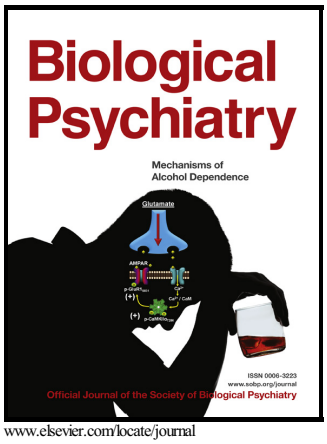

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ADHD remission is linked to better neurophysiological error detection and attention-vigilance processes

(short title: Cognitive and EEG markers of ADHD remission)

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ABSTRACT

Background: The processes underlying persistence and remission of attention-deficit/hyperactivity disorder (ADHD) are poorly understood. We aimed to examine whether cognitive and neurophysiological impairments on a performance monitoring task distinguish between ADHD persisters and remitters.

Methods: On average six years after initial assessment, 110 adolescents and young adults with childhood ADHD (87 persisters, 23 remitters) and 169 age-matched controls were compared on cognitive-performance measures and event-related potentials (ERPs) of conflict monitoring (N2) and error processing (ERN, Pe) from an arrow flanker task with low- and high-conflict conditions. ADHD outcome was examined with parent-reported symptoms and functional impairment measures using a categorical (DSM-IV) and a dimensional approach.

Results: ADHD persisters were impaired compared to controls on all cognitive-performance and ERP measures (all $p<0.05$). ADHD remitters differed from persisters, and were indistinguishable from controls, on the number of congruent (low-conflict) errors, reaction time variability (RTV), ERN and Pe (all $p\leq0.05$). Remitters did not differ significantly from the other groups on incongruent (high-conflict) errors, mean reaction time and N2. In dimensional analyses on all participants with childhood ADHD, ADHD symptoms and functional impairment at follow up were significantly correlated with congruent errors, RTV and Pe ($r=0.19$-0.23, $p\leq0.05$).

Conclusions: Cognitive and neurophysiological measures of attention-vigilance and error detection distinguished ADHD remitters from persisters. These results extend our previous findings with other tasks (Cheung et al. 2015), and indicate that such measures are markers of remission and candidates for the development of non-pharmacological interventions.

INTRODUCTION

The identification of cognitive and neural processes underlying the trajectories of persistence and recovery from childhood-onset disorders during the transition to adulthood has the potential to prevent negative long-term outcomes (1, 2). Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder affecting 5-6% of children and adolescents worldwide (3, 4). ADHD often persists into adulthood, where the prevalence rate is around 2-3% (5), with severe impact on many aspects of individuals' lives (6, 7). Although in a proportion of cases ADHD symptoms reduce to subclinical levels from childhood to adulthood (8), little is known about the compensatory processes and enduring deficits of ADHD.

It has been proposed that the cognitive processes associated with persistence of ADHD across development may be separate from those linked to the remission of the disorder (9). However, empirical data to date are inconsistent with regard to the exact pattern of cognitive impairments that distinguish ADHD remitters from persisters. While some studies comparing ADHD remitters and persisters have linked remission to better executive function performance (1, 10), other studies have found no differences between ADHD remitters and persisters in adolescence and adulthood on measures of executive functions (11-15).

The assessment of neurocognitive processes using cognitive and brain activity data may allow a deeper understanding of the developmental trajectories of ADHD. Our recent investigation of adolescents and young adults with childhood ADHD assessed on a range of cognitive, event-related potential (ERP) and electroencephalography (EEG) measures found that ADHD remitters differed from persisters, but not from controls, on preparation-vigilance measures (RTV, omission errors, ERP activity of response preparation, and delta and theta activity) and actigraph data on movement. Executive-function processes of inhibition and working memory (commission errors, digit span

backwards and ERP activity of inhibitory control), instead, were not sensitive to ADHD persistence/remission, as ADHD remitters showed an intermediate pattern between persisters and controls, without significant differences from either group (14). Further combined investigations of cognitive and neurophysiological data may aid our understanding of the mechanisms underlying ADHD remission and persistence.

Neurocognitive impairments in ADHD include deficits in performance monitoring, an essential cognitive ability in goal-directed behavior to monitor ongoing performance and adjust response selection (16-18). The investigation of performance-monitoring impairments with ERP parameters, including the N2 and the error-related negativity (ERN or Ne) and positivity (Pe), in individuals with ADHD may provide new information to elucidate the neurocognitive pathways of remission. The N2 is a fronto-central stimulus-locked negative deflection mostly observed 200-400 ms after the presentation of stimuli inducing high conflict (such as incongruent stimuli) and when a correct response is made (17, 19). This ERP reflects a conflict-monitoring process, as it results from the conflict arising from two competing responses and evaluation of the correct response (19). When a participant makes an error, the ERN, a fronto-central response-locked negative deflection at around 0-150 ms is observed, followed by the Pe, a centro-parietal positive enhancement at around 200-400 ms after response (20-22). The ERN is thought to reflect unconscious activity of a generic response-monitoring system immediately after a mistake is made, while the Pe is thought to represent conscious error processing to adjust response strategy (23).

