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Frontal brain asymmetry in adult attention-deficit/hyperactivity disorder (ADHD): Extending the motivational dysfunction hypothesis

Philipp M. Keune [a,b,*], Eva Wiedemann [c], Alexander Schneidt [c], Michael Schönenberg [c]

[a] Klinikum Bayreuth, Department of Neurology, Hohe Warte 8, 95445 Bayreuth, Germany
[b] Otto-Friedrich-University of Bamberg, Department of Physiological Psychology, Bamberg, Germany
[c] Institute of Psychology, Department of Clinical Psychology, Eberhard Karls University, Tübingen, Schleichstraße 4, 72076 Tübingen, Germany

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HIGHLIGHTS

- Frontal EEG alpha asymmetry was examined in adult ADHD patients on two measurement occasions, separated by two weeks.
- An alpha asymmetry pattern reflecting elevated approach motivation was associated with pronounced ADHD symptoms and alpha asymmetry displayed sufficient test–retest reliability.
- Results support a motivational dysfunction hypothesis of adult ADHD.

ABSTRACT

Objective: Attention-deficit/hyperactivity disorder (ADHD) involves motivational dysfunction, characterized by excessive behavioral approach tendencies. Frontal brain asymmetry in the alpha band (8–13 Hz) in resting-state electroencephalogram (EEG) represents a neural correlate of global motivational tendencies, and abnormal asymmetry, indicating elevated approach motivation, was observed in pediatric and adult patients. To date, the relation between ADHD symptoms, depression and alpha asymmetry, its temporal metric properties and putative gender-specificity remain to be explored.
Methods: Adult ADHD patients ($n = 52$) participated in two resting-state EEG recordings, two weeks apart. Asymmetry measures were aggregated across recordings to increase trait specificity. Putative region-specific associations between asymmetry, ADHD symptoms and depression, its gender-specificity and test–retest reliability were examined.
Results: ADHD symptoms were associated with approach-related asymmetry (stronger relative right-frontal alpha power). Approach-related asymmetry was pronounced in females, and also associated with depression. The latter association was mediated by ADHD symptoms. Test–retest reliability was sufficient.
Conclusions: The association between reliably assessable alpha asymmetry and ADHD symptoms supports the motivational dysfunction hypothesis. ADHD symptoms mediating an atypical association between asymmetry and depression may be attributed to depression arising secondary to ADHD. Gender-specific findings require replication.
Significance: Frontal alpha asymmetry may represent a new reliable marker of ADHD symptoms.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is being increasingly recognized as a disorder which may persist throughout adulthood, and in recent years, numerous attempts have been made to identify neural underpinnings of ADHD symptoms. Results from several studies suggest that these underpinnings may involve abnormal structural and functional hemispheric asymmetries (for reviews see: Konrad and Eickhoff, 2010; van Ewijk et al., 2012). In this context, a basic notion holds that undermined relative right-hemispheric functions involved in

* Corresponding author. Tel.: +49 921 400 751947.
E-mail address: pmkeune@gmail.com (P.M. Keune).

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the regulation of attention and arousal may contribute to ADHD symptoms (Almeida et al., 2010; Fassbender and Schweitzer, 2006; Hale et al., 2009b, 2010b). Complementary notions highlight the importance of potentially disrupted interhemispheric connectivity (Hale et al., 2009a; Roessner et al., 2004).

In support of the role of abnormal hemispheric asymmetries, several studies utilizing electroencephalographic (EEG) resting-state assessments have revealed an atypical pattern of frontal EEG asymmetry in pediatric and adult ADHD patients (Baving et al., 1999; Hale et al., 2009b; Keune et al., 2011b). These studies originated from the approach–withdrawal model of hemispheric asymmetry, according to which functional asymmetry, specifically in anterior regions, may be indicative of approach vs. withdrawal-related response dispositions (Coan and Allen, 2004; Davidson, 2004; Harmon-Jones et al., 2010). In this line of research, EEG alpha power (8–13 Hz) is commonly regarded as an inverse indicator of underlying cortical activity and stronger relative right-hemispheric anterior alpha power has been identified as a correlate of elevated approach motivation in healthy and abnormal groups (Allen et al., 2004a). In a series of studies utilizing self-report measures, Mitchell and Nelson-Gray (2006) and Mitchell (2010) suggested that ADHD might represent a disorder of motivational dysfunction, involving abnormally elevated approach tendencies. While to date, integrative work on this matter is sparse, findings on abnormal alpha asymmetry in ADHD support this suggestion.

1.1. Abnormal alpha asymmetry in ADHD

Early work by Baving et al. (1999) revealed that in a pediatric sample, males were characterized by abnormal, approach-related alpha asymmetry, i.e. pronounced relative right-hemispheric anterior alpha activity. This pattern was also observed in children with conduct problems (Rybak et al., 2006). More recently, Hale et al. (2009b) reported on a similar asymmetry pattern in adult ADHD patients, which was observed during a resting-state and a cognitive task, relative to a healthy comparison group. Frontal regional specificity, which is predicted by the approach–withdrawal model (Allen et al., 2004a; Harmon-Jones et al., 2010), was not explicitly addressed in the latter study, however, recent attempts have shown that abnormal asymmetry in adult ADHD approximates notions of the approach–withdrawal model (Keune et al., 2011b). Considering data which supports a genetic influence by showing familial loading, as well as the presence of this phenotype in children and adults, abnormal frontal alpha asymmetry may hence be ontogenetically stable in ADHD (Baving et al., 1999; Hale et al., 2010a, 2009b; Keune et al., 2011b). In this context, complementary work has also started to examine various approach-related traits in ADHD and related groups and provides convergent support regarding the relevance of abnormal frontal asymmetry for pronounced approach dispositions (Jaworska et al., 2012, 2013; Keune et al., 2012b).

1.2. Associations between alpha asymmetry and ADHD symptoms

While self-reported behavioral approach tendencies were shown to be associated with ADHD symptoms (Mitchell, 2010), studies on the relation between alpha asymmetry and ADHD symptoms have provided mixed results.

In the initial work by Hale et al. (2009b), approach-related increased relative right-hemispheric alpha activity was "*generally associated with greater numbers of ADHD symptoms*" (p. 2082). Nevertheless, it should be noted that this observation was made in a post-hoc analysis, may have been affected by Type-I error inflation and that regional specificity was not addressed. Similarly, in the study of our group (Keune et al., 2011b), which involved a limited sample size, an association between alpha asymmetry and pronounced approach motivation was not observed. To our knowledge, the question whether the regression of alpha power on ADHD symptoms varies as a function of region and hemisphere, in line with the approach–withdrawal model, remains to be addressed by appropriate statistical means. The latter issue was of primary importance for the current work.

