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ORIGINAL CONTRIBUTION

EEG theta and beta power spectra in adolescents with ADHD versus adolescents with ASD + ADHD

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Abstract Attention problems are common in youngsters with attention deficit hyperactivity disorder (ADHD) as well as in adolescents with combined autism spectrum disorder (ASD) and ADHD. However, it is unknown whether there is psychophysiological overlap and/or a difference in electroencephalogram (EEG) power spectra between ADHD and comorbid ASD and ADHD (ASD + ADHD), on and off stimulant medication. To explore potential differences and overlap, measures of theta and beta power in adolescents diagnosed with ADHD ($n = 33$) versus adolescents with combined ASD + ADHD ($n = 20$), categorized by stimulant medication use (57 % of the total sample), were compared. EEG measures were acquired in three conditions: (1) resting state, eyes closed (2) resting state, eyes open and (3) during an oddball task. In addition, performance on the d2 attention test was analyzed. Adolescents with ADHD displayed more absolute theta activity than adolescents with ASD + ADHD during the eyes open and task conditions, independent of stimulant medication use. In addition, only the adolescents with ADHD showed an association between diminished attention test performance and increased theta in the eyes open condition. Results of the current study suggest that although there is behavioral overlap between ADHD characteristics in adolescents with ADHD and adolescents with combined ASD + ADHD, the underlying psychophysiological mechanisms may be different. Adolescents with ASD + ADHD exhibited fewer of the EEG physiological signs usually associated with ADHD, although there was an overlap in attentional problems between the groups. This may indicate that treatments developed for ADHD work differently in some adolescents with ASD + ADHD and adolescents with ADHD only.

Keywords EEG · ADHD · Autism · Theta · Beta · Stimulant medication

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Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders with a worldwide prevalence of between 5.9 and 7.1 % [1]. Additionally, ADHD co-occurs with autistic spectrum disorders (ASDs) in around 28 percent of youngsters with ASD [2]. Even though comorbidity of ADHD symptoms in ASD is common, in the DSM-IV [3], ADHD cannot be classified as a comorbid disorder, but ADHD symptoms are considered part of ASD. In contrast, the new DSM-V now states that, when criteria for ASD and ADHD are met, both diagnoses should be assigned [4]. Stimulant medication that seems effective for ADHD treatment [5] is also prescribed in cases of comorbid ASD and ADHD (ASD + ADHD). However, although stimulant medication seems also an effective treatment for ADHD in youngsters with combined ASD + ADHD [6], the reported stimulant medication response rate of 49 % in ASD + ADHD [7] is lower than the 77 % response rate in ADHD [8]. The lower response rate to stimulant medication suggests that, although there is behavioral overlap between ADHD with and without ASD, the psychophysiological mechanisms underlying attentional problems may be different in these groups. Potential differences in psychophysiology could indicate that ADHD treatment like stimulant medication might exert its effect differently in combined ASD + ADHD than in ADHD only.

Electro-encephalogram (EEG) power spectra have often been used to assess psychophysiological functioning in ADHD. The most robust finding in ADHD is increased theta power [9–11] mainly in frontocentral areas [10] and, to a lesser extent, decreased beta activity [9, 11]. The theta (4–7 Hz) and beta (13–30 Hz) bands of the power spectrum have been related to measures of vigilance and attention, respectively, at the behavioral level [12], and during childhood show maturational changes: decreasing slow wave activity (including theta) and increasing fast wave activity (including beta) [13]. Specifically, theta power seems to be negatively associated with vigilance or alertness, with high theta corresponding to an underaroused [10, 12, 14] and unfocused state [14]. In contrast, beta power seems to be positively associated with attention [10, 12, 14], with decreased beta also associated with an unfocused state [12]. Taken together, these studies provide support for the hypothesized maturational lag [15] and the in the seventies generated under arousal theories of ADHD [16]. However, there are also several studies that did not replicate the theta difference between ADHD and typically developing (TD)adults [17, 18] and youngsters [19].

The abnormal pattern of theta and beta activity in youngsters with ADHD can be partly normalized by stimulant medication use [14, 20–22], which typically decreases theta activity and increases beta activity. A subpopulation of youngsters with ADHD shows excessive frontal beta instead of decreased beta [23]. These youngsters respond differently to stimulant medication, showing a reduction in beta [24]. Overall, it seems that stimulant medication in youngsters with ADHD results in power spectra that are more similar to those of TD youngsters.

Youngsters with ASD show increased relative theta compared to TD youngsters [25, 26], similar to youngsters with ADHD [15, 20, 27, 28]. In addition to increased relative theta, youngsters with ASD also show differences in absolute and relative beta; however, studies show mixed results. Adults with ASD show increased occipital relative beta [25] and young children with ASD have been shown to have increased absolute beta [29] relative to TD participants, but there is also a finding of decreased absolute beta, particularly in the right hemisphere, in children with ASD [26]. EEG power spectra in children with a primary diagnosis of ADHD and ASD have been little studied. The clearest result of the only study that compared children with a primary diagnosis of ADHD with and without autistic characteristics [30] was an increase in relative beta in children with ADHD with autistic characteristics compared to those with only ADHD. Although theta power did not differentiate the groups, this study also found a greater increase in theta from frontal to central regions in children with autistic characteristics [30]; it must be noted that in this study no formal DSM-IV [3] diagnosis of ASD was required. Taken together, these findings may point to a psychophysiological dissociation between ADHD with and without ASD, despite the behavioral overlap between the conditions.

Previous research on the psychophysiological effects of stimulant medication has focused mainly on adolescents with ADHD [14, 20–22]. The relationship between attentional problems and EEG power spectra in ADHD and ASD + ADHD, both on and off medication, remains unknown. A better understanding of potential underlying differences between the conditions could explain why adolescents with ASD + ADHD [7] have a less favorable response to stimulant medication than adolescents with ADHD [8]. If the underlying mechanisms of the conditions are similar, attentional problems in ASD + ADHD might be treated similarly to those in ADHD, for example with stimulant medication. However, differences in EEG power spectra between ADHD and ASD + ADHD would suggest that treatment options for the attentional problems should be specific for each subgroup. This study aimed to explore psychophysiological differences between these groups in terms of EEG power spectra, comparing stimulant-medicated and stimulant-free adolescents with a primary diagnosis ADHD with adolescents with a combined diagnosis

of ASD and ADHD. Increased levels of theta power have been related to ADHD [9–11] as well as to ASD [25, 26]. There are indications for group-based increased beta in children [29] and adults [25] with ASD, whereas increased beta is only related to ADHD in a subpopulation of approximately 20 percent [23]. Previous studies showed less theta power in stimulant-medicated adolescents with ADHD than stimulant-free adolescents with ADHD [14, 20–22]. In addition, developmental changes show a decrease in mainly slow wave theta activity during adolescence [31]. Combining these assumptions we expected that: (1) adolescents with ADHD and combined ASD + ADHD would show similar levels of theta activity (2) adolescents with ASD + ADHD show more beta activity (3) stimulant-medicated adolescents would show less theta activity than stimulant-free adolescents, irrespective of diagnosis, and (4) older adolescents would show less theta activity than younger adolescents.