In ADHD, N2 attenuation in the flanker task has been reported in children and adults with ADHD (24-26), although two smaller studies failed to replicate this finding (27, 28). With regard to ERN and Pe attenuation in ADHD, a recent meta-analysis found an overall ERN attenuation in performance monitoring tasks (29). Pe attenuations in ADHD samples were significant in Go/NoGo tasks, but not flanker tasks. Yet, data on these ERPs in individuals with ADHD are overall limited, and study samples

have remained small. Furthermore, studies have not, to date, investigated the association between neurophysiological performance monitoring and ADHD persistence and remission. One recent study showed that ERN and Pe deficits may be improved with motivational incentives or methylphenidate medication in ADHD groups (30), suggesting malleability of the error-processing impairments in ADHD.

In the present study, we aimed to extend our recent findings (14) by investigating cognitive and neurophysiological impairments from a performance monitoring task in adolescents and young adults with persistent and remitted ADHD. We examined ADHD outcome with parent-reported symptoms and functional impairment measures using both a categorical (DSM-IV) and a dimensional approach. Based on our previous results and evidence of potentially malleable neurophysiological error processing, we predicted that cognitive measures underlying non-executive processes and ERPs of error processing (ERN/Pe) would distinguish between ADHD persisters and remitters, and represent markers of remission. We further predicted that cognitive indices of executive control would not vary with persistence or remission of ADHD. No formal predictions were made for ERP measures of conflict monitoring (N2), owing to absence of any evidence suggesting a possible association with remission or persistence of ADHD.

METHODS AND MATERIALS

Sample

The sample consists of 279 participants, who were followed up on average 5.8 years (SD=1.1) after initial assessments: 110 had a diagnosis of DSM-IV combined-type ADHD in childhood (10 sibling pairs and 90 singletons) and 169 were control participants (76 sibling pairs and 17 singletons) (14, 31). Participants with ADHD were initially recruited from specialized ADHD clinics (32), and control participants from schools in the UK. Information on any diagnosed neurodevelopmental and psychiatric conditions and medication use were collected through neuropsychiatric screening. Exclusion criteria at both assessments included: IQ < 70, autism, epilepsy, brain disorders and any genetic or medical disorder associated with externalizing behaviors that might mimic ADHD. Other comorbidities were not excluded in order to have an ADHD sample that is representative of the clinical population. At follow up, we excluded six control participants who met DSM-IV ADHD criteria based on the parent-reported Barkley Informant Rating Scale (33) and six participants with ADHD who had missing parent ratings of clinical impairments. Two participants with childhood ADHD, who did not meet ADHD symptom criteria but met clinical levels of impairment at follow up, were also excluded to minimise heterogeneity in the sample.

Among those with childhood ADHD, 87 (79%) continued to meet clinical (DSM-IV) levels of ADHD symptoms and impairment (ADHD 'persisters'), while 23 (21%) were below the clinical cut-off (ADHD 'remitters') (31). Among ADHD remitters, 14 displayed ≥ 5 items on either the inattention or hyperactivity/impulsivity symptom domains, but did not show functional impairment. ADHD persisters, remitters and controls did not differ in age, but there were significantly more males in the remitted group than in the other two groups, with no females among ADHD remitters (Table 1). Participants attended a single research session for clinical, IQ and cognitive-EEG assessments. Almost

half (47%) of the participants with childhood ADHD were being treated with stimulant medication at follow up. Those who were on medication scored significantly higher on ADHD symptoms ($F=11.34$, $p<.01$) and functional impairment ($F=5.22$, $p<.01$) than those who were not taking medication. However, the proportion of participants on medication did not differ between ADHD persisters and remitters ($\chi^2=1.95$, $p=.16$). A 48-hour ADHD medication-free period was required prior to assessments. Three ADHD persisters (3.4%) were also on antidepressant medication, but were not asked to stop taking them for ethical reasons. These participants were included in all analyses as their exclusion did not alter the results. Parents of all participants gave informed consent following procedures approved by the London-Surrey Borders Research Ethics Committee (09/H0806/58).

ADHD diagnosis

The diagnostic interview for ADHD in adults (DIVA) (34) was conducted by trained researchers with parents of the ADHD probands, to assess DSM-IV-defined ADHD presence and persistence. Raw scores for inattention and hyperactivity/impulsivity symptoms (range 0-9 for each dimension) were generated for each participant. Evidence of impairment commonly associated with ADHD was assessed with the Barkley's functional impairment scale (BFIS) (33) during interviews with parents. Each item ranges from 0 (never or rarely) to 3 (very often). Participants were classified as 'affected' at follow-up if they scored ≥ 6 in either the inattention or hyperactivity/impulsivity domains on the DIVA and ≥ 2 on two or more areas of impairments on the BFIS. We defined ADHD outcome using a categorical definition of persistence based on diagnoses, as well as a dimensional approach based on levels of symptoms of ADHD and impairments measured as continuous traits.

IQ assessment

An estimate of IQ was derived with the vocabulary and block design subtests of the Wechsler Abbreviated Scale of Intelligence (WASI) (35).

