



The reinforcing value of delay escape in attention deficit/hyperactivity disorder: An electrophysiological study

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ABSTRACT

The delay aversion hypothesis argues that the tendency for impulsive choice (preference for smaller sooner over larger later rewards) is motivated by the escape of negative affective states associated with delay. This model predicts that individuals with ADHD find the imposition of delay before an outcome or event especially aversive and its escape reinforcing. Consistent with this, fMRI studies show that ADHD is associated with amygdala hyper-sensitivity to cues of delay. However, evidence that delay escape is reinforcing is lacking. Here we extend fMRI research by using electrophysiological methods to study the reinforcing properties of delay-escape in ADHD. Thirty controls and 25 adolescents with ADHD aged 10–15 years performed the Escape Delay Incentive (EDI) task- in which pre-target cues indicated three conditions: i) CERTAIN DELAY: delay would follow a response irrespective of response speed ii) CONDITIONAL DELAY: delay would only follow if the response was too slow and iii) NO DELAY: delay would follow the response whatever the speed. We focused on the Contingent Negative Variation (CNV), a cue-evoked marker of motivated response preparation, across two time windows (CNV1 and CNV2). We took measures of parent, teacher and self-rated ADHD symptoms, task performance (RT) and self-rated delay aversion. We isolated CNV components and compared these between ADHD and controls. Adolescents with ADHD displayed a larger CNV2 to the CONDITIONAL DELAY than the CERTAIN DELAY cues compared to controls. However, this effect was not mirrored at the performance level and was unrelated to self-reported delay aversion. Our study provides the first ERP evidence that delay escape differentially reinforces neural activation of attention preparation in ADHD cases. Future studies should examine the impact of varying cognitive load on task EDI performance.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder affecting about 5% of children and adolescents (Polanczyk et al., 2015). ADHD is associated with atypical responses to emotional and motivationally significant experiences (Chronaki et al., 2015; Knutson and Greer, 2008). For instance, research has consistently shown that individuals with ADHD are especially sensitive to the imposition of a delay prior to reinforcement (Plichta et al., 2009). This leads to impulsive choice defined as the preference for small immediate over large delayed rewards (Marco et al., 2009). Alterations in different

neuro-psychological processes are likely implicated in impulsive choice in ADHD (Sonuga-Barke et al., 2016). These include exaggerated discounting of delay rewards (Marx et al., 2018) or impaired executive control which may contribute to failures to suppress responses in favor of immediacy (Olson et al., 2007; Toplak et al., 2005). According to the delay aversion hypothesis, this pattern of choice is maintained, in part, through a process of negative reinforcement – whereby the preference for immediate rewards is reinforced by escape from the negative affect experienced while waiting for the delayed reward option-which individuals with ADHD find especially aversive (Van Dessel et al., 2018). From a neurobiological perspective this model makes two core

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predictions. First, that cues signaling impending delay should activate networks of brain regions known to be associated with the coding of negative affect (e.g., amygdala, temporal pole). Second, that cues signaling that delay can be avoided through successful engagement with an attention demanding task which would activate brain networks required to mobilize attentional preparation prior to an upcoming target. Such networks include the salience (e.g., anterior insula, anterior cingulum) -which codes the motivational significance of such cues- and attention (e.g., dorsolateral frontal cortex) networks which subsequently ensure sufficient focus and motivated engagement with tasks for effective performance to occur (Holroyd and Yeung, 2012; Rossi et al., 2009).

Magnetic Resonance Imaging (fMRI) studies confirm the first prediction – that people with ADHD display amygdala hyperactivation to cues of delay (Lemiere et al., 2012; Wilbertz et al., 2013). Most recently Van Dessel et al. (2018) contrasted brain activation to three different pre-target cues in a reaction time task indicating three conditions- i) that delay would follow a response irrespective of response speed (CERTAIN DELAY) ii) that delay would only follow if the response was too slow (CONDITIONAL DELAY) and iii) that no delay would follow the response whatever the speed (NO DELAY). Results showed greater delay-related activation in amygdala and dorsolateral prefrontal cortex to CERTAIN DELAY cues relative to NO DELAY cues in ADHD - consistent with these cues being processed by individuals with ADHD as especially negatively valenced. However, these fMRI studies have not yet provided evidence to support the second part of the delay aversion hypothesis - that escape from delay is especially reinforcing in ADHD and increases brain activity within networks required for the mobilization of attentional resources to optimize response preparation. For instance, Van Dessel et al. (2018) found no evidence that CONDITIONAL DELAY cues differentially (compared to CERTAIN DELAY) activated regions within salience or attentional networks in the ADHD group.

