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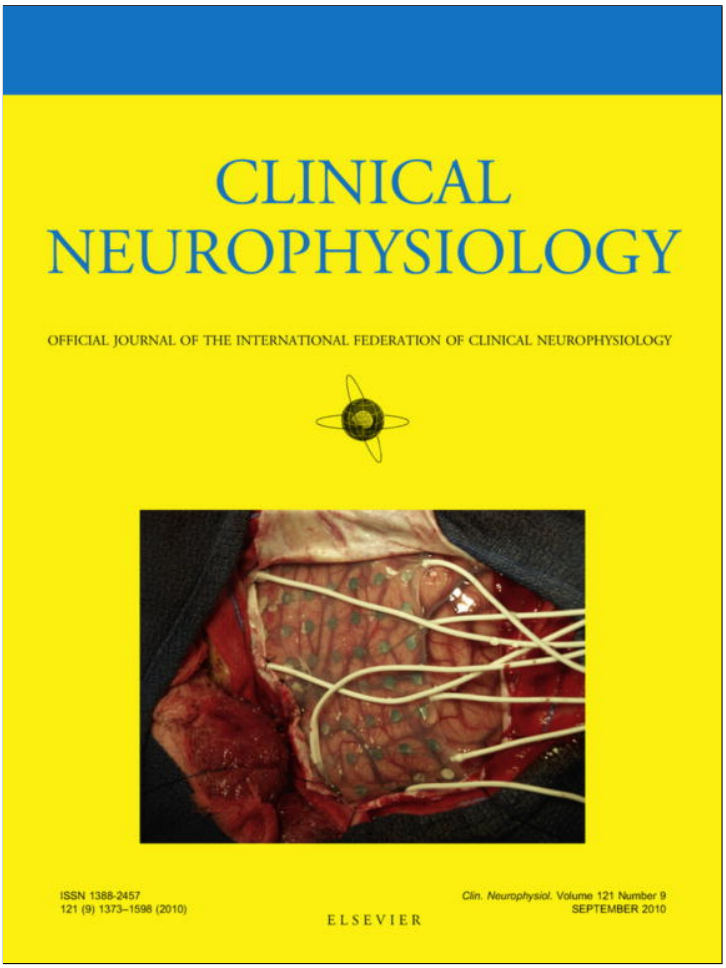

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EEG-vigilance and response to stimulants in paediatric patients with attention deficit/hyperactivity disorder

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ABSTRACT

Objective: In a pilot study it was investigated whether assessment of EEG-vigilance is useful for the prediction of treatment outcome in ADHD patients.
Methods: Resting EEG recordings of 49 unmedicated ADHD patients and 49 age-matched controls were analyzed. Vigilance level was determined for 1-s segments with a computer-based algorithm, distinguishing six stages from higher vigilance stages A1, A2 and A3 with dominant alpha activity to lower stages B1 and B2/3 with low amplitude non-alpha and increasing theta and delta activity and further onto stage C characterizing sleep onset. Treatment outcome was measured as changes in continuous performance test (CPT) results from baseline after at least 4 weeks of medication.
Results: ADHD patients spend less time in higher A1-stages (ADHD = 66%, controls = 81%) and showed more switching between vigilance stages (ADHD = 26.02%, controls = 19.09%), indicating a more unstable vigilance regulation. Patients with less stable vigilance showed a worse pre-treatment CPT performance but achieved a better post-treatment result compared to patients with more stable vigilance regulation. These differences did not reach statistical significance.
Conclusions: Signs of vigilance instability where found in ADHD patients compared to controls. Those patients with a higher degree of vigilance instability seemed to benefit more from stimulant medication.
Significance: This is the first investigation of EEG-vigilance in ADHD-patients. Results are limited by a short recording time but the results strongly suggest further investigation of the vigilance regulation in ADHD patients.
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1. Introduction

Attention deficit/hyperactivity disorder (ADHD) is one of the most prevalent psychiatric disorders in children and adolescents, affecting 3–7% of school aged children (Cormier, 2008). It has been shown that in many cases symptoms will remain into adulthood (Davidson, 2008). Children with ADHD have a high risk of developing comorbid affective substance abuse disorders (Bukstein, 2008; Daviss, 2008; Young, 2008) and ADHD is associated with impairments in educational, neuropsychological and social functioning.

Considerable research has been carried out investigating the neurophysiology of ADHD (reviewed by di Michele et al., 2005). Studies using quantified EEG (qEEG) have consistently shown a distinct profile, characterised by an increase in slow activity (i.e. theta and delta) and decreased power in fast (i.e. beta) frequencies (Clarke et al., 1998; Lazzaro et al., 1998; reviewed by Barry et al., 2003). The elevation of theta activity was found to remain present from childhood to adulthood (Bresnahan et al., 1999; Bresnahan and Barry, 2002).