1.3. Methodological issues: test–retest reliability of alpha asymmetry in ADHD

Besides this primary issue, in the current work, a basic methodological question was supposed to be addressed. In particular, while it may be inferred from previous studies, that abnormal asymmetry in ADHD is ontogenetically stable, to our knowledge there have been no attempts to examine whether alpha asymmetry in adult ADHD displays sufficient test–retest reliability. This is noteworthy for several reasons: firstly, alpha asymmetry is known to involve trait and state components (Coan et al., 2006; Hagemann et al., 2005; Keune et al., 2012a, 2013; Stewart et al., 2011). While some studies have reported that it is reasonably stable in certain psychiatric groups (e.g. unipolar depression; Allen et al., 2004b), others have observed temporal shifts and potential plasticity (Barnhofer et al., 2007; Debener et al., 2000; Keune et al., 2011a; Moscovitch et al., 2011). As it remains unclear, whether alpha asymmetry displays sufficient test–retest reliability in ADHD, the possibility to interpret results of studies on abnormal alpha asymmetry in this group remains limited. This is the case, since abnormality of a neurophysiologic phenotype such as approach-related asymmetry might be observable in cross-sectional studies due to temporal fluctuations of mean values and/or unsystematic progression of variance over time (Hofstadt-van Oy et al., 2014).

Secondly, there have been numerous attempts to utilize alpha asymmetry as an outcome measure in psychotherapeutic intervention studies, especially with regards to mindfulness-based interventions (Barnhofer et al., 2007; Davidson et al., 2003; Keune et al., 2011a, Keune et al., 2013; Moyer et al., 2011; Moynihan et al., 2013). As mindfulness training is known to exert general salutatory effects, it is also becoming increasingly popular in case of ADHD (Keune and Perczel-Forintos, 2010; Mitchell et al., 2013; van de Weijer-Bergsma et al., 2012; Zylowska et al., 2008) and alpha asymmetry might represent a candidate for an outcome measure in this context. However, before it may be utilized as such a measure, its basic methodological features require examination.

1.4. Depression and gender-differences in alpha asymmetry

There are several additional issues which remain to be addressed. Firstly, it remains to be explored, how symptoms of depression, which are frequent in adult ADHD, relate to frontal alpha asymmetry. The contemporarily prevailing view holds that depressive symptoms are associated with withdrawal-related asymmetry. Despite some inconsistencies, the latter association was repeatedly shown in case of unipolar depression (Carvalho et al., 2011; Coan and Allen, 2004; Harmon-Jones et al., 2010; Reid et al., 1998; Segrave et al., 2011). Should this relation also be valid for ADHD, one may suggest that abnormal approach-related asymmetry might be attenuated in patients with signs of depression (Keune et al., 2011b).

On the other hand, it needs to be considered that the occurrence of depression is related to the presence of ADHD symptoms. While abnormal alpha asymmetry and ADHD symptoms are already observable in pediatric patients (Baving et al., 1999), depression usually emerges after the onset of ADHD, reflecting accumulating difficulties in adapting to environmental challenges (Daviss, 2008). Given common variance of approach-related ADHD symptoms and depression, ADHD may hence represent a disorder in

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which signs of depression are associated with an approach-related asymmetry pattern.

It is also noteworthy that gender-specific patterns in alpha asymmetry were observed in both, ADHD and depression. In a pediatric ADHD sample examined by Baving et al. (1999), particularly boys were characterized by an abnormal approach-related alpha asymmetry pattern when compared to healthy controls, whereas the opposite pattern was obtained for girls. In a more recent study by Stewart et al. (2010), withdrawal-related asymmetry in women with lifetime major depression was associated with the severity of current depressive symptoms (i.e. in line with the approach–withdrawal model), whereas this relationship was not consistently observed in males. To date, in case of adult ADHD, information on putative gender-specific patterns of alpha asymmetry and the relation between alpha asymmetry and depression is sparse.

1.5. Purpose of the current work

The purpose of the current work was to address the issues outlined above for the first time. The basic question whether ADHD symptoms are related to specifically frontal EEG alpha asymmetry in line with the approach–withdrawal model and the motivational dysfunction hypothesis, was of primary importance (see Section 1.2). Accordingly, we hypothesized ADHD symptoms to be related to stronger relative right-hemispheric alpha activity, specifically in anterior regions. In addition, the basic methodological aspect was examined (test–retest reliability; Section 1.3). To address these issues, individuals suffering from ADHD participated in two resting-state EEG recordings, separated by two weeks. Psychiatric history, ADHD symptoms and current depressive symptoms were examined in an extensive diagnostic procedure. In an additional analysis, putative gender-specific patterns in alpha asymmetry and the relation between depression and alpha asymmetry were considered (Section 1.4).

2. Methods

2.1. Participants and diagnostic procedure

Recruitment occurred in the context of a larger project which examined putative effects of EEG neurofeedback training in adult ADHD. However, no training occurred prior to, or between assessments of the current study. Patients were recruited via advertisements in local newspapers in the area of Tübingen, Germany, and referred by the University's outpatient psychotherapeutic clinic. The diagnostic procedure has been described elsewhere (Keune et al., 2011b) and consisted of several interviews and self-report measures. The German version of the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) was administered to each candidate. For specific ADHD diagnostics, the Homburger ADHD Scales for Adults (HASE; Rösler et al., 2008a) were utilized. This procedure comprises German versions of the Wender-Reimherr-Interview (WRI; Rösler et al., 2008b), a structured interview addressing psychopathologic characteristics relevant for ADHD, the Wender Utah Rating Scale for Adults (WURS-K; Retz-Junginger et al., 2002), which addresses putative ADHD symptoms during childhood, as well as an ADHD self-rating scale (ADHD-SB; Rösler et al., 2004). To rule out aggravation tendencies, the Amsterdam Short-Term Memory test was administered, which tests aggravation of cognitive deficits (Schagen et al., 1997; Schmand and Lindeboom, 2005). Inclusion criteria involved an age range between 18 and 65 years and a confirmed ADHD diagnosis based on the HASE diagnostics. Participants who suffered from current or lifetime bipolar or psychotic disorder, or a neurological disorder were excluded from participation.