Task

The task was an adaptation of the Eriksen Flanker paradigm designed to increase cognitive load as used in previous studies (24, 25, 36). In each trial a central black fixation mark was replaced by a target arrow (a black 18 mm equilateral triangle). Participants had to indicate whether this arrow pointed towards the left or right by pressing corresponding response buttons with their left or right index fingers. Two flanker arrows identical in shape and size to the target appeared 22 mm above and below the centre of the target arrow 100 ms prior to each target arrow. Both flankers either pointed in the same (congruent) or opposite (incongruent) direction to the target. As such, conflict monitoring is maximal during the incongruent condition. When the target appeared, both target and flankers remained on the screen for a further 150 ms, with a new trial being presented every 1650 ms. Two hundred congruent and 200 incongruent trials were arranged in 10 blocks of 40 trials over 13 minutes. For further details on the task see Supplement 1. Cognitive-performance measures of mean reaction time (MRT), RTV (SD of RTs) and number of errors (left-right errors occurring when participants chose the wrong left or right response) were calculated separately for congruent and incongruent conditions.

Electrophysiological recording and processing

The EEG was recorded from a 62 channel DC-coupled recording system (extended 10–20 montage), using a 500 Hz sampling-rate, impedances under 10 kΩ, and FCz as the recording reference. The

electro-oculograms (EOGs) were recorded from electrodes above and below the left eye and at the outer canthi. EEG data were analyzed using Brain Vision Analyzer 2.0 (Brain Products, Germany). Raw EEG recordings were down-sampled to 256 Hz, re-referenced to the average of all electrodes (turning FCz into an active channel), and filtered using Butterworth band-pass filters (0.1-30 Hz, 24 dB/oct). All trials were visually inspected for electrical artifacts or obvious movement, and sections of data containing artifacts were removed manually. Ocular artifacts were identified using the infomax Independent Component Analysis algorithm (ICA) (37). Sections of data containing artifacts exceeding ± 100 μV or with a voltage step greater than 50 μV were automatically rejected. Baseline correction was applied using the -300 to -100 ms pre-target (-200 to 0 ms pre-flanker) interval.

Analyses of ERPs of performance monitoring were restricted to incongruent trials, as the task used in this study is known to elicit strong N2, ERN and Pe components in high-conflict, but not in low-conflict, conditions (24, 25, 36). Data were segmented based on (1) stimulus-locked incongruent trials where a correct response was made and (2) response-locked (error-related) incongruent trials where an incorrect response was made. Individual averages were created based on each condition, requiring ≥ 20 clean segments for each participant. After averaging, the electrodes and latency windows for ERP analyses were selected based on previous studies (23-25, 38), topographic maps and the grand averages (Figures 1-2). The N2 was measured as maximum negative peak at Fz and FCz between 250-450 ms after target onset. The ERN was defined with respect to the preceding positivity (PNe, -100-50 ms) and measured at FCz between 0-150 ms. This peak-to-peak measure has proven to be a robust measure of this component (20, 23, 39) and was favored over a peak-to-baseline (maximal amplitude) measure as the former distinguished ADHD from controls in independent samples using this version of the Eriksen flanker task (24, 25, 40); it was therefore the ideal candidate in relation to ADHD remission/persistence (for further details see Supplement 1). The Pe was measured as maximum positive peak at CPz between 150-450 ms after an erroneous response on incongruent trials.

Statistical analyses

For RTV and errors we tested overall effects of group (ADHD persisters, remitters, controls), condition (congruent, incongruent) and group*condition interaction using random intercept models in Stata (StataCorp, College Station, TX) to control for genetic relatedness of the sibling pairs in a repeated-measures design. A random intercept model was also run to test the effect of group, scalp site (Fz, FCz) and group*site interaction on the N2. ERN and Pe were analyzed with regression models with dummy variables to identify overall group effects, controlling for sibling relatedness with the 'robust cluster' command in Stata. Age correlated significantly with several of the cognitive-ERP measures (Table S1, Supplement 1), and was therefore included as a covariate in group analyses. On measures that indicated a group effect, post-hoc regressions were performed. The majority of our sample consisted of males (80%), and thus primary analyses were performed on the whole sample without accounting for sex differences. As groups were not matched on gender (no female in the sample remitted from ADHD) (Table 1), analyses were re-run with the females (15 ADHD persisters and 41 controls) removed. Cohen's d effect sizes are presented along with means, SDs and test statistics for the group analyses (Table 2), where 0.20 is considered a small effect, 0.50 a medium effect and 0.80 a large effect (41). Pearson correlations examined which measures correlated with DIVA ADHD symptom scores and functional impairment, in those with a childhood ADHD diagnosis, with age and gender included as covariates.

As ADHD persisters had a lower IQ than remitters (Table 1) (14), and higher IQ in childhood was associated with ADHD remission at follow-up in this sample (31), all analyses were also re-run controlling for IQ. All cognitive-ERP measures were skewed and log-transformed to normal. Three participants (ADHD persisters) were excluded from the N2 analysis and 39 (13 ADHD persisters (15%), 3 ADHD remitters (13%), 23 controls (14%)) from the ERN/Pe analysis due to having < 20

artifact-free ERP segments, similar to previous studies using this paradigm (24, 25) and reflecting a similar exclusion ratio across groups.