Methods

Participants

This study used a sample of 53 adolescents recruited for an intervention study for adolescents with clinical ADHD symptoms. Prior to the start of the study, approval was obtained from the Medical Ethics Committee for Mental Health Institutions in The Netherlands (Ref. no: NL 24776.097.08 CCMO). The study took place in three centers of child and adolescent psychiatry (GGzE, GGz Breburg, Reinier van Arkel group) in the southern part of The Netherlands. Written informed consent was obtained from all participants. For participants aged less than 18 years, parents also provided written informed consent. The sample was the same as in Bink et al. [32], with the exclusion of five adolescents because of poor quality of the EEG data and the addition of two patients: one who enrolled later in the study and one who had been excluded from the earlier study because of missing oddball task-performance data. This patient was included as the EEG data could be used.

Two diagnostic groups of male adolescents aged between 12 and 22 years old were included in the study. The first group consisted of 33 adolescents with a clinical DSM-IV [3] primary diagnosis of ADHD, including combined (C) subtype ($n = 16$), inattentive (IA) subtype ($n = 16$), and hyperactive/impulsive (HI) subtype ($n = 1$). The second group consisted of 20 adolescents with a primary diagnosis of ASD, including Asperger's syndrome ($n = 6$) and pervasive developmental disorder—not otherwise specified (PDD-NOS; $n = 14$). Adolescents with ASD also had a notification of clinical ADHD with symptoms sufficient for a full ADHD diagnosis. ADHD symptoms were verified by a DSM-IV based Dutch semi-structured ADHD interview for adults [33] and the Mini International Neuropsychiatric Interview (MINI; [34], [35]). In the ASD group, DSM-IV ADHD subtype included C ($n = 5$), IA ($n = 4$), HI ($n = 2$), NOS ($n = 2$) and seven participants had clinical ADHD symptoms without given subtype. Exclusion criteria were IQ < 80, neurological disorders, schizophrenia and other psychotic disorders, depression, attachment disorder or anxiety disorder, medication use other than stimulant medication and use of cannabis in the 24 h prior to physiological assessment.

Stimulant medication use was monitored through an intervention questionnaire based on the Dutch national basic ADHD program for children and adolescents [36]. Adherence to prescribed medication was verified by asking the adolescents whether they had been taking their medication as prescribed before the EEG measurement. Overall, the adolescents reported to take their medication before or during breakfast before the assessment. In total, 30 (57 %) of the adolescents used stimulant medication. In the ADHD group, 19 (58 %) used stimulant medication: 6 used immediate release methylphenidate and 13 used sustained release methylphenidate. In the ASD + ADHD group, 11 (55 %) used stimulant medication: 1 used immediate release methylphenidate and 10 used sustained release methylphenidate. Two adolescents in the ASD + ADHD group used low doses (0.5 and 1.5 mg per day) of antipsychotic medication (Risperdal®) in addition to their stimulant medication. Because the doses were low, in combination with stimulant medication use, potential impact on the outcome measures was considered minimal.

Comorbid disorders were allowed: participants with substance-related disorders ($n = 2$), conduct disorders ($n = 3$), and reading disorder ($n = 2$) were included in the ADHD group. In the ASD + ADHD group, participants with conduct disorder ($n = 1$) and reading disorder ($n = 1$) were included.

Measures

Group characteristics

The group characteristics are listed in Table 1. The measures reported are Global Assessment of Functioning (GAF) score, the DSM-IV [3] based ADHD-rating scale [37, 38] which is an adapted form of DuPaul et al. [39], the MINI subscales for inattention and hyperactivity/impulsivity (HI), the Autism-Spectrum Quotient (AQ)-adolescent version for individuals with normal intelligence [40, 41], the Child Behavior Checklist (CBCL) and the Youth Self Report (YSR) [42], and the WISC-III or the WAIS-III full-scale total intelligence quotient (TIQ) [43, 44]. Further information about the reported group characteristics can be found elsewhere [32].