In an initial online survey, 140 individuals who felt that they were affected by ADHD symptoms and had an interest to participate in neurofeedback training, completed relevant self-report measures. Out of this pool, 96 right-handed individuals (49 females) who reported pronounced ADHD symptoms received an appointment for the entire diagnostic procedure. An ADHD diagnosis was confirmed in 65 cases (30 female; ADHD subtypes: 63 combined, 1 inattentive, 1 hyperactive). Subsequently, EEG data was obtained at an initial assessment (Time 1) and again after an interval of two weeks (Time 2) for 54 of these ADHD patients. One case was excluded from the analysis due to insufficient amount of artifact-free EEG data (see Section 2.2 for a detailed description of criteria). Data of another participant was not included because it represented an outlier, i.e. asymmetry values exceeded ±3 standard deviations of respective mean values obtained for frontal sites. The final dataset hence consisted of 52 cases. Demographic and clinical data is presented in Table 1.

2.2. Procedure, EEG recording and analysis

The current study was approved by the ethical committee of the University of Tübingen. All participants provided written informed consent. Resting-state assessments at Time 1 and Time 2 were conducted by means of a 24-channel EEG System (NeXus-32, Mindmedia, Netherlands). Measurements on each occasion involved eight one-minute trials, four with eyes open (O), four with eyes closed (C), which were presented in counterbalanced order (COCOOCOC). Participants were instructed to minimize movements and eye blinks during the recording. Recordings were obtained for 13 sites (F3, F4, F7, F8, Fz, C3, C4, Cz, P3, P4, Pz, M1, M2) with Ag/AgCl electrodes and a common average reference scheme, at a sampling rate of 512 Hz. Data analysis followed standard procedures (Allen et al., 2004a) and is illustrated in Fig 1. An algorithm was applied which excluded parts of each dataset contaminated by artifacts, using a rejection criterion of ±75 μV to rule out the influence of eye blinks on frontal channels. Subsequently, each one-minute trial was divided into one-second segments (50% overlap). A Hamming window was used which tapered data at the distal 10% of each epoch and a fast Fourier transform (FFT) was applied, yielding measures of spectral power (μV^2) in bins of 1 Hz. Spectral power was

Table 1
Demographics and clinical characteristics.

Characteristic	ADHD patients ($N = 52$)
Age (M, SD)	36.37, 9.43
Sex (female/male)	25/27
ADHD Type (N)	
Combined/inattentive/hyperactive	50/1/1
Medication (yes/no)	25/27
Comorbidity (N)	
Mood disorders	
Lifetime major depression	21
Current major depressive episode	None
Lifetime dysthymia	None
Current dysthymia	1
Anxiety disorders	
Current generalized anxiety disorder	2
Current social phobia	5
Current agoraphobia	2
Eating disorders	
Binge-eating type/bulimic	1/1

Note: M = mean, SD = standard deviation; medicated patients involved: methylphenidate $N = 10$, tricyclic antidepressants $N = 1$, selective serotonin reuptake inhibitors $N = 4$, cortisone $N = 1$, isotretinoin $N = 1$, L-tryptophan = 1, thyroxin $N = 10$.

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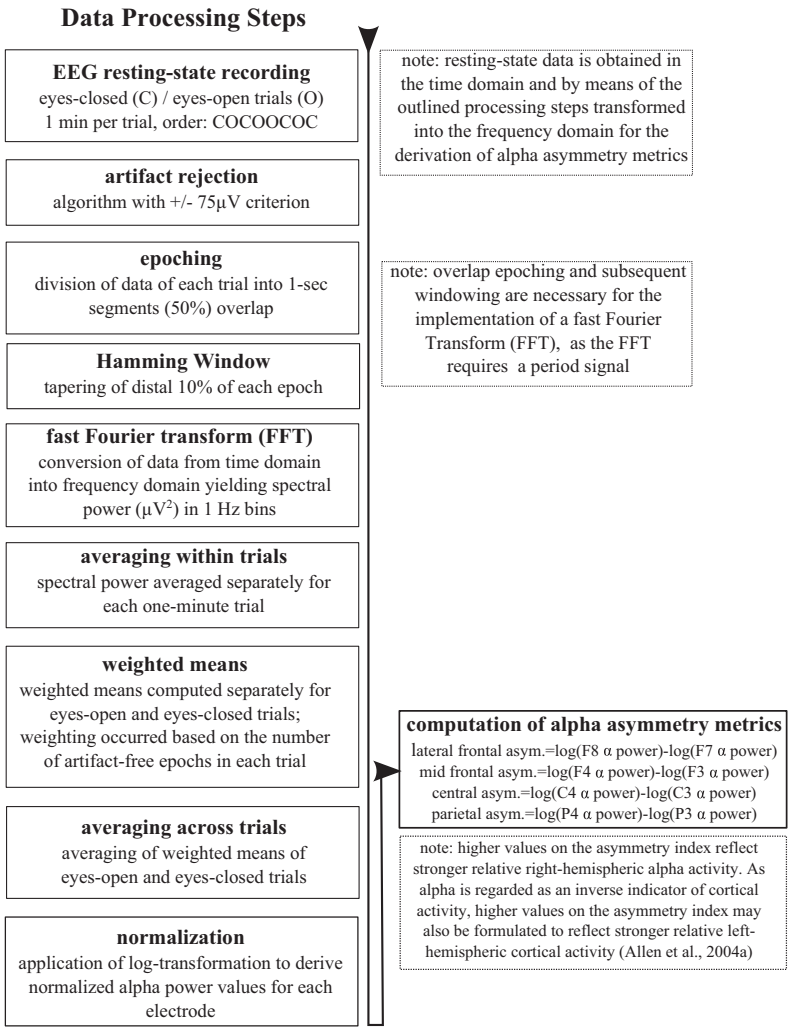

Fig. 1. Schematic outline of EEG data acquisition and processing to derive asymmetry metrics for lateral frontal, mid-frontal, central and parietal sites. For a detailed description of underlying assumptions see also Allen et al. (2004a). Note that the analysis was performed twice, for resting-state data obtained at Time 1 and data obtained at Time 2. Subsequently, normalized alpha and alpha asymmetry values obtained at Time 1 and Time 2 were averaged for each site to derive aggregate scores with increased trait specificity.

averaged separately for each of the eight one-minute trials. Subsequently, weighted means of power spectra were computed for each electrode, separately for eyes-open and eyes-closed trials. Weighting occurred based on the number of artifact-free data segments within each trial of the eyes-open and eyes-closed trials, respectively. Afterwards spectra of eyes-closed and eyes-open trials were averaged, yielding measures of spectral power for each electrode. As the distribution of alpha power values tends to be skewed (Allen et al., 2004a), a log-transformation was applied. Alpha asymmetry measures were computed by subtracting left from right-hemispheric alpha power values of each symmetrical site, i.e. lateral frontal (F7/F8), mid-frontal (F3/F4), central (C3/C4) and parietal (P3/P4; example for lateral frontal sites: [log F8 alpha power – log F7 alpha power]). The resulting measures involve both, state and trait components (Coan et al., 2006; Hagemann et al., 2005). Trait-specificity of alpha asymmetry may be increased if state-specific fluctuations are reduced, e.g. by averaging asymmetry measures across several measurement occasions (Hagemann, 2004; Hagemann et al., 2005). Hence, in a final step, asymmetry measures obtained at Time 1 and Time 2 were averaged for each of the four regions.

