Article

Indices of Heart Rate Variability and Performance During a Response-Conflict Task Are Differently Associated With ADHD and Autism

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Abstract

We investigated autonomic arousal, attention and response conflict, in ADHD and autism. Heart rate variability (HRV), and behavioral/electrophysiological indices of performance, were recorded during a task with low and high levels of response conflict in 78 children/adolescents (7–15 years old) with ADHD, autism, comorbid ADHD+autism, or neurotypical. ANOVA models were used to investigate effects of ADHD and autism, while a mediation model was tested to clarify the relationship between ADHD and slower performance. Slower and less accurate performance characterized ADHD and autism; however, atypical electrophysiological indices differently characterized these conditions. The relationship between ADHD and slower task performance was mediated by reduced HRV in response to the cue stimulus. Autonomic hypo-arousal and difficulties in mobilizing energetic resources in response to sensory information (associated with ADHD), and atypical electrophysiological indices of information processing (associated with autism), might negatively affect cognitive performance in those with ADHD+autism. *(J. of Att. Dis. XXXX; XX(X) XX-XX)*

Keywords

ADHD, autism spectrum disorders, autonomic nervous system, heart rate variability, comorbidity, response conflict

Introduction

ADHD and autism are developmental conditions that typically emerge during early childhood. While inattention and hyperactivity/impulsivity are characteristic of children with ADHD, autism is characterized by social communication and interaction difficulties, restricted and repetitive behaviors, interests, or activities (American Psychiatric Association, 2013). Autism and ADHD highly co-occur; it has been estimated that 20% to 50% of individuals with ADHD also show symptoms of autism, and 30% to 80% of those with autism show symptoms of ADHD (Rommelse et al., 2010). The neurobiological mechanisms underpinning the phenotypic overlap between these conditions are not yet known. Measuring neurocognitive functions that are similarly/differentially impaired in ADHD and autism may help identify pathways of shared risk that explain the comorbidity between them.

There are relatively few published studies comparing ADHD and autism on neuro-cognitive measures. One recent review of studies comparing executive function between ADHD and autism reported mixed findings with many areas of overlap between the two conditions (Craig et al., 2016). The review identified a slightly greater tendency for difficulties

with task-switching and conflict monitoring in autism, compared with a greater tendency for difficulties with attention and inhibitory control in ADHD. Profiles of executive functions in those with co-occurring ADHD and autism (from hereon, ADHD+autism) are unclear. Different models have been proposed to clarify how the co-occurrence of autism and ADHD might influence executive functions. Tye et al. (2014) reported that children with comorbid ADHD+autism are likely to present with atypicalities separately found in both disorders, consistent with an *additive* model of comorbidity. Rommelse et al. (2017) reported that executive function deficits are likely

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to be more severe in those with ADHD+autism, but proposed that this population might show a separate profile of atypicalities compared to those with ADHD- and autism-only, supporting an *interactive* model of comorbidity. It is unclear whether in the domain of executive functions, the additive or interactive models apply.

Arousal regulation refers to the ability to control the mechanisms that characterize wakefulness and responsivity to the environment (Lacey, 1967), and it is intrinsically linked to cognitive function via integration of autonomic and central nervous system signals (Aston-Jones & Cohen, 2005; Aston-Jones et al., 2000). More specifically, electrophysiological and autonomic processes that support orienting of attention, have been proposed to reflect the co-activation of the locus coeruleus-norepinephrine (LC-NE) and the autonomic nervous systems (Nieuwenhuis et al., 2011). Chronic states of hypo-arousal and reduced vigilance have been found in ADHD during cognitive tasks, especially when the tasks used were less engaging and more monotonous (Bellato et al., 2020). Conversely, the profile of autistic individuals is less clear and more heterogeneous, with some studies showing that cognitively demanding tasks elicit hyperarousal (e.g., increased heart rate) in autistic individuals (Guy et al., 2014; Kushki et al., 2013; Patriquin et al., 2019; Porges et al., 2013). This suggests a possible differentiation between ADHD and autism, reflecting atypical arousal regulation in both conditions, but with a greater tendency for hypo- arousal in ADHD and hyper-arousal in autism. In support of this differentiation, behavioral signs of reduced vigilance and alertness, including increased intra-individual response time variability (Kofler et al., 2013) have been found specifically associated with ADHD and not with autism (Karalunas et al., 2014). Opposite profiles of autonomic arousal, that is, hypo-arousal in ADHD and hyper-arousal in autism, might therefore contribute to slightly different atypicalities in executive functioning found in these populations.

We designed an experimental paradigm challenging motor preparation and response conflict, to investigate whether the presence of symptoms of ADHD and autism in a sample of children and adolescents, affected autonomic arousal, task performance, and electrophysiological markers. A secondary aim of the study was to determine whether autonomic arousal was related to motor preparation and inhibitory control in this task (reflected in performance and electrophysiology), and whether these relationships also differed between the clinical groups. During each trial (see paragraph "Experimental paradigm" for more details about the task), the presentation of a cue stimulus (a green or red fixation cross) was followed by a target stimulus (an arrow pointing right or left). In low-demand trials (i.e., when the fixation cross was green), participants were required to press a response button corresponding with target direction (e.g., left button in response to a left-pointing arrow).

Conversely, when the fixation cross was red (high-demand trials), the requirement was to press the button in the opposite direction of the target stimulus.

We investigated short-term fluctuations in heart rate (HR), that is, heart rate variability (HRV), a measure that mirrors the synergistic functioning of the two branches of the autonomic nervous system (ANS); the sympathetic (SNS), and the parasympathetic nervous systems (PNS). In response-conflict paradigms such as the one designed for the present study, SNS-mediated HR accelerations are expected after the onset of cue stimuli that trigger response preparation. Conversely, target stimuli that involve decision making and response initiation, are more likely to be accompanied by decelerations in HR, reflecting greater parasympathetic regulation of the ANS. Activation of frontal brain systems, in response to task-relevant sensory stimuli, have been found to predict increased cardiac decelerations, which were subsequently found associated with less variable and more accurate performance (Ribeiro & Castelo-Branco, 2019).

