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Brain Topogr (2013) 26:135–151
DOI 10.1007/s10548-012-0258-6

ORIGINAL PAPER

Diagnostic Value of Resting Electroencephalogram in Attention-Deficit/Hyperactivity Disorder Across the Lifespan

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Received: 18 May 2012 / Accepted: 11 September 2012 / Published online: 9 October 2012
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Abstract The resting electroencephalogram (EEG) reflects development and arousal, but whether it can support clinical diagnosis of attention-deficit/hyperactivity disorder (ADHD) remains controversial. Here we examined whether theta power and theta/beta ratio are consistently elevated in ADHD and younger age as proposed. Topographic 48-channel EEG from 32 children (8–16 years) and 22 adults (32–55 years) with ADHD and matched healthy controls ($n = 30$ children/21 adults) was compared. Following advanced artefact correction, resting EEG was tested for increased theta and theta/beta activity due to ADHD and due to normal immaturity. Discriminant analyses tested classification performance by ADHD and age using these EEG markers as well as EEG artefacts and deviant attentional event-related potentials (ERPs). No consistent theta or theta/beta increases were found with ADHD. Even multivariate analyses indicated only marginal EEG power increases in children with ADHD. Instead, consistent developmental theta decreases were observed, indicating that maturational lags of fewer than 3 years would have been detected in children. Discriminant analysis based on proposed simple spectral resting EEG markers was successful for age but not for ADHD (81 vs. 53 % accuracy). Including ERP markers and EEG artefacts improved discrimination, although not to diagnostically useful levels. The lack of consistent spectral resting EEG abnormalities in ADHD despite consistent developmental effects casts doubt upon conventional neurometric approaches towards EEG-based ADHD diagnosis, but is consistent with evidence that ADHD is a heterogeneous disorder, where the resting state is not consistently characterised by maturational lag.

Electronic supplementary material The online version of this article (doi:10.1007/s10548-012-0258-6) contains supplementary material, which is available to authorized users.

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Keywords Attention-deficit/hyperactivity disorder (ADHD) · Electroencephalogram (EEG) · Brain maturation · Resting state · Theta · Beta

Abbreviations

ADHD	Attention-deficit/hyperactivity disorder
CD	Conduct disorder
CNV	Contingent negative variation
DA	Discriminant analysis
Goodsegs	Artefact-free segments
CPT	Continuous performance tests
CTRL	Healthy control group
Ec	Eyes-closed
EEG	Electroencephalogram
Eo	Eyes-open
EOG	Electrooculogram
ERP	Event-related potential
ICA	Independent component analysis
ODD	Oppositional defiant disorder
R	Pearson correlation coefficient

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common psychiatric disorder with childhood onset that often persists throughout the lifespan. Its severe combined form is characterized by symptoms of inattention, hyperactivity, and impulsivity. Clinical diagnosis of ADHD relies on assessing behavioural symptoms and impairment through interviews and questionnaires following standard diagnostic manuals (e.g. DSM-IV; AAP 2000). Objective and reliable biological markers of ADHD would provide a valuable addition. Due to their relation to arousal, attention, and development (Matousek and Petersen 1973), neurophysiological measures of brain functioning are promising ADHD markers (Barry and Clarke 2009; Clarke et al. 2001a). Despite an early report on both spectral electroencephalogram (EEG) and visual event-related potentials (ERPs) markers in ADHD (Callaway et al. 1983), no such marker has yet reached clinical acceptance (Banaschewski and Brandeis 2007; Barry et al. 2003a, b; Cortese 2012). Instead ADHD is increasingly considered a heterogeneous disorder involving multiple pathways and neurophysiological subtypes (Clarke et al. 2011; Cubillo et al. 2012; Durston et al. 2011; Pennington 2006; Sonuga-Barke et al. 2010; Willcutt et al. 2010). Still, spectral resting EEG abnormalities, and mainly increased theta/beta ratio due to increased theta (4–7 Hz) continue to be reported as a consistent characteristic of ADHD (Barry et al. 2009; Callaway et al. 1983; Chabot and Serfontein 1996; Clarke et al. 2001c; Lansbergen et al. 2011; Shi et al. 2012; Snyder et al. 2008). Some groups even recommend them as useful diagnostic add-ons (Magee et al. 2005; Snyder and Hall 2006).

Since these markers reliably reflect development (Gasser et al. 1988; John et al. 1980; Matousek and Petersen 1973), they can also detect developmental lag, which has long been implicated in ADHD (Callaway et al. 1983). Structural and functional findings support a delay of nearly 5 years for peak thickness of frontal cortex (Shaw et al. 2007), and delayed maturation of inhibition-related ERPs in ADHD (Doehnert et al. 2010, 2012). This neurodevelopmental rationale and the simplicity of resting EEG recordings in ADHD has generated much research towards clinical translation.

A theta increase, particularly for relative fronto-central theta or theta/beta ratio is considered the most consistent marker of ADHD across resting states (eyes-closed (ec) and eyes-open (eo)), DSM-IV subtypes, sex, and age groups, although the deviance varies with several factors and is less pronounced in adults (Barry and Clarke 2009; Barry et al. 2003a; Bresnahan and Barry 2002; Clarke et al. 1998, 2001c, 2002a, b; Dupuy et al. 2011; Koehler et al. 2009; Lansbergen et al. 2011; Satterfield et al. 1972; Shi et al. 2012). In children, the theta and theta/beta increase appears most prominent for those with ADHD combined type (Clarke et al. 2001d) and without comorbid oppositional defiant disorder (ODD) or conduct disorder (CD) (Clarke et al. 2002a). In their meta-analysis, Snyder and Hall (2006) included nine studies that discriminated ADHD (according to DSM-IV criteria) from controls using increased theta and/or reduced beta resting EEG power. They calculated mean effect sizes of 1.31 for theta, −0.51 for beta power, and an impressive 3.08 for theta/beta ratio, corresponding to sensitivity and specificity both exceeding 90 %. The theta findings appear particularly robust in ADHD, with only a few studies having published failures to replicate theta or theta/beta abnormalities (Loo et al. 2009; Swartwood et al. 2003; van Dongen-Boomsma et al. 2010). However, a recent cluster analysis found theta increased in 3/5 clusters (60 %) but reduced in the other two clusters (40 %) of children with ADHD, thus clearly emphasizing the heterogeneity of spectral EEG in ADHD (Clarke et al. 2011). The beta attenuation seems even less consistent, particularly for adolescents and adults with ADHD (Bresnahan et al. 1999). About 20 % of children with ADHD combined type even show a beta excess (Clarke et al. 2001e) with additional EEG profiles also being reported (Chabot et al. 1996; Chabot and Serfontein 1996; Clarke et al. 2001c, 2011).

Regarding EEG-based classification, two studies reported high sensitivity and specificity (90/94 % (Snyder et al. 2008) and 87/94 % (Monastra et al. 2001)) for separating children and adolescents with ADHD from controls using the theta/beta ratio from a single (vertex) electrode. This

suggests that one simple marker is sufficient to reliably distinguish patients with ADHD from controls in a wide age range. While the ADHD group in the study of Monastra et al. (2001) had to meet additional non-DSM-IV selection criteria like impaired test performance and questionnaire scores, the multisite study of Snyder et al. (2008) used only DSM-IV criteria and blind EEG scoring. A third study (Magee et al. 2005) used DSM-IV criteria in a more narrow age range of 7–13 years plus multivariate classification including further electrodes and frequency bands. A 95 % sensitivity but only 40 % specificity was obtained for discriminating children with ADHD from controls, and only 1/12 of the variables entering the discriminant function reflected theta power. Although sensitivity/specificity increased to 89/80 % after clustering the ADHD group on resting EEG characteristics, this study underlines the considerable EEG heterogeneity in childhood ADHD also reported by others (Chabot and Serfontein 1996; Clarke et al. 1998, 2001b, c, d, e, 2011; Lansbergen et al. 2011; Magee et al. 2005). A recent study also failed to classify children with ADHD, despite 25 % of the patients showing elevated theta activity when compared to controls from a database (Ogrim et al. 2012).

Task-related markers of attentional brain functions also discriminate patients with ADHD from controls (Banaschewski and Brandeis 2007; Barry et al. 2003b). Reduced ERP components including the preparatory contingent negative variation (CNV), the attentional cue and target P300, and the inhibitory NoGo P300 are the best markers of ADHD in children (Banaschewski et al. 2003, 2004; Valko et al. 2009; van Leeuwen et al. 1998) and adults (Fallgatter et al. 2005). Clinical applications have rarely been recommended due to the moderate discrimination obtained and the task-specific setups required. Discriminant analysis using ERP-based classification of ADHD and control groups found lower discrimination than studies using resting EEG markers, with sensitivity/specificity of 71/77 % for children and 57/63 % for adolescents (Smith et al. 2003), consistent with older studies. However, a recent report claimed 91 % sensitivity and specificity for classifying adults with and without ADHD using Go-NoGo ERPs and nonlinear support vector machine classification of ICA components (Mueller et al. 2011). Although these intriguing findings illustrate the power of advanced multivariate methods, an independent validation remains essential.

