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Age dependent electroencephalographic changes in attention-deficit/hyperactivity disorder (ADHD)

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HIGHLIGHTS

- ADHD effects on resting (eyes-closed) EEG strongly depend on age and frequency.
- Support vector machine classification of ADHD adults *versus* controls yielded a good cross validated sensitivity of 67% and specificity of 83% using EEG power and central frequency.
- ADHD children were not classified convincingly with these markers, and thus, altered maturation may only characterize persistent ADHD.

ABSTRACT

Objective: Objective biomarkers for attention-deficit/hyperactivity disorder (ADHD) could improve diagnostics or treatment monitoring of this psychiatric disorder. The resting electroencephalogram (EEG) provides non-invasive spectral markers of brain function and development. Their accuracy as ADHD markers is increasingly questioned but may improve with pattern classification.
Methods: This study provides an integrated analysis of ADHD and developmental effects in children and adults using regression analysis and support vector machine classification of spectral resting (eyes-closed) EEG biomarkers in order to clarify their diagnostic value.
Results: ADHD effects on EEG strongly depend on age and frequency. We observed typical non-linear developmental decreases in delta and theta power for both ADHD and control groups. However, for ADHD adults we found a slowing in alpha frequency combined with a higher power in alpha-1 (8–10 Hz) and beta (13–30 Hz). Support vector machine classification of ADHD adults *versus* controls yielded a notable cross validated sensitivity of 67% and specificity of 83% using power and central frequency from all frequency bands. ADHD children were not classified convincingly with these markers.
Conclusions: Resting state electrophysiology is altered in ADHD, and these electrophysiological impairments persist into adulthood.
Significance: Spectral biomarkers may have both diagnostic and prognostic value.

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1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common psychiatric disorder affecting children, adolescents, and adults. The prevalence of ADHD in children is around 5% (Polanczyk and Rohde, 2007), and varies from 3% to 16% in adults depending on the diagnostic criteria (Faraone and Biederman, 2005). ADHD is associated with serious socio-economical consequences, resulting from difficulties with social interactions, inattention at school or work, and a higher risk of psychological maladjustment (Faraone et al., 2000), leading to a loss in productivity and increased societal healthcare costs (Biederman et al., 2006).

Clinical diagnosis of ADHD is based on structured interviews and questionnaires assessing behavioral symptoms according to standardized diagnostic manuals (DSM-IV and DSM-5, (American Psychiatric Association, 2000, 2013)), although research diagnostics increasingly focus on the neural systems affected (Cuthbert and Insel, 2013). The observed heterogeneity of ADHD highlights the need for more objective and precise diagnostic and prognostic approaches such as advanced pattern classification analyses (Clarke et al., 2011; Poil et al., 2013). Biomarkers based on electroencephalography (EEG) measurements are both inexpensive and non-invasive, making them suitable for screening purposes or for following treatment outcomes (Clarke et al., 2002a). These biomarkers may add an additional dimension to the current diagnostic criteria of ADHD, e.g., with respect to identification of relevant sub-groups. In addition, spectral markers of EEG slowing reflect effects of maturational lag, inattention, hypoarousal, and control deficits found in ADHD. As a result, EEG biomarkers have been explored extensively in ADHD, but have not yet achieved clinical acceptance.

The most common effect reported in the literature is an increase in theta (4–7 Hz) power or theta/beta ratio, measured during rest over fronto-central regions in subjects with ADHD (Arns et al., 2013; Barry et al., 2003, 2009; Bresnahan et al., 1999; Clarke et al., 2001a; Magee et al., 2005; Snyder and Hall, 2006). The validity of this effect presumed to represent a form of EEG slowing related to maturational lag and hypoarousal has, however, been questioned by recent studies which failed to observed theta or beta effects (in both theta/beta ratio and power) (Liechti et al., 2013; Loo et al., 2009, 2013; van Dongen-Boomsma et al., 2010). The lack of theta effect may be caused by differences in methodology or by the general heterogeneity of ADHD and control groups (Arns et al., 2013; Clarke et al., 2011; Liechti et al., 2013; Loo et al., 2013). Combining EEG with skin conductance measures of arousal has further challenged the proposed link between theta/beta levels and hypoarousal, and instead suggests that increased alpha levels reflect reduced arousal in both ADHD and control children (Barry et al., 2009). Similarly, slower alpha peak or central frequencies have been implicated in ADHD (Arns et al., 2008). In sum, several thorough recent studies (Liechti et al., 2013) and reviews (Arns et al., 2013; Clarke et al, 2013) suggest that findings of elevated theta and theta/beta ratios in ADHD exhibit considerable more heterogeneity, relate less clearly to hypoarousal, and yield less consistent results across the life span in recent work than claimed previously.

This study aims to clarify the potential diagnostic or prognostic value of EEG spectral biomarkers through a better understanding of age-related changes in these biomarkers. Evidence from previous studies indicates that the developmental changes in ADHD subjects are characterized by a delayed maturation of spectral biomarkers at rest (Clarke et al., 2002b), inhibition related activation deficits (Doehnert et al., 2010; Rubia et al., 1999), and structural changes in, for example, frontal cortex (Shaw et al., 2007). While we could not confirm such delays for spectral theta and beta power of ADHD children and adults in an earlier study (Liechti et al., 2013), combining a wider range of frequency bands and measures with multidimensional classification could provide more sensitivity. Therefore, we hypothesized that ADHD patients would show a different developmental trajectory compared with healthy subjects in EEG power and central frequency biomarkers (Arns et al., 2013; Clarke et al., 2001b).

Since traditional log-linear regression analysis has previously been shown to characterize EEG developmental trajectories closely (Wackermann and Matousek, 1998), we expect this analysis to reveal different developmental trajectories between ADHD and control subjects based on the delayed maturation theory. We further employ a binary multi-dimensional classification method, i.e., a support vector machine (SVM), to investigate whether the combined spectral EEG biomarkers (power and central frequency) could provide additional information that may give better separations between groups (ADHD *versus* healthy and "young" *versus* "adult" subjects) than classification based on single biomarkers alone. Classification analysis during rest or task has previously shown good accuracy in classifying several disorders, such as schizophrenia, depression, Alzheimer's disease (Lehmann et al., 2007; Orrù et al., 2012; Poil et al., 2013; Übeyli, 2010), and ADHD (Abibullaev and An, 2012; Cheng et al., 2012; Dai et al., 2012; Eloyan et al., 2012; Hart et al., 2013; Mueller et al., 2011; Tenev et al., 2013). A recent pattern classification competition of resting state functional MRI data from a large number of ADHD and control subjects (>200 children and adolescents with ADHD) yielded cross-validated group discrimination from 55% (compared to 33% obtained by chance, Colby et al. 2012) to 78% (Eloyan et al. 2012; reduced to 61% for an external data set), and exceeded classification based on single markers (Dai et al., 2012). We thus hypothesize that whole-brain pattern analysis using resting state EEG markers will similarly improve individual classification of ADHD patients.