In a previously published systematic review (Bellato et al., 2020), we reviewed studies that investigated relationships between HRV and executive functions in ADHD in tasks like the one we used here, which challenged response inhibition, response conflict or response regulation. Although some studies did not find any differences in HRV during executive function tasks between people with ADHD and controls (see for example, Keage et al., 2006; McQuade & Breaux, 2017; Perrin et al., 2014), other studies found ADHD-specific effects which were dependent on the pace, cognitive demand or difficulty of the task. For example, Börger and van der Meere (2000) found reduced HR decelerations in anticipation of task relevant stimuli requiring a response (go-signals) in children with ADHD compared with typical controls, and delayed HR acceleration after the manual response (i.e., button press), as well as longer RTs. These effects were specific to a slow-paced condition of the go/no-go task, suggesting that a slow stimulus event-rate is more likely to challenge attention and arousal regulation in ADHD than a faster event-rate. Jennings et al. (1997) found that a group of boys with ADHD did not show any changes in HR preceding successful response inhibition during a stop signal task, unlike neurotypical controls who displayed cardiac decelerations before successfully inhibiting a motor response. Furthermore, Dykman et al. (1982) and Groen et al. (2009) found that children with ADHD displayed reduced fluctuations in HR in relation to task-relevant stimuli, when compared with controls (using a visual search task and a selective attention task, respectively). Investigating short-term HRV (i.e., HR accelerations and decelerations in relation to task-relevant stimuli) might therefore help to identify ADHD-specific atypicalities in autonomic arousal mechanisms, which might be associated with executive function difficulties in people with this condition.

To our knowledge, only two studies in autism have used an inhibitory control task (stop-signal task) and investigated associations with HRV. Kuiper et al. (2017) reported that reduced HRV was associated with worse task performance in a sample of autistic adults. Kushki et al. (2014) reported marginally elevated HR in their autistic group as compared to neurotypicals, indicating hyper-arousal at rest, which persisted throughout a battery of cognitive tasks (including the stop-signal task); although, no group differences in HRV were specifically observed during the inhibitory control task. How a profile of hyperarousal might affect specific functions of inhibitory control or conflict monitoring in autism is, therefore, unclear.

In the present study we measured changes in heart rate in relation to cue and target stimuli and manual responses, during a response-conflict paradigm, in children and adolescents with ADHD, autism, comorbid ADHD+autism, and neurotypical controls. Performance was measured by computing mean reaction times (RTs) and the percentage of correct responses; neural processes related to cue processing and response conflict processing were indexed by latency and amplitude of the N2 and the P3 ERPs; and autonomic function was indexed by HR (mean HR) and changes in the inter-beat interval in relation to stimuli and responses (HRV). We predicted HR accelerations in response to cue stimuli in neurotypical participants, and HR decelerations after the onset of target stimuli and manual responses (Hypothesis 1; H1). A profile of hypo-arousal and reduced ability to up-regulate arousal in response to task-relevant stimuli was expected in those with ADHD, reflected in longer IBIs and smaller change in IBIs in response to task-relevant stimuli when compared to those without ADHD (H2). Based on the limited previous literature in autism, it was difficult to make a strong prediction about HRV findings in those with this condition; however, we predicted to find signs of hyper-arousal (e.g., faster HR; therefore, shorter inter-beat intervals) in line with the study by Kushki et al. (2014) (H3). We also predicted slower and less accurate performance, that is, slower RTs and reduced percentage of correct responses in those with ADHD (H4) in line with previous literature (Karalunas et al., 2014); reduced P3 and N2 amplitudes in ADHD, and reduced N2 amplitude in autism (H5). Moreover, we tested whether the additive or the interactive models of comorbidities were supported by our data, by modelling both main effects of ADHD and autism and their interaction. Specifically, we tested whether children with co-occurring ADHD+autism displayed worse task performance and different atypical autonomic indices of autonomic (HRV) and electrophysiological functioning (N2 and P3 ERPs) in comparison to children with a single diagnosis (interactive model), or if they presented an additive profile of atypicalities separately present in ADHD and autism (additive model).

Methods

Recruitment and Ethical Considerations

The present work is based on data collected for the SAAND study ("Studying Attention and Arousal regulation in Neurodevelopmental Disorders"), carried out at the University of Nottingham, UK. Ethical approval for the main study was obtained from the UK National Research Ethics Committee and the Health Research Authority; written parental consent and children's assent was obtained before they took part to the study. Children between 7 and 15 years of age diagnosed with, or under clinical assessment for, ADHD and/or autism, and neurotypical children from the local community, were recruited between September 2017 and March 2019. Children receiving pharmacological treatment for ADHD with stimulants withdrew their medication for at least 24 hr before the testing session. Participants were excluded from the study if they had any neurological conditions, such as epilepsy or Tourette's syndrome; if they were on non-stimulant medication (e.g., atomoxetine, guanfacine or clonidine); if they or their parent/legal guardians were unhappy with stimulant medication being withdrawn for 24 hr; or if they did not speak fluent English. Children were not excluded if they had other mental health conditions (including anxiety, depression, oppositional defiant or conduct disorder), or intellectual disability (children with IQ < 70 were not excluded from the study).

Clinical Assessment

The evaluation of symptoms of ADHD and autism was derived from parent- and teacher-report Conners' Rating Scales (CRS-3; Conners, 2008) and Social Communication Questionnaire (SCQ; Rutter et al., 2003). The parent-report Development and Well-Being Assessment (DAWBA; Goodman et al., 2000) gave a computer-generated measure of children and adolescents' prosocial behaviors and psychopathology, including the probability of meeting diagnostic criteria for ADHD and autism. The Autism Diagnostic Observation Schedule, Second Edition (ADOS-2; Lord et al., 2012) and the Wechsler Abbreviated Scale of Intelligence (WASI-II; Wechsler, 2011) were administered to children by trained researchers, to evaluate the presence of clinical symptoms of autism and to obtain a measure of intellectual functioning, respectively. A consensus research diagnosis of autism and/or ADHD was made in consultation with two experienced child and adolescent psychiatrists (CH and PK) by using combined information from all measures presented above.

Participants were categorized (a) in the ADHD group if they had CRS-3 T-scores > 65 in either the Inattention, Hyperactivity or Global ADHD Indices, and the DAWBA reported a high probability (>75%) of meeting DSM-5 criteria for a diagnosis of ADHD; (b) in the Autism group if they had ADOS-2 Total scores > 7, indicating the presence of

Table 1. Main Socio-Demographic and Clinical Characteristics of the Sample.