Table 1 Group characteristics

	Total $n = 53$ Mean (SD	ASD + ADHD $n = 20$ Mean (SD)	ADHD $n = 33$ Mean (SD)	F	η_p^2	Stimulant-medicated $n = 30$ Mean (SD)	Stimulant-free $n = 23$ Mean (SD)	F	η_p^2
Age in years	15.42 (2.88)	15.60 (2.62)	15.30 (3.07)	0.13	0.00	14.63 (2.22)	16.43 (3.36)	5.52*	0.10
GAF-score	55.11 (6.45)	54.50 (6.10)	55.48 (6.73)	0.29	0.01	55.00 (6.65)	55.26 (6.33)	0.02	0.00
AQ-adolescent version[a]	25.58 (8.02)	32.45 (5.36)	21.41 (6.33)	42.35***	0.45	24.63 (8.10)	26.80 (7.93)	0.95	0.02
ADHD-rating scale[b]									
Inattention	4.75 (2.24)	4.90 (2.25)	4.67 (2.26)	0.13	0.00	4.47 (2.22)	5.13 (2.24)	1.15	0.02
Hyperactivity/ impulsivity (H/I)	3.45 (1.89)	3.70 (2.06)	3.30 (1.79)	0.55	0.01	3.73 (1.96)	3.09 (1.76)	1.54	0.03
Childhood inattention	6.04 (2.67)	5.65 (2.83)	6.27 (2.58)	0.67	0.00	6.07 (2.68)	6.00 (2.71)	0.01	0.00
Childhood H/I	4.94 (2.78)	4.20 (2.75)	5.39 (2.75)	2.35	0.04	5.10 (2.80)	4.74 (2.82)	0.22	0.00
MINI ADHD inattention	5.38 (2.48)	5.00 (2.53)	5.61 (2.46)	0.74	0.01	5.27 (2.50)	5.52 (2.50)	0.14	0.00
MINI ADHD H/I	3.72 (2.26)	3.60 (2.39)	3.79 (2.22)	0.08	0.00	3.80 (2.14)	3.61 (2.46)	0.09	0.00
CBCL Total Problems	62.57 (28.89)	72.95 (28.27)	56.27 (27.81)	4.42*	0.08	59.63 (26.08)	66.39 (32.39)	0.71	0.01
Internalizing problems	14.47 (9.54)	17.55 (10.37)	12.61 (8.62)	3.51	0.06	13.00 (7.71)	16.39 (11.39)	1.67	0.03
Externalizing problems	18.79 (11.53)	21.80 (11.06)	16.97 (11.59)	2.24	0.04	17.80 (10.68)	20.09 (12.68)	0.51	0.01
Attention problems	11.83 (3.50)	12.80 (3.62)	11.24 (3.34)	2.55	0.05	11.87 (3.30)	11.78 (3.81)	0.01	0.00
YSR Total problems	47.42 (20.58)	54.30 (21.43)	43.24 (19.18)	3.79	0.07	46.03 (17.47)	49.21 (24.35)	0.31	0.01
Internalizing problems	9.17 (5.79)	10.90 (6.09)	8.12 (5.43)	2.97	0.06	8.70 (5.33)	9.78 (6.42)	0.45	0.01
Externalizing problems	15.51 (9.66)	17.85 (9.89)	14.09 (9.38)	1.92	0.04	14.97 (9.04)	16.22 (10.57)	0.22	0.00
Attention problems	9.26 (3.14)	8.85 (3.59)	9.52 (2.87)	0.55	0.01	9.10 (2.89)	9.48 (3.50)	0.19	0.00
TIQ	101.83 (10.74)	104.90 (11.60)	99.97 (9.90)	2.71	0.05	102.53 (11.75)	100.91 (9.44)	0.29	0.01

Data are means (SD); *df* (1.51)

H/I Hyperactivity/impulsivity

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

[a] Autism Spectrum Quotient (AQ)- adolescent version is a parent report

[b] The ADHD-rating subscales are retrospective self-reported current and childhood symptoms

Cognitive measures

The d2 attention test [45] was administered and the raw scores of the total number of processed items (TN) and total correctly processed items (C) were analyzed, both can be seen as measures of selective attention. The d2 attention test is a paper–pencil test comprising 14 lines with d and p, with one to four dots. In 20 s per line, the participant has to try to cancel out the d's with two dots. After 20 s, the participant has to shift immediately to the subsequent line. [46].

Physiological measures

The EEGs were recorded between 10am and 11am. Where applicable, stimulant medication was taken with breakfast, before the measurement. No caffeine or nicotine intake was allowed during the 2 h prior to physiological assessment.

The EEG recordings were performed in combination with a subset of the Brain Resource Company (BRC; Ultimo, Australia) test battery. This included a baseline condition in which participants had to sit quietly with their eyes open for 2 min and closed for 2 min. Subsequently, they performed an auditory oddball task lasting 6 min. The auditory oddball task is an attention test in which relevant stimuli need to be processed and irrelevant stimuli need to be ignored. In this task, a 75 dB tone lasting 50 ms, with a rise and fall of 5 ms, was presented binaurally by headphones with an inter-stimulus interval of 1.0 s. Low-frequency standard tones (500 Hz) were presented 280 times and intermixed with infrequent (60 presentations in 6 min) high target tones (1,000 Hz); the tones were presented in quasi-random order. Adolescents were asked to press the answer box with both index fingers as fast as they could on hearing the high frequency 1,000 Hz target tone. EEGs were recorded using the 10–20 system using a Quick-Cap with 26 EEG electrodes and impedance <5 kΩ. Horizontal electrooculograms (EOG) were recorded with two electrodes placed 1.5 cm lateral to the lateral canthi of the eyes. Vertical EOGs were recorded with electrodes above and below the middle of the eye with the upper electrode placed 3 mm above the eyebrow and the other electrode 1.5 cm below the lower eye-lid. A Neuroscan NuAmps amplifier recorded the signals with a sampling frequency of 500 Hz, 100 Hz low-pass anti-aliasing filter, and 32 bit, DC high-pass filter.

Electroencephalogram recordings were analyzed with Brain Vision Analyzer v2.0 (Brain Products GmbH, Germany). Reference to linked mastoids was calculated off-line; a high-pass filter of 0.5 Hz, 12 dB/octave and a low-pass filter of 30 Hz, 48 dB/octave were applied. Ocular correction was applied as in Gratton et al. [47]. Data of the three conditions were segmented in 2 s epochs. For the oddball task, the segmentation was done irrespective of stimuli presentation. Automatic raw data inspection was applied with a maximum allowed voltage step between samples of 50 μV/ms, maximum allowed difference of 120 μV in each segment, and permitted amplitude range of −100 to 100μV. Data were marked as bad 200 ms before and after a detected artifact, the lowest permitted activity in intervals was 0.5 μV with an interval length of 50 ms. Fast Fourier transformation (FFT) with a 20 % Hamming window was applied for tapering, and averages over the artifact-free epochs per channel were calculated. At least 30 artifact-free epochs had to be available for a channel to be included.

For each condition, the mean included channels and the minimum number of epochs for the included channels were considered. During the eyes closed condition, mean included channels were: $M = 25,\ 64$, SD = 0.29 with a minimum number of epochs of $M = 57,\ 64$, SD = 8.04. During the eyes open condition, mean included channels were: $M = 25.89$, SD = .32 with a minimum number of epochs of $M = 58.81$, SD = 4.35. During task condition mean included channels were: $M = 25.87$, SD = .34 with a minimum number of epochs of $M = 172.66$, SD = 21.72. For the three conditions, there were no differences in mean included channels or minimum number of epochs between the two diagnostic groups or between stimulant-medicated and stimulant-free adolescents. Mean absolute power (μV^2) was exported to SPSS for the following frequency bands: theta 3.5–7.5 Hz, and beta 12.5–25 Hz. To increase the comparability of the results, the frequency bands used were similar to those used in previous studies in ADHD by Clarke et al. [20, 22–24, 30]. A $\log_{10}$ transformation was applied to all measures to give a Gaussian distribution.