2. Methods and materials

2.1. Subjects

The study involved a large sample of 116 subjects, including 48 ADHD patients and 68 control subjects. We studied 19 children with ADHD and 22 control children, 7 adolescents with ADHD, and 19 control adolescents. The adult group consisted of 22 adults with ADHD, and 27 control adults (Tables 1–3). The control group was recruited from nearby regular schools, personal contacts, and through advertisement at public science presentations, while patients were mostly recruited from our university clinics specializing in child or adult ADHD. These subjects are different from the subjects included in the Liechti et al. (2013) study. The subject groups were matched for handedness, gender, and estimated IQ. The control subjects did not report any current or previous neurological or psychiatric diagnoses. For the SVM analysis we used the adult group, which was age matched and did not take antidepressants drugs, in order to avoid potential interactions from age and antidepressants drugs. This subgroup included 11 ADHD subjects (median age 32 years, $SD = 14$, 6 males, IQ = 111, $SD = 18$, 10 on Methylphenidate (i.e., Ritalin or Concerta), and 25 control subjects (median age 30 years, $SD = 10$, 10 males, IQ = 115, $SD = 17$). All ADHD adults were recruited from the Psychiatric University Clinic Zürich, and underwent a clinical interview and screening for comorbidities by a consultant psychiatrist with expertise in adult ADHD. The ADHD children were recruited by the Department of Child & Adolescent Psychiatry of the University of Zurich. The Kiddie-SADS-Present and Lifetime Version (K-SADS-PL) clinical

Table 1
Group characteristics of adults with ADHD and controls.

	n (f)	Mean (*SD*)	Median	Range	*p*
Age					
ADHD	22 (12)	37.9 (11.3)	38.4	[23.7:61.1]	0.26[b]
Control	27 (17)	34.1 (10.5)	28.2	[21.0:53.3]	
Estimated IQ					
ADHD	22	103.1 (19.9)	107	[69.0:141.0]	0.12[a]
Control	25	111.6 (16.5)	114	[80.0:145.0]	
Corsi Block Span Task					
Normal Span					
ADHD	22	5.3 (1.3)	5	[3.0:9.0]	0.40[b]
Control	27	5.4 (1.0)	5	[3.0:8.0]	
Suppression Span					
ADHD	22	7.1 (2.3)	7	[4.0:12.0]	0.08[b]
Control	27	8.1 (1.6)	8	[5.0:11.0]	
WURS-k Sum					
ADHD	22	34.0 (14.5)	36	[6.0: 53.0]	<0.001[a]
Control	27	12.2 (9.8)	10	[0.0:38.0]	
CAARS-S:L (ADHD-Index)					
ADHD	22	64.2 (9.2)	65	[48.0:81.0]	<0.001[b]
Control	27	44.5 (5.9)	43	[36.0: 62.0]	
CAARS-O:L (ADHD-Index)					
ADHD	18	64.3 (11.6)	64	[44.0:83.0]	<0.001[a]
Control	27	46.7 (6.2)	49	[37.0:58.0]	
Medication					
ADHD	Ritalin (n = 10); Concerta (n = 6); Oral contraceptives (n = 1); Trittico (n = 2); Focalin (n = 2); Wellbutrin (n = 1)*; Valdoxan (n = 1)*; Remeron (n = 1)*; Dafalgan (n = 1)*; Cannabis (n = 1)*; Tegretol (n = 1)*; Temesta (n = 1)*; Amitriptylin (n = 1)*; Prednison (n = 1); Aspirin (n = 2)*; Beta blocker (n = 1)*				
Control	Finasterid (n = 1); Verrumal (n = 1)*; Dafalgan (n = 1); L-Tyroxin (n = 1); Contraceptives (n = 5); Antibiotics (n = 2)				
Comorbidities					
ADHD	Sleep problems (n = 1); Epilepsy (n = 1)*				
Control	Hashimoto's thyroiditis (n = 2)				

Notes: *n* (f) = total number (females); ADHD = attention-deficit/hyperactivity disorder; WURS = Wender Utah Rating Scale; CAARS = Conners' Adult ADHD Rating Scales; SD = Standard Deviation.
[a] Two-tailed two-sample *t*-test.
[b] Wilcoxon rank sum test.
* Those subjects were not included in the subgroup "non-antidepressant, non-antiepileptic".

interview (Delmo et al., 2001) was performed for all children with ADHD to ensure the diagnosis of combined ADHD and to exclude subjects with comorbidities (Kaufman et al., 1997).

Subjects taking stimulants were asked to interrupt their medication at least 48 h before the neuropsychological assessment and at least 72 h before the measurements. All participants were asked to withdraw from caffeine, alcohol, and cigarettes for at least 6 h before the recordings.

ADHD symptoms were assessed with the German version of the Conners Adult ADHD Rating Scale-Self/Other (Christiansen et al., 2013), and the German short form of the Wender-Utah Rating Scale (WURS-k, (Retz-Junginger et al., 2003)). For the children we used the Conners-3D (Lidzba et al., 2013) and the strength and difficulties questionnaire (Goodman, 1997) in its German adaptation (Woerner et al., 2004). Four subtests of the HAWIK-4 (Petermann and Petermann, 2008) were used to estimate the intelligence of our children, namely Digit symbol coding, Similarities, Block Design and Digit Span, which were shown to be the strongest predictors for full IQ (Waldmann, 2008). For the adults we used the WIE-III (von Aster et al., 2006) and selected the equivalent subtests to those in the children group. Additionally, we used an electronic version of the Corsi block tapping task (normal and suppression) to assess the visuo-spatial short term working memory capacity of our children and adults (Beblo et al., 2004). All subjects gave their informed consent. The study was approved by the local ethics committee in accordance with guidelines of the Helsinki Declaration. Participants received 60 CHF in vouchers for the participation in this study.

2.2. Electroencephalography recordings

The EEG was recorded using two BrainAmp amplifiers (Brain Products, Munich, Germany). The EEG was recorded in DC mode at a resolution of 0.1 μV, with a 250 Hz low-pass filter. A 2.5 min eyes closed resting-state EEG recording was acquired. Data were sampled at 5000 Hz with a 3.3 mV input range, and off-line re-sampled to 500 Hz. EEG was recorded from sixty scalp electrode locations. All electrode positions of the 10–20 system plus the following 10–10 system sites were used: Fpz, AFz FCz, CPz, POz, Oz, Iz, F5/6, FC1/2/3/4/5/6, FT7/8/9/10, C1/2/5/6, CP1/2/3/4/5/6, TP7/8/9/10, P5/6, PO1/2/9/10, OI1/2 (total 60 scalp channels). O1/2 and Fp1/2 were placed 2 cm laterally from the standard positions for more even coverage (Halder et al., 2005). F1 served as the recording reference, and F2 served as the ground electrode. Two additional electrodes were placed below the outer canthus of each eye and two further electrodes were positioned adjacent to the sternum and on the left chest close to the heart, to record the electrocardiogram. Electrode impedances were kept below 30 kΩ.