[Table 1 about here]

RESULTS

Group differences

An overall group effect emerged on all cognitive-performance and ERP measures (Table 2, Figures 1-2). Post-hoc analyses showed that ADHD persisters had significantly higher MRT, RTV, number of errors, enhanced N2 (at Fz, but with a trend for reduction at FCz, pointing to topographic differences, as shown in Figure S1, Supplement 1) and reduced ERN and Pe compared to controls, with small-to-large effect sizes. Significant differences between ADHD remitters and persisters emerged on congruent and incongruent RTV, congruent errors, ERN and Pe, with medium-to-large effect sizes. ADHD remitters did not differ from persisters on MRT in either condition, on incongruent errors and N2, with null-to-small effect sizes. ADHD remitters and controls significantly differed on incongruent RTV, with a medium effect size, and at trend-level with small effect sizes for incongruent errors and incongruent MRT.

Controlling for IQ, group effects on MRT in both conditions and N2 at FCz were non-significant (Table 2). Differences between remitters and persisters became non-significant in incongruent RTV, and trends in ERN and Pe. Remitters and controls differed at trend-level in incongruent RTV, but not in incongruent errors. Results for other variables remained unchanged. When repeating the analyses with females removed, the difference between ADHD persisters (n=63) and remitters (n=20) became a trend for the ERN and non-significant for the Pe. Given the small female sample sizes (n=15; of

which only n=11 with data on ERN and Pe) and the discrepancy in the size of male and female groups, sex differences were not directly tested. Yet, the effect sizes in the male-only sample (d=0.47 for the ERN, d=0.34 for the Pe) were comparable or only slightly reduced compared to those of the full sample. Remitters significantly differed from controls on incongruent MRT, congruent and incongruent RTV, but not on incongruent errors. All other results remained unchanged. For further details see Supplement 1.

[Table 2 about here]

Associations with ADHD symptoms and impairments

Among those with childhood ADHD (n=110), both ADHD symptoms and impairment at follow up significantly correlated with the Pe (Table 3). ADHD symptoms also significantly correlated with RTV in both conditions, and functional impairment with congruent errors and at trend level with incongruent RTV and N2 at Fz. When IQ was controlled for, the correlation of ADHD symptoms or impairment with RTV became non-significant, and the correlation between functional impairment and congruent errors became a trend (Table 3).

[Table 3 about here]

DISCUSSION

In this first large scale investigation of cognitive and neurophysiological performance monitoring in adolescents and young adults with ADHD we found that ADHD remitters had enhanced cognitive processes of attention-vigilance (RTV and congruent errors) and neurophysiological error processing (ERN and Pe) compared to persisters. Attention-vigilance measures and conscious error processing

were also associated with the continuum of ADHD symptoms and impairment at follow up. Conversely, measures of executive control (incongruent errors), speed of processing (MRT) and neurophysiological conflict monitoring (N2) did not distinguish remitters from persisters, thus were not sensitive to remission or persistence of the disorder. Processes of attention-vigilance and neurophysiological error processing can be markers of remission from ADHD, and may be sensitive to the effects of training or compensatory mechanisms.

RTV, measuring intra-individual variability in RT, and number of congruent errors in the low-conflict condition distinguished ADHD remitters from persisters, but not from controls, and were also correlated with continuous ratings of ADHD symptoms and impairment. Impairments in such measures in the congruent condition of the flanker task may result from lapses in attention, and index attention-vigilance processes. Neurophysiological measures of error processing (ERN and Pe), showed the same association with ADHD remission. Conscious error processing (Pe) also correlated with the continuous ADHD symptoms and functional impairments at follow up. Of note, the group difference observed on this peak-to-peak ERN were likely explained by the voltage change from the PNe to the negative ERN peak (see Supplement 1). This measure captures the response-locked oscillatory pattern immediately before and after an error is made, and as such may reflect early attentional processes linked to automatic error detection. Conversely, incongruent errors in the high-conflict condition, likely reflecting a failure in executive control, and MRT in left-right responses at every trial, likely measuring speed of processing in this task that induces high cognitive demands, did not distinguish ADHD remitters from persisters. Similarly, neurophysiological conflict monitoring (N2) did not differ between ADHD groups, potentially indicating suboptimal parallel stimulus processing regardless of remission/persistence (17, 42). Remitters also showed lower RTV in the incongruent condition than persisters, but were still impaired compared to controls. Given the higher levels of executive control elicited in the incongruent condition, this could result from joint

influences of both attention-vigilance and executive processes. Therefore, RTV in the incongruent condition may be less sensitive to remission than in the congruent condition.