	NT	ADHD-only	Autism-only	ADHD + autism	Group differences
N	21	19	14	24	—
Males/females	13/8	12/7	10/4	21/3	—
Age, years (*SD*)	11.38 (2.44)	11.01 (2.18)	10.57 (2.02)	11.03 (1.40)	None
WASI—FSIQ (*SD*)	117.81 (9.83)	107.84 (9.97)	108.93 (14.76)	104.58 (19.72)	ADHD + autism < NT
SCQ—Total score (*SD*)	3.33 (3.02)	14.53 (7.18)	17.29 (5.12)	20.8 (6.99)	NT < ADHD-only, autism-only and ADHD + autism; ADHD + autism > ADHD-only
CRS-3—ADHD Global index (*SD*)	48.38 (4.72)	89.05 (2.04)	77.71 (13.20)	86.54 (5.80)	NT < autism-only < ADHD-only and ADHD + autism
Comorbid diagnoses (*N* per group)					
°Anxiety	—	6	7	9	
°Depression	—	1	2	5	
°CD/ODD	—	12	7	16	
°Tics	—	2	1	4	

clinically significant symptoms of autism, SCQ total score > 15, and the DAWBA reported a high probability of meeting DSM-5 or ICD-10 criteria for a diagnosis of autism; (c) in the comorbid ADHD + autism group if they met research diagnostic criteria for both autism and ADHD (as defined above). Children recruited as neurotypical controls (NTs) were not included in this study if they had a family history of either ADHD or autism, if the clinical assessment showed the presence of clinically significant symptoms of ADHD (CRS-3 T-scores > 65) or autism (SCQ Total Score > 15), or elevated probability (>75%, as reported by the DAWBA) of meeting DSM-5 or ICD-10 criteria for a diagnosis of any other condition, including mood and anxiety disorders.

Sample Characteristics

A total of 106 children and adolescents were included in the final database of participants for the main study; of these, 78 completed the task we are presenting in this paper (Age: mean = 11.04 years; *SD* = 2.00 years; 56 males, 22 females). There was no difference in sample characteristics (including gender distribution, age, IQ, or symptom severity) between those who did and did not complete the testing session. Among these, 21 children were assigned to the control group of neurotypical participants; 19 children had a diagnosis of ADHD (but not autism), 14 had a diagnosis of autism (but not ADHD), while 24 met criteria for both conditions (ADHD + autism). Table 1 summarizes the main characteristics of the sample, including the number of participants displaying comorbid symptoms of anxiety, depression, conduct disorder/oppositional defiant disorder and tics, for each group.

Experimental Paradigm

We designed an adapted version of the Preparing to Overcome Prepotency task (POP; Cho et al., 2006) to investigate preparation and inhibition of motor responses and conflict monitoring in conditions with different levels of cognitive demand. Children were instructed to press the left or right button on a response box as soon as possible after the appearance of a target, a left or right arrow. In half of the trials, the cue preceding the arrow was a green fixation cross, and this indicated that the motor response required after the onset of the target stimuli should have been congruent with the arrow direction (e.g., pressing the right button in response to the right arrow; low-demand trials). In the other half of trials, the cue was a red fixation cross, indicating that the behavioral response required after target presentation should have been contralateral to the direction of the target arrow (e.g., pressing the left button if the red fixation cross was followed by a right arrow; high-demand trials).

Visual stimuli were presented in the center of a computer screen with a dark grey background: cue stimuli were presented for 1500 ms and were followed by target stimuli, which were presented for 1500 ms. While there was no temporal interval between the offset of the fixation cross and the presentation of the arrow, there was an interval of 500 ms between the offset of the target stimuli and the start of a new trial (Figure 1). The task was comprized of 8 blocks of 36 trials each (288 trials in total). Before presenting the first block of the task, detailed instructions were given to the participants, who completed 20 practice trials. At the end of every block, a 50-s break was followed by a 10-s visual countdown which indicated the re-starting of the task. Participants were told about the presence of the breaks, but they were not aware of the total duration of the task. There was a short interval between the end of the break after the fourth task block, and before the beginning of the fifth task block, during which children's comfort was monitored by the researchers.

Procedure

A 64-channel Biosemi® headcap was used to record EEG at 512 Hz. Four additional electrodes were placed around the
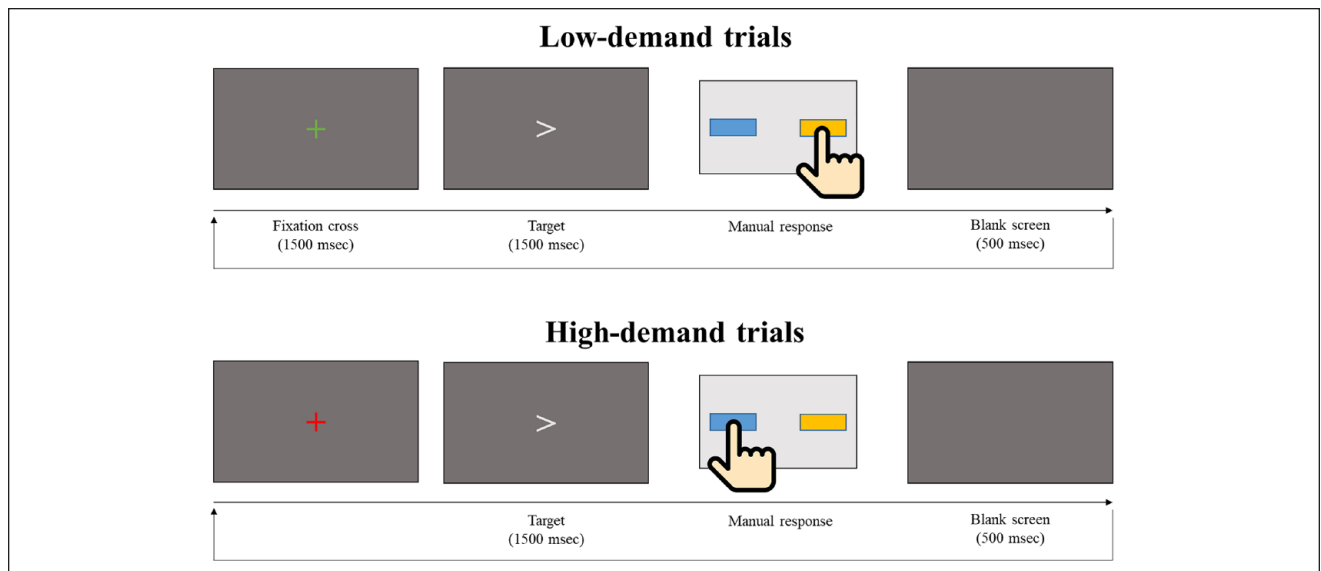
Figure 1. POP task diagram.