2.3. EEG processing

EEG data were processed offline using the Brain Vision Analyzer software (version 2, Brain Products, Munich, Germany) and the Neurophysiological Biomarker Toolbox (http://www.nbtwiki.net/) (Hardstone et al., 2012; Poil et al., 2013). Transient artifacts such as muscle artifacts (on average 8 s) were

Table 2
Group characteristics of adolescents with ADHD and controls.

	n (f)	Mean (*SD*)	Median	Range	*p*
Age					
ADHD	7 (3)	15.1 (1.9)	14.6	[12.2:17.5]	0.55[a]
Control	19 (11)	15.6 (1.7)	15.8	[12.2:18]	
Estimated IQ					
ADHD	7	107.9 (17.8)	105.0	[81.0:128.0]	0.48[a]
Control	18	113.2 (11.7)	113.5	[97.0:133.0]	
Corsi Block Span Task					
Normal Span					
ADHD	7	5.3 (1.5)	5	[3.0:7.0]	0.47[b]
Control	19	5.8 (1.0)	6	[4.0:8.0]	
Suppression Span					
ADHD	7	6.7 (0.8)	7	[5.0:7.0]	0.02[b]
Control	19	8.5 (1.9)	8	[5.0:11.0]	
Conners Parents ADHD-index					
ADHD	7	68.9 (6.7)	71.0	[54.0:73.0]	<0.001[b]
Control	16	49.8 (12.5)	47.5	[31.0:68.0]	
SDQ Parents Total					
ADHD	7	18.0 (6.2)	20	[9.0:24.0]	0.002[a]
Control	15	6.5 (4.6)	5	[1.0: 16.0]	
Medication					
ADHD	Ritalin (n = 3); Concerta (n = 2); Symbicord (n = 1); Cannabis (n = 1)				
Control	Oral contraceptives (n = 1); Mepha-Isotretinoin (n = 1); Antihistamin (n = 1)				
Comorbidities					
ADHD	F81.0 Reading and writing problems (n = 1); F40.2 Isolated Phobia (needles, n = 1)				
Control	F40.2 Specific Phobia (Heights, n = 1); Bruxismus (n = 1); F40.2 Specific Phobia (Needles, n = 1)				

Notes: *n* (f) = total number (females); ADHD = attention-deficit/hyperactivity disorder; WURS = Wender Utah Rating Scale; CAARS = Conners' Adult ADHD Rating Scales; SD = Standard Deviation.
[a] Two-tailed two-sample *t*-test.
[b] Wilcoxon rank sum test.

removed from the EEG before independent component analysis (ICA). Data were digitally high-pass filtered for ICA cleaning (0.5 Hz, finite impulse response filter, and 4 s Hanning window). An extended ICA was calculated to decompose the measured signal into EEG and artifact components (Delorme and Makeig, 2004). Components assigned to either eye blink or muscle artefacts were excluded from the back projection. The EEG was then transformed to the average reference, and resampled to 200 Hz. There was no significant difference between the number of rejected ICA components (number of removed components: ADHD: 8 ± 3 (median ± *SD*); Control: 8 ± 4), or the length of signal rejected as transient artifacts.

The power spectral density was estimated using Bartlett's method, whereby the EEG signal was segmented into windows of 1024 points (5.12 s) and convolved with an equal length symmetric Hamming window.

The EEG (absolute) power was quantified as the integrated area of the EEG power spectrum for each respective frequency band; namely, delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), alpha-1 (8–10 Hz), alpha-2 (10–13 Hz), beta (13–30 Hz), and gamma (30–45 Hz).

We evaluated the central frequency in the same frequency bands. The central frequency was calculated based on previous studies (Klimesch, 1999; O'Gorman et al., 2013). The central frequency is a power weighed frequency, which provides an estimate on the dominant frequency in a given frequency band.

2.4. Linear regression analysis

A linear regression analysis on power values was performed with the Matlab statistics toolbox using the LinearModel function (MATLAB and Statistics Toolbox Release 2012b, The MathWorks, Inc., Natick, Massachusetts, United States), which uses QR decomposition to solve the least-square fitting problem. The explained (i.e., modelled) variance was calculated as the square-root of the Pearson correlation between the real and predicted age. The prediction error of the fit was calculated as the difference between the real age and the predicted age.

2.5. SVM classification

To classify subjects as belonging to ADHD or control groups using multiple biomarkers, we used a least-square SVM with a Gaussian radial basis kernel as implemented in the LSSVM Matlab toolbox (Pelckmans et al., 2002; Suykens and Vandewalle, 1999) (http://www.esat.kuleuven.be/sista/lssvmlab/). A SVM is a method to perform binary classification by identification of separation hyper-planes in a multi-dimensional space. This multi-dimensional space is constructed by kernel based mapping from the input data. The hyper-planes are found by optimizing the margin between the hyper-plane and the data points (the support vectors). The regularization parameter (determining the error margin) and the squared kernel bandwidth were tuned using leave-one-out cross-validation with the classification accuracy as the cost function. The input to the SVM was the median across channels that showed a significant difference between ADHD and control subjects using a Student's *t*-test ($p < 0.05$, uncorrected). For biomarkers with no significant effects between ADHD and control, biomarker data from all channels were averaged before being entered into the SVM. For the SVM analysis we used the adult group that was age matched and did not take antidepressants drugs in order to avoid potential interactions from age and antidepressants drugs. We report median sensitivity and specificity values from a 2-fold cross-validation made with 100 replications (see Section 2.6below).

Table 3
Group characteristics of children with ADHD and controls.

	n (f)	Mean (*SD*)	Median	Range	*p*
Age					
ADHD	19 (9)	10.6 (1.1)	10.6	[8.6:13.1]	0.78[a]
Control	22 (8)	10.8 (1.7)	10.8	[8.1:14.7]	
Estimated IQ					
ADHD	19	99.2 (12.9)	96.0	[83.0:125.0]	0.004[b]
Control	22	111.8 (15.7)	113.0	[68.0:132.0]	
Corsi Block Span Task Normal Span					
ADHD	19	4.26 (0.9)	4.0	[3.0:6.0]	0.03[b]
Control	22	4.82 (0.6)	5.0	[4.0:6.0]	
Suppression Span					
ADHD	19	5.42 (1.46)	5.0	[3.0:8.0]	0.23[a]
Control	22	6.00 (1.60)	6.0	[3.0:9.0]	
Conners Parents ADHD-index					
ADHD	19	69.7 (5.2)	73.0	[58.0:73.0]	<0.001[b]
Control	22	54.0 (7.8)	54.5	[41.0:71.0]	
SDQ Parents Total					
ADHD	19	19.0 (7.0)	17.5	[10.0:34.0]	<0.001[b]
Control	22	6.0 (3.6)	5.5	[1.0:15.0]	
Medication					
ADHD	Ritalin (n = 10); Concerta (n = 3); Antibiotics (n = 1); Dexamine (n = 1); Similasan (n = 1)				
Control					
Comorbidities					
ADHD	F81.0 Reading and writing problems (n = 1); F98.0 Enuresis (n = 1); F40.2 Specific Phobia (n = 4); F82 Specific developmental disorder d motor functions (n = 2); F81.2 dyscalculia (n = 1)				
Control	Sub-clinical attention problems (n = 1)				

Notes: *n* (f) = total number (females); ADHD = Attention-Deficit/Hyperactivity Disorder; WURS = Wender Utah Rating Scale; CAARS = Conners' Adult ADHD Rating Scales; SD = Standard Deviation.
[a] Two-tailed two-sample t-test; subscript.
[b] Wilcoxon rank sum test.

2.6. Classification measures

To evaluate the outcome of our classification we use three different measures:

- Sensitivity: defined as the (number of correctly classified ADHD subjects)/(number of ADHD subjects).
- Specificity: defined as the (number of correctly classified control subjects)/(number of control subjects).
- Matthew correlation coefficient: explains the correlation between the outcome and the expected outcome (Baldi et al., 2000).

A Matthew correlation coefficient higher than 0.18, sensitivity higher than 63%, and specificity higher than 63%, means that the classification is significantly different from a random classification (Monte Carlo simulation, 5000 iterations, $n = 36$ (the smallest group size tested in the SVM (adult groups)), $p < 0.05$; these results depend on the sample size, such that the threshold levels are lower for larger sample sizes). Perfect classification would give a Matthew correlation coefficient of 1, sensitivity of 100%, and a specificity of 100%.

