5cm below the middle of the left bottom eye-lid. Skin resistance was < 5 K Ohms and above 1K 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 40dB 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, and were told that this condition would last for 3 minutes. Following this, subjects were asked to rest quietly with their eyes closed for the duration of the recording, and were told that this condition would last for three minutes.

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. Subjects 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 X 1 cm checkerboards) were randomly interwoven with the letter stimuli. Subjects were instructed to ignore the “checkerboards”. Subjects were given a brief practice session to clarify the task instructions. Subjects were told that this task would last for 8 minutes. Reliability and validity data of these tasks are reported elsewhere [5, 25, 31].

2.6 Psychophysiological variables

Average 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), next the average power spectra were calculated. Epochs were rejected if the signal at three or more sites exceeded 100 uV 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 Heart Rate) were obtained from an ECG lead at the wrist during Eyes Open and Eyes Closed condition.

2.7 EEG Phenotype Rating

For all 98 subjects a full individual report was obtained with the EOG corrected [16] raw EEG for EO and EC condition. Furthermore, a Brain Resource Company ‘Neurofeedback’ report was obtained containing individual data compared to the International Brain Database consisting of 5000 normative subjects. Data were first rated by the first author and after that 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 1 or more EEG Phenotypes. See Johnstone et al. [19] for an elaboration of all EEG Phenotypes. Below find a brief description of the EEG Phenotypes and the exact definitions used in this study:

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: Real frontal slow required a visual inspection of the raw EEG. The finding of slow activity which could not be considered either frontal alpha or a slowed alpha peak frequency as per Niedermeyer & 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 one is mentioned under ‘Frontal Lobe Disturbances’.

3) Low Alpha Peak Frequency (Low APF): Alpha Peak Frequency findings were interpreted dependent on age in agreement with Niedermeyer & Lopes da Silva [24]. An alpha peak frequency of lower than 9 Hz was considered a slow alpha peak frequency. For ages below 9 years of age this 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 uV (as per definition of Niedermeyer & Lopes da Silva [24]) and centre 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 subtype 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 the research of 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 standard site.

8) Temporal Alpha: This phenotype was classified as showing 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 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 Strattera. Four were treated with Strattera, and were hence excluded from the analysis, in order to focus the treatment outcome results specifically on stimulant medication. All remaining 45 subjects were treated with a stimulant: Methylphenidate (n=38) or Dexamphetamine (n=7). No control subjects received medication.

2.9 Statistical analysis

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 vs. 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 measure tests were 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 vs. not present) and as the dependent variable autonomic measures (HR or HRV).

3.0 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 .90 or better, though with the persistent eyes open alpha and frontal alpha phenotypes showing the lowest inter-rater reliability. Table 1 shows the number of subjects per EEG Phenotype sub-group, together with the exact Kappa values. Note that for this study phenotype classification was used only when both raters agreed on the EEG Phenotype classification.

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3.2. Prevalence of EEG phenotypes

Figure 3 shows the prevalence of the different EEG Phenotypes in ADHD and Normal controls. There were no significant age differences between the EEG Phenotype groups. The ADHD group tended to show a higher occurrence of ‘Frontal 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 ADHD and Control groups. Only the difference for low voltage EEG (p=.050) and slow alpha peak frequency (p=.074) tended towards significance. This lack of effect is probably due to the low subject numbers per subgroup.
Figure 3: The occurrence of the different EEG Phenotypes for both ADHD and the matched Control group. 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.

Figure 4 below shows the Eyes Open spectral plots for 3 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 grouping. In the Frontal Slow phenotype, the ADHD group has more frontal slow EEG power when 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).
Figure 4: The 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 controls 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’ (or 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 is explained by the EEG Phenotype. Finally, note the exaggeration for the respective EEG Phenotypes in the ADHD group as compared to the Control group (as demonstrated by the shadowed black or red area in the left graphs showing the difference between the ‘Normal EEG group’ vs. the respective ‘Phenotype’ group).
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 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=.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).