participant's eyes, to record vertical and horizontal eye movements, and two were positioned on the earlobes as reference. Pre-processing of EEG signal (carried out with Brainstorm; Tadel et al., 2011), included band-pass filtering (0.05–30 Hz); exclusion of bad segments, flat or extremely noisy channels; independent component analysis (ICA) and re-referencing to the average scalp signal. The EEG signal was segmented into epochs locked to the onset of the cue and the target stimuli (-200 ms; $+1500$ ms). Epochs with electrical activity outside the range $\pm 100\,\mu V$ were rejected, and single-subject ERP waveforms were extracted (cue- and target-locked, for low- and high-demand trials). The latency and amplitude of the cue- and target-locked P3 were determined by extracting the maximal positive peak in EEG signal (at electrode Pz) between 250 and 400 ms after the onset of cue- and target stimuli, while the most negative peak (at electrode FCz) in the time window 100 to 250 ms was identified to extract the latency and amplitude of the N2 in response to target stimuli.

HR signal was recorded from two electrodes placed on participants' wrists, and band-pass filtered (8–20 Hz), to reduce the baseline fluctuation of the cardiac signal and minimize the impact of artifacts or high frequency noise (Fedotov, 2016). Automatic detection of cardiac beats was carried out in Brainstorm (Tadel et al., 2011), followed by visual correction of potentially erroneous or missing peaks, before calculating the Inter-Beat Intervals (IBI), calculated as the time (in ms) between successive heartbeats.

We calculated measures of performance speed and accuracy (RTs, percentage of correct responses), and HR accelerations and decelerations with respect to the onset of the cue- and target stimuli, and manual responses. To calculate
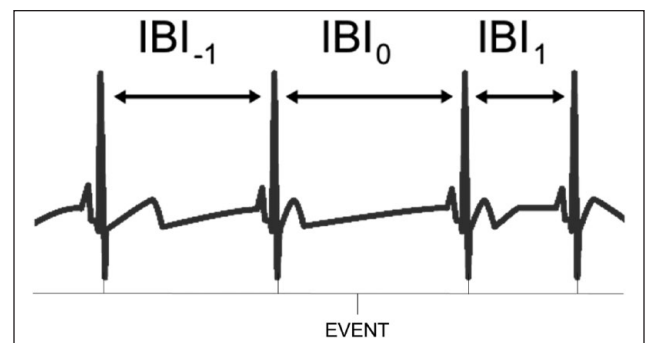

Figure 2. Visual representation of inter-beat-intervals around events' onset.

HR accelerations and decelerations in response to the three events of interest (cue-onset, target-onset, and button-press), we extracted the IBI preceding the event (IBI_{-1}), the IBI during which the event occurred (IBI_0), and the IBI following the event (IBI_1) (Figure 2).

Statistical Analyses

The effects of ADHD and autism were represented by two binomial between-subjects factors (i.e., ADHD-factor and autism-factor; 0=no; 1=yes) reflecting the presence (or not) of a diagnosis of ADHD or autism in an individual. In this way, we were able to compare children with and without ADHD (0: NT and autism-only; 1: ADHD-only and ADHD+autism) and children with or without autism (0: NT and ADHD-only; 1: autism-only and ADHD+autism) to test specific effects related to one condition or the other.

Moreover, we could investigate the impact of a comorbid clinical diagnosis of ADHD+autism (in case we found an interaction between ADHD- and autism-factors) or the profile of a specific group in comparison with the others (in case parallel main effects of both ADHD and autism were found).

The following statistical analyses were conducted in SPSS v26 (IBM). Firstly, to measure the effects of ADHD and autism on task performance, separate one-way ANOVAs were conducted on the percentage (%) of overall correct responses (an index of performance accuracy), and on mean RTs (calculated for correct trials only; an index of response speed) with ADHD and autism (each with 2-levels: yes/ no) as between-subjects factors. Secondly, to measure effects of ADHD and autism on electrophysiological markers, separate repeated measures ANOVAs were conducted on the latency and amplitude of the following ERPs: the cue-locked parietal P3, the target-locked fronto-central N2 and the target-locked parietal P3. In these ANOVAs, Cognitive Demand (2-levels; low- and high-demand) was the within-subjects factor, while ADHD and autism (2-levels: yes/ no) were the between-subjects factors. Thirdly, IBIs in relation to the cue stimuli, the target stimuli, and the manual responses, were investigated through separate repeated measures ANOVA. Each of these ANOVAs included Time (3-levels; IBI_{-1}, IBI_0, and IBI_1) and Cognitive Demand (2-levels; low- and high-demand) as the within-subjects factors; and ADHD and autism (2-levels: yes/ no) as between-subjects factors. Response accuracy (2-levels; correct and incorrect) was added as an additional within-subjects factor in the analysis of IBI in relation to the manual responses. Although it was not a primary outcome measure of the study, we also calculated average heart rate (i.e., number of beats per minute; BPM) to give further insight into general functioning of the autonomic system in the sample: reduced HR is usually interpreted as an index of hypo-arousal, while increased HR reflects hyper-arousal. A univariate ANOVA on average HR measured during the POP task was therefore carried out with ADHD and autism (2-levels: yes/ no) as between-subjects factors.

Greenhouse-Geisser adjusted degrees of freedom are reported for those variables where sphericity was violated (this was evaluated through Mauchly's tests). When significant main effects and interactions arising from these analyses were followed up with pairwise comparisons of the four groups (NTs, ADHD-only, autism-only, ADHD+autism), *p*-values were adjusted for multiple comparisons using the Benjamini-Hochberg (BH) method, which is based on the Bonferroni method but also controls for the false discovery rate (FDR), that is, the proportion of false positives which may be present among the rejected hypotheses (Benjamini & Hochberg, 1995).

Bivariate correlations between clinical symptoms (SCQ Total score; CRS-3 Global Index), ERPs (cue-P3, target-N2, and target-P3 amplitude), behavioral measures of task performance (RTs and percentage of correct responses) and IBIs (in relation to cue- and target stimuli, and in relation to manual responses); were carried out to investigate the presence of associations between autonomic arousal, attentive and cognitive mechanisms; and clinical symptoms of ADHD or autism.