To sum up, whether neurophysiological candidate ADHD markers can be used remains a critical question, which needs further clarification through methodologically sound controlled studies. Our study aimed to evaluate the diagnostic potential of conventional spectral resting EEG markers for ADHD and developmental lag throughout the lifespan. To this end, we analysed resting EEG in children and adults with ADHD, for whom we had published task-related attentional and inhibitory ERP deficits measured as reductions of cue CNV and NoGo P300 amplitudes (Valko et al. 2009). We hypothesized that patients would show significantly higher theta power and theta/beta ratio than healthy controls. Secondly, resting state theta and theta/beta were expected to be better age- and ADHD-classifiers than the task-related ERP markers.

Materials and Methods

Subjects

Subjects with ADHD were recruited from 71 families in the Zurich multimodal family assessment study on ADHD (MFAA; Valko et al. 2009) building on the International Multi-centre ADHD Gene (IMAGE) project (Brookes et al. 2006). Children with ADHD combined subtype (DSM-IV), aged 8–16 years, IQ $\geq$80 were diagnosed using the semi-structured clinical diagnostic interview PACS (parental account of children's symptoms; Taylor et al. 1986) plus Conners' teacher rating scale—revised (CTRS; Conners et al. 1998b). For further details, see Valko et al. (2009; 2010). Adults with ADHD were identified among the parents of these children. Inclusion criteria were scores within the clinical range on an ADHD-self report scale of a questionnaire for adults on current ADHD symptoms (ADHS-SB, Rosler et al. 2004; $\geq$15) as well as on a retrospective self-rating questionnaire on ADHD childhood symptoms (German short version of the Wender-Utah-Rating Scale, WURS-k, Retz-Junginger et al. 2002; Ward et al. 1993; $\geq$27). Controls were recruited from local schools and sports clubs, and by staff members, and had to score below the subclinical cutoff on the Conners' Parent Rating Scale—Revised ($T < 60$ on CPRS; Conners et al. 1998a) or the ADHS-SB and WURS-k, respectively, as in our previous work (Valko et al. 2009, 2010).

For children and adults, ADHD and control groups were matched on age, IQ, and gender (see Table 1). All participants were free of psychotropic medication and patients on stimulant medication suspended treatment at least 48 h before testing. The ADHD groups were identical with Valko et al. (2009). From the control groups one child was excluded for resting EEG spikes and one adult for missing resting EEG. For additional analyses, the two groups of children were further split according to their median age. All participants and children's parents gave informed, written consent and the study was approved by the local Ethics Committee.

Experimental Procedures

Subjects were tested neurophysiologically in a 2.5 h session. Resting EEG during separate 3 min eo and ec conditions, and

Table 1 Group characteristics for children and adults with attention-deficit/hyperactivity disorder (ADHD) and healthy control (CTRL) subjects

	ADHD	CTRL	df	*p*
Children	$n = 32$	$n = 30$		
Male/female	20/12	18/12	60	n.s.
Age [years]				
Mean (SD)	11.1 (2.1)	11.2 (2.1)	60	n.s.
Range	8.1–15.7	8.7–15.9		
Younger subgroups	$n = 16$	$n = 15$		
Mean (SD)	9.47 (0.84)	9.45 (0.69)	29	n.s.
Range	8.1–10.8	8.7–10.8		
Older subgroups	$n = 16$	$n = 15$		
Mean (SD)	12.81 (1.54)	12.85 (1.65)	29	n.s.
Range	10.9–15.7	10.8–15.9		
Estimated IQ (HAWIK-III)				
Mean (SD)	120.8 (13.9)	119.7 (16.5)	60	n.s.
Stimulant medication	7 (con), 8 (rit)	–	2[a]	<0.001
CPRS [*t*-scores]				
Inattention	72.7 (12.3)	47.3 (5.2)	60	<0.001
Hyperactivity/impulsivity	77.6 (11.9)	46.0 (3.6)	60	<0.001
Total	76.8 (10.3)	46.5 (4.3)	60	<0.001
CTRS [*t*-scores]				
Inattention	65.1 (10.6)	50.2 (6.7)	58[b]	<0.001
Hyperactivity/impulsivity	68.7 (12.7)	49.6 (9.1)	58[b]	<0.001
Total	68.8 (11.2)	49.7 (6.6)	58[b]	<0.001
SDQ P–hyperactivity [raw scores]	7.6 (2.2)	1.6 (1.4)	60	<0.001
SDQ T–hyperactivity [raw scores]	6.6 (2.5)	2.1 (1.9)	58[b]	<0.001
CBCL [*t*-scores]				
Internalising problems	60.8 (8.8)	44.1 (9.3)	58[b]	<0.001
Externalising problems	68.1 (10.1)	45.4 (7.8)	58[b]	<0.001
Comorbidities				
ODD/CD	11			
Depression	3			
Reading difficulties	8			
Dyslexia	3			
Adults	$n = 22$	$n = 21$		
Male/female	11/11	11/10	41	n.s.
Age [years]				
Mean (SD)	42.7 (4.4)	44.0 (4.7)	41	n.s.
Range	32.2–53.0	38.1–55.2		
Estimated IQ (WAIS)				
Mean (SD)	111.7 (11.9)	112.9 (12.9)	41	n.s.
Stimulant medication	6	–		
ADHD-SB [sumscore]	23.2 (7.0)	6.1 (4.3)	41	<0.001
WURS-k [total score]	37.0 (7.3)	7.7 (6.3)	41	<0.001
Comorbidities				
Reading difficulties	10	3		

Stimulant medication: ritalin (rit), concerta (con); instruments to further quantify ADHD symptoms in children: Conners' Parent (CPRS; Conners et al. 1998a) and Teacher Rating Scale (Conners et al. 1998b) with DSM-IV items; strength and difficulties questionnaire (SDQ, Goodman 1997) from parents (P) and teacher (T) with hyperactivity item; child behavior checklist (CBCL, Achenbach et al. 1991) with items: internalizing, externalizing, and attention problems; IQ based on four subscales of the German version of the Wechsler intelligence scale for children III (HAWIK-III): vocabulary, block design, arithmetic, and picture arrangement (Schallberger 2005); possible comorbidities, such as oppositional defiant disorder (ODD), conduct disorder (CD), reading difficulties, and previously received diagnosis of dyslexia, derived from parental account of children's symptoms (PACS) and anamnestic data. For adults, IQ was estimated by taking the arithmetic mean of the German Wechsler adult intelligence scale (WAIS) subtests vocabulary and block design (Tewes 1991). ADHD-self report scale of a questionnaire for adults on current ADHD symptoms (ADHS-SB); retrospective self-rating questionnaire on ADHD childhood symptoms: German short version of the Wender-Utah-Rating scale (WURS-k). Reading disability according to a reading questionnaire (Lefly and Pennington 2000)

[a] Pearson's Chi-square test

[b] Not available for two control subjects

a short period of vertical and horizontal eye movements was followed by cognitive ERP tests including cued continuous performance tests (CPT). The present paper focuses on resting EEG but includes comparisons with published CPT data (Valko et al. 2009). Subjects sat in an electrically shielded video-controlled room with their head on a chin rest. They were asked to minimise motion and eye movements during recordings. Subjects fixated on a monitor during eo, and held their index fingers on their eyelids to facilitate eye closure and reduce eye movement during the ec condition.

Recordings

Data were recorded from an extended 10–20 system montage including 46 EEG and two electrooculogram (EOG) electrodes (Ag/AgCl; Valko et al. 2009) using elastic caps (Easy Cap, FMS, Munich), Synamp amplifiers (Neuroscan, El Paso, TX, USA), 500 Hz sampling rate, DC-70 Hz filter setting, Fpz referencing, and impedances kept below 20 kOhm.

Data Processing and Analysis

The EEG was analysed using Brain Vision Analyzer (Version 1.05.0005, Brain Products, Gilching, Germany). After combining the eo and ec data files, EEG was filtered offline (0.1–70 Hz band-pass, Butterworth, 24 dB/Oct plus 50 Hz notch filter), and initially re-referenced to Fz for ocular artefact correction using independent component analysis (ICA). The ICA followed automatic rejection of large technical and movement artefacts, and in four subjects with slow EEG drifts, a high-pass filter of 0.5 Hz. After average referencing, remaining artefacts exceeding ±150/±100 μV (children/adults) were rejected semiautomatically. To avoid EEG distortion, a narrow band rejection filter at 16.66 Hz (0.1 Hz width, fourth order) eliminated artefacts from a nearby railway track. The clean EEG was segmented into 2.048 s epochs for fast Fourier transform (FFT) power density computation (full spectrum) using 10 % Hanning windowing. Four frequency bands (delta: 1.5–3.5 Hz, theta: 3.5–7.5 Hz, alpha: 7.5–12.5 Hz, beta: 12.5–25 Hz) were analysed for absolute and relative power and the theta/beta ratio. At least 20 artefact-free epochs were averaged per condition.