Patients with ADHD do not represent a homogenous group from the neurophysiologic perspective. Arns et al. (2008) demonstrated that ADHD patients with increased slow wave qEEG activity (i.e. more theta than normal) might actually consist of two sub-groups: one group with a slowed alpha peak frequency (APF), which is misclassified as "slow" activity, and another group with real elevated theta (and a normal alpha frequency). Though a reduction in beta activity is characteristic for the group average in ADHD, in about 20% of individual patients an excess in beta-power has been found (Chabot and Serfontein, 1996; Clarke et al., 2001a; Arns et al., 2008). Several EEG-defined sub-types of ADHD have been proposed. Besides the rare excess beta type (interpreted as over-aroused), a sub-group with an increase in high-amplitude theta and a reciprocal decrease in beta activity (interpreted as sign of

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cortical hypoarousal) as well as a group with increased slow wave and deficiencies of fast wave activity (suggesting a maturational lag) have been described (Clarke et al., 2001a, b, 2002b).

ADHD can effectively be treated with neurofeedback, psychotherapeutic and pharmacological interventions (Arns et al., 2009; Benner-Davis and Heaton, 2007; Ghuman et al., 2008; Knight et al., 2008). In the latter case, psychostimulants are considered the first line approach (Plizska, 2007; Soileau, 2008). Although their effectiveness and safety has been proven (Lerner and Wigal, 2008; Rostain, 2008) a considerable number of patients does not clinically respond to stimulant medication (Swanson et al. 1993; Greenhill et al., 1999).

Therefore, many attempts have been made to use the EEG as a predictor for treatment response (Satterfield et al., 1973; Chabot et al., 1999; Hermens et al., 2005b; Loo and Barkley, 2005; Arns et al., 2008). Psychostimulants have been shown to normalize the EEG activity towards the pattern found in healthy controls (Clarke et al., 2002d, 2003, 2007; Hermens et al., 2005a). The usefulness of EEG for response prediction is suggested by findings that subgroups of ADHD patients with different EEG profiles respond differently to stimulant medication (Suffin and Emory, 1995; Clarke et al., 2002a, c; Arns et al., 2008).

Recently, a pathogenetic model was proposed focussing on the unstable vigilance regulation found in manic patients (Hegerl et al., 2008a, 2009). According to this model, vigilance instability may result in a vigilance auto-stabilization behaviour, which is reflected in hyperactivity, sensation seeking, and distractibility. In a recent paper, Hegerl et al. (2010) discussed similarities in symptoms and pathophysiology of mania and ADHD, arguing that EEG-vigilance might be a pathogenetic factor in the development of ADHD, too. The therapeutic effect of psychostimulants in ADHD thus results from their vigilance enhancing properties.

This concept is based on the description of vigilance stages (e.g. Ulrich, 2002), which refer to distinct states of global brain activation (Olbrich et al., 2009), observable on the continuum ranging from full wakefulness to sleep onset. Several classification systems have been proposed, which are based on characteristic EEG features of these stages. The following stages can be separated (Loomis et al., 1937; further developed by Roth, 1961; Bente, 1964):

- An activated state with a lack of dominant alpha activity.
- Stage A with dominant alpha activity corresponding to relaxed wakefulness (further divided into sub-stages A1, A2 and A3 according to the degree of alpha anteriorisation.
- Stage B with low amplitude non-alpha (sub-stage B1) and increasing theta and delta activity (sub-stages B2 and B3) corresponding with stage I (drowsiness) according to Rechtschaffen and Kales (1968).
- Stage C with vertex waves, sleep spindles or K-complexes characterizing sleep onset and corresponding to stage II sleep according to Rechtschaffen and Kales (1968).

An unstable vigilance regulation would result in more frequent declines to lower vigilance stages, characterized – as described above – by a decline in posterior alpha activity and increase in theta and delta activity mainly in frontal areas. The qEEG profile of someone remaining in lower vigilance stages throughout an EEG recording would thus appear as what has consistently been shown in qEEG studies in ADHD: decreased alpha and increased theta activity. However, there are important methodological differences between the EEG-vigilance approach and quantitative EEG. Although EEG recordings of several minutes are performed in qEEG studies, generally only a few artefact free segments are chosen from the continuous EEG recording. Depending on the quality of the recording and the number of artefacts, the required amount of segments can be taken at the very beginning of a recording or after several minutes. The EEG-vigilance approach questions this procedure, since there are inter-individual differences in the temporal stability of EEG-vigilance. While most individuals will toggle between vigilance stages during resting conditions (physiologic vigilance regulation), there are those remaining unaltered in one stage (hyperstable vigilance regulation), whereas others show rapid declines to lower vigilance stages (unstable vigilance regulation). Especially in cases of unstable vigilance, the position of segments extracted for qEEG is of crucial importance for the obtained results.

An important advantage of the vigilance approach is that it is theory driven. When classifying vigilance stages, the power and temporal dynamics in the four main frequency bands are compared according to criteria derived from earlier works on the neuroelectric activity and its changes in the transition period between wakefulness and sleep onset (Bente, 1964; Ulrich, 2002), which have been confirmed by contemporary research (DeGennaro et al., 2001; Tsuno et al., 2002; Cantero et al., 2002; Strijkstra et al., 2003; Kaida et al., 2006; Marzano et al. 2007).