2.7. Statistics

To test for group differences we used a student's *t*-test on all channels in group comparisons, and subsequently corrected for multiple comparisons using as a minimum binomial correction (Poil et al., 2011), or the more conservative Hochberg step-up correction where possible. Hochberg correction is as conservative as Bonferroni correction, but has better power (Hochberg and Benjamini, 1990). Bootstrap confidence intervals were used to test for significant differences between variance explained values, as defined by no overlap between the 0 and the 95th percentile difference confidence interval. Confidence intervals were calculated using non-parametric bias corrected and accelerated bootstrap ($n = 5000$) (DiCiccio and Efron, 1996). Two-way ANOVA was

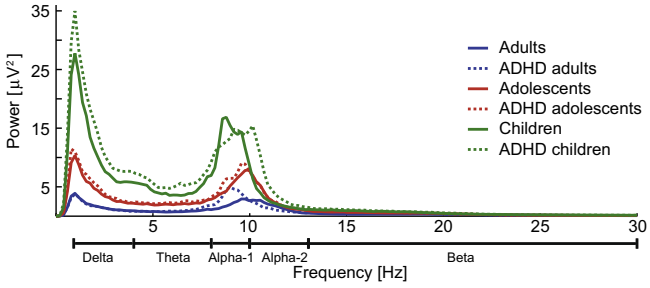

Fig. 1. Spectral power is differentially impaired in ADHD depending on age group. Grand average power spectrum of eyes-closed rest EEG (averaged across all channels) from different age groups for control (*line*) and ADHD (*dashed line*) children (*green*), adolescents (*red*), and adults (*blue*). The power spectrum reveals clear developmental differences and differential effects of ADHD depending on the age group. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

performed using Matlab. We used a significance threshold of $p = 0.05$, corrected for multiple comparisons for all tests.

3. Results

3.1. The power spectrum of the resting-state electroencephalography is sensitive to development and ADHD

In keeping with the known developmental trajectory of the power spectrum of the resting-state electroencephalogram (Gasser et al., 1988; Wackermann and Matousek, 1998), we observed the typical developmental pattern; such as, low frequency band (delta–theta) power decreases with development in both control and ADHD subjects (Fig. 1). In the children we observe higher delta and alpha-2 power in ADHD in mainly the frontal region compared with control children (binomial correction, $p < 0.05$) (Figs. 1 and 2A). The higher alpha-2 power could indicate a shift in alpha frequency as seen in Fig. 1, but this did not reach significance (Fig. 2A, right panel, $p > 0.05$, binomial correction). We observe no differences between ADHD and controls in the adolescent group (binomial corrected, $p > 0.05$, data not shown). In the adult group, we found higher beta power (binomial corrected, $p < 0.05$) in the frontal midline and bilaterally in the parietal and occipital regions as well as lower alpha central frequency (binomial corrected) in fronto-parietal regions in ADHD compared to control subjects (Fig. 2B, for t-values see Supplementary Fig. S2). We also repeated

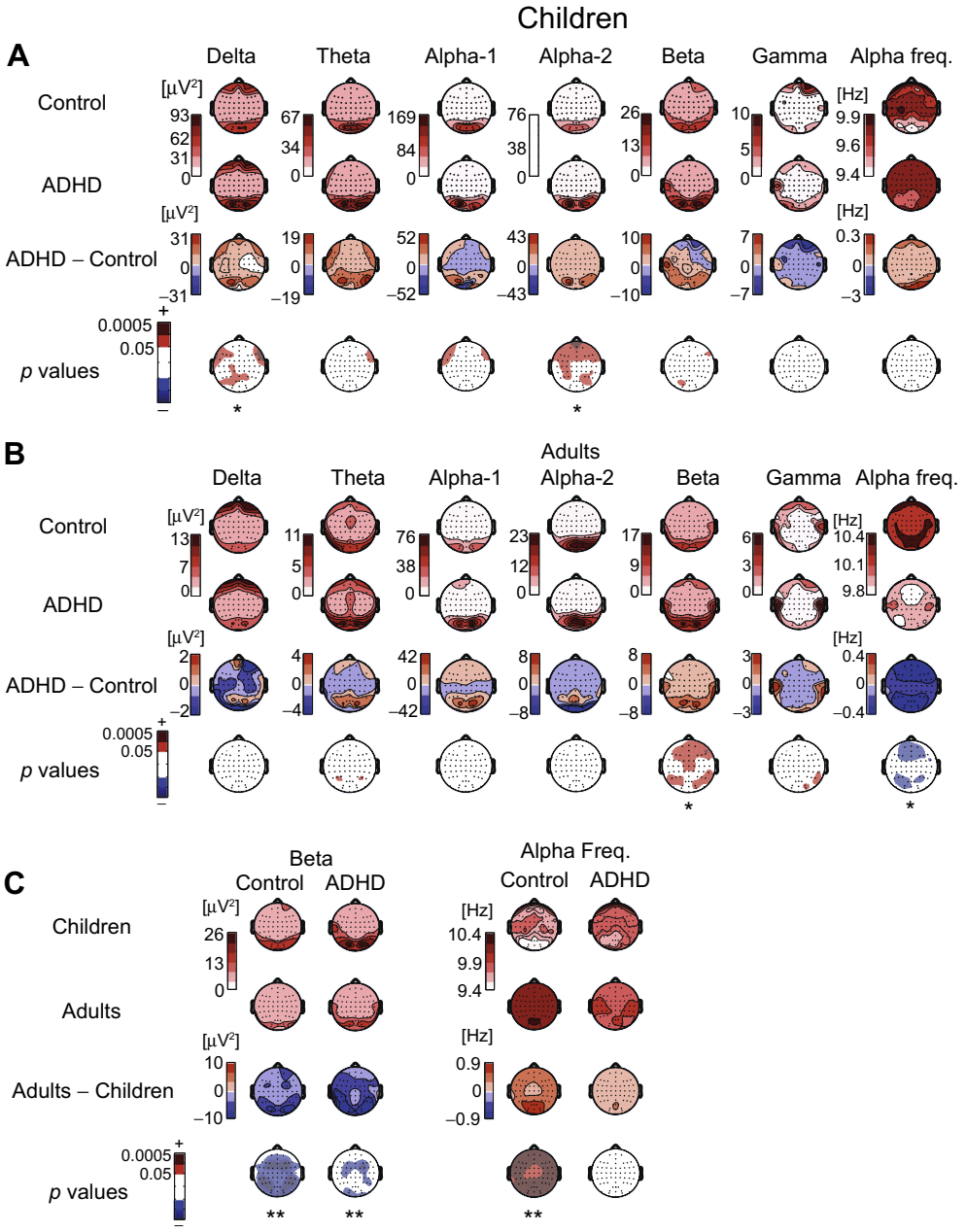

Fig. 2. ADHD children have higher alpha-2 power, whereas adults have higher beta power and lower alpha frequency. (A) Topographic plots of power for different frequency bands for children. Unpaired t-test. We only observe ADHD effects in alpha-2 (10–13 Hz) power and delta (1–4 Hz) power (binomial corrected, $p < 0.05$). *Binomial corrected, **Hochberg corrected. (B) Same as in (A), but for adults. We only observe ADHD effects in beta (13–30 Hz) power and central alpha frequency (binomial corrected, $p < 0.05$). (C) Topographic plots of developmental differences in beta power and alpha frequency. Beta power is lower in adults compared with children in both ADHD and control subjects, but the difference includes more electrodes in control subjects than ADHD. The alpha frequency is higher in control adults compared with children, but not in ADHD. *Binomial corrected, **Hochberg corrected.

this analysis on the adult group excluding subjects taking antidepressants and antiepileptic drugs (and excluding subjects from both groups for age matching), and found equivalent effects in beta power and alpha central frequency ($n = 11$, ADHD-subjects, Supplementary Fig. S3).