For replication purposes, this analysis was repeated following Clarke et al. (2001c), using artefact rejection thresholds, instead of ICA correction, for EEG (children: ±200 μV, adults: ±150 μV) and EOG (±50 μV) channels, approximated ear referencing (using the average of TP9/10 and FT9/10, van Leeuwen et al. 1998, see also Gottselig et al. 2004), 0.5–70 Hz band-pass filter, and region analyses (averaged power measures within three sagittal regions: frontal (Fp1/2′, Fpz, F3/4, F7/8, Fz), central (T3/4, C3/4, Cz) and posterior (T5/6, P3/4, Pz, O1/2′, Oz).

Statistical Analysis

The bandwise (theta, beta, theta/beta) repeated-measures analysis of variance (ANOVA) focused on resting EEG measures separately for three midline electrodes (Fz, Cz, Pz) with clinical (ADHD, controls) and age (children, adults) groups as between-subjects factor, and condition (ec, eo) as within-subjects factor. In additional multivariate analyses (MANOVAs), midline electrode (Fz, Cz, Pz) was included as additional within-subjects factor. For children, analogous (M)ANOVAs compared younger with older children.

In the supplementary replication analyses "region" (frontal, central, parietal) instead of "electrode" was used as factor. A separate ANOVA was calculated for the number of artefact-free segments (goodsegs) that entered the FFT analyses. Since children suffering from ADHD and ODD/CD have been reported to show diminished ADHD abnormalities (Clarke et al. 2002a), an additional analysis excluded ADHD subjects with suspected ODD/CD (11/32). Supplementary analyses were also run with age as a covariate, for drug naive children (11/32) and with only those control children scoring also below (sub) clinical cutoffs on all CPRS and CTRS DSM-IV ADHD subscales (25/30).

Given the focus on ADHD markers, significant ADHD effects and interactions were followed-up by posthoc analyses. Two-tailed independent sample *t* test was used for descriptive and topographic (*t*-maps) group comparisons. To test the relationship between the EEG measures and age, the Pearson correlation coefficient (*r*) was calculated using $\log_{10}$ transformed power for different frequency bands (delta, theta, alpha, beta). The level of significance was set at $p < 0.05$. Trends ($p < 0.1$) and approached trends ($p < 0.2$) are only reported for critical ADHD effects.

To distinguish ADHD from control, and younger from older children, separate discriminant analyses (DA) were used. Neurophysiological measures were entered using minimised Wilks' lambda at each step. Resting EEG (theta, beta, theta/beta at Cz for ec, eo) and ERP measures (NoGoP300, cueCNV at Pz for CPT and the flanker version, CPTF; see also Table 4) were tested separately, and in combination with goodsegs. Only variables contributing substantially to discrimination (with probability of F to enter set at 0.2 and to remove at 0.3; Smith et al. 2003) entered the stepwise analyses. Sensitivity, specificity, and overall classification accuracy were calculated. An additional DA focused on slower and more frontal resting EEG (delta, theta at Cz, Fz for ec, eo).

Results

Group differences were found on all ADHD symptom measures, while IQ, age and gender proved closely

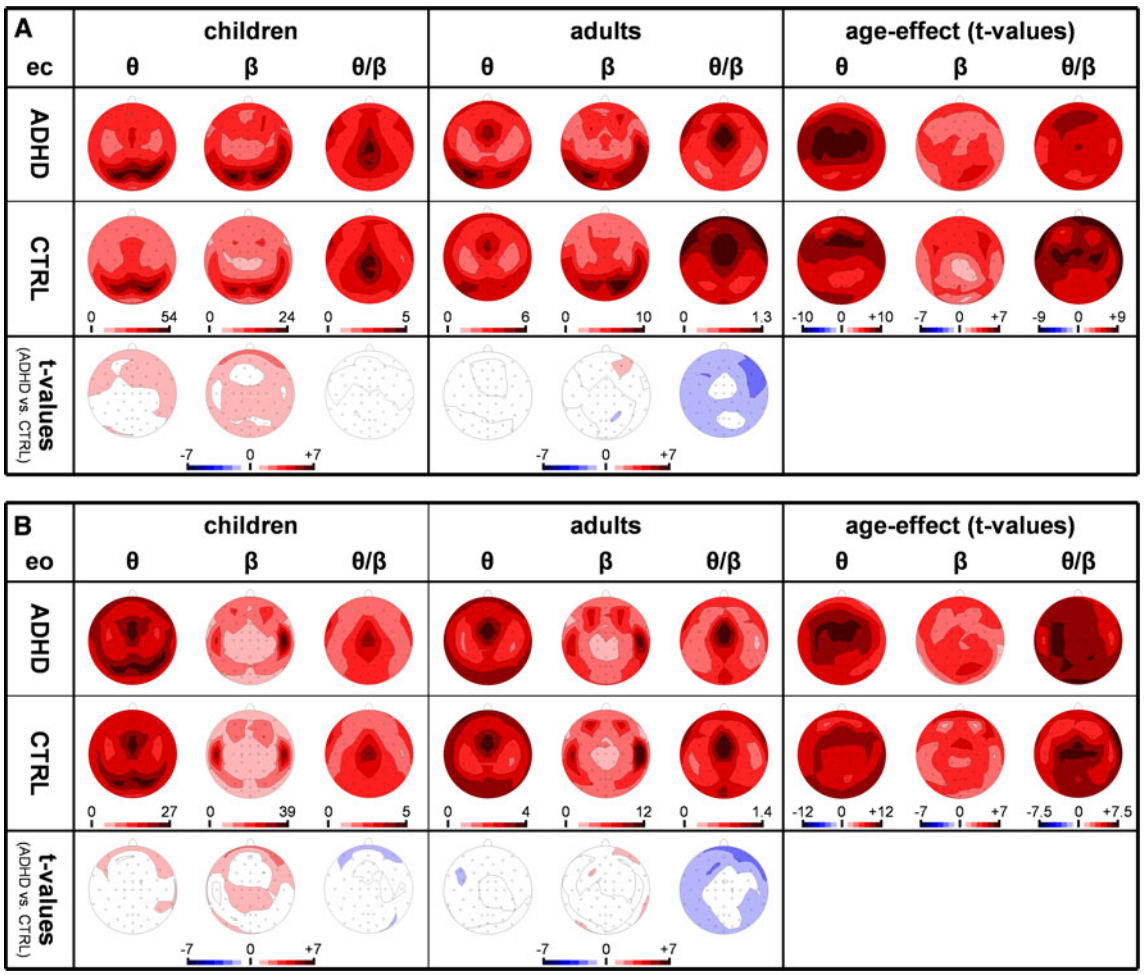

Fig. 1 Spectral analysis of children's and adults' resting EEG (ICA-corrected, average referenced) for **a** eyes-closed (ec) and **b** eyes-open (eo) conditions. Absolute power [μV^2] for theta (θ) and beta (β) frequency bands and theta/beta (θ/β)-ratio. The *t*-maps [*t* values] illustrate attention-deficit/hyperactivity disorder (ADHD)-related and younger-age-related effects (ADHD versus healthy controls (CTRL), bottom; children versus adults, right column). Scales below the corresponding topographic maps in $\mu V^2/t$ values, respectively

matched (Table 1). Mapping theta and beta power, and theta/beta ratio revealed typical topographies but no significant ADHD-related differences in any *t*-map for children or adults (Fig. 1). After splitting younger and older children, increased theta power emerged at one single electrode (Cz) in older ADHD children with eo (Fig. 2). Age effects due to increased power with younger age were prominent for children versus adults (Fig. 1) in all bands, and for younger compared to older children for theta power and theta/beta ratio (Fig. 2). The MANOVAs (Tables 2, 3) revealed no significant main effects of ADHD, neither for theta nor beta power, nor for theta/beta ratio (all p values >0.2).

Theta Power

Absolute theta had a fronto-central peak, plus posterior bilateral peaks, which were particularly prominent in children and ec (Figs. 1, 2). For the full groups, neither increased theta with ADHD (MANOVAs, Table 2, $p > 0.2$, Fig. 1), nor interactions or trends involving ADHD were found. When testing electrodes separately, a significant interaction between ADHD and condition at Fz indicated a greater increase in theta power with eye closure in ADHD than in control subjects, particularly in children (ADHD $\times$ age $\times$ condition, $p = 0.078$). There were no ADHD-related significances or trends at Cz. Children had much more theta power than adults ($p < 0.001$) and a larger theta increase with eye closure (age $\times$ condition; $p < 0.001$), particularly at Pz (age $\times$ condition $\times$ electrode; $p < 0.001$).