For a dataset of a respective measurement occasion to be included in the statistical analysis, at least 80 artifact-free segments across eyes-open and eyes-closed trials were required. A one-minute trial was rejected from further analysis if there were less than 10 artifact-free segments available. The application of these criteria resulted in the rejection of one dataset. Box-plots were used to screen alpha asymmetry values for outliers and one dataset in which mid-frontal asymmetry at Time 2 exceeded three standard deviations of the mean asymmetry value was excluded. In sum, 52 datasets were considered in the final statistical analysis. Kolmogorov–Smirnov tests indicated that alpha asymmetry values of each site showed a normal distribution at Time 1 and Time 2 (all *p*-values >.05).

2.3. Quantification of ADHD symptoms and depression

In order to quantify ADHD symptoms, the self-rating scale (ADHD-SB; Rösler et al., 2004) which was used during the diagnostic procedure was utilized. On this self-report measure, individuals evaluate the presence and intensity of 18 ADHD criteria according to DSM-IV on a scale from 0 to 3 (0 = "*does not apply*"; 3 "*symptom strongly present*"). The ADHD-SB yields a global measure of ADHD symptoms ($ADHD_{Global}$), calculated as the sum of scores on all 18 criteria of the questionnaire, which showed a normal distribution according to a Kolmogorov–Smirnov test (*p*-value >.05). In

consideration of risk of Type I error inflation, the $ADHD_{Global}$ scale was chosen as the primary parameter of ADHD symptoms. The scale comprises subscales representing inattentiveness ($ADHD_{Inattentiveness}$), hyperactive behavior ($ADHD_{Hyperactivity}$) and impulsive behavior ($ADHD_{Impulsivity}$).

For the assessment of depressive symptoms, a 15-item questionnaire was used (Allgemeine Depressionskala, ADS-K; English: General Depression Scale; Hautzinger and Bailer, 1993), which addresses the severity of depressive symptoms during the last two weeks. Items are rated on a scale from 0 to 3 and the sum of all items represents the depression parameter. Depression scores showed a normal distribution according to a Kolmogorov–Smirnov test (p-value >.05).

2.4. Statistical analysis

2.4.1. Primary purpose: alpha asymmetry and ADHD symptoms

The statistical analysis followed standard procedures for this line of research (Hewig et al., 2004). For the primary analysis, which addressed the question whether specifically frontal EEG alpha asymmetry is associated with ADHD symptoms in adult patients, a repeated-measures analysis of variance (ANOVA) was implemented, using alpha power values which had been aggregated across Time 1 and Time 2 for each electrode. The model included the factor Region with four levels (lateral frontal: F7/F8, mid-frontal: F3/F4, central: C3/C4, parietal: P3/4) and the factor Hemisphere with two levels (left vs. right). Scores of the ADHD-SB self-report measure, i.e. the $ADHD_{Global}$ scale were z-transformed and entered as a covariate. In a secondary analysis, z-transformed values of the subscales were also entered as covariates, in separate models. The resulting respective statistical models tested whether the regression of alpha power on self-reported ADHD symptoms varied as a function of Region and Hemisphere, as would be reflected by a significant three-way interaction, Region × Hemisphere × Self-report scale. To examine subsequently, which region contributed to the association between alpha asymmetry and ADHD symptoms, Pearson correlations were computed between asymmetry scores of the four regions (lateral frontal, mid-frontal, central, parietal) on the one hand, and self-report scales for which three-way interactions emerged, on the other hand. In the correlation analysis, a Bonferroni-correction was applied in consideration of the primary $ADHD_{Global}$ scale and the four electrode pairs. Consequently, a value of $p < .0125$ ($p = .05/4$) was set as the threshold of significance.

2.4.2. Test–retest reliability of alpha asymmetry

To address the issue of test–retest reliability, Pearson correlations were used to examine systematicity of variance across measurement occasions. Asymmetry scores of each region at Time 1 were correlated with those obtained at Time 2.

2.4.3. Gender-specificity, alpha asymmetry and depression

Gender-specific patterns in alpha asymmetry were explored by means of a repeated measures ANOVA, involving the same factors Region and Hemisphere as outlined in Section 2.4.1 with Gender as a between-subjects factor. In addition, gender-differences in depression (ADS-K), and ADHD symptoms ($ADHD_{Global}$ and subscales), were examined by means of Bonferroni-corrected t-tests.

A putative relation between alpha asymmetry and lifetime major depression was explored by means of a repeated measures ANOVA, involving the same factors Region and Hemisphere as outline above, and Lifetime Depression as a between-subjects factor. In order to examine the association between alpha asymmetry and current signs of depression, the same repeated ANOVA model as described in Section 2.4.1 was implemented with z-transformed ADS-K depression scores as a covariate.

3. Results

3.1. Alpha asymmetry and ADHD symptoms

The ANOVA revealed that the regression of alpha activity on ADHD symptoms varied as a function of Region and Hemisphere, as reflected by a significant three-way interaction Region × Hemisphere × $ADHD_{Global}$, $F(3,150) = 2.94$, partial $\eta^2 = 0.06$, as well as significant interactions Region × Hemisphere × $ADHD_{Inattentiveness}$, $F(3,150) = 3.03$, partial $\eta^2 = 0.06$ and Region × Hemisphere × $ADHD_{Hyperactivity}$, $F(3,150) = 3.01$, partial $\eta^2 = 0.06$ (all p-values <.05). Interactions remained significant when medication status was entered as an additional covariate. The interaction Region × Hemisphere × $ADHD_{Impulsivity}$, $F(3,150) = 0.65$, partial $\eta^2 = 0.01$, $p > .05$, did not reach significance.

Correlations between alpha asymmetry and self-report measures are displayed in Table 2. In case of both, $ADHD_{Global}$ and $ADHD_{Inattentiveness}$, significant correlations with alpha asymmetry obtained for lateral frontal sites emerged (Fig. 2a and b). These consistently positive correlations indicated that ADHD symptoms were associated with stronger relative right-hemispheric alpha activity. There were no significant correlations for any further regions (all p-values >.0125).