Initial regions of interest (ROIs) were based on a principal components analysis (PCA) of the frequency bands for the electrodes with covariance matrix, varimax rotation and Kaiser normalization. Missing values were replaced by mean imputation. A frontocentral area and a parietal-occipital area were defined for the different conditions and frequency bands. To improve comparability with areas defined in other reports, three ROIs were derived: anterior (Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4), central (C3, Cz, C4, Cp3, CPz, Cp4, T3, T4) and posterior (P3, Pz, P4, O1, Oz, O2, T5, T6). ROI values were, therefore, calculated for the different frequency bands across the three conditions as the mean of the respective electrodes.

Data analyses

All analyses were performed using SPSS version 19.0. Values of $p < 0.05$ were considered statistically significant. Differences in group characteristics were analyzed with a one-way ANOVA or a Chi square test (χ^2) with Fisher exact correction. Generalized Linear Model (GLM) univariate ANCOVAs were conducted for the measures of the d2 test of attention, with age as covariate and diagnostic group (ADHD or ASD + ADHD) and stimulant medication use (stimulant-medicated and stimulant-free) as between-subjects factors. GLM repeated-measures (RM) ANCOVAs were conducted separately for the absolute and relative power measures, with age as covariate, ROI as within-subject factor, and diagnostic group and stimulant medication use as between-subjects factors. The full factorial models were tested. All ROI effects were evaluated using multivariate test criteria, a method known to be robust against violations of sphericity [48]. Effect sizes are expressed as proportion of explained variance in partial η^2 (η_p^2). Post hoc pairwise comparison with Bonferroni correction for multiple comparisons was performed, and the adjusted difference (AD) and 95 % confidence interval (95 % CI) have been reported where applicable.

To control for the effects of other comorbidities and the use antipsychotic medication, post hoc analysis were performed with the exclusion of the adolescents with comorbid disorders and the adolescents using antipsychotic drugs. This post hoc group included 26 with ADHD [15 (58 %) stimulant medicated] and 16 adolescents with ASD + ADHD (8 (50 %) stimulant medicated). Post hoc stepwise linear regressions were performed separately for diagnostic group (ADHD and ASD + ADHD) with the measures of the d2 attention test (TN and C) as dependent variables. Four sets of independent variables were analyzed in each behavioral condition (eyes closed, eyes open and task) for all ROIs: (1) absolute theta (2) absolute beta. Because of multicollinearity between the independent variables, only the variable with the strongest association to the d2 test attention measures was considered.

Results

Group characteristics

Group characteristics are summarized in Table 1. The two diagnostic groups (ADHD and ASD + ADHD) did not differ in age (see Table 1). In total, 30 (57 %) adolescents used stimulant medication. Stimulant medication use was equally distributed over the diagnostic groups, with 19 (58 %) adolescents with ADHD and 11 (55 %) with combined ASD + ADHD using stimulant medication, $\chi^2(1, 51) = .00$, $p > .05$. In addition, the mean prescribed dose in mg for the stimulant-medicated adolescents was similar in the ADHD group ($n = 19$, $M = 34.74$, SD = 13.02), and the ASD + ADHD group ($n = 11$, $M = 35.27$, SD = 17.35; $F(1, 28) = 0.01$, $p > .05$, $\eta_p^2 = 0.00$). However, the average age of the stimulant-free adolescents (ADHD: $M = 16.21$, SD = 3.87; ASD + ADHD: $M = 16.78$, SD = 2.54) was somewhat older than that of the stimulant-medicated adolescents (ADHD: $M = 14.64$, SD = 2.38; ASD + ADHD: $M = 14.63$, SD = 2.19). This age difference was similar in the ADHD group and the ASD + ADHD group, $F(3,49) = 0.12$, $p > 0.05$, $\eta_p^2 = .00$. Stimulant-free and stimulant-medicated adolescents did not differ significantly in other group characteristics.

The AQ adolescent confirmed that the ASD + ADHD group exhibited more autism symptoms than the ADHD group. For the ASD + ADHD group, parents reported more total behavioral problems on the CBCL. The two diagnostic groups did not differ in other group characteristics.

Post hoc analysis for the group without comorbid disorders shows similar results for the group characteristics. The only exception to this is the reported CBCL attention problems: Parents report more attention problems for adolescents with ASD + ADHD, $M = 12.56$, SD = 3.98 than for adolescents with ADHD, $M = 10.27$, SD = 2.93, $F(1,40) = 4.60$, $p = 0.038$, $\eta_p^2 = 0.10$.

Cognitive performance

D2 attention test performance (TN and C) was similar for the two diagnostic groups, see Table 2. In addition, stimulant-free and stimulant-medicated adolescents did not differ in terms of d2 attention test performance. Older adolescents performed better than younger adolescents in terms of both TN and C.

EEG

Electroencephalogram outcomes are summarized in Table 3 and shown in Fig. 1.

Diagnostic group and stimulant medication use

Absolute theta power differed between the adolescents with ADHD and the adolescents with ASD + ADHD during the eyes open and task conditions. During the eyes open condition, adolescents with ADHD displayed more absolute theta than adolescents with ASD + ADHD, $AD_{ADHD - ASD + ADHD} = 0.11$, 95 %CI: 0.004–0.21, $p = 0.043$. During the task condition, adolescents with ADHD also showed more absolute theta than adolescents with ASD + ADHD, $AD_{ADHD - ASD + ADHD} = 0.11$, 95 %CI: 0.01–0.22, $p = 0.039$. There was no diagnostic group difference in absolute theta during the eyes closed condition, $AD_{ADHD - ASD + ADHD} = 0.10$, 95 %CI: −0.03–0.23, $p = 0.129$. Differences in absolute theta are shown in Fig. 1. There were no main effects of stimulant medication use on absolute theta and no interaction involving stimulant medication use. Absolute beta power revealed no main effects of diagnostic group or stimulant medication use.