For children, ADHD neither resulted in increased theta (Table 3). The interaction between ADHD, condition, and electrode (topography) reached a trend ($p = 0.065$). When testing electrodes separately, there was a greater theta power increase at Fz with eye closure in ADHD than in control children (ADHD $\times$ condition, $p < 0.05$), but no ADHD-related effects or trends at Cz. Accordingly, no ADHD-related differences approached significance for

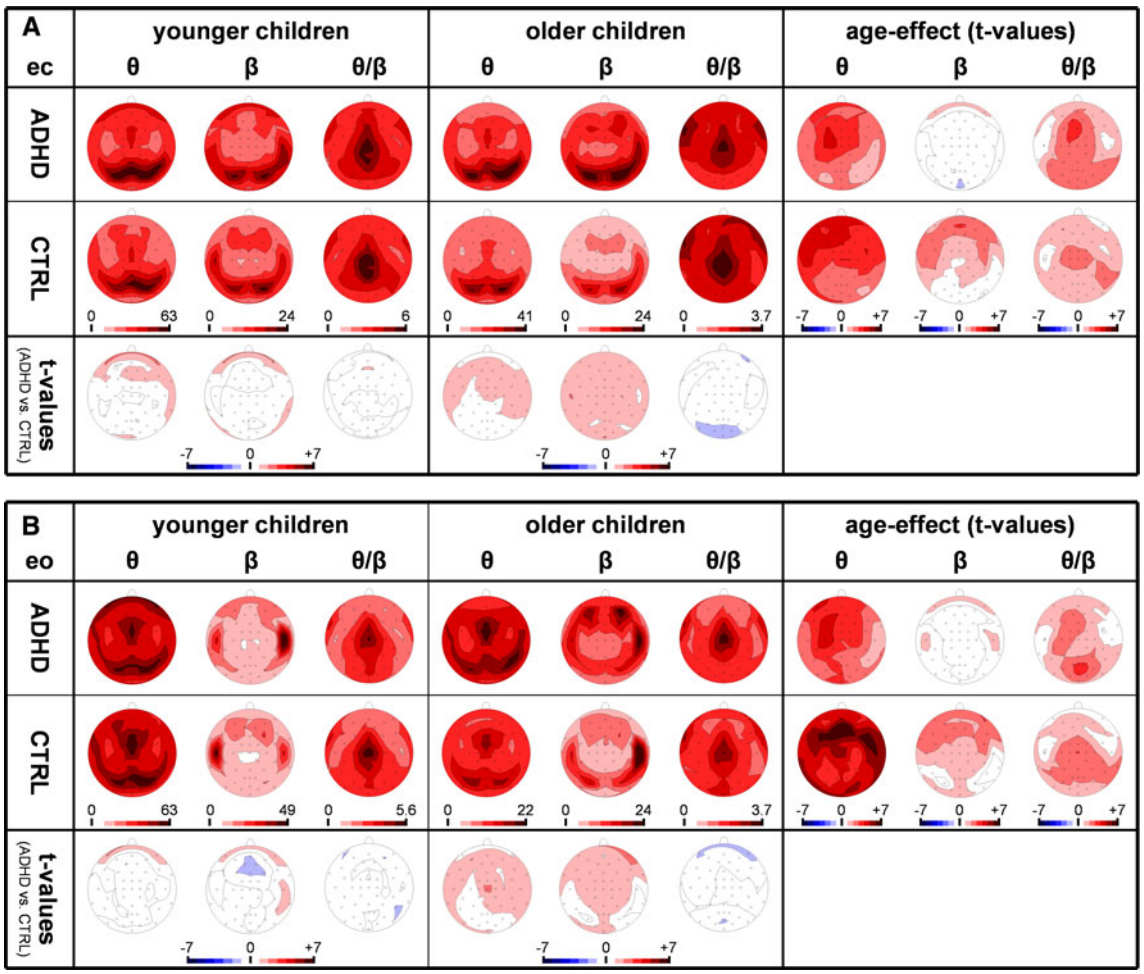

Fig. 2 Spectral analysis of children's resting EEG (ICA-corrected, average referenced) for **a** eyes-closed (ec) and **b** eyes-open (eo) conditions. Absolute power [μV^2] for theta (θ) and beta (β) frequency bands and theta/beta (θ/β)-ratio. The *t*-maps [*t* values] illustrate attention-deficit/hyperactivity disorder (ADHD)-related and younger-age-related effects (ADHD versus healthy controls (CTRL), bottom; younger versus older children, right column). Scales below the corresponding topographic maps in $\mu V^2/t$ values, respectively

younger children, but in older children with ADHD, theta power at Cz during eo was increased compared to control children. This increase reached a trend with ec, and approached trends at Fz (both conditions) and Pz (eo). Younger children showed significantly more theta power than older children ($p < 0.001$).

Beta Power

Absolute beta displayed characteristic bilateral posterior topographies during ec, and a frontal bilateral distribution with additional focal peaks at temporal sites prone to muscle artefacts with eo (Figs. 1, 2). Children with ADHD showed a trend for increased beta power, particularly at EOG electrodes. No differences were found in adults. Children showed greater beta power than adults throughout (*t*-maps Fig. 1, right columns).

Over all subjects, the MANOVAs (Table 2) indicated no ADHD-related effects (see also Fig. 1). Only a trend suggested an ADHD × condition × age interaction ($p = 0.066$). When testing electrodes separately, there was only a single trend (ADHD × condition × age interaction at Fz; $p = 0.087$) for greater beta power increase with eye closure in ADHD children. Children had more beta power than adults ($p < 0.001$).

For children's groups, no ADHD-related effects were found (Table 3). Testing electrodes separately revealed no main effect of ADHD but a trend (ADHD × condition interaction) at Fz suggesting greater increase in beta power with eye closure in ADHD than in control children ($p = 0.081$). At Cz, there were no ADHD-related effects, interactions or trends. Age effects were inconsistent except for a significant frontal beta increase in younger compared to older control children (Fig. 2).

Table 2 Summary of ICA-corrected absolute theta and beta band power and theta/beta ratio in children and adults

A																B						
		Children						Adults						All									
		ADHD		CTRL		*t* test		ADHD		CTRL		*t* test		*t* test		ADHD status				Age		Cond
		($n = 32$)		($n = 30$)		(32/30)		($n = 22$)		($n = 21$)		(22/21)		(54/51)			× cond	× age	× cond × age		× cond	
		M	*SD*	M	*SD*	*t*	*p*	M	*SD*	M	*SD*	*t*	*p*	*t*	*p*	(1, 101) (η_p^2)	(1, 101) (η_p^2)	(1, 101) (η_p^2)	(1, 101) (η_p^2)	(1, 101) (η_p^2)	(1, 101) (η_p^2)	(1, 101) (η_p^2)
θ: Absolute power [μV^2]																						
Fz	eo	24.82	*9.43*	23.98	*9.43*	0.35	0.73	3.55	*2.82*	3.59	*1.91*	−0.05	0.96	0.23	0.82	0.84	**4.16***	0.72	3.17^{t}	172.59***	12.42**	32.20***
	ec	32.46	*14.50*	27.14	*11.08*	1.62	0.11^{+}	4.97	*8.24*	4.70	*3.59*	0.14	0.89	1.05	0.30	(0.008)	(0.040)	(0.007)	(0.030)	(0.631)	(0.110)	(0.242)
Cz	eo	24.35	*9.38*	23.41	*10.86*	0.37	0.71	3.40	*2.49*	3.22	*1.57*	0.29	0.78	0.29	0.77	0.17	0.11	0.13	0.23	167.0**	26.82***	42.06***
	ec	31.27	*11.06*	29.43	*16.28*	0.52	0.60	4.04	*4.69*	4.03	*2.82*	0.01	1.00	0.36	0.72	(0.002)	(0.001)	(0.001)	(0.002)	(0.623)	(0.210)	(0.294)
Pz	eo	21.45	*11.58*	19.80	*10.51*	0.59	0.56	2.38	*2.14*	2.36	*1.20*	0.03	0.98	0.44	0.66	0.29	0.22	0.33	0.30	85.57***	30.93***	36.53***
	ec	41.64	*24.88*	36.73	*32.27*	0.67	0.50	3.02	*3.76*	3.26	*2.23*	−0.25	0.81	0.53	0.59	(0.003)	(0.002)	(0.003)	(0.003)	(0.459)	(0.234)	(0.266)
β: Absolute power [μV^2]																						
Fz	eo	10.12	*10.63*	9.55	*6.81*	0.25	0.80	3.39	*2.54*	3.36	*2.61*	0.05	0.96	0.25	0.80	0.11	0.92	0.16	2.99^{t}	17.78***	0.10	11.37**
	ec	11.27	*12.58*	9.62	*7.21*	0.63	0.53	3.97	*3.17*	4.25	*3.64*	−0.26	0.79	0.52	0.61	(0.001)	(0.009)	(0.002)	(0.029)	(0.150)	(0.001)	(0.101)
Cz	eo	7.32	*5.39*	5.99	*3.30*	1.16	0.25	3.51	*3.18*	3.22	*2.60*	0.33	0.75	1.11	0.27	0.78	0.11	0.83	2.01	13.71***	0.82	36.47***
	ec	8.43	*5.88*	6.71	*3.93*	1.34	0.19^{+}	4.43	*4.06*	4.77	*4.47*	−0.26	0.80	0.92	0.36	(0.008)	(0.001)	(0.008)	(0.020)	(0.119)	(0.008)	(0.265)
Pz	eo	8.95	*7.42*	6.93	*4.36*	1.30	0.20	3.22	*2.49*	3.45	*2.54*	−0.31	0.76	1.04	0.30	0.61	0.01	1.84	2.52	18.63***	2.55	54.28***
	ec	12.07	*9.56*	9.06	*6.62*	1.43	0.16^{+}	4.47	*3.69*	5.58	*5.48*	−0.78	0.44	0.91	0.37	(0.006)	(0.000)	(0.018)	(0.115)	(0.156)	(0.025)	(0.350)
θ/β: Ratio																						
Fz	eo	3.28	*1.50*	3.23	*1.89*	0.10	0.92	1.25	*0.73*	1.33	*0.63*	−0.36	0.72	0.01	1.00	0.01	0.00	0.18	0.61	59.50***	5.46*	12.19**
	ec	3.79	*1.71*	3.63	*1.90*	0.36	0.72	1.28	*1.00*	1.47	*1.00*	−0.64	0.53	0.07	0.94	(0.000)	(0.000)	(0.002)	(0.006)	(0.371)	(0.051)	(0.108)
Cz	eo	4.33	*2.07*	4.42	*2.31*	−0.16	0.88	1.35	*0.79*	1.42	*0.72*	−0.31	0.76	−0.15	0.88	0.09	0.08	0.00	0.09	82.9***	9.70**	2.97^{t}
	ec	4.79	*2.46*	4.87	*2.53*	−0.13	0.89	1.16	*0.73*	1.35	*0.92*	−0.72	0.47	−0.21	0.83	(0.001)	(0.001)	(0.000)	(0.001)	(0.451)	(0.088)	(0.029)
Pz	eo	3.17	*1.68*	3.41	*1.99*	−0.52	0.61	0.86	*0.50*	0.93	*0.47*	−0.48	0.63	−0.44	0.66	0.25	0.04	0.03	0.03	65.30***	16.52***	15.29***
	ec	4.38	*2.79*	4.63	*3.55*	−0.31	0.76	0.78	*0.53*	0.96	*0.65*	−1.01	0.32	−0.35	0.73	(0.002)	(0.000)	(0.000)	(0.000)	(0.393)	(0.141)	(0.131)