To our knowledge, there are no studies using the EEG-vigilance approach in patients with ADHD. One reason might be the difficulty to obtain undisturbed resting EEGs from hyperactive patients, but also the increased time, expense and methodological problems. To evaluate whether or not this added effort is justifiable, we performed a pilot study, reanalyzing data published by Arns et al. (2008). Our intention was to investigate the association between EEG-vigilance and the therapeutic effect of psychostimulants in ADHD. The following hypotheses were tested:

a. States of lower vigilance occur more often in patients with ADHD as compared to healthy controls.
b. Those ADHD patients with a lower vigilance level will benefit more from treatment with vigilance stabilizing agents such as psychostimulants.

2. Methods

2.1. Subjects

Data from 49 boys with ADHD (average age = 11.33; range 6–17) and 49 control boys (matched on age, gender and education; average age = 11.92; range 7–18) were drawn from the Brain Resource International Brain Database (see Gordon, 2003; Gordon et al., 2005). Exclusion criteria were a personal or family history of mental illness, brain injury, neurological disorder, serious medical condition, drug/alcohol addiction; and a family history of genetic disorders. All subjects voluntarily gave written informed consent.

The ADHD patients had been referred by a paediatrician and their diagnosis was confirmed by a semi-structured interview based on DSM-IV criteria for ADHD, as well as being 1 SD above the norm for inattentive or hyperactive/impulsive indices of the Connors Parent Rating Scales. A portion of the data supporting the paediatrician's diagnosis was missing for three participants. Since no ADHD sub-group analysis was to be performed, those three patients' data were not excluded from analysis. For the other patients mean scores and SDs on the subscales were: inattentive: mean = 8.909, SD = 1.27; hyperactive/impulsive: mean 5.28; SD = 2.90 and impulsive: mean = 1.91; SD = 1.16. Twenty-two subjects met DSM-IV criteria for ADHD of predominantly inattentive sub-type, two subjects met criteria for ADHD of predominantly hyperactive-impulsive sub-type and 22 subjects met criteria for the combined ADHD sub-type.

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2.2. Procedure

On the assessment day electroencephalographic and neuropsychological assessments took place in the following order: EEG data was recorded for 2 min with eyes open (EO) and for 2 min with eyes closed (EC), followed by a continuous performance test (CPT). After having received medication for at least 4 weeks, the ADHD patients again performed the CPT. Change in CPT results was used as a measure for response to treatment.

During the CPT, a series of letters (B, C, D and G) were presented for duration of 20 ms with an interstimulus interval of 2.6 s. When the same letter appeared twice in a row, subjects had to press two buttons with each index finger. The CPT contained 125 stimuli in total: 20 of which were pseudo-randomly presented target letters, 85 background letters, and 20 additional distractor stimuli (black and white checkerboards), which were randomly interwoven with the letter stimuli but had to be ignored by the subjects. The CPT was fully computerized, presented on a touch screen monitor and subjects' responses were recorded via touch-screen presses. The task instruction equally stressed response accuracy and speed. Subjects were told that the task would be 8 min long and performed a brief practice session. Reliability and validity data of these tasks are reported elsewhere (Paul et al., 2005; Clark et al., 2006).

2.3. Treatment

At the time of the baseline assessment 49 ADHD patients were either medication naïve ($n = 30$) or free of medication for at least 48 h ($n = 19$). No control subjects received medication. All ADHD patients had been taking a prescribed medication for at least 4 weeks at the time of the CPT re-test. Patients were required to take their prescribed dose 60 min before the testing session. 45 subjects were treated with psychostimulants (methylphenidate: $n = 38$; dexampetamine: $n = 7$), while four patients were treated with atomoxetine. When analyzing treatment effects on CPT performance, those four patients treated with atomoxetine were excluded.

2.4. Psychophysiological data acquisition

The EEG was recorded in a sound and light attenuated room, controlled at an ambient temperature of 22 °C. EEG data were acquired from 26 channels: Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4, T3, C3, Cz, C4, T4, CP3, CPz, CP4, T5, P3, Pz, P4, T6, O1, Oz and O2 (Quickcap; NuAmps; 10–20 electrode international system), referenced to averaged mastoids with a ground at Fpz. Horizontal eye-movements were recorded with electrodes placed 1.5 cm lateral to the outer canthus of each eye. Vertical eye movements were recorded with electrodes placed 3 mm above the middle of the left eyebrow and 1.5 cm below the middle of the left bottom eye-lid. Skin resistance was below 5 kΩ and above 1 kΩ for all electrodes. A continuous acquisition system was employed and EEG data were EOG corrected offline (Gratton et al., 1983). An additional ECG lead was placed on the arm. The sampling rate of all channels was 500 Hz. A low pass filter with attenuation of 40 dB per decade above 100 Hz was employed prior to digitization.