Post hoc analyses revealed that when only adolescents without other comorbid disorders or Risperdal use were considered, theta is significantly higher in the ADHD-only group compared to the ASD + ADHD group for all three conditions: eyes closed $AD_{ADHD - ASD + ADHD} = 0.14$, 95 %CI: 0.009–0.28, $p = .038$, eyes open $AD_{ADHD - ASD + ADHD} = 0.14$, 95 %CI: 0.03–0.25, $p = 0.038$, task $AD_{ADHD - ASD + ADHD} = 0.14$, 95 %CI: 0.02–0.25, $p = 0.019$.

Age effects

Age by topography interactions are summarized in Table 3. Note: age was taken into consideration because the mean age of stimulant-medicated adolescents was younger than that of stimulant-free adolescents.

Table 2 GLM ANOVA of the d2 attention test with age as covariate

D2 attention test	TOTAL	ASD + ADHD	ADHD	Diagnostic group		Stimulant-medicated	Stimulant-free	Stimulant medication		Age		
	Mean (SD)	Mean (SD)	Mean (SD)	F	η^2_p	Mean (SD)	Mean (SD)	F	η^2_p	F	η^2_p	B_{Age}
Total group	$n = 53$	$n = 20$	$n = 33$			$n = 30$	$n = 23$					
Total processed items (TN)	421.60 (67.96)	422.35 (70.27)	421.15 (67.61)	0.06	0.00	419.33(62.24)	424.57 (76.11)	1.89	0.04	25.65***	0.35	14.64***
Total correct items (C)	164.75 (26.17)	166.15 (32.73)	163.91 (21.78)	0.00	0.00	164.60(25.01)	164.96 (28.17)	2.11	0.04	20.41***	0.29	5.22***
Post hoc group	$n = 42$	$n = 16$	$n = 26$			$n = 23$	$n = 19$					
Total processed items (TN)	427.31 (69.23)	441.13 (64.70)	419.00 (71.79)	0.01	0.00	423.39(62.82)	432.32 (77.76)	1.65	0.04	37.81***	0.50	18.07***
Total correct items (C)	167.62 (27.56)	172.31 (33.35)	164.73 (23.57)	0.00	0.00	167.43(26.88)	167.84 (29.10)	2.52	0.06	33.67***	0.48	7.07***

Data are means (SD); total group $df(1.48)$ and post hoc group $df(1.37)$

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

There was a decrease in Theta power with age. Specifically, within-subjects contrasts reveal that the reduction of absolute theta power in older adolescents during the eyes closed condition was linear and greatest in the posterior region and smaller at more anterior scalp locations, $F(1,48) = 7.29$, $p = 0.01$, $\eta^2_p = 0.13$. During the eyes open and the task conditions, a general decrease in absolute theta with age was seen. Absolute beta power decreased with age during the eyes open and the task conditions. Similar results were seen for the post hoc group. In summary, absolute power decreased with age for theta and beta frequency bands.

Region

During the eyes closed condition, beta differed across ROIs (see also Fig. 1). Within-subjects contrast shows a quadratic pattern, $F(1,48) = 6.49$, $p = 0.01$, $\eta^2_p = 0.12$; pairwise comparisons show that beta was greatest in the posterior region, $AD_{posterior\text{-}anterior} = 0.05$, 95 %CI: 0.01–0.09, $p < 0.01$; $AD_{posterior\text{-}central} = 0.06$, 95 %CI: 0.03–0.09, $p < 0.001$.

During the eyes closed condition, the post hoc group also shows that beta differs across ROIs, with within-subjects contrast showing a quadratic pattern, $F(1,37) = 5.26$, $p = 0.03$, $\eta^2_p = 0.12$; pairwise comparisons showed that beta was greatest in the posterior region, $AD_{posterior\text{-}anterior} = 0.06$, 95 %CI: 0.01–0.11, $p = 0.01$; $AD_{posterior\text{-}central} = 0.07$, 95 %CI: 0.03–0.10, $p < 0.001$. Although the post hoc group shows an interaction for theta with ROI, with within subjects contrast showing a linear pattern, $F(1,37) = 6.55$, $p = 0.02$, $\eta^2_p = 0.15$; pairwise comparisons do not show a significant differences between the different ROIs.

Post hoc d2 attention test performance, theta and beta power

In Table 4, the associations between d2 attention test performance and theta and beta power are summarized separately for the two diagnostic groups. Low theta during the eyes closed condition was associated with a higher TN than high absolute theta; in the ADHD group, this applied to central theta and in the ASD + ADHD group it applied to posterior theta. During the eyes open condition, low posterior theta was associated with a higher TN in the ADHD group, but not in the ASD + ADHD group. During the task condition, low posterior theta was associated with a higher TN than high posterior theta in both diagnostic groups. The ADHD group also showed an association between low theta and C in the central regions during the eyes closed condition and in the posterior region during the eyes open and task conditions. C was not related to theta in the ASD + ADHD group. Low absolute central beta during the eyes open and task conditions was associated with high TN in the ADHD group, but not in the ASD + ADHD group.

Post hoc analyses with the group without other comorbid disorders or Risperdal reveal that low posterior theta and posterior beta in all conditions were associated with high TN and high C for the group with ADHD only, whereas for the ASD + ADHD group only low posterior theta during the eyes closed condition was associated with high TN.

Table 3 EEG results for each frequency band by region, diagnostic group, stimulant medication use and age