Table 2 continued

C

ADHD status								Age				Cond		Elect	
	× cond	× age	× elect	× cond × age	× cond × elect	× age × elect	× cond × age × elect		× cond	× elect	× cond × elect		× elect		
(1, 101) (η_p^2)	(1, 101) (η_p^2)	(1, 101) (η_p^2)	(2, 100) (η_p^2)	(1, 101) (η_p^2)	(2, 100) (η_p^2)	(2, 100) (η_p^2)	(2, 100) (η_p^2)	(1, 101) (η_p^2)	(1, 101) (η_p^2)	(2, 100) (η_p^2)	(2, 100) (η_p^2)	(1, 101) (η_p^2)	(2, 100) (η_p^2)	(2, 100) (η_p^2)
θ: Absolute power [μV^2]															
0.43	0.74	0.41	0.47	0.78	2.29^{+}	0.53	1.44	149.75***	31.15***	2.38^{t}	13.25***	44.81***	13.21***	0.79	
(0.004)	(0.007)	(0.004)	(0.626)	(0.008)	(0.044)	(0.011)	(0.028)	(0.597)	(0.236)	(0.045)	(0.209)	(0.307)	(0.209)	(0.016)	
β: Absolute power [μV^2]															
0.43	0.08	0.82	0.10	3.45^{t}	1.34	1.33	0.57	19.76***	0.18	9.66***	3.84*	46.63***	15.80	11.32***	
(0.004)	(0.001)	(0.008)	(0.002)	(0.033)	(0.026)	(0.026)	(0.011)	(0.164)	(0.002)	(0.162)	(0.071)	(0.316)	(0.240)	(0.185)	
θ/β: Ratio															
0.11	0.04	0.01	0.24	0.16	0.07	0.26	0.09	78.74***	14.40***	22.18***	6.44**	12.76***	10.80***	33.94***	
(0.001)	(0.000)	(0.000)	(0.005)	(0.002)	(0.001)	(0.005)	(0.002)	(0.438)	(0.125)	(0.307)	(0.114)	(0.112)	(0.178)	(0.404)	

(A) Resting EEG data (ICA-corrected, average referenced) given as mean (M) ± standard deviation (SD) comparing subjects with attention-deficit/hyperactivity disorder (ADHD) versus healthy control subjects (CTRL) including post hoc *t* tests for children, adults and all subjects (children + adults). (B) Repeated-measures ANOVA per midline electrode (Fz, Cz, Pz) and EEG measure with between-subjects factors: ADHD status (ADHD, CTRL), age (children, adults) and within-subjects factor condition (cond): eyes-open (eo), eyes-closed (ec). (C) Repeated-measures ANOVA per EEG measure with electrode (elect) as within-subjects factor

Significances for ADHD and age effects including their interactions: $^{+}$ $p < 0.2$; ^{t} $p < 0.1$; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Theta/beta Ratio

The theta/beta ratio had a central distribution (Figs. 1, 2) with more power at Cz than at Fz/Pz ($p < 0.001$, Tables 2, 3). There was no increase with ADHD but with younger age for all groups and conditions (Figs. 1, 2). The MANOVAs over all subjects revealed no ADHD-related effects or trends; consistent with separate electrodewise analyses ($p > 0.2$). Children had a larger theta/beta ratio than adults ($p < 0.001$). Similarly, theta/beta ratio was increased ($p < 0.001$) and had a different topography (interaction: age × electrode; $p < 0.05$) in younger compared to older children.

Maturational Resting EEG Changes in Children

Negative correlations with children's age were found for all EEG power measures. Strong maturational power reductions ($p < 0.01$) were found for theta. Negative correlations were maximal in frontal regions and with ec, and higher in controls than in ADHD (Fig. 3, accounting for up to 80 % of the variance; for details and other frequency bands see online resources: Table S1, Fig. S2).

EEG Quality

The goodsegs entering the analyses without ICA correction tended to be lower with ADHD ($F(1,101) = 3.74$, $p = 0.056$) and was lowest in ADHD children (ADHD × age: $F(1,101) = 9.97$, $p < 0.01$; ADHD children: 37, CTRL children: 52, ADHD adults: 72, CTRL adults: 68). Children had fewer good segments than adults ($p < 0.001$), particularly with ec (age × condition: $p < 0.001$).

Multiband and Replication Analyses in Children

The MANOVAs including both theta and beta bands as a factor also revealed no significant ADHD main effect ($p > 0.2$). Significant interactions involving ADHD suggested a greater power increase with eye closure in ADHD than in control subjects, more pronounced at Pz than at Fz/Cz (ADHD × condition x electrode: $F(2,57) = 3.54$, part. $\eta^2 = 0.111$, $p = 0.035$), and opposite ADHD power deviations at Fz for younger ($\theta\uparrow$, $\beta\downarrow$) versus older ($\theta\uparrow$, $\beta\uparrow$) children (ADHD × age × band × electrode: $F(2,57) = 3.60$, part. $\eta^2 = 0.112$, $p = 0.034$). The strong age main effect ($p < 0.001$) interacted with frequency band ($p < 0.001$) due to more EEG power in children than in adults, particularly for theta.

Supplementary analyses using relative theta and beta power, recalculated linked-ear reference, and amplitude-based artefact rejection, neither revealed any ADHD effect, while age effects remained stable (online resource Fig. S1,

Table 3 Summary of ICA-corrected absolute theta and beta band power and theta/beta ratio in children