We observed significant developmental changes in beta power and alpha central frequency in control subjects in all regions between children and adults (Hochberg correction, Fig. 2C). However, in ADHD we only found a small region of developmental change between children and adult in beta power in fronto-central and occipital regions (Hochberg correction, Fig. 2C), and no significant changes in alpha central frequency (Fig. 2C).

To understand these results better we also performed a two-way ANOVA with diagnosis and age-group (children and adults) as the two factors. To reduce the number of multiple comparisons we only performed the ANOVA in the four biomarkers reported to show significant differences between control and ADHD above. The ANOVA revealed a significant effect of age-group in all these biomarkers (delta, alpha-2 and beta power, and alpha frequency) (Hochberg corrected), but only an effect of diagnosis in beta power (bionomial corrected). However, a significant interaction between the two factors was found in the three other biomarkers (delta, alpha-2 power and alpha frequency).

3.2. EEG biomarkers follow log–log linear relationship with age

In order to quantify the developmental trajectory of EEG changes further, we fitted a log-linear regression model to the power in different frequency bands (see Section 2). Based on the well-known age-related changes in delta and theta power, we first investigated a log-linear regression model consisting only of delta and theta power (Fig. 3A). We found a strong log-linear relation between the changes in the power in delta and theta, and age in control subjects (Fig. 3A). Delta and theta power explained on average 68% of the variance in control subjects (Fig. 3C). The log-linear regression fitted to control subjects also fitted the ADHD subjects quite well with on average 70% explained variance (Fig. 3C).

We then investigated if biomarkers other than delta and theta power would follow a similar log–log linear model (Fig. 3B). For the control subjects, after fitting a log linear model of alpha, alpha-1, alpha-2, beta, and gamma power and central frequency combined, we observed a similar quality of fit to that found for

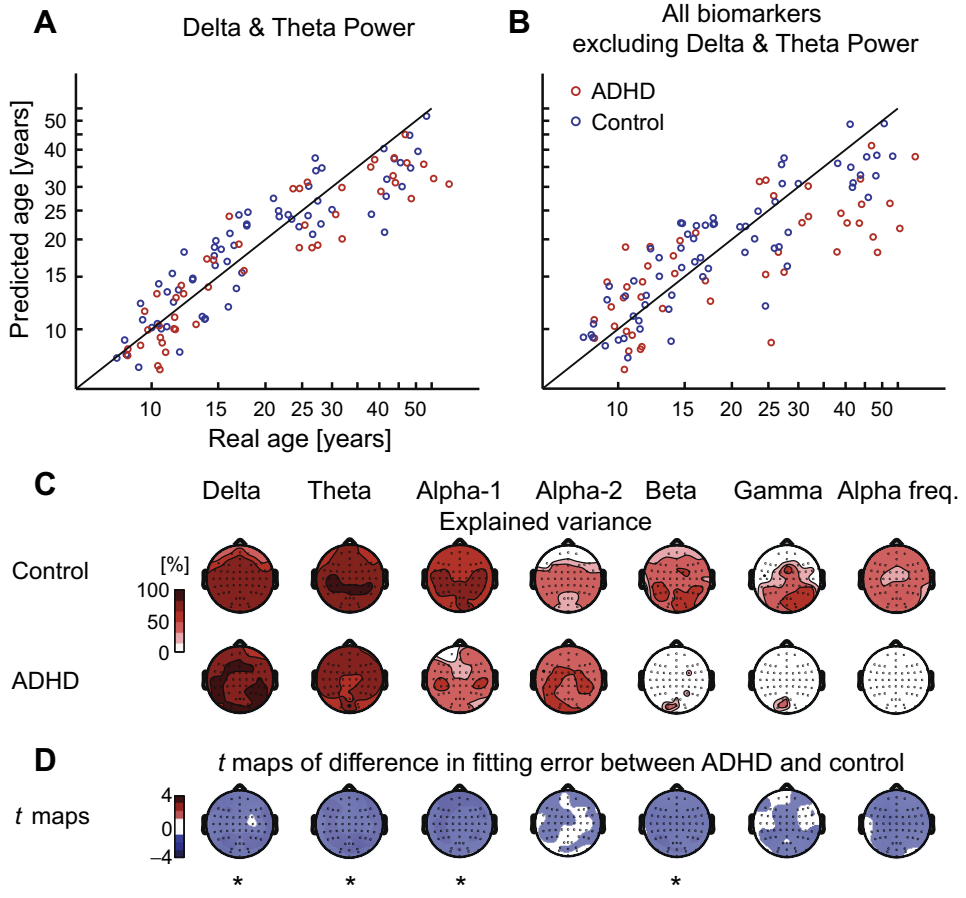

Fig. 3. Linear regression analysis reveals that delta and theta power are sensitive to developmental effects, but not to ADHD dependent developmental impairments. (A) Log-linear regression analysis including only delta and theta power, fitted using control subjects for Control (*blue*) and ADHD (*red*). Log linear regression gives a good prediction of developmental effects. Results in this figure were based on an average across all channels. The black line shows the perfect fit between real and predicted age. (B) Log-linear regression analysis including alpha-1, alpha-2, beta, gamma power, and central frequency, fitted using control subjects for control (*blue*) and ADHD (*red*). The ADHD adult subjects are predicted to be younger than their real age. Results in this figure were based on an average across all channels. The black line shows the perfect fit between real and predicted age. (C) Explained variance is high for delta and theta power in both ADHD and control, but lower in ADHD compared with control in other frequency bands. Topographic plots of explained variance for the correlation real age *versus* predicted age based on log-linear regression of control subjects. (D) Significant negative differences in the deviation from perfect age prediction between controls and ADHD subjects in delta, theta, alpha-1, and beta power. Topographic *t*-value maps (two tail *t*-test). Blue means ADHD deviates more negatively than control from perfect fit of real age *versus* predicted age from log-linear regression of control subjects. Significant effects at $p \sim 0.05$ level are at $t \sim \pm 2$. *Significant, binomial corrected, $p < 0.05$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the delta and theta power (71% explained variance, Fig. 3C). However, we also observed that the EEG markers from ADHD subjects – when analysed using the regression model fitted using control subjects – were poorly fitted (43% explained variance, bootstrap test, $p < 0.05$), such that ADHD subjects appear to show a younger EEG profile relative to that predicted by their real age (one-tail Wilcoxon signed rank test, $p < 0.05$) (Fig. 3B). In a similar fashion we found that adult control subjects were predicted to be older if fitted using a model trained on all ADHD subjects (one-tail Wilcoxon signed rank test, $p < 0.05$) (*data not shown*).

We next explored individual biomarkers using the log-linear regression model to characterize the explained variance and the difference between deviations from a perfect prediction of age (Fig. 3C and Supplementary Fig. S4). We found strongly reduced explained variance in beta power (26% (percentage points difference, averaged across significant channels, $p < 0.05$, binomial, bootstrap test) and gamma power (17%), alpha central frequency (24%), and a moderately reduced explained variance in theta (12%, 13 significant channels), and alpha-1 (27%, only significant in 6 channels) power in ADHD (Fig. 3D). This result is clearly coupled with the atypical development in beta power and central alpha frequency described above (Fig. 2C). Delta, theta, alpha-1, and beta power predicted the age significantly worse (and younger) in ADHD than control subjects (*t*-test, binomial corrected, $p < 0.05$, Fig. 3D).