2.5. Vigilance classification

Only data from the EC condition was used for vigilance classification, since the current classification criteria refer to resting conditions with closed eyes. For vigilance analysis we used BrainVision Analyzer (Brain Products GmbH, Germany) software. After reading the data into the Analyzer we applied a low pass (>70 Hz), high pass (<0.5 Hz) and notch (50+/−2.5 Hz) filter and divided the EEG recording into 2 s segments, resulting in 60 segments for each data set. The segmented EEGs underwent a semi-automatic artefact correction, focussing mainly on those channels crucial for vigilance analysis (F3, F4, O1 and O2). Segments containing muscle, movement or technical artefacts were marked and not classified into a vigilance stage but not excluded in order to maintain the original time course. On average 8.98% of all segments (SD = 7.98) were marked as containing artefacts. One subject from the control group had to be excluded from further analysis since artefacts were found in 35% of all 2-s-segments.

Each data set was visually scanned for periods of actual sleep onset (defined as the onset of stage 2 sleep). No subject exhibited signs of actual sleep onset, thus no segments were classified as stage C.

Classification of vigilance stages A and B was executed using a validated computer algorithm (Hegerl et al., 2008b; Olbrich et al., 2009), which uses the frequency spectrum from 2 to 25 Hz and calculates power in the four main frequency bands (delta, theta, alpha and beta). The edge definitions of the frequency bands were not fixed (besides delta at 2–4 Hz) but adapted to the individual alpha peak frequency (APF) at occipital sites. APF was determined by searching the interval from 7.5 to 12.5 Hz in 0.5 Hz steps for the frequency range with the highest power. Individual APF was set as mean peak frequency at sites O1 and O2. An alpha band rage of 4 Hz was centred at the individual APF (+/−2 Hz). The resulting frequency range was considered the alpha band. Range of theta and beta bands were then determined according to the alpha band (Theta = 4 Hz to beginning of alpha band; beta = end of alpha band to 25 Hz). Each segment was then assigned to a respective vigilance stage based on the proportion of power in the four frequency bands, comparing frontal power (F3 and F4) to occipital (O1 and O2) power (see Fig. 1).

2.6. Statistics

For each vigilance stage its mean percentage of all non-artefact segments was calculated. Differences in the prevalence of vigilance stages was tested using a General Linear Model (GLM) with group (ADHD vs. Controls) as inter-subject factor and vigilance stage (A1, A2, A3, B1, B2/3) as intra-subject factor. Post-hoc analyses were performed with Bonferroni-Correction.

Subjects were classified to vigilance types according to the most prevalent vigilance stage. In cases of equal amount of two or more vigilance stages no classification was performed. Chi-square-tests were used to test differences in the occurrence of vigilance types between the ADHD group and controls.

CPT error scores (false positives, false negatives and total errors) were subjected to a square-root transformation in order to reduce skew in the distribution. Since many subjects made zero mistakes, we follow a recommendation of Freeman and Tukey (1950) and used the equation X′ = X**0.5 + (X + 1)**0.5.

Medication effects on CPT scores were tested using repeated measurement ANOVAs with time (pre vs. post-treatment) as intra-subject factor and vigilance type (low vs. high vigilance) as inter-subject factor.

3. Results

3.1. Prevalence of EEG-vigilance stages

During the 2 min of resting EEG with eyes closed, A1-stages were most prevalent in both groups (ADHD: 66.3%; controls: 81.0%), followed by B2/3 stages (ADHD: 24.0%; controls: 14.3%), whereas stages A2, A3 and B1 were rarely found. GLM analysis confirmed a significant main effect of vigilance stage ($F = 487.6$; $p = 0.000$), no significant main effect for group ($F = 2.0$; $p = 0.160$),

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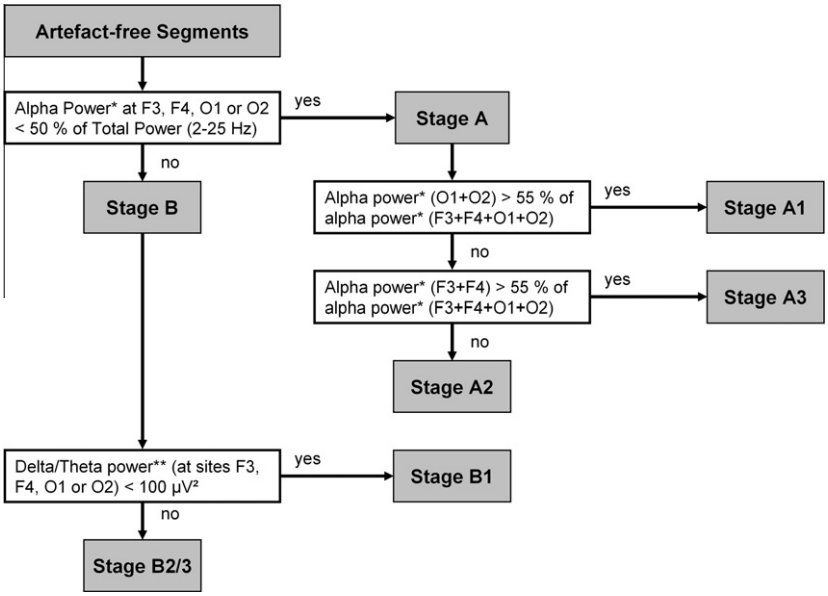