Based on the results of these analyses (see paragraph "Relationships between performance, ERPs and HRV" in the "Results" section), a mediation model was tested to investigate the direct effect of ADHD on RTs (path c′), the indirect effect of ADHD on HRV fluctuations in response to cue stimuli (path a) and the indirect effect of HRV fluctuations in response to cue stimuli on RTs (path b). Confidence intervals (95%) were calculated using bias-corrected 10,000 bootstrap resampling. This analysis was carried out in JASP (JASP Team, 2020).

Results

Performance: Response Time and Accuracy

The one-way ANOVA conducted to investigate the effects of ADHD and autism on RTs revealed a significant main effect of ADHD ($F_{1,74}=4.383$; $p=.040$; $\eta^2_p=.056$) reflecting longer RTs in those with ADHD (ADHD-only and ADHD+autism; mean=894.000 ms; $SE=19.473$ ms) than those without (NT and autism-only; mean=812.763 ms; $SE=29.642$ ms). There was also a significant interaction between ADHD and autism on RTs ($F_{1,74}=5.381$; $p=.023$; $\eta^2_p=.068$). To further investigate this interaction, we compared RTs between the four diagnostic groups (NTs, ADHD-only, autism-only, ADHD+autism). As shown in Figure 3, neurotypical children had faster RTs compared to children with ADHD-only ($p=.012$; BH-corrected), children with autism-only ($p=.034$; BH-corrected), and children with ADHD+autism ($p=.003$; BH-corrected). There were no differences between children with autism-only and ADHD-only ($p=.734$; BH-corrected), between children with autism-only and ADHD+autism ($p=.877$; BH-corrected), or between children with ADHD-only and ADHD+autism ($p=.681$; BH-corrected). There was no statistically significant main effect of autism on RTs ($F_{1,74}=1.736$; $p=.192$; $\eta^2_p=.023$).

There were significant main effects of autism ($F_{1,74}=11.036$; $p=.001$; $\eta^2_p=.130$) and ADHD ($F_{1,74}=8.424$; $p=.005$; $\eta^2_p=.102$) on the percentage of correct responses, but no statistically significant interaction between ADHD and autism ($F_{1,74}=0.231$; $p=.632$; $\eta^2_p=.003$). Those with ADHD (ADHD-only and ADHD+autism; mean=71.4%; $SE=2.5$%) performed worse than those without (NTs and autism-only; mean=82.5%; $SE=2.8$%); and those with autism (autism-only and ADHD+autism; mean=70.6%; $SE=2.8$%) performed worse than those without (NTs and ADHD-only;
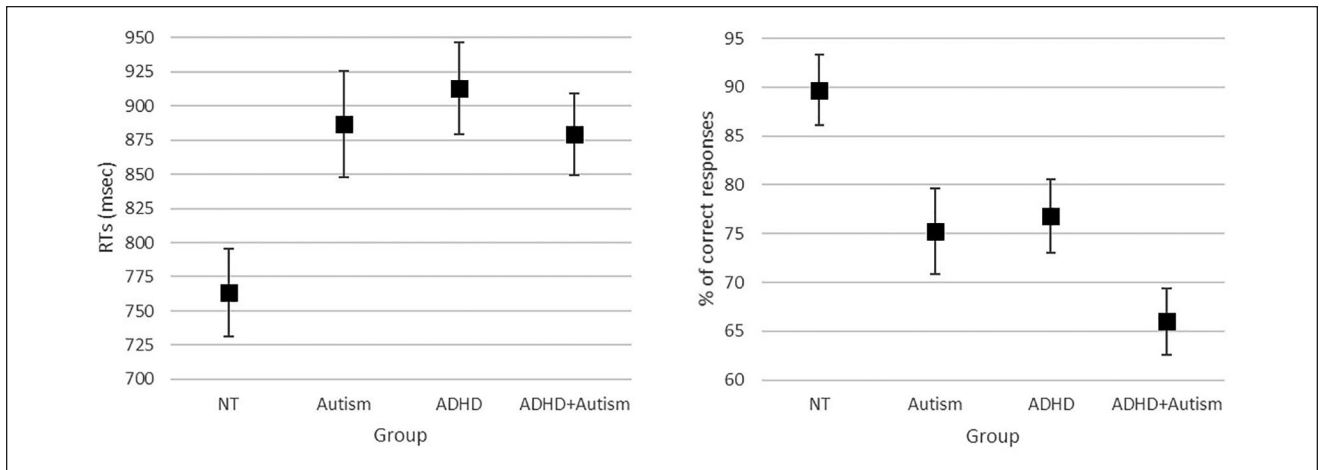
Figure 3. Comparison of average RTs (left) and percentage of correct responses (right) between the groups.
Note. Error bars indicate the *SE* of the mean.

mean = 83.3%; *SE* = 2.6%). To fully characterize these significant main effects of ADHD and autism, we conducted follow-up comparisons between the four diagnostic groups and found that neurotypical children showed better performance accuracy, reflected in increased percentage of correct responses, compared to children with ADHD-only (*p* = .032; BH-corrected), children with autism-only (*p* = .032; BH-corrected) and children with ADHD + autism (*p* < .001; BH-corrected). Children with ADHD-only showed a marginally significantly increased percentage of correct responses compared to those with ADHD + autism (*p* = .054; BH-corrected) (Figure 3). No other comparisons were statistically significant (ADHD-only vs. autism-only: *p* = .784; BH-corrected; autism-only vs. ADHD + autism: *p* = .121; BH-corrected).

ERPs

We found significant main effects of autism on cue-P3 latency ($F_{1,68}$ = 5.789; *p* = .019; η^2_p = .078), cue-P3 amplitude ($F_{1,67}$ = 11.914; *p* = .001; η^2_p = .151) and target-N2 latency ($F_{1,67}$ = 5.219; *p* = .026; η^2_p = .072) but not on target-N2 amplitude ($F_{1,67}$ = 0.001; *p* = .984; η^2_p < .001). More specifically, in children with autism (autism-only and ADHD + autism) the parietal cue-P3 peaked earlier (*M* = 334.264 ms; *SE* = 5.424 ms) and was reduced in amplitude (*M* = 2.336 μV; *SE* = 0.432 μV), compared to children without autism (NT and ADHD-only; latency: *M* = 352.697 ms; *SE* = 5.160 ms; amplitude: *M* = 4.104 μV; *SE* = 0.403 μV). Moreover, the fronto-central target-N2 had longer latencies in children with autism (*M* = 171.684 ms; *SE* = 1.721 ms) than without (*M* = 166.164 ms; *SE* = 1.620 ms). Main effects of ADHD were not statistically significant on cue-P3 latency ($F_{1,68}$ = 0.760; *p* = .386; η^2_p = .011) and amplitude ($F_{1,68}$ = 0.589; *p* = .445; η^2_p = .009), or on target-N2 latency ($F_{1,68}$ = 2.107; *p* = .151; η^2_p = .030) and