A															B						
		Younger children						Older children						All							
		ADHD		CTRL		*t* test		ADHD		CTRL		*t* test		*t* test		ADHD status				Age		Cond
		($n = 16$)		($n = 15$)		(16/15)		($n = 16$)		($n = 15$)		(16/15)		(32/30)			x cond	x age	x cond x age		x cond	
		M	*SD*	M	*SD*	*t*	*p*	M	*SD*	M	*SD*	*t*	*p*	*t*	*p*	(1, 58) (η_p^2)	(1, 58) (η_p^2)	(1, 58) (η_p^2)	(1, 58) (η_p^2)	(1, 58) (η_p^2)	(1, 58) (η_p^2)	
θ: Absolute power [μV^2]																						
Fz	eo	29.49	*9.05*	31.12	*5.99*	−0.59	0.56	20.14	*7.43*	16.85	*6.27*	1.33	0.19^{+}	0.35	0.73	1.97	7.00*	0.35	1.88^{+}	36.16***	2.59^{+}	40.57***
	ec	39.67	*14.70*	34.48	*8.76*	1.18	0.25	25.26	*10.38*	19.81	*7.90*	1.64	0.11^{+}	1.62	0.11^{t}	(0.033)	(0.108)	(0.006)	(0.031)	(0.384)	(0.043)	(0.412)
Cz	eo	28.70	*10.87*	31.25	*8.70*	−0.72	0.48	20.00	*4.82*	15.56	*6.06*	2.27	0.03^{*}	0.37	0.71	0.35	0.25	2.07^{+}	0.01	33.87***	3.02^{t}	52.86***
	ec	37.26	*11.36*	38.72	*16.83*	−0.29	0.78	25.27	*6.87*	20.13	*9.00*	1.79	0.08^{t}	0.52	0.60	(0.006)	(0.004)	(0.034)	(0.000)	(0.369)	(0.049)	(0.477)
Pz	eo	25.70	*11.61*	26.45	*9.81*	−0.19	0.85	17.20	*10.18*	13.15	*6.15*	1.33	0.19^{+}	0.59	0.56	0.54	0.39	0.41	0.03	12.36***	3.37^{t}	50.16***
	ec	50.25	*24.25*	48.65	*38.97*	0.14	0.89	33.04	*23.10*	24.81	*18.28*	1.09	0.28	0.67	0.50	(0.009)	(0.007)	(0.007)	(0.001)	(0.176)	(0.055)	(0.464)
β: Absolute power [μV^2]																						
Fz	eo	8.80	*5.39*	11.87	*8.44*	−1.22	0.23	11.44	*14.16*	7.22	*3.64*	1.12	0.27	0.25	0.80	0.21	3.14^{t}	2.35^{+}	0.09	0.082	1.06	4.08*
	ec	9.55	*5.52*	11.73	*8.74*	−0.84	0.41	12.98	*17.03*	7.52	*4.67*	1.20	0.24	0.63	0.53	(0.004)	(0.051)	(0.039)	(0.002)	(0.001)	(0.018)	(0.66)
Cz	eo	7.08	*5.64*	6.79	*3.60*	0.17	0.87	7.56	*5.31*	5.20	*2.88*	1.52	0.14^{+}	1.16	0.25	1.58	1.06	0.89	0.3	0.031	3.28^{t}	23.80***
	ec	7.74	*5.38*	7.27	*3.63*	0.28	0.78	9.11	*6.45*	6.16	*4.26*	1.49	0.15^{+}	1.34	0.19^{+}	(0.026)	(0.018)	(0.015)	(0.005)	(0.001)	(0.054)	(0.291)
Pz	eo	8.51	*6.27*	8.20	*4.82*	0.15	0.88	9.38	*8.60*	5.65	*3.56*	1.56	0.13^{+}	1.30	0.20	1.90	1.59	1.06	0.18	0.15	0.13	44.99***
	ec	11.33	*7.38*	10.37	*7.21*	0.37	0.72	12.81	*11.55*	7.76	*5.93*	1.52	0.14^{+}	1.43	0.16^{+}	(0.032)	(0.027)	(0.018)	(0.003)	(0.003)	(0.002)	(0.437)
θ/β: Ratio																						
Fz	eo	3.88	*1.43*	3.92	*2.38*	−0.06	0.96	2.67	*1.34*	2.55	*0.85*	0.30	0.77	0.10	0.92	0.07	0.29	0.30	2.43^{+}	12.41**	0.81	15.77***
	ec	4.68	*1.56*	4.24	*2.29*	0.63	0.53	2.90	*1.40*	3.02	*1.21*	−0.24	0.81	0.36	0.72	(0.001)	(0.005)	(0.001)	(0.040)	(0.176)	(0.014)	(0.214)
Cz	eo	4.98	*1.95*	5.57	*2.62*	−0.71	0.48	3.68	*2.04*	3.27	*1.15*	0.69	0.50	−0.16	0.88	0.23	0.00	0.37	1.65	15.69***	3.15^{t}	9.79**
	ec	5.88	*2.57*	6.10	*2.86*	−0.22	0.83	3.69	*1.83*	3.65	*1.37*	0.07	0.94	−0.13	0.89	(0.000)	(0.000)	(0.006)	(0.028)	(0.213)	(0.052)	(0.144)
Pz	eo	3.75	*1.62*	4.16	*2.40*	−0.57	0.58	2.59	*1.57*	2.65	*1.11*	−0.14	0.89	−0.52	0.61	0.18	0.00	0.11	0.00	9.67**	3.24^{t}	23.92***
	ec	5.39	*2.88*	5.86	*4.45*	−0.35	0.73	3.37	*2.36*	3.41	*1.76*	−0.05	0.96	−0.31	0.76	(0.003)	(0.000)	(0.002)	(0.000)	(0.143)	(0.053)	(0.292)

Table 3 continued

C

	ADHD status							Age				Cond		Elect
	× cond	× age	× elect	× cond × age	× cond × elect	× age × elect	× cond × age × elect		× cond	× elect	× cond × elect		× elect	
	(1, 58) (η_p^2)	(1, 58) (η_p^2)	(2, 57) (η_p^2)	(1, 58) (η_p^2)	(2, 57) (η_p^2)	(2, 57) (η_p^2)	(2, 57) (η_p^2)	(1, 58) (η_p^2)	(1, 58) (η_p^2)	(2, 57) (η_p^2)	(2, 57) (η_p^2)	(1, 58) (η_p^2)	(2, 57) (η_p^2)	(2, 57) (η_p^2)
θ: Absolute power [μV^2]														
	0.90	1.18	0.85	0.73	0.04	2.88^{t}	0.71	0.85	27.19^{***}	3.78^{t}	0.26	1.39	58.55^{***}	19.18^{***}	1.92
	(0.015)	(0.020)	(0.014)	(0.025)	(0.001)	(0.092)	(0.024)	(0.029)	(0.319)	(0.061)	(0.009)	(0.047)	(0.502)	(0.402)	(0.063)
β: Absolute power [μV^2]														
	1.03	2.67^{+}	1.77^{+}	0.86	0.23	1.97^{+}	1.38	0.02	0.102	1.11	0.20	0.26	30.74^{***}	17.66^{***}	17.22^{***}
	(0.017)	(0.044)	(0.030)	(0.029)	(0.004)	(0.064)	(0.046)	(0.001)	(0.002)	(0.019)	(0.007)	(0.009)	(0.346)	(0.383)	(0.377)
θ/β: Ratio														
	0.03	0.02	0.09	0.40	0.57	0.12	1.31	0.84	14.19^{***}	3.14^{t}	3.50^{*}	1.49	21.72^{***}	11.29^{***}	44.88^{***}
	(0.000)	(0.000)	(0.002)	(0.014)	(0.010)	(0.004)	(0.044)	(0.029)	(0.197)	(0.051)	(0.109)	(0.050)	(0.272)	(0.284)	(0.612)

(A) Resting EEG data (ICA-corrected, average referenced) given as mean (M) ± standard deviation (SD) comparing children with attention-deficit/hyperactivity disorder (ADHD) versus healthy control children (CTRL) including post hoc *t* tests for younger, older and all children (younger + older children). (B) Repeated-measures ANOVA per midline electrode (Fz, Cz, Pz) and EEG measure with between-subjects factors: ADHD status (ADHD, CTRL), age (children, adults) and within-subjects factor condition (cond): eyes-open (eo), eyes-closed (ec). (C) Repeated-measures ANOVA per EEG measure with electrode (elect) as within-subjects factor

Significances for ADHD and age effects including their interactions: $^{+}$ $p < 0.2$; ^{t} $p < 0.1$; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Tables S2, S3). In particular, no relative theta increases were found for ADHD. The only significant ADHD effect in the main analysis (increased theta at Cz for eo in older children; $p = 0.031$) was reduced to a trend ($p = 0.059$, Table S3) using the replication approach. A single significant interaction involving ADHD indicated increased beta power with eye closure in children with ADHD (ADHD × condition; $p = 0.037$). Re-analysing exclusively ADHD children without comorbid ODD/CD, medication naive children, control children without subclinical ADHD symptoms, or using the regional average (Table S4) instead of the single electrode approach revealed neither significant ADHD-related main effects nor interactions.

Classification Analyses

No resting EEG measure succeeded in ADHD classification (Table 4) except for goodsegs. Stepwise DA retained only "β_Cz_ec" with an overall classification accuracy of 53 %. Theta power (ec) in combination with goodsegs correctly classified ADHD from control children in about 70 % of the cases. Regarding age, DA retained factors "θ_Cz_eo" and "θ/β_Cz_ec", and correctly classified younger from older children in 74–87 % of the cases, which even improved (80–90 %) using EEG and goodsegs measures. Using ERP measures improved classification, but maximally reached a sensitivity/specificity of 65/60 % retaining only "NoGoP300_CPT". Combining resting EEG and ERP measures, correctly predicted group membership for about 63 % of ADHD and CTRL children. The best ADHD classification (72/73 %) was reached using "goodsegs_ec", "NoGoP300_CPT" and "θ_Cz_eo". Regarding age, a maximal sensitivity/specificity of 81/90 % was reached. Explorative addition of slower (delta) and more frontal (Fz) EEG markers, increased overall EEG-based ADHD classification to 66 %, while age classification remained above 80 %.

Discussion

The present study investigated the consistency of presumed ADHD markers from childhood to adulthood and how they relate to maturational lag. We could not replicate the commonly reported EEG abnormalities in ADHD like theta increase and beta decrease but observed highly consistent maturational changes.