Fig. 1. Overview over the algorithm used to classify continuous 2-second EEG-segments from 2 min of resting-EEG with eyes closed. Segments containing artefacts were not classified. *, ** Frequency bands were not fixed, but adapted to individual alpha peak frequency (APF). Alpha band was considered as the 4 Hz band around the individual APF (+/−2 Hz). The frequency spectrum above 4 Hz until start of the alpha band was considered as theta band, while beta band was defined as the frequency range from the individual alpha band to 25 Hz.

but a significant vigilance * group interaction ($F = 2.7$; $p = 0.037$). As hypothesized, post-hoc analyses with Bonferroni Correction (see Table 1) showed that ADHD patients spent significantly less time in A1-stages than controls, and compared to controls tended to remain longer in the rare A2-stages. Comparable results were found when age was included as a covariate.

As can be seen in Fig. 2, these differences remained stable over the whole recording period. There was no detectable decrease in the prevalence of A1-stages, either in the ADHD group or in the control group during the 2 min of recording. However, when comparing the percentage rate of stage-switches (corrected for switches into, between and out of segments containing artefacts), ADHD patients were shown to switch between different vigilance stages more often than controls (ADHD: 26.02%; Controls: 19.09%; $T = 1.749$; $p_{(1\text{-tailed})} = 0.042$), indicating a less stable vigilance regulation in ADHD.

Subjects were classified according to the predominant vigilance stage over the whole recording period. 38 subjects in the ADHD group (77.6%) and 43 subjects in the control group (89.6%) were classified as "A1-type", 10 ADHD patients (20.4%) and 4 controls (8.3%) as "B2/3-type", and 1 subjects from both groups was classified as "B1-type". Chi-square-tests revealed no significant differences in the relation of these vigilance types between the ADHD and Control group ($X^2 = 2.870$, $p = .238$).

3.2. Changes in continuous performance test (CPT)

For all analyses of vigilance regulation on CPT performance and response to psychostimulants, "low vigilance" ADHD patients (remaining predominantly in B2/3-stages) were compared "high vigilance" ADHD patients (showing mostly A1-stages). Those excluded from analysis include the four patients treated with atomoxetine, the one patient with predominant B1-stages, as well as five patients who did not complete the follow-up CPT. Therefore data of 40 ADHD patients were analyzed for CPT and medication response.

After 4 weeks of treatment with stimulant medication, a significant reduction in false positives, false negatives and total errors was found. Also, the standard deviation of the reaction time did significantly decline; though there was no significant reduction in reaction time (see Table 2). When performing a median split of the pre-treatment reaction times (slow group: RT < 565 ms; fast group: RT = />565 ms), a regression to the mean became evident – those who exhibited faster pre-treatment reaction times (fast group, $n = 22$) tended to slow down under stimulant medication ($M_{pre} = 491.50$, $M_{post} = 558.68$, $T = -1.863$, $p = 0.077$) whereas those who had rather slow pre-treatment reaction times (slow group, $n = 18$) significantly accelerated their performance ($M_{pre} = 753.61$, $M_{post} = 604.81$, $T = 4.997$, $p = 0.000$). However, Chi-square-tests

Table 1
Differences in the incidence of vigilance stages in ADHD patients compared to controls. For each vigilance stage its mean proportion of the whole recording (corrected for artefacts) is shown. When age was included as a covariate, this had no effect on the results.

	ADHD ($n = 49$) (%)	Controls ($n = 48$) (%)	p (1 tailed)[a]	Co-variable (age) p (1 tailed)[a]
A1-stages	66.30	81.01	0.008**	0.007**
A2-stages	4.29	1.45	0.015*	0.012*
A3-stages	1.98	1.00	0.128	0.126
B1-stages	3.46	2.21	0.297	0.267
B2/3-stages	23.98	14.33	0.035	0.037

[a] Bonferroni-corrected significance level set at **p(5%) = 0.01, *p(10%) = 0.02.

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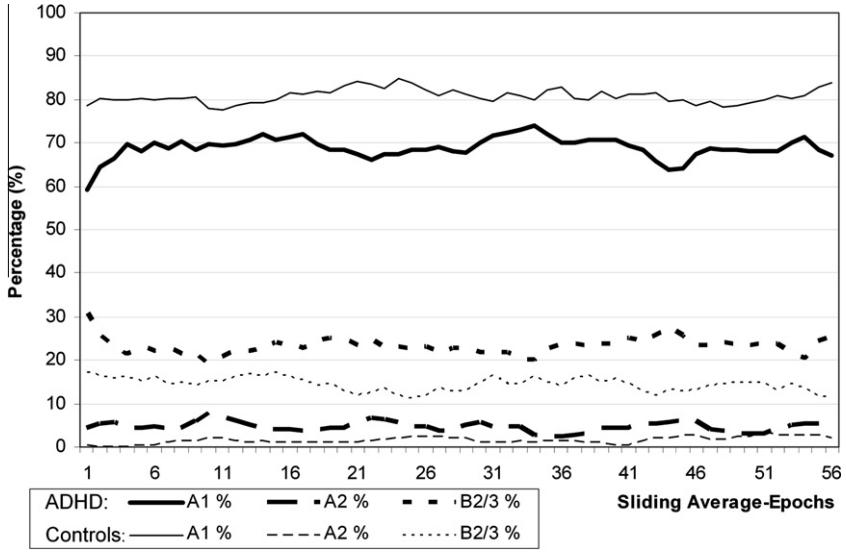