Condition	Frequency band	ROI[a]		ADHD or ASD + ADHD		ROI, ADHD or ASD + ADHD and stimulant medication		Age		ROI and Age		Anterior	Central	Posterior
		F	η_p^2	F	η_p^2	F	η_p^2	F	η_p^2	$F(2,47)$	η_p^2	B_{Age}	B_{Age}	B_{Age}
Total group		*df*(2.47)		*df*(1.48)		*df*(2.47)		*df*(1.48)		*df*(2.47)				
Eyes closed	Theta	2.79	0.11	2.38	0.05	0.57	0.02	25.72***	0.35	3.82*	0.14	−0.05***	−0.06***	−0.07**
	Beta	4.44*	0.16	0.04	0.00	0.33	0.01	2.27	0.05	2.34	0.09	−0.02	−0.01	−0.02
Eyes open	Theta	1.78	0.07	4.32*	0.08	2.98	0.11	32.54***	0.40	2.98	0.11	−0.05***	−0.05***	−0.06***
	Beta	1.05	0.04	1.59	0.03	2.60	0.10	5.09*	0.10	0.65	0.03	−0.03*	−0.02	−0.02*
Task	Theta	0.52	0.02	4.52*	0.09	1.96	0.08	31.91***	0.40	2.43	0.09	−0.05***	−0.05***	−0.06***
	Beta	0.12	0.01	1.54	0.03	1.18	0.05	5.08*	0.10	0.04	0.00	−0.02*	−0.02*	−0.02*
Post hoc group		*df*(2.36)		*df*(1.37)		*df*(2.36)		*df*(1.37)		*df*(2.36)				
Eyes closed	Theta	3.49*	0.16	4.65*	0.11	1.19	0.06	26.61***	0.42	4.64*	0.16	−0.05***	−0.06***	−0.07***
	Beta	3.79*	0.17	0.07	0.00	0.81	0.04	3.97	0.10	1.79	0.09	−0.02	−0.02	−0.03*
Eyes open	Theta	2.69	0.13	6.52*	0.15	3.05	0.15	27.27***	0.42	4.70*	0.21	−0.04***	−0.05***	−0.06***
	Beta	0.67	0.04	1.08	0.03	3.63*	0.17	6.93*	0.16	0.42	0.02	−0.03*	−0.02*	−0.03*
Task	Theta	1.20	0.06	6.02*	0.14	1.55	0.08	29.45***	0.44	4.09*	0.19	−0.05***	−0.06***	−0.06***
	Beta	0.05	0.00	1.52	0.04	1.42	0.07	9.79**	0.21	0.13	0.01	−0.03**	−0.03**	−0.03**

The total group comprises adolescents with ADHD and ASD and other comorbid disorders. The post hoc group comprises adolescents with only ADHD and ASD, excluded for this group*** were adolescents with other comorbid disorders or those using antipsychotic medication

* $p<0.05$, ** $p<0.01$, *** $p<0.001$

[a] The regions of interest (ROIs) Anterior, Central and Posterior were included. Variables and interactions were included in the table only if there was a significant main effect of the variable or an interaction for at least one of the frequency bands. Stimulant medication showed no between-groups effect and was, therefore, not included

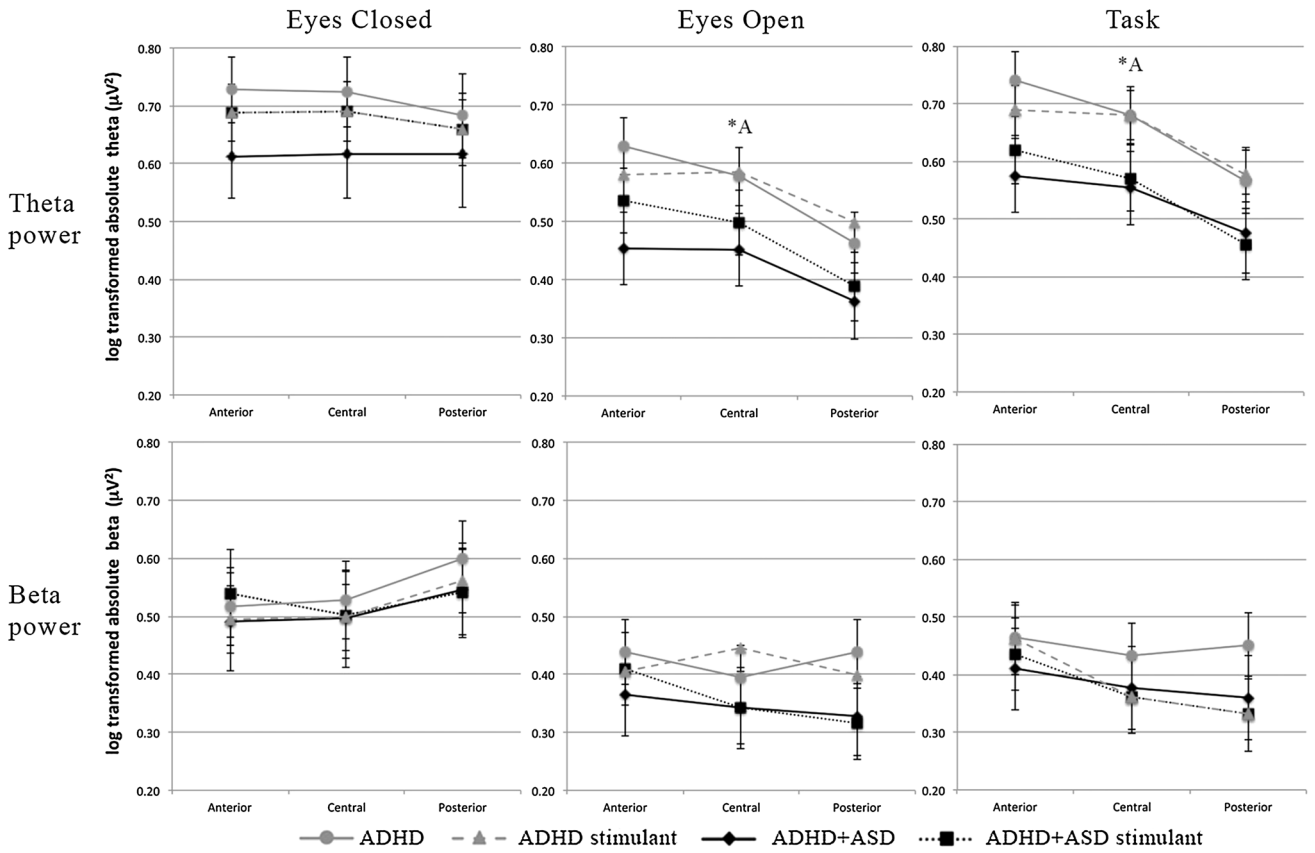

Fig. 1 Power as a function of region for the ADHD and ASD + ADHD groups, on and off stimulant medication. Note: Estimated marginal means are shown for $\log_{10}$ transformed absolute power (μV2) with standard error bars for each ROI and the evaluated covariate age 15.42 years for each condition (eyes closed, eyes open and task), for stimulant-free and stimulant-medicated adolescents with ADHD and for stimulant-free and stimulant-medicated adolescents with ASD + ADHD; *Asterik A* absolute theta was higher during the eyes open and task conditions for adolescents with ADHD than adolescents with ASD + ADHD, irrespective of stimulant medication use

Overall, absolute theta was associated with attention test performance, in all three conditions in the ADHD group. In the ASD + ADHD group, there was an association between posterior absolute theta and TN during the eyes closed. In general, the associations between attentional performance and theta were the most pronounced in the posterior region.