amplitude ($F_{1,68}$ = 2.246; *p* = .139; η^2_p = .032). There were no significant interactions between ADHD and autism factors on cue-P3 latency ($F_{1,68}$ = 1.139; *p* = .290; η^2_p = .016) and amplitude ($F_{1,68}$ = 0.080; *p* = .779; η^2_p = .001), on target-N2 latency ($F_{1,68}$ = 0.596; *p* = .443; η^2_p = .009) or amplitude ($F_{1,68}$ = 0.812; *p* = .371; η^2_p = .012).

Following up a marginally significant interaction Cognitive Demand * ADHD on target-N2 amplitude ($F_{1,68}$ = 3.323; *p* = .073; η^2_p = .047) showed that children with ADHD (ADHD-only and ADHD + autism) had reduced target- N2 during high-demand trials (*M* = −2.987 μV; *SE* = 0.344 μV), compared to children without ADHD (NT and autism-only: *M* = −4.043 μV; *SE* = 0.387 μV; *p* = .048). This difference was not significant for low-demand trials (*p* = .412).

Heart Rate Variability

Cue stimulus. The ANOVA investigating the effects of Time, Cognitive Demand and ADHD/autism on IBIs in relation to the cue stimulus, showed significant main effects of ADHD ($F_{1,74}$ = 4.187; *p* = .044; η^2_p = .054) and autism ($F_{1,74}$ = 5.333; *p* = .024; η^2_p = .067): those with ADHD had longer IBIs in relation to the cue stimulus (i.e., slower HR) than those without, while those with autism had shorter IBIs (i.e., faster HR) than those without (see Supplemental Material S1 for full statistics). When following these main effects with pairwise comparisons of the four groups, children with ADHD-only showed longer IBIs than children with autism-only; and marginally longer IBIs compared to children with ADHD + autism, and NT children (see Supplemental Material S1 for full results). These results are supported by findings showing that children with ADHD-only had reduced average heart rate (i.e., slower HR), compared to children with autism-only and children with ADHD + autism; and
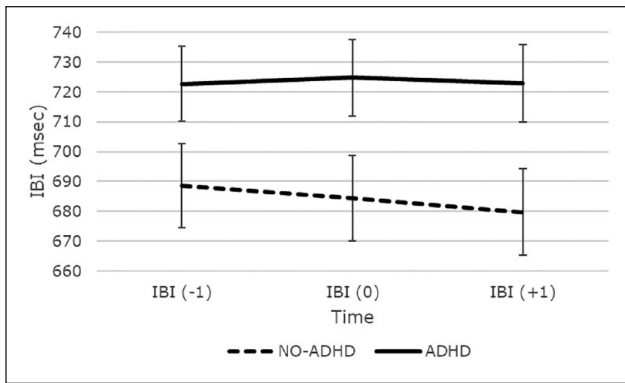
Figure 4. Mean IBI in relation to cue stimuli at different timepoints, for children with and without ADHD.
Note. Error bars indicate the *SE* of the mean.

marginally reduced heart rate than neurotypical children throughout the entire task (see Supplemental Material S2).

The ADHD*autism interaction was not statistically significant ($F_{1,74}=0.590$; $p=.445$; $\eta^2_p=.008$). There was also a significant effect of Time ($F_{1,74}=4.004$; $p=.049$; $\eta^2_p=.051$) and a significant interaction ADHD * Time ($F_{1,74}=4.399$; $p=.039$; $\eta^2_p=.056$), but not a statistically significant effect of Cognitive demand ($F_{1,74}=0.126$; $p=.724$; $\eta^2_p=.002$) or any other interactions. More specifically, while in those without ADHD (NT and autism-only) $IBI+_1$ was shorter than IBI_0 (indicating HR acceleration in response to the cue stimulus; mean difference$=4.692$ ms; $SE=1.817$ ms; $p=.012$), this effect was not present in those with ADHD (ADHD-only and ADHD+autism), who did not show any significant differences between IBI_0 and $IBI+_1$ in relation to the cue stimulus (mean difference$=1.813$ ms; $SE=1.617$ ms; $p=.266$; see Figure 4).

Target stimulus. When investigating the effects of Time, Cognitive demand and ADHD/autism on IBIs in relation to the target stimulus, we found a significant main effect of ADHD ($F_{1,74}=4.999$; $p=.028$; $\eta^2_p=.063$), and a significant main effect of autism ($F_{1,74}=4.949$; $p=.029$; $\eta^2_p=.063$), which, when further investigated, were due to longer mean IBI in those with ADHD than those without, and shorter mean IBI in those with than without autism (see Supplemental Material S1 for full statistics). The ADHD*autism interaction was not statistically significant ($F_{1,74}=0.633$; $p=.429$; $\eta^2_p=.008$).

There was also a statistically significant main effect of Time ($F_{1,74}=4.043$; $p=.048$; $\eta^2_p=.052$) but not a statistically significant effect of Cognitive demand ($F_{1,74}=1.648$; $p=.203$; $\eta^2_p=.022$) or any other interactions. IBI_0 was shorter than IBI_{-1}, indicating an acceleration in HR in the interval during which the target appeared on the screen (mean difference$=2.688$ ms; $SE=0.872$ ms; $p=.003$; $\eta^2_p=.114$). Conversely, after the target onset there was a

deceleration in HR, irrespective of the type of response required, since $IBI+_1$ was longer than IBI_0 (mean difference$=3.094$ ms; $SE=1.162$ ms; $p=.009$; $\eta^2_p=.087$).

Manual response. When analyzing IBIs in relation to the manual response, we found a marginally significant main effect of ADHD ($F_{1,74}=3.900$; $p=.052$; $\eta^2_p=.050$) and a statistically significant main effect of autism ($F_{1,74}=4.517$; $p=.037$; $\eta^2_p=.058$). When further investigating these main effects, we found that children with ADHD-only had marginally longer IBIs than those with Autism-only, ADHD+Autism and neurotypical children (see Supplemental Material S1). The ADHD*autism interaction was not statistically significant ($F_{1,74}=0.850$; $p=.360$; $\eta^2_p=.011$).