3.2. Test–retest reliability of alpha asymmetry measures

Information regarding test–retest reliability of alpha asymmetry measures is provided in Table 3. Measures of test–retest reliability were highly significant for eyes-closed and eyes-open conditions, as well as for the two conditions combined.

3.3. Gender-specificity, alpha asymmetry and depression

3.3.1. Gender-specific differences

Mean alpha asymmetry scores of males and females are displayed in Fig. 3. There was a gender-specific expression of alpha activity across hemispheres and examined regions, as reflected by a significant three-way interaction, Region × Hemisphere × Gender, $F(3,150) = 3.97$, partial $\eta^2 = 0.07$, $p < .01$, which remained significant when medication status was considered as a covariate, $F(3,147) = 4.00$, partial $\eta^2 = 0.08$, $p < .01$. Bonferroni-corrected simple comparisons for each region revealed significantly stronger relative right-hemispheric anterior alpha activity in females compared to males in lateral and mid-frontal regions, whereas no significant differences emerged for central and parietal sites (Table 4). Females also scored significantly higher on the depression self-report measure (ADS-K; females: $M = 23.20$, $SD = 6.57$; males: $M = 18.33$, $SD = 8.06$; $t(50) = 2.38$, $p = 0.01$). There was no gender-specific difference in scores on the $ADHD_{Global}$ scale or its subscales (all p-values >.10).

Table 2
Pearson correlations between frontal alpha asymmetry measures and ADHD symptoms.

ADHD symptoms	Global	Inattentiveness	Hyperactivity	Impulsivity
Region (electrode pair)				
Lateral frontal (F7/F8)	.38**	.32*	.28	.24
Mid-frontal (F3/F4)	.20	.24	.11	.06
Central (C3/C4)	.10	−.04	.06	.23
Parietal (P3/P4)	−.17	−.20	−.26	.11

Note: See Section 2.3 for references and description of the ADHD symptom scales. Scatterplots of flagged correlations are displayed in Fig. 2a and b.
** $p < .005$.
* $p < .0125$.

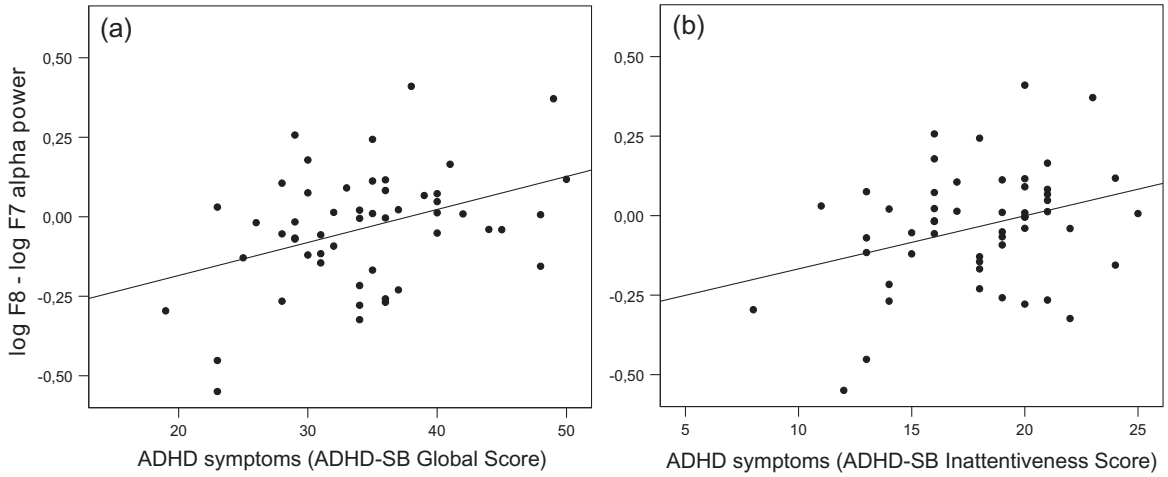

Fig. 2. Correlations between lateral frontal alpha asymmetry and $ADHD_{Global}$ symptoms (a), as well as $ADHD_{Inattentiveness}$ symptoms (b), as assessed by ADHD-SB self-report measure (see text for references). Higher values on the asymmetry index reflect stronger relative right-hemispheric alpha activity.

Table 3
Test–retest reliability of alpha asymmetry across Time 1 and Time 2.

Trials	Eyes-closed and eyes open	Eyes open	Eyes-closed
Region (electrode pair)			
Lateral frontal (F7/F8)	.43**	.50**	.40**
Mid-frontal (F3/F4)	.35**	.36**	.38**
Central (C3/C4)	.68**	.62**	.66**
Parietal (P3/P4)	.48**	.48**	.55**

Note: Reliability assessed by Pearson correlations.
** $p < .01$.

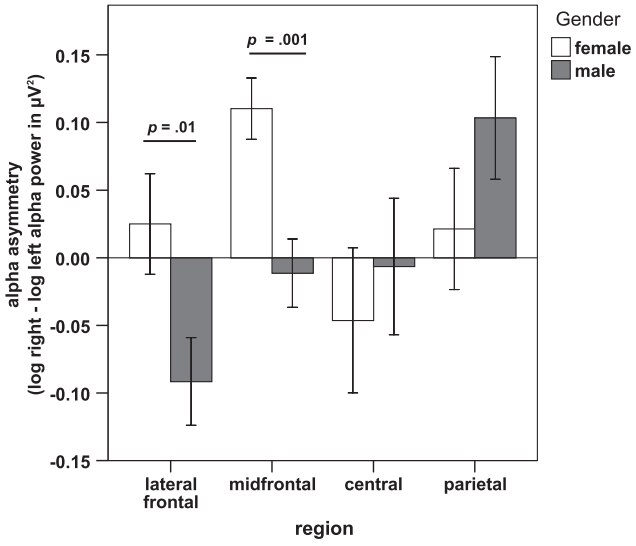

Fig. 3. Mean alpha asymmetry displayed by region and gender. Higher values on the asymmetry index reflect stronger relative right-hemispheric alpha activity. Error bars represent standard errors.

3.3.2. The relation between alpha asymmetry and depression

Overall, the current sample included $N = 21$ individuals (age: $M = 36.20$, SD = 8.31, 10 females) with a history and $N = 31$ individuals (age: $M = 36.48$, SD = 10.25, 15 females) without a history of depression. These groups did not differ with regards to their gender distribution, $\chi^2(1,52) = 0.003$, $p > .10$. Alpha asymmetry values were not affected by the occurrence of lifetime major depression, Region × Hemisphere × Lifetime Depression, $F(3,150) = 1.45$, partial $\eta^2 = 0.03$, $p > .05$.