Our consistent maturational effects (Gasser et al. 1988; John et al. 1980; Matousek and Petersen 1973; Ogrim et al. 2012) provide strong evidence that the data would have allowed reliable detection of maturational lag as often implicated in ADHD. While maturational lag has been found to play a role for inhibitory control deficits

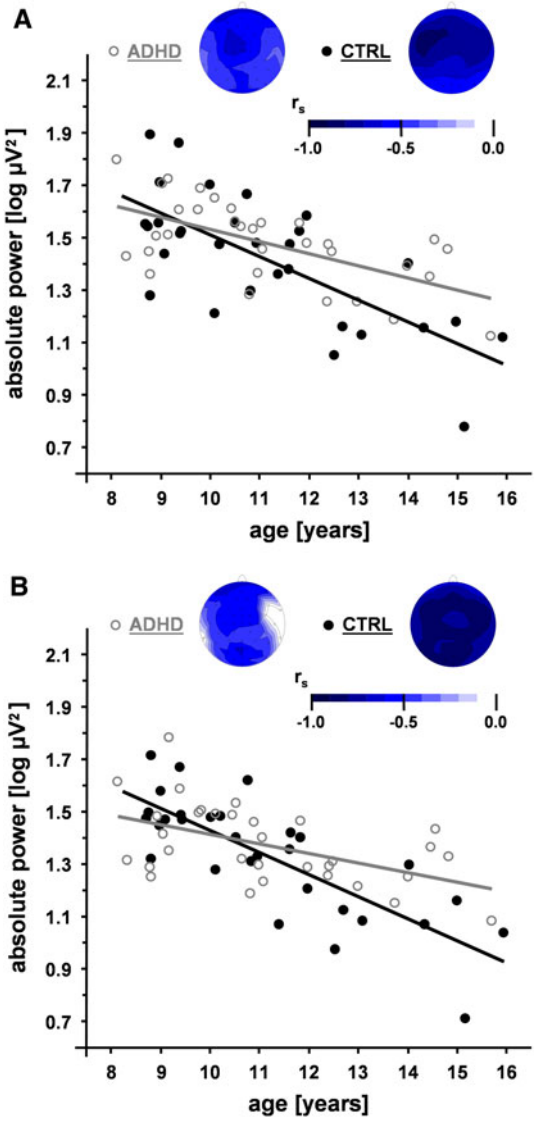

Fig. 3 Theta power increase during development for children from 8.5 to 16 years. Linear regression and correlation (r) were calculated using $\log_{10}$ transformed absolute power for the theta band power. Log theta power at electrode Cz and regression lines are plotted for attention-deficit/hyperactivity disorder (ADHD, open gray circles) and control (CTRL, black) groups during **a** eyes-closed (ec) and **b** eyes-open (eo) condition. Topographical distribution for both groups and conditions is illustrated on correlation-maps with r values plotted for $p < 0.05$. **a** ADHD: $b = -0.046$, $t(30) = -4.28$, $p < 0.001$, $r = -0.615$, $p < 0.001$; CTRL: $b = -0.083$, $t(28) = -5.37$, $p < 0.001$, $r = -0.712$, $p < 0.001$; r_{ADHD} vs. r_{CTRL}: Fisher's $Z = 0.65$, $p = 0.513$ **b** ADHD: $b = -0.037$, $t(30) = -3.29$, $p = 0.003$, $r = -0.515$, $p = 0.003$; CTRL: $b = -0.084$, $t(28) = -6.87$, $p < 0.001$, $r = -0.792$, $p < 0.001$; r_{ADHD} vs. r_{CTRL}: Fisher's $Z = 1.90$, $p = 0.058$

(Doehnert et al. 2010, 2012) its role for the resting EEG may be limited to specific EEG-defined ADHD subtypes (Clarke et al. 2011, 2002c; Magee et al. 2005). The typical attentional and inhibitory ERP abnormalities found in the same ADHD groups (reported elsewhere, Valko et al. 2009) confirm that the lack of neurophysiological ADHD markers is specific for the resting EEG.

The lack of EEG abnormalities in our adults with ADHD could partly reflect that they were not clinically referred but diagnosed based on self reports. However, this explanation fails to account for the reliable ERP abnormalities observed (Valko et al. 2009). This is in line with other recent failures to replicate consistent theta and/or theta/beta increases in ADHD (Loo et al. 2009; Ogrim et al. 2012; Swartwood et al. 2003; van Dongen-Boomsma et al. 2010), but contrasts with most other reports (Bresnahan and Barry 2002; Bresnahan et al. 2006; Dupuy et al. 2011; Hermens et al. 2004, 2005; Hobbs et al. 2007; Koehler et al. 2009; Lazzaro et al. 1999; Shi et al. 2012). Compared to the literature (summarised in online resource Table S5), the theta/beta ratios of the control children are near the upper limit, and those of the ADHD children near the lower limit of the published studies, but they are still in the range of published values. Considering the sensitivity of EEG band power to age, but also to different frequency band widths, analyses, and recording settings, these figures and comparisons, however, have to be treated with caution. This does not alter the fact that the present study is the first not to replicate major theta or theta/beta abnormalities in children and adults with proven ERP abnormalities. Our finding is particularly intriguing because the children met the full DSM-IV criteria for ADHD combined type reported to have the most pronounced resting EEG abnormalities (Clarke et al. 2001d). The only ADHD-related deviance in uncorrected posthoc tests was limited to a single electrode (Cz) in older children with eo (using ICA correction only). No other ADHD-related effect reached conventional uncorrected significance levels for children or adults. This is roughly in line with the findings from Ogrim et al. (2012), but contrasts with recent reports about consistent resting EEG abnormalities (Shi et al. 2012). For relative theta power and theta/beta ratio widely considered as the most robust ADHD markers, mean decreases rather than increases were even found, and absolute beta power tended to be increased rather than decreased in ADHD. Despite controlling for multiple factors such as EEG analysis, resting condition, age, severity of ADHD, and comorbidity with ODD/CD or developmental disorders, no consistent resting EEG abnormality was found in ADHD, even after excluding also control children with any subclinical ADHD symptoms to meet more restrictive criteria than previous work (Clarke et al. 2001a). Since some research suggests that alpha peak slowing may contribute to theta activity increases (Lansbergen et al. 2011), we also examined group differences in individual alpha peak frequency (ec condition, see also online resource Fig. S2a) directly. There were no significant ADHD effects ($F(1,101) = 0.029$, $p = 0.866$), neither for children

(ADHD: 9.45 ± 1.23 Hz, CTRL: 9.23 ± 1.16 Hz) nor for adults (ADHD: 9.74 ± 1.53 Hz, CTRL: 10.04 ± 1.09 Hz), although the developmental increase in individual alpha peak frequency was replicated (children versus adults: $F(1,101) = 5.010$, $p = 0.027$). There were also no significant ADHD effects on individual alpha peak amplitudes. Thus, the lack of theta increases was not accompanied by an individual alpha peak frequency slowing.

Subtle ADHD-related deviance was only detected post-hoc in older children (discussed above) or for interactions with the resting condition. The theta reduction with age tended to be less consistent and pronounced in ADHD than in control children, consistent with increased heterogeneity in ADHD, and with increased theta deviance in adolescence. ADHD patients also produced a greater theta power increase at Fz to eye closure than controls, replicating previous reports that resting condition interacts with ADHD (Lansbergen et al. 2011; van Dongen-Boomsma et al. 2010). Nevertheless, using classical spectral EEG markers, ADHD classification proved unsuccessful, even after combining theta, beta, and theta/beta markers. In contrast to others (Monastra et al. 2001; Snyder et al. 2008), overall EEG-based ADHD classification accuracy was below 60 % and remained poor when including artefact time and/or ERP markers. Instead, younger and older children were discriminated with up to 85 % overall accuracy despite using variables selected for ADHD abnormalities.

Our topographic state of the art EEG analyses could have contributed to this lack of sensitivity, since the EEG data from children and from ADHD patients contained more movement and eye artefacts. However, using conventional artefact rejection yielded even less evidence for spectral ADHD deviance than ICA, which corrects better for pure eye artefacts. Both procedures consistently detected the maturational EEG effects. Still, artefact-free EEG time was a better ADHD marker than any spectral EEG measure (Table 4). This result suggests that artefacts may have confounded previous EEG differences between clinical (or developmental) groups.

Our extensive additional analyses did not identify any convincing explanation why other studies found consistent theta or theta/beta increases in ADHD. We suspect that several factors including subtle differences in referral or recruiting like using additional criteria for impairment (Monastra et al. 2001) may have contributed to the inclusion of more ADHD patients with maturational lag at rest in other studies. In addition, our advanced EEG approach using ICA correction and our close matching for age and gender may have precluded artefactually high performance of EEG-based ADHD classification. Another possible explanation for the lack of EEG abnormalities in our study may be the short (6 min) duration of our EEG recordings. Other studies select a similar number of segments, but from up to 20 min EEG (Clarke et al. 2002a). In case EEG abnormalities emerge only during prolonged recordings, these may reflect a more rapid vigilance decrement in ADHD, which should be studied systematically. For diagnostics, shorter test durations are particularly important to ensure efficient and reliable approaches, which require a minimum of expertise with as few rejects as possible.

Filtering railway-related noise at 16.66 Hz led to some artificial, but marginal reduction in beta band power and a corresponding increase in the theta/beta ratio. Our very narrow band rejection filter (0.1 Hz width fourth order) suppressed only a small proportion (<5 %) of the beta band (see also power density spectra in online resource Fig. S2). Although this situation has to be kept in mind when comparing our data with literature values (online resource Table S5), it does not influence any comparison between our groups and conditions, as all were recorded and analysed under the same conditions. Filtering in the beta band can also not explain the lack of theta increases, which have been considered to be the most robust ADHD marker across the wide age range covered here.