To elucidate the age-related EEG effects amongst ADHD and controls in more detail, we divided our subjects into two groups: young (age <18 years, $n = 63$, 38 ADHD subjects) and old (age >20 years, $n = 49$, 27 ADHD subjects). For subjects below the age of 18 years, mainly delta and theta power showed high explained-variance with respect to the log-linear fit describing the developmental changes with no difference between control and ADHD subjects (not significant, bootstrap test, $p > 0.05$, Fig. 4A). The variance explained by the log-log model for subjects below age 18 years was only different between ADHD and control for beta power (12%, bootstrap $p < 0.05$). We did not observe any difference in the error of predicted age between control and ADHD for subjects below age 18 years (Fig. 4B). In the young age group, the developmental trajectories of power in ADHD in all frequency bands were not significantly different from those of control subjects. For the older age group, we observe lower explained variance in ADHD subjects in delta (2%, averaged across all channels) and theta (36%) power (bootstrap test, Fig. 4C). Theta, alpha-1, beta power and alpha frequency predict a younger age of ADHD subjects compared with their real age (Fig. 4D).

Next we investigated whether a SVM classification might reveal hidden separation boundaries that would classify ADHD better than the univariate tests. Using a SVM with multiple biomarkers, namely the power in all frequency bands as well as central frequency (in all frequency bands), we obtained a classification of adult ADHD with a sensitivity of 67 ± 33% (median ± interquartile range), specificity of 83 ± 33%, and a Matthew correlation coefficient of 0.5 ± 0.3 (Fig. 5A). The classification performance was good in all channels (Fig. 5B), and significantly different from a random classification (see Section 2). For children, the SVM performed

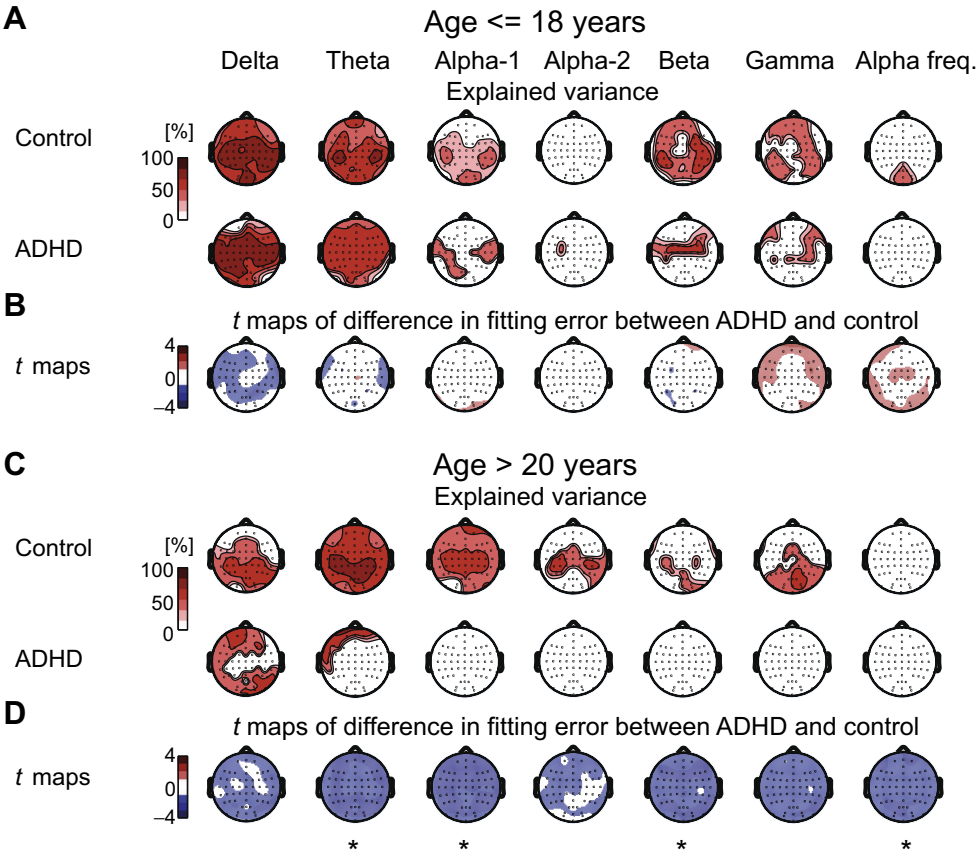

Fig. 4. Frontal and parietal theta, alpha-1, and beta power predict a lower age for old ADHD patients, but no effects are observed for younger ADHD patients. (A) Topographic plots of explained variance (based on the log-linear regression of control subjects across all age groups) for the correlation of real age *versus* predicted age for subjects with age below or equal 18 years. (B) Topographic *t*-maps of the difference between the predicted age using log-linear regression analysis and the real age using different spectral EEG biomarkers for ADHD patients with age below or equal 18 years. (C) Same as in (A), but for subjects above age 20 years. (D) Same as in (B), but for subjects with age above 20 years. Frontal and parietal alpha-1 and mid-central and parietal beta predict lower ages of the older ADHD patients. *Significant (binomial corrected, $p < 0.05$).

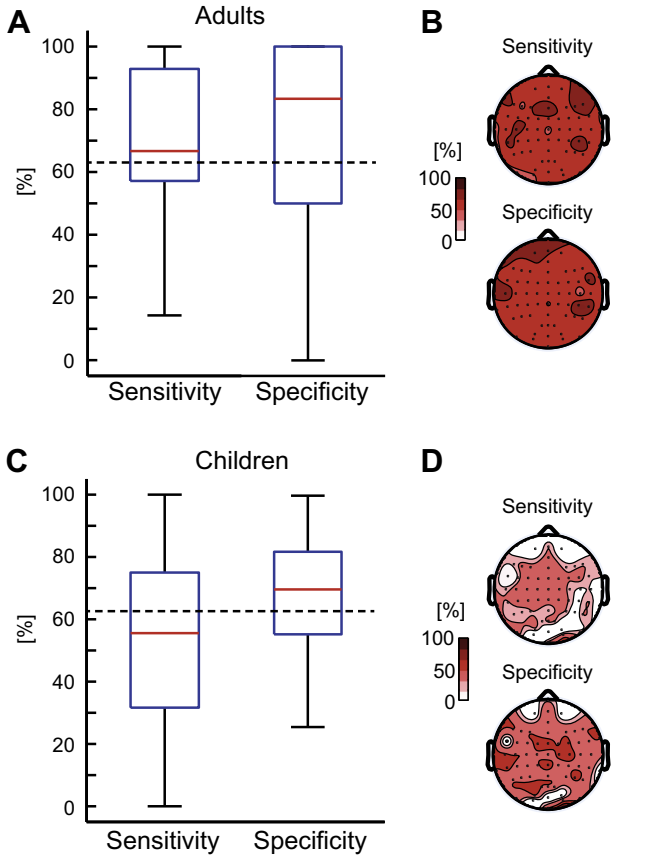

Fig. 5. Support vector machine classification gives good classification of adult subjects, but not of children. (A) Support vector machine classification of adult ADHD subjects (without antidepressants and anti-epileptic drugs) *versus* adult control subjects (age-matched), using power and central frequency in all frequency. Good classification is found with sensitivity around 67 ± 33% and specificity around 83 ± 33%. Boxplot of 2-fold cross-validated statistics (n = 100). The boxplot shows the media, 25th and 75th percentiles, the whiskers show extend of data up to 1.5 times the interquartile range. The dashed line indicates a significant classification performance (i.e., not random). (B) Topographic plot of the sensitivity and specificity based on SVM analysis of biomarkers from each channel. (C) Same as in (A), but for children. Poor classification is found with sensitivity 56 ± 43%, and specificity 70 ± 27%. (D) Same as in (B), but for children.