When the relation between alpha asymmetry and current depressive symptoms was examined, a marginally significant linear trend emerged, Region × Hemisphere × ADS-K, $F(1,50) = 3.14$, partial $\eta^2 = 0.06$, $p = .08$, which reached significance when medication status was considered as a covariate, Region × Hemisphere × ADS-K, $F(1,49) = 4.44$, partial $\eta^2 = 0.08$, $p < .05$. Depression scores showed a positive correlation with lateral frontal asymmetry (F7/F8: $r = .27$, $p < .05$; Fig. 4), while correlations in mid-frontal, central and parietal regions were not significant (F3/F4: $r = .14$; C3/C4: $r = -.04$; P3/P4: $r = -.13$; all p-values >.05). This implies that depressive symptoms showed a similar association with stronger relative right-frontal alpha activity as $ADHD_{Global}$ scores (see Section 3.1).

3.3.3. Mediation model: ADHD symptoms as a mediator between asymmetry and depression

It should be noted that the correlation between depressive symptoms and stronger relative right-frontal alpha activity (i.e. approach-related asymmetry), stands in contrast to the repeatedly observed association between depression and withdrawal-related asymmetry. As outlined in Section 1.4, depression frequently arises due to ADHD symptoms (Daviss, 2008), which implies common variance of the two parameters. With regards to the current results, this would also suggest a putatively mediating role of ADHD symptoms in the atypical correlation between depressive symptoms and approach-related asymmetry. A conceptual outline of a corresponding mediation model is provided in Fig. 5. In order to illustrate the possibility of a mediation analysis, intercorrelations between the relevant variables, i.e. lateral frontal alpha asymmetry (F7/F8), depressive symptoms (ADS-K) and $ADHD_{Global}$ symptoms, are summarized in Table 5. While the mediation analysis referred to the entire sample due to required statistical power, the same intercorrelations were also computed for male and female subgroups to derive further descriptive information. Lateral frontal asymmetry was selected to reduce Type-I error inflation, as this parameter had previously shown an association with $ADHD_{Global}$ symptoms and depressive symptoms.

As displayed in Table 5, besides the correlations between alpha asymmetry and depression (Fig. 4) and alpha asymmetry and ADHD symptoms (Fig. 2a), also depression and ADHD symptoms were significantly correlated (Fig. 6). Consequently, the devised

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Table 4
Alpha asymmetry in male and female ADHD patients.

	Males M (SD)	Females M (SD)	*t*-Statistic	*p*-Value
Region (electrode pair)				
Lateral frontal (F7/F8)	−0.092 (0.169)	0.025 (0.186)	2.37	0.010
Mid-frontal (F3/F4)	−0.011 (0.131)	0.110 (0.113)	3.56	0.001
Central (C3/C4)	−0.007 (0.262)	−0.046 (0.268)	0.54	0.296
Parietal (P3/P4)	0.103 (0.236)	0.021 (0.224)	1.29	0.102

Note: *M* = mean, SD = standard deviation.

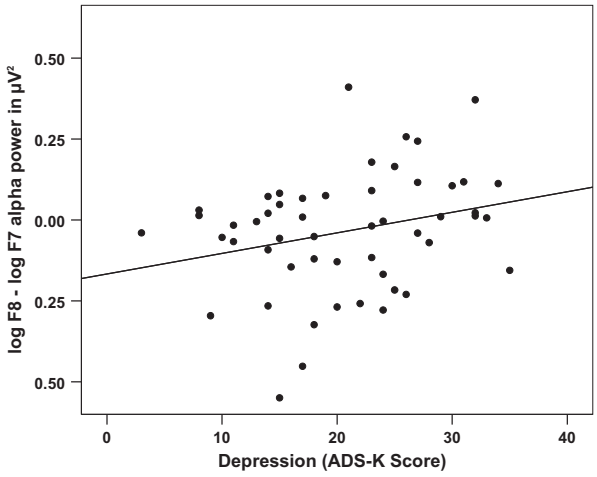

Fig. 4. Scatterplot of the correlation between lateral frontal alpha asymmetry and depressive symptoms. Higher values on the asymmetry index reflect stronger relative right-hemispheric alpha activity.

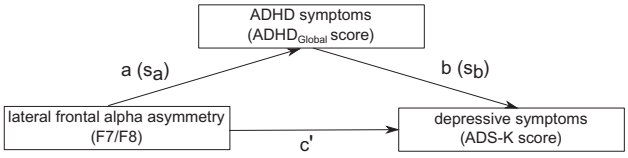

Fig. 5. Conceptual outline of the assumed mediating function of ADHD symptoms in the association between stronger relative right-hemispheric anterior alpha activity and depressive symptoms (c′). As summarized in Table 5, alpha asymmetry was positively correlated with ADHD and depressive symptoms, and both types of symptoms were correlated. Following a regression analysis which identified ADHD symptoms as a partial mediator of the relation between alpha asymmetry and depressive symptoms (Table 6), a Sobel test could be implemented using the raw regression coefficient between alpha asymmetry and ADHD symptoms (a) and its standard error (Sa), as well as the raw coefficient between ADHD and depressive symptoms (b) and its standard error (Sb).

mediation model could be tested. It is noteworthy that the correlation between alpha asymmetry and depression in the whole sample appeared to be driven by the occurrence of the same correlation in the female subsample, whereas the correlation was absent in males. As indicated, due to required statistical power, the mediation analysis focused on the entire sample, nevertheless, the analysis was also repeated for the female sample, results of which are accessible in Supplement S1.

Following suggestions of Coan and Allen (2004), a regression analysis was implemented to test the mediation model. In this analysis, alpha asymmetry was regressed on the mediator (ADHD symptoms) and on depressive symptoms separately. Subsequently both, alpha asymmetry and ADHD symptoms were regressed on depressive symptoms. In support of a mediating role of ADHD symptoms, the correlation between alpha asymmetry and depression was attenuated during the latter step (Table 6).

A Sobel test (Sobel, 1982) was used to formally determine the mediating role of ADHD symptoms in the relation between alpha asymmetry and depression. To this end, respective raw regression coefficients between alpha asymmetry and ADHD symptoms, ADHD and depressive symptoms, as well as respective standard errors were used (Fig. 5). A significant result of the Sobel test confirmed that the relation between alpha asymmetry and depression was partially mediated by ADHD symptoms ($Z = 2.12$, SE = 3.10, $p < .05$).

While a similar attenuation of the correlation between alpha asymmetry and depression occurred in the female subsample as ADHD symptoms were added to the regression model, the Sobel test did not reveal a significant result in this case (Supplement S1).