Fig. 2. Time course of vigilance stages A1, A2 and B2/3 in ADHD-patients compared to healthy controls during 2 min of resting-EEG with closed eyes. On the *x*-axis, consecutive sliding average-epochs are presented, which have been calculated from the 60 2 to second segments (epoch 1: averaged amount of vigilance stages from segments 1–5, epoch 2: segments 2–6, epoch 3: segments 3–7, . . ., epoch 56: segments 56–60).

($X^2 = 0.240$; $p = 0.887$) revealed no association of reaction time (slow vs. fast group) with ADHD sub-types (inattentive vs. hyperactive/impulsive vs. combined).

Pre-post-treatment CPT-results were compared between the "low vigilance" ($n = 10$) and the "high vigilance" ($n = 30$) patients. The "low vigilance" group achieved worse pre-treatment results as compared to the "high vigilance" group on all CPT scores (slower RT with higher SD, more FP, FN and ER) and, after stimulant medication, improved more on all scores, resulting in better post-treatment performance as compared to the "high vigilance" group (see Fig. 3). However, repeated measurement ANOVAs showed a main effect of time (pre vs. post-treatment) for all CPT results besides the reaction times, but no significant main effect of vigilance group. For total errors, there was a tendency for a vigilance *time interaction (see Table 3).

4. Discussion

In this work, we investigated the vigilance regulation of patients with ADHD. It has been hypothesized that an unstable vigilance regulation is a trait characteristic of ADHD and that some ADHD symptoms, e.g. hyperactivity, might be part of an autoregulatory vigilance stabilization behaviour (Hegerl et al., 2010). Since vigilance stabilizing agents such as psychostimulants are effective in the treatment of ADHD, we assumed that those patients with more pronounced vigilance instability should benefit the most from stimulant treatment.

Table 2
Changes in the pre- and post-treatment continuous performance test scores of 40 ADHD patients receiving stimulant treatment.

		Pre	Post	T	*p* (2-tailed)
Reaction time (in ms, RT)	M	609.45	579.48	1.025	0.312
	SD	176.72	158.36		
Standard deviation (in ms, SD)	M	263.00	199.50	2.733	0.009
	SD	135.65	91.417		
False positive errors (FP)*	M	5.11	4.17	2.946	0.005
	SD	2.73	2.79		
False negative errors (FN)*	M	3.64	2.76	2.729	0.009
	SD	1.77	1.40		
Total errors (TE)*	M	6.35	5.09	3.600	0.001
	SD	2.81	2.69		

* Square root transformed data.

We could confirm the first hypotheses as ADHD patients spend less time in stages of higher vigilance (A1-stages) as well as demonstrating more fluctuations in their vigilance level, seen as a higher number of stage switches. These findings remained significant when age was included as a co-variable, though some may still critique our results as being due to maturation effects. This argument is based on the fact that cortical rhythms such as alpha develop in a certain temporal order during youth and adolescence. It could be argued that vigilance stages are not validly classifiable in children, since the definition of vigilance stages depends on the spatio-temporal distribution of cortical rhythms, mainly the occurrence (or non-occurrence) of alpha. However, according to Niedermeyer (2005), a stable alpha rhythm can be found in children aged 6–10 years, but only gradually reaches the mature frequency of 10/s. A vigilance classification depending on a rigid definition of the alpha band (8–12 Hz), would therefore underestimate the occurrence of A-stages, since a slowed alpha would be considered as theta. This was taken into account when the individual APF was used as basis for vigilance classification. However, intermixture of posterior slow activity can be found quite often in the fusiform alpha waves in younger children. Whether or not slow EEG-activity reflects lower vigilance or immaturity can not be answered from this study (for a detailed discussion see Ulrich, 2002).

To test our second hypothesis (more severe vigilance dysregulation should benefit the most from psychostimulants), changes in continuous performance test (CPT) results were used to assess medication response. Swanson (1985) recommended objective laboratory measures of inattention as appropriate measures for monitoring pharmacological effects in children. Comparing results of repeated CPT performances of unmedicated ADHD patients, Soreni et al. (2009) found the CPT to yield a reliable measure of inhibitory control (false positive errors) and acceptable reliability estimates for reaction times and reaction time variability.