Primary analyses did not control for IQ, as lower-mean IQ in ADHD samples represents one of multiple cognitive processes underlying ADHD pathophysiology (43, 44), and the etiological influences shared between ADHD and IQ are largely separate from those shared with other cognitive impairments (45-47). Thus by removing IQ effects when investigating the relationship between ADHD and cognitive-ERP variables one may also control for features of ADHD related to IQ (48, 49). In this sample ADHD remission was associated with higher IQ measured both in childhood and at follow up (14, 31). As such, it may be that higher IQ represents a potential compensatory mechanism. To test the association between cognitive-ERP measures and remission/persistence beyond the influence of IQ, we also repeated the analyses covarying for IQ. When controlling for IQ, overall group differences for MRT were no longer significant, suggesting that group differences on this measure may reflect ADHD impairments related to IQ. Moreover, remitters were more similar to persisters in some markers of remission (RTV, ERN and Pe) when removing the IQ effects. This further points to an association between IQ and better cognitive-neurophysiological profiles in ADHD remitters.

The present study extends the findings in our previous investigation that used a cued continuous performance test (CPT-OX), a four-choice RT task and WASI measures of IQ and digit span (14). Attention-vigilance and error detection showed a similar pattern to that found in our previous analyses for preparation-vigilance measures (RTV, omission errors, ERP activity of response preparation, and delta and theta activity), while executive control (measured by incongruent errors), speed of processing (MRT for left-right responses) and conflict monitoring (N2) did not distinguish remitters from persisters, similar to measures of inhibition and working memory in our previous investigation (14). ADHD remitters showed an intermediate pattern between persisters and controls

on this latter group of measures: they showed no significant differences from either group on the N2, but trend-level differences from controls on incongruent errors and MRT, suggesting that the latter two measures may potentially represent markers of enduring deficits. Our findings align with four recent studies reporting no differences between ADHD remitters and persisters in executive control (11-14), but not with two earlier studies that suggested a link from ADHD remission to better executive function (1, 10). More broadly, our findings are in line with evidence for a separation of ADHD neurocognitive impairments into bottom-up and top-down processes supported by genetically-sensitive studies (32, 50). Our results are also consistent with reports of ADHD-sensitive improvement following rewards in RTV and ERPs of error processing (30, 51, 52), suggesting that such processes are malleable and may improve with the additional allocation of cognitive arousal and motivational incentives in ADHD samples. Future studies may further characterize the relationship between ADHD outcome and performance/conflict monitoring processes by using tasks with different ratios of congruent and incongruent trials, which may produce stronger enhancement of conflict processes (53), potentially coupled with single-trial measures to examine trial-to-trial adjustments (54).

A limitation of this study is that, despite the large sample size, the low ADHD remission rate at follow-up resulted in a relatively small group of remitters. Therefore we could not rule out the possibility that some non-significant differences between remitters and other groups could be due to low power. However, we observed medium-to-large effect sizes (d=0.44-0.75) between persisters and remitters in measures representing markers of remission, but small or negligible effect sizes (d=0.02-0.28) in measures not sensitive to ADHD outcome at follow-up, suggesting this study had sufficient power to detect the major correlates of remission with the current sample sizes. Secondly, when we repeated the analyses for males only, differences between remitters and persisters in the ERN and Pe were reduced. However, the small sample of females did not allow a direct examination of sex differences. Future studies, including a higher number of female participants, are needed to

further investigate these processes also in females. Finally, our sample included young adults as well as adolescents, who are still undergoing rapid cortical maturation. While we controlled for age in all analyses, future follow-up assessments with participants having reached adulthood and when more ADHD participants may have remitted could clarify matters further.

Overall, we report that attention-vigilance and neurophysiological error processes were impaired in ADHD persisters but not in remitters, and may be sensitive to compensatory mechanisms in those who remit from the disorder. These processes may be targets for non-pharmacological interventions or behavioral training aimed at alleviating some of the long-term outcomes of ADHD. Conversely, cognitive measures of executive control, speed of processing and conflict monitoring were not sensitive to ADHD remission/persistence. Considering the importance of using a broad range of cognitive and neural measures in investigating the mechanisms underlying neurodevelopmental disorders (2), our cognitive and neurophysiological investigation provides an improved understanding of the trajectories to ADHD remission and persistence. Future studies should aim to investigate the neural sources and neurobiological mechanisms underlying these markers of remission, in order to pave the way towards the development of new interventions aimed at stimulating processes that are sensitive to remission to reduce severe long-term outcomes of the disorder.

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FINANCIAL DISCLOSURES

Prof Philip Asherson has received funding for research by Vifor Pharma, and has given sponsored talks and been an advisor for Shire, Janssen–Cilag, Eli-Lilly, Flynn Pharma and Pfizer, regarding the diagnosis and treatment of ADHD. All funds are received by King's College London and used for studies of ADHD. Prof Tobias Banaschewski has served as advisor or consultant for Bristol Myers-Squibb, Develco Pharma, Lilly, Medice, Novartis, Shire and Vifor Pharma; he has received conference attendance support and conference support or speakers honoraria from Janssen McNeil, Lilly, Medice, Novartis and Shire, and has been involved in clinical trials conducted by Lilly and Shire. All other authors report no biomedical financial interests or potential conflicts of interest.

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FIGURES

Figure 1. Grand average response-locked ERPs of the ERN at FCz electrode between 0-150 ms (A) and the Pe at CPz electrode between 150-450 ms (B) after an erroneous response on the incongruent trials for ADHD persisters (ADHD-P, in red), ADHD remitters (ADHD-R, in green) and control participants (Controls, in black), with topographic maps.