Discussion

The current study explored differences between adolescents with ADHD and ASD + ADHD, on and off stimulant medication, in attention test performance and EEG theta and beta power. The main results revealed that although behavioral and neuropsychological measures of attention were similar in adolescents with ADHD and ASD + ADHD, absolute theta was elevated in adolescents with ADHD compared to adolescents with ASD + ADHD during the eyes open and task conditions, irrespective of stimulant medication use of the adolescents.

In line with the only previous study, to our knowledge, comparing power spectra in children with ADHD and ASD + ADHD [30], no differences between these groups in terms of absolute theta were observed during an eyes closed condition. Extending the protocol used by Clarke et al. [30], in which only an eyes closed condition was investigated, we recorded power spectra during an eyes open and a task condition, which revealed overall greater absolute theta in adolescents with ADHD than in adolescents with ASD + ADHD. Post hoc analysis with exclusion of adolescents with other comorbid disorders and those using Risperdal confirm differences in theta during eyes open and task condition, and also differences during the eyes closed condition were found. It is notable that in ADHD increased theta power during resting state conditions [9–11], mainly in frontocentral regions [10], was the most robust finding. Theta is associated with an underaroused [10, 12, 14] and unfocused state [14]. It could be suggested that with their eyes open and during the task condition, adolescents with ADHD in the present study were characterized by a more underactive and unfocused

Table 4 Dependence of the d2 attention test on theta and beta power for ADHD and ASD + ADHD groups

Frequency band	D2	Condition	ADHD				ASD + ADHD			
			ROI	β	R^2	F	ROI	β	R^2	F
Total group						*df*(1.31)				*df*(1.18)
Theta	TN	Eyes closed	Central	−0.580	0.337	15.74***	Posterior	−0.548	0.300	7.71***
	C	Eyes closed	Central	−0.409	0.167	06.22*	–	–	–	–
	TN	Eyes open	Posterior	−0.605	0.366	17.91***	–	–	–	–
	C	Eyes open	Posterior	−0.462	0.213	08.41**	–	–	–	–
	TN	Task	Posterior	−0.581	0.338	15.82***	Posterior	−0.469	0.220	5.08*
	C	Task	Posterior	−0.430	0.185	07.04*	–	–	–	–
Beta	TN	Eyes open	Central	−0.355	0.126	04.46*	–	–	–	–
	TN	Task	Central	−0.464	0.215	08.51**	–	–	–	–
Post hoc group						*df* (1.24)				*df* (1.14)
Theta	TN	Eyes closed	Posterior	−0.708	0.501	24.07***	Posterior	−0.507	0.257	4.83*
	C	Eyes closed	Posterior	−0.667	0.445	19.27***	–	–	–	–
	TN	Eyes open	Posterior	−0.728	0.529	27.01***	–	–	–	–
	C	Eyes open	Posterior	−0.698	0.466	22.86***	–	–	–	–
	TN	Task	Posterior	−0.722	0.521	26.12***	–	–	–	–
	C	Task	Posterior	−0.678	0.459	20.40***	–	–	–	–
Beta	TN	Eyes closed	Posterior	−0.442	0.196	5.84*	–	–	–	–
	C	Eyes closed	Posterior	−0.442	0.195	5.82*	–	–	–	–
	TN	Eyes open	Posterior	−0.507	0.257	8.30**	–	–	–	–
	C	Eyes open	Posterior	−0.516	0.267	8.73**	–	–	–	–
	TN	Task	Posterior	−0.650	0.423	17.60***	–	–	–	–
	C	Task	Posterior	−0.564	0.318	11.17**	–	–	–	–

Separate stepwise regressions were performed for the total groups: ADHD ($n = 33$) and ASD + ADHD ($n = 20$). TN and C were the dependent variables. Independent variables were: (1) theta and (2) beta. Only significant models are reported, β = standardized regression coefficients; post hoc analyses were performed for both group without comorbid disorders: ADHD ($n = 26$) and ASD + ADHD ($n = 16$)

TN total processed items, *C* total correct items

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

state than adolescents with ASD + ADHD. This may indicate that underarousal is a better explanation for attentional problems in adolescents with ADHD than in adolescents with ASD + ADHD; the attentional problems in ASD + ADHD may result from other brain dysfunctions, such as abnormal neuronal connectivity [26, 49] and top-down processing problems [50], rather than from frontocentral underarousal per se. In healthy adults, frontocentral theta has also been positively related to sustained attention and working memory during cognitive complex tasks [51, 52]. Accordingly, an alternative explanation for the relation between ADHD and theta activity might be that the theta activity is the result of an applied strategy to compensate for attention problems. In addition, in healthy adults the stimuli-related early theta activity directly after stimuli presentation seems strongly related to the event-related potential (ERP) P300 [53]. The P300 has also been previously positively related to selective attention and working memory [54]. Whereas theta activity direct after stimuli presentation was similar for TD children and children with ADHD only, increased stimulus-related theta, between 200 and 450 ms after stimuli presentation, was related to the presence of ADHD symptomatology in children [55]. In the current study, theta activity during the whole task condition was considered, irrespective of stimuli presentation. Considering that theta was elevated in the ADHD compared to the ASD + ADHD group, it would be interesting for future research to see if this difference in theta can be further localized in specific theta event-related oscillations and ERP components.

It is remarkable that the difference in absolute theta between the diagnostic groups was present irrespective of stimulant medication use, because other studies have reported decreased theta and increased beta after stimulant medication use [14, 20–22]. However, although stimulant medication partly normalizes theta and beta power, children with ADHD do not reach similar theta and beta levels as TD children [20, 22]. Furthermore, the decrease in frontal theta in children with ADHD associated with stimulant

medication use has been related to parent-reported behavioral improvement [56]. As the adolescents with ASD + ADHD in our study did not show as much absolute theta as adolescents with ADHD, this suggests either that stimulant medication works differently in youngsters with ASD + ADHD or is less effective than in youngsters with ADHD only.