worse with a sensitivity of 56 ± 43%, specificity of 70 ± 27% (Fig. 5C), and Matthew correlation of 0.2 ± 0.2, which is within the range of random classification (see Section 2). We also tested whether the EEG-based classification of the children would improve when separating the ADHD and control groups further by excluding those with potentially subclinical or milder impairment based on their symptom scores. To this end we excluded all control children with Conners scores >62 (n = 3, suggestive of subclinical impairment), and all children with ADHD but Conners scores <62 (n = 2, consistent with milder impairment). The results indicated only slightly better overall classification, with somewhat higher Sensitivity (63 ± 38%) and reduced Specificity (67 ± 22%). The topographic map comparisons for ADHD effects in these further separated groups of children also remained largely unchanged, indicating again nonsignificant classification for the theta and beta bands as well as for the theta/beta ratio. Only the increase in alpha-2 power in ADHD children became more prominent and suggested faster posterior alpha, while the differences in the delta band became even less prominent (Supplementary Fig. S5). This finding confirms our univariate observation that spectral biomarkers are not sufficiently altered in the eyes-closed resting EEG of ADHD children for these biomarkers to be used for automatic classification.

4. Discussion

This study investigated a group of ADHD and control subjects across a broad age range using EEG during an eyes-closed resting state with spectral biomarkers. We observed that adult ADHD subjects have higher beta power and lower alpha central frequency than adult control subjects, whereas ADHD children have higher delta power and higher alpha-2 power than control children. We show that a log-linear model of the EEG spectral changes can explain the developmental changes in most frequency bands in both control and ADHD. However, when our model is fitted to control subjects, the adult ADHD subjects are predicted to have a younger age than their real age. We showed that this is caused by atypical age-related changes in the theta, alpha-1 and beta frequency bands. This confirms our hypothesis that ADHD subjects have a differential maturation profile relative to control subjects. The SVM classification confirmed the univariate analysis, as only in adults specificity (and to less extent sensitivity) values different from random classification (in contrast to children).

Our findings suggest that adult ADHD is associated with atypical developmental changes in EEG biomarkers, and thus provide further support for the notion that ADHD in adults is a valid clinical diagnosis (Faraone et al., 2000; Moncrieff and Timimi, 2011; Tyrie and Knibbs, 2012).

4.1. Elevated beta power and lower alpha frequency in ADHD adults

In our sample, ADHD adults demonstrated elevated beta power combined with a lower alpha frequency in ADHD adults, but these effects were not seen in ADHD children. The typical finding in children with ADHD is a lower beta power relative to controls (Barry et al., 2003). However, elevated beta activity has been observed in a sub-group of children with ADHD, who are more likely to be diagnosed with ADHD combined type and have low IQ (Clarke et al., 2001a). This finding is consistent with observations from our study where we only have combined type ADHD subjects, although our ADHD subjects have average or above average IQ.

Elevated alpha and beta power have also previously been observed in ADHD adults (Bresnahan and Barry, 2002), although other studies did not find higher beta power in adults (Bresnahan et al., 2006; Koehler et al., 2009; Liechti et al., 2013). Variable results have also been found on alpha power, with some studies reporting elevated alpha power, and others reporting lower alpha power (Chabot and Serfontein, 1996; Clarke et al., 2011; Koehler et al., 2009; Woltering et al., 2012). These variable findings again highlight the diverse nature of ADHD. The difference in findings between studies may be caused by differences in subject ages, associated with strong developmental changes, or by different diagnostic standards of ADHD between studies.

Elevated beta power could index the presence of some form of combined type of ADHD. At least in children, it was shown that absolute EEG beta power is elevated in girls with the combined types relative to girls showing more inattentive symptoms (Dupuy et al., 2013), but that girls with ADHD showed lower absolute beta EEG power than controls. Even in college students with ADHD, reduced alpha and beta power were seen compared to a nonclinical comparison group (Woltering et al., 2012). These findings of different beta power manifestations might index anomalous arousal mechanism and hyperactive-impulsive symptoms, which are not present in control subjects, and which persist into early adulthood. Thus, one can speculate if the description of ADHD should comprise not only few isolated dysfunctions but also show rather include more complex models integrating the heterogeneity of the clinical manifestations of ADHD (Cortese et al., 2012). Findings from structural and functional neuroimaging on ADHD suggest

the involvement of developmentally abnormal brain networks related to cognition, attention, emotion and sensorimotor functions but also (as shown in this study) that ADHD children and adults show persistent altered EEG power and frequency, compared with controls. Our results emphasize rather broad changes of EEG power in ADHD relative to controls (Fig. 3D), supporting the notion of disrupted network functions in ADH. These significant changes in EEG power could be linked to alterations on the molecular level (e.g., dysfunctions in the dopaminergic, adrenergic, serotoninergic and cholinergic pathways) or to genetic dispositions (e.g. a heritability of ~60–75% suggests that a plethora of genes interact with environmental factors to increase the susceptibility to ADHD). Indeed, EEG power effects persist into adulthood (Fig. 5), which makes it likely that resting state EEG classification approaches might be a useful tool capturing some of this molecular-genetic dysfunctions. Taken in combination with previous findings in the literature, results from the present study underscore the need for larger study samples of this inhomogeneous patient population.

4.2. Atypical development in old but not young subjects

Our results suggest that different spectral measures are affected in ADHD patients at different developmental stages. The higher beta power and lower central alpha frequency observed in adult ADHD subjects relative to control subjects (Fig. 2B) is consistent with weaker developmental changes in these markers between ADHD children and adults (Fig. 2C). The ANOVA analysis partially confirmed this with a significant interaction between age-group and diagnosis in alpha frequeny. The atypical development seen in ADHD from childhood to adulthood therefore seems to underlie the ADHD effects we observe in adults (Callaway et al., 1983; Shaw and Rabin, 2009).

Our exploration of the developmental changes using linear regression modelling and SVM revealed effects that did not appear in pure one-to-one absolute power band group comparisons, suggesting that statistical methods that integrate data across multiple age groups may reveal new and otherwise hidden information with regard to developmental and disease-related effects. These methods may also be relevant for other disorders where developmental changes occur. Specifically, we observed that older ADHD subjects had a predicted age younger than their real age if modelled using theta, alpha-1, or beta power. This relates well to a recent observation of ADHD effects only in older children (age ~13 years) but not in younger children (age ~9 years) (Liechti et al., 2013). This pattern can be considered a type of maturational lag characterizing only the older ADHD subgroup. That no such abnormality was found in children could reflect an ADHD effect on late maturation, but would be unrelated to the prominent behavioural abnormalities of ADHD children. Alternatively, it may indicate that a developmental lag seen in the EEG profile is a marker of persistent ADHD, which is by definition more strongly represented in the older ADHD group. This intriguing hypothesis would imply that those ADHD children with developmental lag patterns are at particular risk to develop persistent ADHD, and could be tested through longitudinal studies. A maturational lag hypothesis of ADHD has previously been suggested (Clarke et al., 2002b), and ADHD has been linked to a delay of cortical maturation (Shaw and Rabin, 2009), and delayed maturation of inhibition related event related potentials (Doehnert et al., 2010, 2012). Our results only partly confirm this hypothesis because we did not find any developmental differences for subjects below age 18 years. Rather we observe a change in the developmental trajectory of older subjects with ADHD. The lack of significant differences in developmental trajectory between children with ADHD and control children may appear surprising, but is consistent with EEG work suggesting that a developmental lag only characterizes subgroups of children with ADHD (Clarke et al., 2002a, 2011), and not typical clinical ADHD groups (Liechti et al., 2013). The lack of a significant developmental effect during adolescence may also be due to the limited number of ADHD adolescents in our sample, giving lower power and a lower dynamic range to fit the developmental changes. One limitation of our study is that although all age groups were recruited and diagnosed using analogous criteria and scales, we cannot exclude the possibility that differences in ADHD assessment methods may contribute to the better ADHD discrimination in adults.