We also found a statistically significant main effect of Time ($F_{1,148}=85.181$; $p<.001$; $\eta^2_p=.535$), but not a statistically significant effect of Cognitive demand ($F_{1,74}=1.478$; $p=.228$; $\eta^2_p=.020$) or Correctness ($F_{1,74}=3.558$; $p=.063$; $\eta^2_p=.046$). IBI_0 was longer than IBI_{-1} (mean difference$=4.759$ ms; $SE=1.416$ ms; $p=.001$; $\eta^2_p=.132$) and $IBI+_1$ was longer than IBI_0 (mean difference$=21.277$ ms; $SE=2.072$ ms; $p<.001$; $\eta^2_p=.588$), indicating that the preparation and initiation of a manual response caused a deceleration in HR, irrespectively of the type of response required. There was a significant interaction ADHD * Demand on response-locked IBIs ($F_{1,74}=4.835$; $p=.031$; $\eta^2_p=.061$), such that children without ADHD (NT and autism-only) exhibited shorter IBIs (i.e., faster HR) during high-demand trials than low-demand (mean difference$=5.754$ ms; $SE=2.517$; $p=.025$; $\eta^2_p=.066$) while children with ADHD (ADHD-only and ADHD+autism) did not show any difference on IBI between low- and high-demand trials (mean difference$=1.656$ ms; $SE=2.240$; $p=.462$; $\eta^2_p=.007$) (Figure 5). No other significant interactions were found.

Relationships Between Performance, ERPs and HRV

As shown in Supplemental Material S3, we found evidence of some associations between HRV, ERPs, and RTs. Among these, we found that larger accelerations in HR after the onset of the cue stimulus were associated with shorter RTs, i.e., faster performance. Considering that children and adolescents with ADHD did not show any changes in HR in response to the cue (unlike those without ADHD, who did show HR accelerations), and showed slower performance to the task (i.e., longer RTs); we investigated through mediation analysis whether the relationship between ADHD and slower RTs was mediated by HR changes in relation to the cue stimulus (i.e., the difference between IBI_0 and $IBI+_1$). As Figure 6 shows, the coefficient for the direct effect of ADHD on RTs (path c′) was 0.369 (95% CI for 10,000
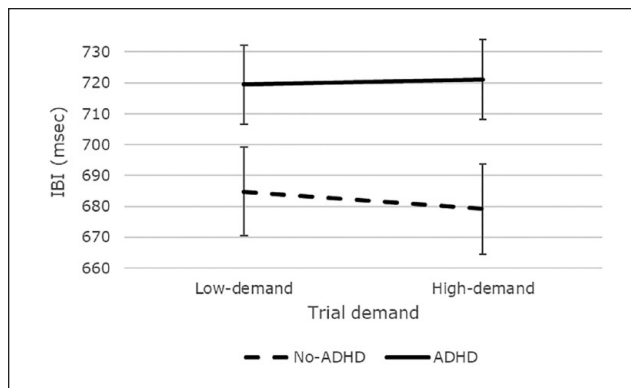
Figure 5. Mean IBI in relation to manual responses during low- and high-demand trials, for children with and without ADHD. *Note.* Error bars indicate the *SE* of the mean.
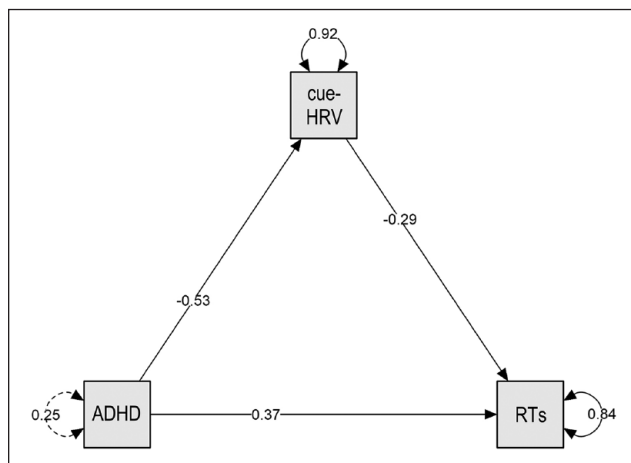

Figure 6. Model investigating the mediated relationship between ADHD, cue-related HRV and RTs (regression estimates are standardized).

bootstrapped samples = [−0.075; 0.794]), while the indirect effect was 0.154 (95% robust CI = [0.034; 0.373]), indicating that the relationship between ADHD and RTs was mediated by changes in HR after the cue stimuli onset (see Supplemental Material S4 for the full statistical output). More specifically, ADHD diagnosis predicted a reduced acceleration in HR after the onset of cue stimuli, and this predicted slower RTs.

Discussion

In the present study, we measured behavioral and electrophysiological indices of performance, and HRV in response to task-relevant stimuli, during a response conflict task; and investigated whether these indices were affected by ADHD and/or autism in a sample of children and adolescents.

We predicted HR accelerations in response to the cue stimulus, and HR decelerations after the onset of the target stimulus and the manual response (button press) (H1). This first hypothesis was supported by our results showing HR accelerations after the onset of the cue stimulus (reflected in shorter $IBI+_1$ than IBI_0). However, this effect was only significant in those without ADHD (NTs and autism-only) but non-significant in those with ADHD (ADHD-only and ADHD+autism), who did not show any changes in HR in response to the cue stimulus. In addition, and also in line with our first hypothesis, decelerations in HR were found across the entire sample after the onset of the target stimulus (reflected in longer $IBI+_1$ than $IBI-_1$), during the preparation of and after the manual response (reflected in longer $IBI+_1$ and IBI_0, compared to $IBI-_1$); irrespective of trial demand. Our findings suggest that the informative cue stimulus triggered a mobilization of energetic resources and a sympathetic nervous system reaction (HR acceleration), but not in those with ADHD. This finding is in line with our second hypothesis (H2), where we predicted to find indices of hypo-arousal and reduced ability to up-regulate arousal in response to task-relevant stimuli in children with ADHD; and with previous evidence of hypo-arousal and reduced ability to up-regulate arousal in response to task-relevant stimuli in this population (reviewed in Bellato et al., 2020). Conversely, irrespective of ADHD or autism diagnoses, the processing of the target stimulus that involved decision making and response initiation/inhibition, elicited HR decelerations which are likely to reflect PNS-driven changes in autonomic function, to facilitate the initiation of quick and correct responses. We expected to find indices of hyper-arousal in relation to autism (H3): our study confirmed this hypothesis, since we found evidence of increased HR during the task in those with autism, but not in relation to specific task-relevant stimuli.