Figure 2. Grand average stimulus-locked ERPs of the N2 at Fz and FCz electrodes between 250-450 ms after incongruent stimuli where a correct response was made for ADHD persisters (ADHD-P, in red), ADHD remitters (ADHD-R, in green) and control participants (Controls, in black), with topographic maps.

Table 1. Sample demographics divided by group, with test for group differences

	ADHD-P	ADHD-R	Ctrl	p	ADHD-P vs Ctrl	ADHD-P vs ADHD-R	ADHD-R vs Ctrl
					p	p	p
Gender (M:F)	72:15	23:0	129:40	.02*	.24	.03*	<.01**
Age, mean (SD)	18.27 (3.03)	18.89 (3.06)	18.77 (2.19)	.15	-	-	-
IQ, mean (SD)	96.20 (15.33)	104.57 (13.63)	109.98 (12.42)	<.01**	<.01**	.02*	.10

Abbreviations: F = females, M = males.

Notes: Group differences on gender were tested via Chi-square test; group differences on age and IQ were tested with regression models. Group differences in gender, age and IQ were previously reported in another paper on this sample (14).

**p<.01; *p<.05.

Table 2. Descriptive statistics and group comparison on cognitive-performance and ERP measures

	ADHD-P	ADHD-R	Ctrl	Group Comparison						Covarying IQ						
	mean (SD)	mean (SD)	mean (SD)	p	ADHD-P vs Ctrl		ADHD-P vs ADHD-R		ADHD-R vs Ctrl		p	ADHD-P vs Ctrl		ADHD-P vs ADHD-R		ADHD-R vs Ctrl	
					d	p	d	p	d	p		d	p	d	p	d	p
Performance																	
Congruent errors	10.89 (17.26)	4.00 (3.85)	4.14 (8.31)	<.01**	**.83**	<.01**	*.75*	<.01**	.04	.95	<.01**	*.55*	<.01**	*.60*	.01**	.09	.89
Incongruent errors	57.87 (20.08)	56.22 (20.75)	48.87 (18.02)	<.01**	*.53*	<.01**	.06	.86	.46	.06†	<.01**	.32	.01**	.06	.98	.37	.11
Congruent MRT (ms)	355.82 (60.39)	339.58 (38.99)	336.25 (33.28)	<.01**	.41	<.01**	.28	0.23	.11	0.63	.28	-	-	-	-	-	-
Incongruent MRT (ms)	449.87 (56.16)	441.94 (33.44)	431.68 (40.75)	<.01**	.40	<.01**	.07	.73	.35	.07†	.44	-	-	-	-	-	-
Congruent RTV (ms)	114.26 (65.70)	83.19 (28.22)	76.24 (21.67)	<.01**	**1.00**	<.01**	*.61*	<.01**	.35	.11	<.01**	*.60*	<.01**	.42	.04*	.14	.25
Incongruent RTV (ms)	119.31 (80.64)	88.18 (32.91)	76.12 (22.84)	<.01**	**.97**	<.01**	.47	.04	*.50*	.02*	<.01**	*.55*	<.01**	.24	.18	.30	.08†
ERPs																	
N2 at Fz	-	-	-	.02	.3	.03	.0	.91	.2	.19	0.0	.2	.02	.0	.88	.2	.20

(μV)	7.23 (3.69)	6.91 (3.61)	6.57 (3.27)		0	*	2		9		3	5		1		6	
N2 at FCz (μV)	-5.8 (3.74)	-6.26 (3.57)	-6.92 (3.81)	.07	.26	.08†	.18	.53	.08	.82	0.11	-	-	-	-	-	-
ERN at FCz (μV)	7.78 (3.37)	9.64 (4.11)	10.08 (4.51)	<.01**	.55	<.01**	*.52*	.05	.06	.86	<.01**	.37	<.01**	.39	.09†	.01	.98
Pe at CPz (μV)	9.36 (4.23)	10.96 (4.06)	11.31 (4.27)	<.01**	.44	<.01**	.44	.05	.02	.88	.03	.32	.03	.36	.06†	.06	.79

Abbreviations: ADHD-P = ADHD persisters, ADHD-R = ADHD remitters, Ctrl = Control group, SD = standard deviation, p = regression model significant testing, d = Cohen's d effect size (0.20 small, 0.50 medium and 0.80 large), Congruent = congruent condition, Incongruent = incongruent condition, MRT = reaction time of correct response to targets, RTV = reaction time variability to targets (i.e. SD of reaction time).

Notes: Data on performance measures were available for the full sample (87 ADHD-P, 23 ADHD-R and 169 controls); data on the N2 were available for 84 ADHD-P, 23 ADHD-R and 169 controls; data on the PNe, ERN and Pe were available for 74 ADHD-P, 20 ADHD-R and 146 controls.

Overall effects of group, condition (on cognitive-performance measures) and site (on the N2) and interaction effects were tested with mixed models and reported in Supplement 1, Table S2. Only group effects were tested on the ERN and Pe, thus regression models (rather than mixed models) were used. Age was also included as a covariate in all analyses and its effects not presented here for simplicity, but available upon requests.