Theta and beta power spectra were not significantly influenced by stimulant medication use. Stimulant medication use is generally associated with decreased theta and increased beta [14, 20–22]. In the current study there were no overall differences in EEG power between stimulant-medicated and stimulant-free adolescents. Baseline differences in age between adolescents on and off stimulant medication in our sample may have contributed to the lack of effects of stimulant medication: the stimulant-free adolescents were, on average, older than stimulant-medicated adolescents. This is in line with former research that showed that despite the persistent nature of ADHD, the majority of adolescents with ADHD discontinue stimulant medication before adulthood [57, 58]. In addition, from childhood to adulthood, there is a decrease in total power and particularly in the slow wave bands including theta power [19, 31]. Since aging [31] as well as using stimulant medication [14, 20–22] results in decreased theta power, the two effects may have cancelled each other out. Another point of consideration is that the stimulant-medicated adolescents continued stimulant medication use on the day of assessment as prescribed and a variety of stimulant medications were used. These stimulant-medicated adolescents were compared with stimulant-free adolescents. Former studies [14, 20–22] that showed an association between decreased theta and stimulant medication use did so in a within-group design: children were tested first stimulant naive or after stimulant washout and thereafter stimulant-medicated. By controlling for individual differences with a within-group design, effects of stimulant medication use might be better demonstrable than with a between groups design. In addition, stimulant medication intake of these studies [14, 20–22] was 1 h before assessment, whereas in the current study the precise time between medication intake and assessment was unknown. Consequently, all the above-mentioned variables might have contributed to the absence of differences in theta and beta power between stimulant-medicated and stimulant-free adolescents.

Increased theta, particularly in the anterior region, is generally thought to be typical for ADHD. In the current study, we observed that high theta was correlated with less total processed stimuli on the d2 attention test for all ROIs. However, this inverse association between theta and d2 attention test performance was most pronounced posterior instead of anterior. This finding is similar to that of Hermens et al. [59] who found an inverse correlation between posterior theta during an eyes open condition and reaction time in TD adolescents but not adolescents with ADHD [59]. It is striking that a lower posterior absolute theta during the eyes open condition was strongly associated with attentional performance in terms of total processed (TN) and total correct processed (C) items in adolescents with ADHD but not in adolescents with ASD + ADHD. It should be noted that due to the smaller size of the ASD + ADHD group, associations had to be stronger to reach significance; but taking this difference in sample size into account, the association was so pronounced in the ADHD group that an association of similar strength in the combined ASD + ADHD would have proved significant, as was the association between TN and posterior theta during the eyes closed and task conditions. Reported attention problems as well as attention task performance were similar for the two diagnostic groups. Combining these findings provides support for the hypothesis that increased theta seems to be associated with attentional problems in ADHD, but less often with attentional problems in ASD + ADHD.

Similar to theta, lower absolute beta, particularly during task condition, was also associated with improved attention test performance in the adolescents with ADHD. For the combined ASD + ADHD group, there were no significant associations between beta and d2 attention task performance. In TD young adults, an increase in absolute beta during attention test performance has been associated with improved visual attention test performance [60]. Similarly, strong positive correlations between absolute beta and attention test performance, as well as parent-reported measures of attention in children with ADHD, have been reported previously [56]. The reverse finding in the current study—a reduction in absolute beta and improved attention test performance—might, therefore, be a reflection of maturation, which is generally accompanied by a decrease in power across all frequency bands, with posterior sites maturing at an earlier age than more frontal sites [31]. In line with the review by Segalowitz et al. [31], the current study found a clear maturation effect, with older adolescents displaying lower theta and beta power. In addition, we observed a maturation effect on attention test performance, with better performance at older ages. Interestingly, the maturation effects in theta and beta power seem more prominent in the ADHD group than in the combined ASD + ADHD group, whereas there were no differences in age or age range between the two groups.

The current results showed overlap in behavioral and cognitive measures of attention, but differences in absolute theta activity between adolescents with ADHD and adolescents with ASD + ADHD. Nevertheless, further systematic research on the psychophysiological aspects of

ADHD and ASD + ADHD and their implications is warranted. A major limitation of the current study is the absence of a control group with TD adolescents. As such, no conclusions can be drawn with respect to whether the theta activity of the adolescents with ADHD was indeed higher than normally seen in adolescents, nor whether the adolescents with combined ASD + ADHD display less or similar levels of theta activity compared to TD adolescents. Further research, including a TD group, is therefore warranted. Moreover, replication of these psychophysiological results in a larger sample size is needed, ideally with a controlled stimulant medication titration trial including physiological baseline measures with stimulant-free adolescents with ADHD, ASD + ADHD, ASD and TD adolescents. Such a titration trial would control for baseline differences in stimulant medication use and age that were observed in the current study. Although we controlled for age statistically, it is possible that stimulant medication use and maturation may affect EEG spectra similarly. The stimulant-medicated adolescents in this study were on average younger than the stimulant-free adolescents, this may have concealed potential effects of stimulant medication use. Secondly, the diagnostic group assignments in this study were based on clinician's decisions using DSM-IV [3] criteria; while this increased the ecological validity of the study, information about specific diagnostic aspects of ASD was not available. Including diagnostic interviews such as the Autism Diagnostic Interview [61] or the Autism Diagnostic Observation Schedule [62] in future research could give more detailed information about specific characteristics of ASD. In addition, while there are indications that EEG patterns in reaction to stimuli might be different for the combined and inattentive subtype [63], the current study did not look at differences between ADHD subtypes because sample sizes of the subtype groups would be too small. However, whereas robust differences in EEG activity between ADHD and TD control groups have been found, there is less evidence available for differences between ADHD subtypes [64]. In the studies that did present differences between ADHD subtypes, the combined subtype seemed to show overall more pronounced deviations than the inattentive subtype as compared to TD children, rather than different deviations [64]. Future research that addresses the abovementioned limitations is warranted to uncover the physiological patterns associated with ADHD, ASD, ASD + ADHD and typical development.

In conclusion, adolescents with ADHD displayed more absolute theta activity than adolescents with ASD + ADHD with their eyes open and during performance of a task. In addition, adolescents with ADHD but not adolescents with ASD + ADHD showed an association between diminished attention test performance and increased theta with their eyes open. The current study suggests that although there is an overlap in behavioral ADHD characteristics between adolescents with ADHD and adolescents with ASD + ADHD, the underlying psychophysiological mechanisms responsible may be different. This finding may help to explain why stimulant medication is less effective in ASD + ADHD than in ADHD. Further research into the psychophysiology of ASD + ADHD is, therefore, warranted.

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Conflict of interest The authors declare that they have no conflict of interest.

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