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=.025) The frontal slow phenotype hence made more false negative errors pre-treatment ( mean = 5; SEM = 1.19;) as compared to post-treatment ( mean = 2; SEM = 0.52;).

Interestingly, as can be seen in figure 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.

In Table 2 below, the percentages of ADHD-subtypes Inattentive, Combined and Hyperactive/Impulsive for the different EEG Phenotypes are shown. It can be seen that there is no 100% relation between the EEG Phenotypes and the ADHD-subtypes based on behavior although there is a trend that the Inattentive sub-type is more associated with the Slow APF and Frontal Alpha EEG subtypes.

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<td>Hyperactive/Impulsive</td>
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Figure 5: Pre-treatment and post-treatment performance for the ADHD group only 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 make more errors as compared to the other groups, and that only the Frontal Slow group responds to treatment with a stimulant (*: P<.05). Also note that there were no treatment effects on reaction times.
3.4 Autonomic arousal

Only the Frontal Slow EEG Phenotype showed significant increased Heart Rate during Eyes Open (F=6.627, df=1; p=.015) and Eyes Closed (F=4.351, df=1; p=.045) conditions as compared to the ‘Normal EEG’ group for both ADHD and the controls group (EEG Phenotype effect). The overall group effects were also significant indicating ADHD patients in the ‘Normal EEG’ and ‘Frontal Slow’ sub-groups have significantly decreased Heart Rate during Eyes Open (F=12.158; df=1; p=.001) and Eyes Closed (F=6.156; df=1; p=.018) as compared to the control group. There were no other significant relationships between EEG Phenotypes and HR or HRV in Eyes Open and Eyes Closed conditions.

**Figure 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 as compared to the Control group.
4.0 Discussion

This study used the EEG Phenotype classification postulated by Johnstone, Gunkelman & 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 .90. Only for Persistent Alpha and Frontal Alpha the inter-rater reliability scores were lower, indicating a lower agreement for those EEG Phenotypes, which could also be due to the lower occurrence of these EEG Phenotypes (<10%). The Phenotype ratings 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 most likely did not have a dramatic effect.

As pointed out in the introduction a large qualitative heterogeneity existed in EEG Phenotypes in the ADHD group as well as in the control group. From table 2 it also became clear that the differences in EEG Phenotypes could not be explained completely by behaviorally diagnostic differences such as ADD or ADHD diagnosis. Indeed more subjects from the control group exhibited a ‘normal EEG’ as compared to the ADHD group; however this was only 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 our knowledge this is the first study assessing individually scored alpha peak frequency as a subgroup 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 figure 4 where for the slow APF groups there is an increased power in the frontal ‘theta band’. Therefore, 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 non specific floor-effects. The Frontal Slow and Slow APF groups both performed worst 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.
In this context it might be argued that ADHD children with frontal slow 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 figure 6) since they already make the fewest False Positive errors, and with a stimulant they even make 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 figure 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.

Interestingly, both groups contained two subjects who displayed Paroxysmal EEG activity, whereas these subjects were not diagnosed with 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 increased resting heart rate during eyes open and eyes closed condition as compared to the ‘normal EEG’ groups for both children with ADHD and the control group, suggesting a lower vagal nerve tone associated with a frontal slow EEG (irrespective of ADHD or control 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 an 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 figure 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

In spite of the high Kappa reliability values, it must be noted that the raters were not blind to the status of the subjects. 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 & Lunt [19] are clearly identifiable EEG patterns which can be classified with good reliability 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 seemed to discriminate ADHD subjects best from the control group, however not significantly. Interestingly, 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. This implicates that all 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 it’s relation to behavior rather than the presence or absence of an EEG phenotype.

Investigating EEG Phenotypes or Neuromarkers seem to be a promising way to classify EEG data, explaining much of the variance, and thereby potentially leading to more specific prospective treatment outcomes.

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