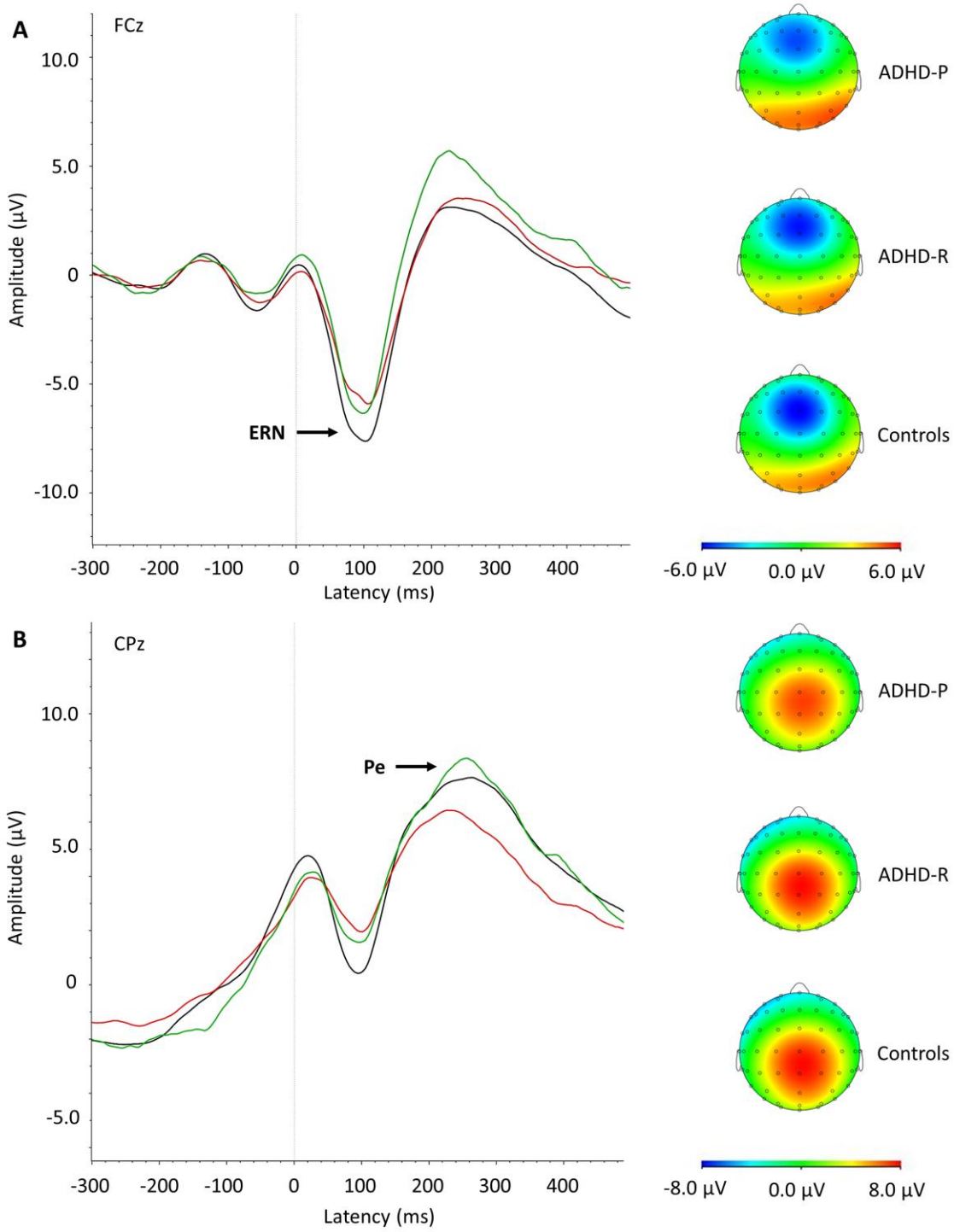
**p≤.01; *p≤.05; †p≤.09.