4. Discussion

Attention-deficit/hyperactivity disorder has been suggested as a disorder involving motivational dysfunction, characterized by excessive approach dispositions (Mitchell (2010)). Abnormal alpha asymmetry (stronger relative right-hemispheric anterior alpha power), indicative of approach motivation may represent an ontogenetically stable trait in ADHD patients (Baving et al., 1999; Hale et al., 2010a, 2009b; Keune et al., 2011b), nevertheless, to date information on a specific association between frontal asymmetry and ADHD symptoms is lacking. Moreover, information on temporal properties of alpha asymmetry in ADHD, as well as on putative gender-differences and the relation to depression is sparse.

4.1. The relation between alpha asymmetry and ADHD symptoms

In the current work, the regression of alpha power on self-reported ADHD symptoms significantly varied as a function of Region and Hemisphere, and specifically in the lateral frontal region, a positive correlation between alpha asymmetry and ADHD symptoms was observed, unaffected by medication status. In accord with our hypothesis, the latter correlation indicates that stronger relative right-frontal alpha activity (i.e. approach-related asymmetry) was associated with elevated ADHD symptoms. While results of previous studies suggested, that such an association might be detectable in ADHD (Hale et al., 2009b; Keune et al., 2011b), to our knowledge, the current study is the first, which examined this relation specifically. The results are generally compatible with notions of the approach–withdrawal model of hemispheric asymmetry, according to which stronger relative right-hemispheric anterior alpha activity represents a neural correlate of approach motivation (Davidson, 2004; Harmon-Jones et al., 2010). They are further compatible with findings on abnormal relative right-hemispheric alpha power in pediatric and adult ADHD patients (Baving et al., 1999; Hale et al., 2009b; Keune et al., 2011b).

In adult ADHD, abnormal alpha asymmetry has recently been specified as approximating notions of the approach–withdrawal model of hemispheric asymmetry (Keune et al., 2011b). Similar notions were devised by Mitchell (2010), according to which ADHD may be regarded as a disorder involving motivational dysfunction.

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Table 5
Intercorrelations between lateral frontal asymmetry, depression and ADHD symptoms.

	Whole sample ($n = 52$)		Females ($n = 25$)		Males ($n = 27$)	
	Depression	$ADHD_{Global}$	Depression	$ADHD_{Global}$	Depression	$ADHD_{Global}$
Asymmetry	.27*	.38**	.42*	.42*	−.01	.35*
$ADHD_{Global}$	.44**		.40*		.44*	

Note: Asymmetry = lateral frontal asymmetry (F7/F8). Depression assessed by ADS-K and ADHD symptoms by the $ADHD_{Global}$ scale; see Section 2.3. for references.
** $p < .01$.
* $p < .05$.

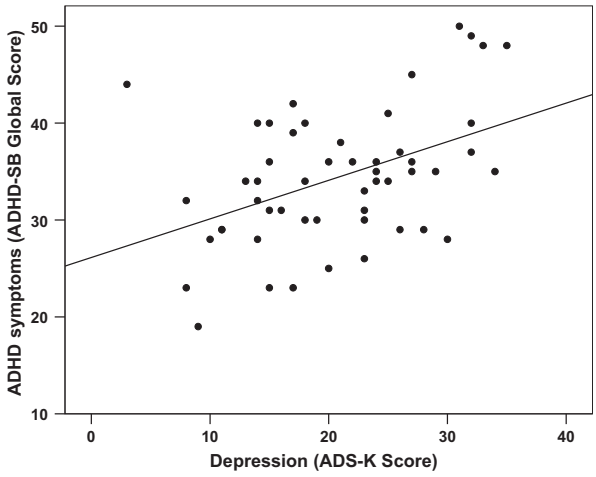

Fig. 6. Scatterplot of the correlation between depressive symptoms and ADHD symptoms.

Table 6
Regression analysis for the identification of ADHD symptoms as a mediator.

Variables	β	t	Total R^2	F
Dependent variable: depressive symptoms (ADS-K) Alpha asymmetry (F7/F8)	.27*	1.94	.07	3.77
Dependent variable: ADHD symptoms ($ADHD_{Global}$) Alpha asymmetry (F7/F8)	.39**	2.99	.15	8.94
Dependent variable: depressive symptoms (ADS-K) ADHD symptoms ($ADHD_{Global}$) Alpha asymmetry (F7/F8)	.40** .11	2.90 0.79	.21	6.37

Note: Regression analysis revealed that the regression between alpha asymmetry and depressive symptoms ($\beta = .27$) dropped when ADHD symptoms were added to the model ($\beta = .11$), identifying ADHD symptoms as a potential partial mediator of the relationship between alpha asymmetry and depression.
** $p < .01$.
* $p < .05$.

As results of the current work suggest a link between ADHD symptoms, as well as approach-related asymmetry, it may serve to consolidate the motivational dysfunction hypothesis of ADHD. Further, it may serve as a basis to integrate the established approach–withdrawal model (Davidson, 2004; Harmon-Jones et al., 2010) with the motivational dysfunction hypothesis (Mitchell, 2010) and provide a comprehensive approach for further studies on abnormal motivation in ADHD.

4.2. Methodological characteristics: test–retest reliability of alpha asymmetry in adult ADHD

The feasibility of alpha asymmetry in this context is supported by its methodological properties which were observed in the current work. Even though several studies have provided important cross-sectional data on alpha asymmetry in ADHD (Baving et al., 1999; Hale et al., 2009b; Keune et al., 2011b), information on the temporal characteristics of alpha asymmetry in this group is sparse in the literature. This is striking, considering potential plasticity and dynamic progression of alpha asymmetry measures, which have been observed in other psychiatric conditions (Barnhofer et al., 2007; Keune et al., 2011a; Moscovitch et al., 2011; but see also Allen et al., 2004b for comparison). In the current work, reliability estimates across two weeks ranged between $r = .35$ and .68, with an estimate of .43 for lateral frontal sites, i.e. the region for which consistent correlations between alpha asymmetry and ADHD symptoms were obtained. Early work on test–retest reliability of alpha asymmetry revealed somewhat higher estimates across an interval of three weeks in healthy individuals (range of $r = .53–.66$; Tomarken et al., 1992). However, reliability estimates of alpha asymmetry were also shown to display considerable variation depending on the examined clinical population, time interval and frequency of repeated resting-state recordings, as well as further methodological features, such as the chosen reference scheme. In case of depression for example, Allen et al. (2004b) report estimates of .54–.66 for frontal asymmetry measures obtained across three assessment sessions throughout eight weeks. Others have reported lower estimates of .30–.48 for lateral and mid-frontal sites in extremely vulnerable, recurrently depressed patients, based on two assessment sessions across the same time interval (Keune et al., 2011a). In this context, a significant estimate of $r = .43$ in the current work may be regarded as reflecting reasonable test–retest reliability and systematic progression of variance across measurement occasions. The latter finding may aid the interpretation of previous work in which abnormal alpha asymmetry was observed in adult ADHD. Nevertheless, as to our knowledge, the current data on test–retest reliability in adult ADHD are the first to be contributed to the literature, future studies appear necessary to explore this characteristic in more detail.