When unmedicated CPT performance was compared to CPT performance with psychostimulants (methylphenidate, dexamphetamine), we found a reduction in omission (false negative) and commission (false positive) errors. Reaction time showed a regression to the mean. These findings are in accordance to existing data on stimulant effects on CPT performance (Losier et al., 1996; Riccio

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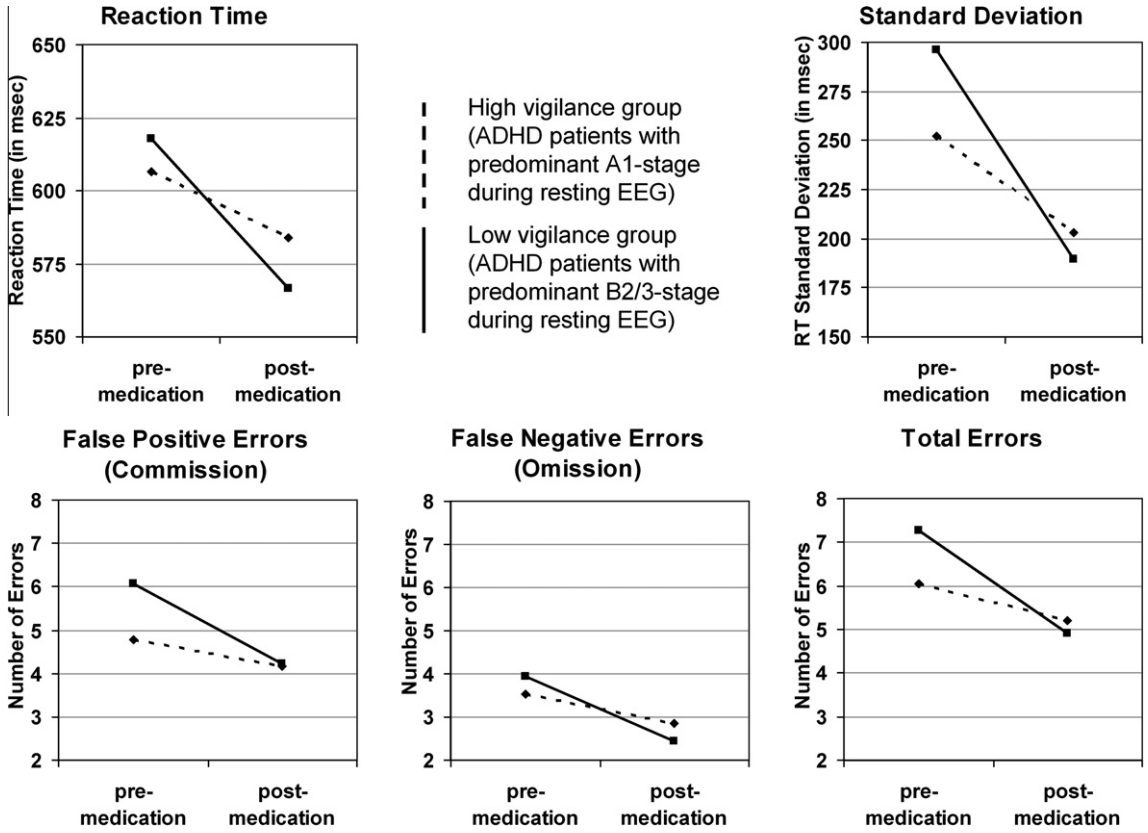

Fig. 3. Results of the ADHD group in the continuous performance test (CPT). Subjects performed the CPT in unmedicated state (pre-treatment) and after at least 4 weeks of medication with stimulants (methylphenidate, dexamphetamine). Shown separately are the results of those ADHD patients whose resting-EEG showed signs of an unstable vigilance (low vigilance group, $n = 10$), resulting in a greater proportion of time spend in lower vigilance stages, compared to those ADHD patients who exhibited predominantly higher A1-stages during the 2 min of resting-EEG (high vigilance group, $n = 30$).

et al., 2001). We also found a reduction in the variability of reaction times, but no significant change in reaction times. In general, ADHD patients had slower and more variable reaction times compared to controls, with medication resulting in faster reaction times and reduced variability (Kavale, 1982; Riccio et al., 2001).

One explanation for the lack of change in reaction times might be that there have been agonistic effects in our population. When patients with slower baseline reaction times were compared to patients who exhibited faster reaction times at baseline, the former were found to become faster under medication, whereas the latter tended to get slower. Though this might simply reflect a regression to the mean, it could also be sign of a reduction of impulsivity in the fast group and more attentional focus in the slow group. Teicher et al. (2004) classified the attentional state of patients during CPT performance and showed that these state measures provided a robust differentiation between controls and ADHD patients, who were less often on task and showed more shifting between attentional states. In the presence of faster reaction times, such attentional lapses do result in instances of prolonged reaction times (Leth-Steenson et al., 2000), making it difficult to detect changes with the usual statistics (Castellanos and Tannock, 2002; Hervey et al., 2006).

Although attentional lapses are consistent with the hypothesis of an unstable vigilance regulation causing performance deficits in prolonged tasks, we were not able to verify that an unstable vigilance regulation could predict response to stimulant medication (our second hypothesis). In general, those ADHD patients, who at baseline demonstrated more signs of an unstable vigilance,

Table 3
Effects of treatment (pre vs. post treatment with psychostimulants) and vigilance type (low vigilance vs. high vigilance) on performance in the continuous performance test. Shown are results of repeated measurement ANOVAs with two-sided significance testing.