We had predicted slower and worse performance in those with ADHD (H4), and worse task performance associated with both ADHD and autism, but with different underlying electrophysiological signatures (H5). In line with these predictions and with previous research (Karalunas et al., 2014; Kofler et al., 2013), we found that slower and less accurate performance characterized children with ADHD and autism, compared to neurotypical controls. However, children with comorbid ADHD+autism performed slightly worse than children with ADHD-only, suggesting that the co-occurring presence of ADHD and autism was related to a more severe impairment in performance accuracy, compared to a single diagnosis of ADHD. These findings therefore support both the additive model of comorbidity (children with ADHD+autism displayed a profile of atypicalities separately reported in those with either ADHD or autism; both at electrophysiological and behavioral level) and the interactive model (children with ADHD+autism had worse performance accuracy than those with ADHD-only), which do not therefore seem mutually exclusive.

We found that atypical electrophysiological indices of information processing (P3 latency and amplitude) and

conflict monitoring (N2 latency and amplitude) were differently associated with ADHD and autism, in line with our predictions (H5). However, contrary to our expectations (we had predicted to find an association between reduced P3 and ADHD) and previous findings in the literature (Tye et al., 2014), children with autism (with or without ADHD) showed reduced P3 in response to cue stimuli, indicating reduced processing of the informative cue-stimulus. In line with previous literature (Craig et al., 2016; Magnuson et al., 2019), those with autism also had a delayed fronto-central N2 in response to target stimuli, suggesting slower conflict processing. Conversely, during high-demand trials only, children with ADHD showed reduced N2 amplitude in response to target stimuli. These findings suggest difficulties in processing the conflicting stimuli in children with ADHD (Kaiser et al., 2020), which were reflected in reduced N2 but only during more cognitively demanding trials. Although the neural response to the cue stimulus was typical in those with ADHD (typical P3 amplitude and latency were found in our sample), this information might not have then been translated into an appropriate autonomic reaction (reflected in a lack of modulation of HRV and consequent atypical allocation of attentional resources to task-relevant stimuli). This is in line with what has been proposed by Nieuwenhuis et al. (2011), who theorized that anatomical overlaps and functional synchronization between electrophysiological (e.g., the P3) and autonomic processes, reflecting the co-activation of the sympathetic nervous system and the locus coeruleus-norepinephrine system (LC-NE), are essential for effective orienting of attention to task-relevant stimuli and further information processing.

Moreover, although a direct association between the amplitude of target-N2 and IBIs in relation to the target stimuli or the manual responses was not found, we found that children without ADHD showed shorter IBIs (i.e., faster HR) before, during and after the button-press, during high-demand trials than low-demand; however, children with ADHD did not show this effect. Reduced N2 and weaker up-regulation of autonomic arousal mechanisms in response to more cognitively challenging trials, might concurrently have a negative effect on task performance in those with ADHD. Although this indirect relationship was not confirmed by our results (no correlations between target-N2 amplitude and RTs, or between target-N2 amplitude and performance accuracy, were found), our secondary analysis showed that a direct relationship between ADHD and slower RTs was mediated by reduced HR acceleration to the cue-stimulus, suggesting that arousal regulation mechanisms are likely to play an important role in ADHD, and that dysregulated autonomic arousal (in the form of hypo-arousal and weak arousal regulation) might underlie executive function deficits usually found in this population. This is in line with theoretical models that proposed deficits in arousal regulation as

core contributors to cognitive deficits in ADHD (Sergeant, 2000; van der Meere et al., 2010).

The present study has some limitations. Although we were able to recruit and test 106 children and adolescents, not every child completed the POP task investigated in the present study, possibly lowering the power of the statistical analyses. The recruitment strategy adopted for the SAAND study might have caused an imbalance in the number of children with ADHD and autism referred to the study, potentially having missed a portion of children presenting less severe clinical presentations (as children were recruited from clinics) or more severe clinical profiles, for whom their parents did not consider the study suitable. Moreover, we could not include children on non-stimulants (because short-term withdrawal is not feasible and these drugs also affect cardiovascular functioning), reducing the representability and generalisability of our sample.

The results from the present study might be useful in the design of future research studies investigating arousal and attention regulation in ADHD and autism. We encourage researchers to design studies which include additional measures of autonomic arousal (such as electro-dermal activity or pupillometry) to gain a fuller understanding of these mechanisms in ADHD. The present study is in line with previous findings of reduced autonomic arousal in ADHD, especially when investigating HR and electro-dermal activity (see Bellato et al., 2020; for a review), and supports the theoretical models suggesting the presence of chronic states of hypo-arousal in people with ADHD (Sergeant, 2000; van der Meere et al., 2010). Further research is needed to understand how this profile of dysregulated arousal may impact people with ADHD in real-world settings, such as at school or in the workplace. Atypicalities in performance are likely to be similarly present in those with autism, however in this population they might be more related to atypical brain functioning (reflected in atypical N2 and P3 ERPs in the present study) and less associated with dysregulated autonomic arousal. Further research is therefore needed to specifically understand how task performance and behavioral symptoms in individuals with ADHD and autism are affected by different types of environment (e.g., where sensory stimulation is controlled), and to investigate the possibility that behaviors such as hyperactivity and restrictive and repetitive behaviors compensate for the effects of dysregulated arousal on attention, executive functioning and behavior.

Conclusion

To our knowledge, the present study has been one of the first to investigate the impact of ADHD and autism on heart-rate variability (HRV) and performance during a cued-stimulus-response task challenging response inhibition and conflict monitoring. We have demonstrated the

presence of atypicalities in stimulus-locked HRV in ADHD, reflected in a profile of reduced HRV in relation to task-relevant cue stimuli and manual responses. Importantly, we demonstrated a relationship between ADHD, reduced HRV in response to informative cue stimuli, and slower task performance. ADHD and autism were differently associated with the presence of atypicalities in electrophysiological indices of conflict monitoring and information processing. Lastly, children with comorbid ADHD+autism showed both an additive profile of behavioural and electrophysiological atypicalities reported in those with a single diagnosis but also a profile characterized by worse task performance than those with a single diagnosis of ADHD.

Author's Note

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Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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