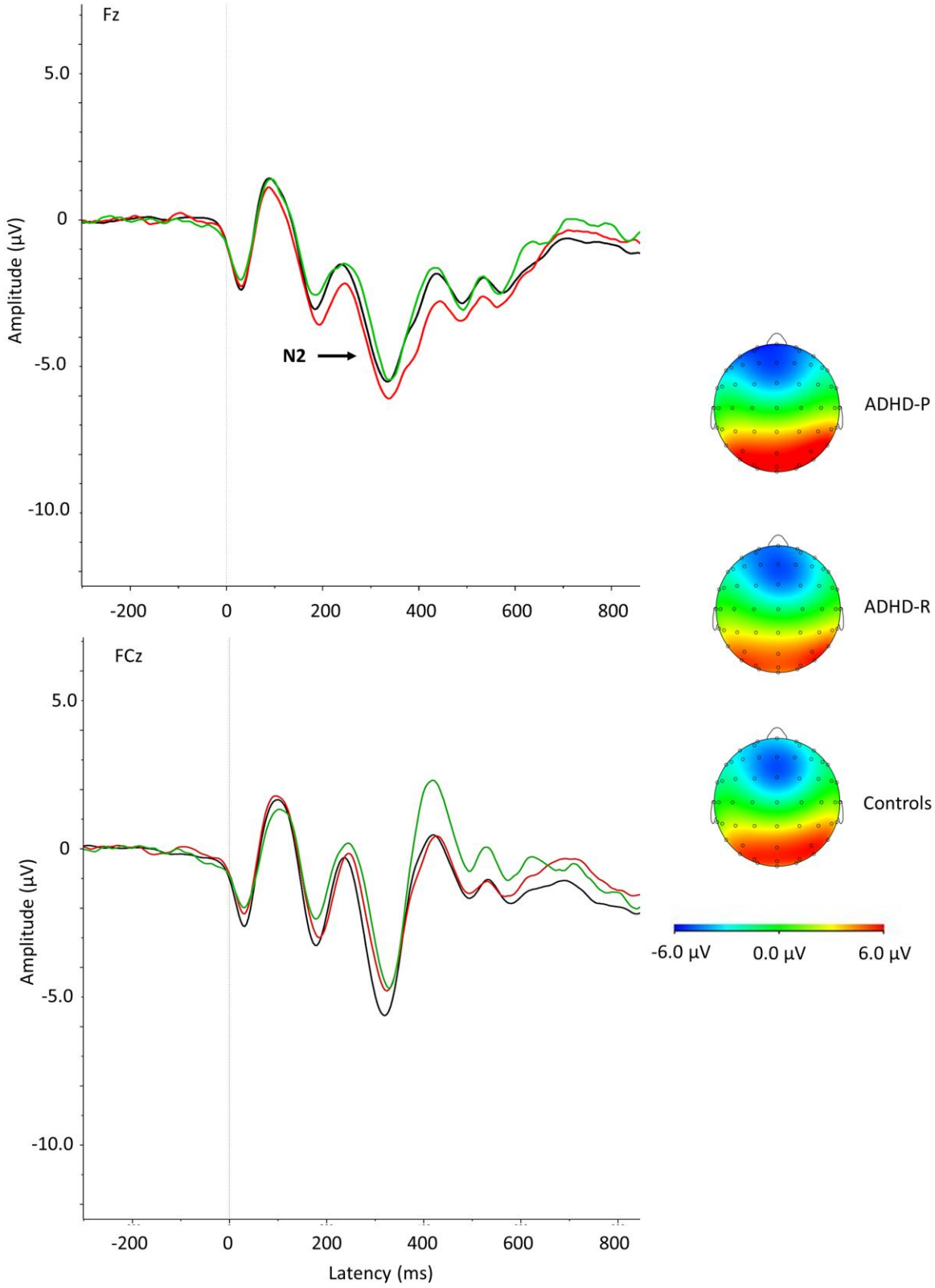
Table 3. Pearson correlations (two-tailed) of cognitive performance and ERP measures with interview-based DIVA ADHD symptoms and clinical impairment within the ADHD group only (n=110), controlling for age and gender (left hand side), and controlling for IQ, age and gender (right hand side)

	ADHD symptoms	Impairment	ADHD symptoms (covarying IQ)	Impairment (covarying IQ)
Congruent errors	0.15	0.21*	0.10	0.17†
Incongruent errors	0.07	0.03	0.05	<0.01
Congruent MRT (ms)	-0.11	0.001	0.07	-0.09
Incongruent MRT (ms)	0.05	-0.07	-0.01	0.14
Congruent RTV (ms)	0.21*	0.13	0.15	0.12
Incongruent RTV (ms)	0.21*	0.18†	0.14	0.10
N2 at Fz (μV)	0.04	0.18†	0.04	0.18†
N2 at FCz (μV)	0.07	0.12	0.10	0.15
ERN at FCz (μV)	-0.01	-0.15	0.03	-0.11
Pe at CPz (μV)	-0.20*	-0.20*	-0.20*	-0.20*

Abbreviations: Congruent = congruent condition, Incongruent = incongruent condition, MRT = reaction time of correct response to targets, RTV = reaction time variability to targets (i.e. SD of reaction time).

*p≤.05; †p≤.09.


A
FCz
10.0
5.0
0
-5.0
-10.0
Amplitude (μV)
ERN
-300
-200
-100
0
100
200
300
400
Latency (ms)
ADHD-P
ADHD-R
Controls
-6.0 μV
0.0 μV
6.0 μV
B
CPz
10.0
5.0
0
-5.0
Amplitude (μV)
Pe
-300
-200
-100
0
100
200
300
400
Latency (ms)
ADHD-P
ADHD-R
Controls
-8.0 μV
0.0 μV
8.0 μV


Fz
5.0
0
-5.0
-10.0
Amplitude (μV)
N2
-200
0
200
400
600
800
FCz
5.0
0
-5.0
-10.0
Amplitude (μV)
-200
0
200
400
600
800
Latency (ms)
ADHD-P
ADHD-R
Controls
-6.0 μV
0.0 μV
6.0 μV