4.3. Gender differences in alpha asymmetry

Besides the basic, consolidating finding of an association between reliably assessable alpha asymmetry and ADHD symptoms, the current work also provides new information referring to gender differences and the relation to depressive symptoms. Previous work on alpha asymmetry has revealed gender-specific findings in ADHD and depression. Stewart et al. (2010) reported on an association between withdrawal-related asymmetry and current depressive symptoms in women with lifetime major depression, whereas the association could not be consistently observed in males. Referring to pediatric ADHD, Baving et al. (1999) found that while preschool boys showed an abnormal approach-related alpha asymmetry pattern relative to healthy controls, the opposite was observed in girls.

In contrast to the design implemented by Baving et al. (1999), the current work did not involve healthy comparisons, and alpha asymmetry was directly compared between males and females.

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Gender-specific findings nevertheless appear to stand in contrast to those from pediatric patients. In our sample, *females* showed pronounced approach-related asymmetry, relative to males, irrespective of medication status. While it was previously suggested that abnormal asymmetry may be an ontogenetically stable phenotype in ADHD (Hale et al., 2009b; Keune et al., 2011b), the current findings therefore hint at an underlying gender-specific development. To our knowledge, similar gender-specific findings in alpha asymmetry in adult ADHD patients have not been reported on before. Consequently these results require replication before such a gender-specific developmental pathway may be confirmed.

4.4. The relation between alpha asymmetry and depression

It is noteworthy that in adult ADHD patients, depressive symptoms showed an atypical relation to frontal alpha asymmetry. According to the contemporarily prevailing view, despite some inconsistencies, depressive symptoms are associated with withdrawal-related asymmetry (Carvalho et al., 2011; Coan and Allen, 2004; Harmon-Jones et al., 2010; Reid et al., 1998; Segrave et al., 2011). Nevertheless in the current sample, depression was associated with stronger relative right-frontal alpha activity, i.e. an approach-related pattern. The fact that ADHD symptoms could be identified as a mediator of this atypical relationship speaks to the robustness of the association between alpha asymmetry and ADHD symptoms. ADHD symptoms and abnormal alpha asymmetry are already observable in pediatric patients (Baving et al., 1999), and depression commonly arises secondary to these conspicuities, partly due to adaptation difficulties (Daviss, 2008). In Section 1.4., we suggested that due to this developmental sequence, ADHD might represent a disorder in which depression is related to approach-related asymmetry. The hypothesis of such an atypical association was confirmed and the finding that ADHD symptoms partially mediated this relationship is in accord with the assumed underlying developmental sequence.

Our results have further theoretical implications for the approach–withdrawal model. They indicate that a psychopathologic phenotype as depression cannot be assorted to either component of this model, without considering the global approach vs. withdrawal-related context of a given disorder, as well as the underlying mechanism due to which such a phenotype develops.

4.5. Limitations and future directions

Results of the current work need to be considered in the context of several limitations. While the sample size was reasonable when compared to previous work (Hale et al., 2009b; Keune et al., 2011b), it was still relatively small and in order to address the relation between alpha asymmetry and ADHD symptoms more thoroughly, it is warranted to replicate the current results in a larger sample. This issue may have been somewhat attenuated by the fact, that the current work involved asymmetry values, which were aggregated across two measurement occasions. The latter method is one of several options which have been suggested to increase trait-specificity of alpha asymmetry, hence reducing state-influences which may interfere with the observation of an association between trait alpha asymmetry and clinical symptoms (Hagemann, 2004; Hagemann et al., 2005). Based on results of the current work, we suggest that the application of this method is also feasible in case of adult ADHD patients. An alternative method to make associations between alpha asymmetry and trait variables of interest more salient was suggested in context of the capability model of frontal alpha asymmetry (Coan et al., 2006). According to this model, such associations may become more salient, if alpha asymmetry is obtained during experimental conditions in which temporary manipulations are implemented, which resemble the trait variable of interest (Coan et al., 2006; Keune et al., 2012a, 2013; Stewart et al., 2011; Verona et al., 2009). While it remains to be determined how such a condition could be devised in ADHD patients, recordings during tasks which challenge attentional capacities might be useful (Hale et al., 2009b).

Another limitation which needs to be considered is that ADHD symptoms and depression were associated with alpha asymmetry values of lateral frontal sites (F7/F8), while a correlation for mid-frontal sites (F3/F4) did not reach significance. This is somewhat incongruent with previous reports on abnormal asymmetry in adult ADHD, where abnormality was observed in case of mid-frontal sites (e.g. Keune et al., 2011b). On the other hand, particularly correlations between alpha asymmetry and ADHD symptoms were obtained in the context of a conservative, Bonferroni-corrected analysis for the primary $ADHD_{Global}$ scale. Referring to the gender-specific findings and the atypical relation between alpha asymmetry and depression, future studies are required to confirm these findings, and to determine whether they may be observed for further frontal regions, particularly if the sample size is increased.

5. Conclusion

The current work provides basic findings which serve to integrate the established approach–withdrawal model of hemispheric asymmetry (Davidson, 2004) with notions according to which adult ADHD represents a disorder involving motivational dysfunction (Mitchell, 2010). Based on the current observations, which complement previous work on abnormal alpha asymmetry in ADHD, we suggest that ADHD symptoms, resembling motivational dysfunction, involve a pattern of frontal brain asymmetry, indicative of approach motivation. This consolidation of the motivational dysfunction hypothesis may be verified by future studies, based on the solid temporal metric properties of alpha asymmetry in adult ADHD, as observed in the current study. The latter characteristic allows the suggestion that alpha asymmetry may be feasible as an outcome measure in psychotherapeutic intervention studies involving ADHD patients, as utilized in other psychiatric groups (Barnhofer et al., 2007; Keune et al., 2011a; Moscovitch et al., 2011).

Besides these basic issues, new gender-specific findings and a mediating role of ADHD symptoms in an atypical relation between alpha asymmetry and depressive symptoms were obtained. These findings suggest that longitudinal studies are necessary to study the developmental pathway of alpha asymmetry in ADHD in more detail.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.clinph.2014.07.008.

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