To sum up, our maturational and ADHD-related findings point to increased heterogeneity of the resting EEG in ADHD. This is consistent with recent multiple pathway models of ADHD, but inconsistent with claims for reliable ADHD diagnosis based on simple EEG markers. This is at least partly in line with others (Barry and Clarke 2009; Clarke et al. 2011; Ogrim et al. 2012), but clearly at odds with Monastra et al. (2001) and Snyder et al. (2008), although it does not exclude that EEG markers are useful to separate ADHD subgroups. Similar to the clinical evaluation of ADHD, neurophysiological classification is challenged by the heterogeneity among these patients and the coexistence of comorbidities and other disorders with similar symptoms. Resting EEG markers proved even less sensitive and less suitable for diagnostic purposes than ERP markers. Combining such markers might assist in the identification of ADHD, but a robust combination has not yet been found. These findings also have important implications for neurofeedback treatment of ADHD, where patients are often trained to reduce their theta power or theta/beta ratio (Heinrich et al. 2007). If these EEG markers are not abnormally elevated, such neurofeedback training lacks a physiological rationale in terms of a unidirectional state normalisation, and training state regulation on demand in both directions may be the better approach (Liechti et al. 2012). Alternatively, the lack of systematic theta/beta deviation in our ADHD groups could also be taken as support for personalized neurofeedback based on the individual quantitative EEG deviations (Arns et al. 2012). However, the large variability of theta and theta/beta markers that we observed also in our control groups

Table 4 ADHD and age classification based on resting EEG and ERP measures

Analysis	Variable	Sensitivity	Specificity	Overall accuracy	Steps	Wilks λ	X^2	Df	p
ADHD classification									
Resting EEG									
	θ_Cz_ec	46.9 %	56.7 %	51.6 %	–	0.995	0.271	1	0.603↑
	θ_Cz_eo	43.8 %	50.0 %	46.8 %	–	0.998	0.134	1	0.714↑
	β_Cz_ec	37.5 %	70.0 %	53.2 %	–	0.971	1.751	1	0.186↑
	β_Cz_eo	37.5 %	66.7 %	51.6 %	–	0.978	1.316	1	0.251↑
	θ/β_Cz_ec	43.8 %	36.7 %	40.3 %	–	1.000	0.018	1	0.893↓
	θ/β_Cz_eo	46.9 %	40.0 %	43.5 %	–	1.000	0.025	1	0.875↓
	Stepwise (6)	37.5 %	70.0 %	53.2 %	1	0.971	1.751	1	0.186[a]
	Goodsegs_ec	71.9 %	63.3 %	67.7 %	–	0.825	11.459	1	0.001↓
	Goodsegs_eo	59.4 %	66.7 %	62.9 %	–	0.921	4.871	1	0.027↓
	Stepwise (8)	68.8 %	73.3 %	71.0 %	3	0.773	15.062	3	0.002[b]
ERP									
	CNV_Pz_CPT	59.4 %	63.3 %	61.3 %	–	0.942	3.586	1	0.058↑
	CNV_Pz_CPTF	62.5 %	60.0 %	61.3 %	–	0.959	2.483	1	0.115↑
	NoGoP300_Pz_CPT	65.6 %	60.0 %	62.9 %	–	0.934	4.093	1	0.043↓
	NoGoP300_Pz_CPTF	68.8 %	56.7 %	62.9 %	–	0.956	2.648	1	0.104↓
	Stepwise (4)	65.6 %	60.0 %	62.9 %	1	0.934	4.093	1	0.043[c]
Resting EEG and ERP									
Stepwise (without goodsegs: 10)		62.5 %	63.3 %	62.9 %	2	0.905	5.863	2	0.053[d]
Stepwise (all: 12)		71.9 %	73.3 %	72.6 %	3	0.765	15.650	3	0.001[e]
Age classification									
Resting EEG									
	θ_Cz_ec	74.2 %	83.9 %	79.0 %	–	0.690	22.055	1	<0.001↑
	θ_Cz_eo	74.2 %	80.6 %	77.4 %	–	0.633	27.230	1	<0.001↑
	β_Cz_ec	64.5 %	29.0 %	46.8 %	–	1.000	0.016	1	0.899↓
	β_Cz_eo	35.5 %	67.7 %	51.6 %	–	0.997	0.202	1	0.653↑
	θ/β_Cz_ec	67.7 %	74.2 %	71.0 %	–	0.777	14.978	1	<0.001↑
	θ/β_Cz_eo	64.5 %	71.0 %	67.7 %	–	0.828	11.217	1	0.001↑
	Stepwise (6)	74.2 %	87.1 %	80.6 %	2	0.594	30.726	2	<0.001[f]
	Goodsegs_ec	74.2 %	64.5 %	69.4 %	–	0.773	15.354	1	<0.001↓
	Goodsegs_eo	61.3 %	67.7 %	64.5 %	–	0.871	8.231	1	0.004↓
	Stepwise (8)	80.6 %	90.3 %	85.5 %	4	0.471	43.708	4	<0.001[g]
ERP									
	CNV_Pz_CPT	51.6 %	45.2 %	48.4 %	–	0.993	0.422	1	0.516↓
	CNV_Pz_CPTF	61.3 %	58.1 %	59.7 %	–	0.977	1.380	1	0.240↑
	NoGoP300_Pz_CPT	61.3 %	54.8 %	58.1 %	–	0.990	0.626	1	0.429↓
	NoGoP300_Pz_CPTF	67.7 %	58.1 %	62.9 %	–	0.887	7.165	1	0.007↓
	Stepwise (4)	67.7 %	58.1 %	62.9 %	1	0.887	7.165	1	0.007[h]
Resting EEG and ERP									
Stepwise (without goodsegs: 10)		83.9 %	87.1 %	85.5 %	4	0.540	35.770	4	<0.001[i]
Stepwise (all: 12)		80.6 %	90.3 %	85.5 %	6	0.421	49.372	6	<0.001[j]

Variables which entered into the stepwise discriminant function analysis (DA) of children (n = 62) comparing children with attention-deficit/hyperactivity disorder (ADHD) and healthy controls (CTRL) and different age groups. Variables are listed with their corresponding sensitivity (ADHD vs. CTRL; younger vs. older children), specificity, overall classification accuracy, associated Wilks λ statistic, Chi-square test (X^2) and p value. Classification based on resting EEG for eyes-closed (ec) and eyes-open (eo) condition at electrode Cz and event-related potential (ERP) markers (contingent negative variation (CNV) after a visual cue and a P300 component after an inhibitory NoGo situation (NoGoP300) for continuous performance task (CPT) and flanker version (CPTF) at electrode Pz (for further details, see Valko et al. 2009). Variables in the order they entered the stepwise DA: [a]β_Cz_ec↑; [b]goodsegs_ec↓, goodsegs_eo↓, θ_Cz_ec↑; [c]NoGoP300_Pz_CPT↓; [d]NoGoP300_Pz_CPT↓, β_Cz_ec↑; [e]goodsegs_ec↓, NoGoP300_Pz_CPT↓, θ_Cz_eo↑; [f]θ_Cz_eo↑, θ/β_Cz_ec↑; [g]θ_Cz_eo↑, goodsegs_eo↓, β_Cz_ec↓, goodsegs_ec↓; [h]NoGoP300_Pz_CPTF↓; [i]θ_Cz_eo↑, θ/β_Cz_ec↑, CNV_Pz_CPT↓, NoGoP300_Pz_CPTF↓; [j]θ_Cz_eo↑, β_Cz_ec↓, goodsegs_eo↓, goodsegs_ec↓, CNV_Pz_CPT↓, CNV_Pz_CPTF↑

suggests that values close to the control group's mean are not prerequisites for normal attentional and inhibitory functions.

Conclusion

The absence of consistent resting EEG abnormalities in the theta and beta band of the present ADHD sample questions the value of neurometric ADHD classification based on these simple spectral resting EEG markers. This finding does not imply a general null hypothesis for all samples, but acknowledges the heterogeneity across ADHD (and control) samples for these markers, which is, however, equally problematic for claims postulating a simple and robust diagnostic ADHD marker. Neither these simple resting EEG nor simple ERP measures permitted sufficiently reliable ADHD diagnosis across subtypes, although these markers have previously proven useful to identify multiple pathways, subtypes, and treatment responses in ADHD.

Acknowledgments This study was supported by the Swiss National Science Foundation (SNSF) grant 32-109591 and by grants from Eli Lilly to H.-C. Steinhausen. Recruitment of ADHD sibling pairs was supported by National Institute of Mental Health Grant R01MH062873 to Steve Faraone (PI) and H.-C. Steinhausen (site PI). We thank the children and their families for participation, Antonia Bak, Gudrun Schneider, Guyslaine Thalmann, Lea Meier, Nadia Mock, and Yamilée Schwitter for help with testing and data processing, and Markus Mächler and Stefano Maurizio for their support with data analysis.

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