4.3. SVM: a useful tool for classifying ADHD adults but not for ADHD children

The SVM analysis demonstrates that spectral markers of electroencephalography are predominantly affected for adult ADHD subjects. Our SVM results in adults should be considered with as preliminary, because of the low number of subjects, and we caution that they may potentially not generalize to a broader population of subjects. However, our SVM classification performed well and with a similar accuracy reported in previous studies (Abibullaev and An, 2012; Cheng et al., 2012; Mueller et al., 2011; Tenev et al., 2013), which found classification accuracy around 70% for ADHD *versus* control classification of adult subjects. Tenev et al. (2013) found better classification performance (accuracy around 80%) by combining information from resting (eyes-open) and task EEG measurements in the classification (see also Liechti et al. (2013)). However, it is difficult to interpret the study by Tenev et al. (2013), because is it unclear which spectral markers were included in the SVM analysis. Task specific cognitive event-related potentials have also shown good classification power of ADHD, ranging from 73% in children using discriminant analysis (Smith et al., 2003) up to a high sensitivity and specificity of 91% using SVM in adults (Mueller et al., 2011), while fMRI based classification of task related activations reached 77% (Hart et al 2013). Our study adds that (in addition to the linear regression analysis) SVM analysis using resting EEG power enables to classify ADHD adults from control adults, indicating that no task is required for a good classification performance. The SVM revealed worse classification of children, in contrast to other studies reporting classification of ADHD children and adolescents with sensitivity and specificity of 90% and 94% (Snyder et al., 2008), or 87% and 94% (Monastra et al., 2001) using the theta/beta power ratio from a single vertex electrode. These results should, however, be viewed cautiously in the light of the lack of theta/beta effects observed in children and adolescents in the present study and other more recent studies (Supplementary Fig. S1) (Arns et al., 2013; Clarke et al., 2011; Loo et al., 2013; Magee et al., 2005). In the study by Magee et al (2005) ADHD children (7–13 years) were classified with a sensitivity of 95%, but only a specificity of 40% (Magee et al., 2005). Similar, Ogrim et al (2012) could not classify children with ADHD, despite the fact that 25% showed elevated theta power when compared to controls (Ogrim et al., 2012). These observations underline the considerable EEG heterogeneity in childhood ADHD, and the inadequacy of theta power as a reliable ADHD classification marker. Our SVM analysis suggests that spectral biomarkers alone are not sufficient for classifying ADHD children, implying that additional biomarkers from the EEG or other modalities may improve the classification significantly (considering children only).

In a recent study ADHD children and adults were examined (relative to healthy controls) by an eyes-closed and eyes-open resting EEG and multivariate analyses while focusing only on theta and beta bands (Liechti et al., 2013). Although strong and consistent developmental theta power decreases were found, theta power was not higher in ADHD. Further, a discriminant analysis using resting EEG (theta and beta) power and event-related potential

measures indicated no contribution of EEG power elevations in children with ADHD. In fact, spectral resting EEG markers led only to a successful discrimination for age but not for ADHD children (as in our study). In this light, the absence of a clear discrimination between healthy children and children with ADHD in our study is not surprising, even though the most promising spectral EEG biomarkers were included in the discrimination analysis.

4.4. Absent ADHD-related effects in theta power

For children we did not observe effects of ADHD in theta power, which is in contrast to the findings of some previous resting EEG studies examining mainly ADHD children (Barry et al., 2003, 2009; Clarke et al., 2001a; Snyder and Hall, 2006; Woltering et al., 2012). However, other EEG studies also did not find theta power effects (Liechti et al., 2013; Loo et al., 2009; Ogrim et al., 2012; Swartwood et al., 2003; van Dongen-Boomsma et al., 2010). It has previously been speculated that the inconclusive findings of theta power effects could be caused by a difference in sub-group (pre-dominantly inattentive *versus* pre-dominantly hyperactive) composition of the ADHD group (Arns et al., 2013; Clarke et al., 2011). However, all ADHD patients in the present study suffered from the combined subtype, reported to exhibit a particularly prominent theta increase (Clarke et al., 1998). Alternatively, different EEG cleaning strategies (Liechti et al., 2013), a trend towards increased theta in the normal controls due to decreasing sleep duration (Arns et al., 2013), or the heterogeneity of ADHD in terms of EEG subtypes have been implicated. Up to nine different EEG sub-types have been suggested to exist in children with and without ADHD (Arns et al., 2008; Chabot and Serfontein, 1996; Clarke et al., 2011; Johnstone et al., 2005), which might explain differences between studies due to uneven sampling of these sub-groups.

We found higher spectral power in all frequency bands in ADHD children compared with control children, although this difference in power only reached significance in the delta and alpha-2 bands. The lack of theta effect may be caused by high variance in this measure (van Dongen-Boomsma et al., 2010). Overall, there is some consensus that theta power cannot be considered a reliable biomarker of ADHD, based on a recent meta-analysis investigating nine studies of in total 1253 ADHD children/adolescents (Arns et al., 2013), although another meta-analysis by (Snyder and Hall, 2006) reached a different conclusion. The delta effects seem bound to lateral eye movements, which very likely is caused by the ADHD subjects moving more during measurements. Our finding of higher alpha-2 power in ADHD children is in contrast to studies either finding lower or equal level of alpha power in ADHD children (Bresnahan et al., 1999; Clarke et al., 1998), although these different findings may be bound to the difference in frequency band between alpha and alpha-2. We also did not observe effects in alpha-1 although this frequency band typically has been associated with attention (Klimesch, 1997), which also shows the importance of dissecting the power spectrum in narrow frequency bands (Klimesch, 1997). It can be speculated that the higher alpha-2 power indicates a compensatory function for ADHD symptoms, since increases in alpha-2 power through neurofeedback training have been associated with higher cognitive performance (Hanslmayr et al., 2005; Zoefel et al., 2011).

5. Conclusion

This study reveals strong atypical development of resting EEG power in theta, alpha-1, beta, and alpha central frequency in ADHD patients. The effects in theta and alpha-1 were obscured by normal developmental changes, but were revealed by linear regression modeling of the developmental effects. Based on classification analysis, we conclude that ADHD is not characterized by a maturational lag, but rather by an atypical developmental trajectory in the adults with ADHD, possibly related to persistence of ADHD in this subject group, and that advanced spectral EEG based classification may identify predictive ADHD markers. These EEG biomarkers may potentially be used for prognostic purposes, e.g., in the identification of the most suitable treatment option for a specific patient group, or for monitoring of treatment response.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.clinph.2013.12.118.

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