	Vigilance type	Pre	Post	Time	Vigilance	Time* vigilance
Reaction time (in ms, RT)	Low	618.00	566.40	$p = 0.283$	$p = 0.954$	$p = 0.675$
	High	606.60	583.83			
Standard deviation (in ms; SD)	Low	295.80	189.30	$p = 0.006$	$p = 0.650$	$p = 0.291$
	High	252.07	202.90			
False positive errors (FP)*	Low	6.07	4.22	$p = 0.001$	$p = 0.483$	$p = 0.100$
	High	4.79	4.16			
False negative errors (FN)*	Low	3.95	2.44	$p = 0.006$	$p = 1$	$p = 0.260$
	High	3.53	2.86			
Total errors (TE)*	Low	7.27	4.93	$p = 0.000$	$p = 0.586$	$p = 0.071$
	High	6.04	5.14			

* Square root transformed data.

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achieved numerically worse results in the CPT during the baseline condition. After 4 weeks of medication with methylphenidate or dexamphetamine they seemed to perform better than patients who had demonstrated a higher vigilance level at baseline. The fact that these differences did not reach statistical significance, suggests that the study might have been underpowered concerning this aspect. Still, floor effects have to be considered, especially concerning error rates. Many patients made very few mistakes even in the unmedicated baseline assessment, and if there is no possibility to improve performance, any attempt to statistically describe an improvement is bound to fail.

Heterogeneity of the patient sample might be a reason for the non-significant results concerning the medication effect. The study sample consisted of patients suffering from different ADHD-subtypes. It has been shown that EEG-abnormalities of the inattentive sub-type are of lesser degree than those of the combined sub-type, although both sub-types displayed the same EEG-profile (Clarke et al. 1998, 2001a, b). No differential hypotheses have been proposed or tested due to the pilot nature of this study, but particularly since no difference would have been suspected according to the concept proposed by Hegerl et al. (2010). An unstable vigilance regulation is assumed to be present in both sub-types, with the combined sub-type merely showing additional vigilance auto-stabilization behaviour. With the suppressed auto-stabilization seen under resting conditions with eyes closed, the model predicts similar vigilance features in both sub-types. Additional heterogeneity of the study sample results from the different medications used. Most patients received methylphenidate, while others were treated with dexamphetamine or atomoxetine. However, dexamphetamine and methamphetamine are classified as stimulant medication and both act by increasing the availability of synaptic dopamine. Thus, a similar clinical effect of both medications was expected. Patients receiving a non-stimulant medication (atomoxetine) were excluded from analysis on the effect of medication on CPT performance.

In a previous publication using the same dataset, Arns et al. (2008) found that treatment outcome could be predicted using an EEG-phenotype approach based on the pre-treatment EEG. It was shown that the frontal slow EEG-phenotype predicted treatment outcome to stimulant medication, which led to speculation about whether frontal slow EEG should be considered a stable trait (EEG Phenotype) or a state (vigilance state). In Fig. 2 it can be seen that the differences in vigilance stages were present over the full 2 min EEG recording and there seemed to be a baseline difference rather than a time effect. This tends to suggest that in ADHD the frontal slow EEG could be regarded as a stable trait (EEG-phenotype), which is supported by the fact that the EEG-phenotype approach did predict treatment outcome. However, the exact cause of the frontal slow EEG is not clear yet, and might still be a result of an unstable vigilance regulation.

One important limitation of this study is the brevity of the available EEG-data. In normal practice, EEG-vigilance classification is based on recordings of 10 min or longer, since differences in vigilance regulation do manifest themselves only after sufficient time. Hegerl et al. (2008b) compared the EEG-vigilance of unmedicated patients with borderline personality disorder (BPD) or obsessive–compulsive disorder (OCD) and healthy controls. BPD patients showed a lower vigilance from the first minute on, controls progressively declined to lower vigilance levels, and OCD patients showed a stable and high vigilance level during 5 min of resting EEG with eyes closed. Yet, during the 5 min these differential time courses did not reach significance. By analyzing vigilance during 2 min of resting EEG in this study, only slight differences could be detected between ADHD patients and healthy controls. Assuming that ADHD patients do generally present with trait-like vigilance instability, one has to argue that it may have been easier to distinguish patients with more or less severe vigilance instability if longer EEG recordings would have been available. Additional limitations include the fact that post-hoc analysis was performed on existing data; therefore some conditions could not be constructed optimally. There was no repeated EEG-recording after medication to verify changes in vigilance regulation and no change-sensitive rating scale for ADHD symptoms was available.

To summarize, in this study we showed that ADHD patients have a less stable vigilance regulation, seen as more switches between vigilance stages and as lower vigilance stages (as compared to healthy controls during 2 min of resting EEG with eyes closed). Although statistical significance was not reached, patients with a more disturbed vigilance regulation seemed to benefit more from medication with vigilance enhancing stimulants. These differences may have been more prominent if longer EEG recordings would have been available. Therefore, based on these very promising pilot data, further research employing longer recordings should be conducted to investigate vigilance regulation in ADHD.

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