This appears to present a conundrum - while for people with ADHD delay imposition is aversive, its escape does not appear to be reinforcing - based on fMRI data. One possibility that needs to be considered is that fMRI lacks the temporal resolution to draw the fine-grained distinctions necessary to isolate and measure the specific components of neural processes that underpin motivated response preparation and attention. Here, to address this point, we will use electrophysiology to isolate one such component the Contingent Negative Variation (CNV; Gómez et al., 2007) known to be central to effective response preparation. This is a slow negative brain potential elicited by an informative cue which signals the onset of an imperative stimulus requiring the participants' attention and response (Walter et al., 1964). The CNV reflects anticipatory attention and effortful processing. It is comprised of two sub-components, an early wave related to the alerting properties of the warning stimulus and a later component related to anticipatory motor response preparation in thalamo-cortico-striatal networks (Brunia et al., 2012) and therefore reflects the motivational salience of the upcoming stimuli (Novak and Foti, 2015). Goldstein et al. (2006) have observed the CNV in two time windows: CNV1 (600 to 800 ms) and CNV2 (1300 to 1500 ms) after the onset of a warning stimulus in a reaction-time paradigm with monetary rewards in 16 young healthy participants. Similarly, Ortega et al. (2013) have measured the cue CNV from 200 ms before the cue to 1400 ms after the cue in a visual-spatial attention task in 10-year old children with ADHD. Previously we have shown that the CNV is enhanced to CONDITIONAL DELAY compared to CERTAIN DELAY cues (Broyd et al., 2012a) and that this effect is correlated with normal variation in ADHD symptoms (i.e., individuals with more ADHD symptoms show greater CNV response to CONDITIONAL DELAY cues). The above study employed a general population adolescent sample, although the sample was enriched with two patients with a clinical diagnosis of ADHD who were recruited through a clinic.

In the current paper, we extended this analysis to test whether the

Table 1
Sample characteristics.

	ADHD		Controls		Comparison	
	Mean	S.D.	Mean	S.D.	t	p value
Child age (years)	11.50	1.40	12.80	1.20	-2.90	0.006
Full scale IQ	96.20	12.60	108.65	11.90	-3.10	0.003
SDQ self-report						
ADHD symptoms	6.60	1.60	2.90	2.00	5.50	< 0.001
Conduct problems	4.90	1.60	1.50	0.90	8.30	< 0.001
SDQ teacher-report						
ADHD symptoms	4.80	2.30	1.70	1.80	3.20	0.004
Conduct problems	0.50	0.80	0.15	0.50	1.20	0.20
SDQ parent-report						
ADHD symptoms	8.80	1.60	2.30	2.30	9.00	< 0.001
Conduct problems	6.10	2.30	1.50	2.15	6.30	< 0.001
ADHD parent-report						
Inattention	21.80	4.80	5.50	4.90	10.10	< 0.001
Hyperactivity-impulsivity	21.70	4.40	5.70	4.40	10.90	< 0.001
Quick delay questionnaire						
Delay aversion	3.45	0.90	2.60	0.80	2.90	0.006
Delay discounting	2.70	0.70	2.00	2.10	2.90	0.007

Note: ADHD Parent-report as measured by DISC-IV. For teacher-SDQ, data were available from 14 controls and 8 adolescents with ADHD. For all other measures, data were available from 28 controls and 15 adolescents with ADHD. 'ADHD symptoms' refer to the hyperactivity subscale of the SDQ assessing hyperactivity and inattention.

CNV of children with a clinical diagnosis of ADHD was differentially activated by CONDITIONAL DELAY compared to CERTAIN DELAY more than for typically developing controls. This provided the first electrophysiological test of the second prediction of the delay aversion hypothesis - that cues signaling the possibility of delay escape are especially negatively reinforcing in ADHD. We predicted that this effect (the CNV difference between the two cue conditions) would be correlated with task performance and self-ratings of delay aversion.

2. Methods

2.1. Participants

Thirty typically developing adolescents (11 girls) and 25 adolescents with ADHD (4 girls), aged 10–15 years were recruited (see Table 1 and Table S1). From the 25 adolescents with ADHD, two adolescents with ADHD dropped out, one was excluded due to a technical error and two were taking atomoxetine (Strattera) and were therefore excluded. Informed written consent was obtained from parents. Written assent was also obtained from adolescents. Adolescents with ADHD were recruited from local child and adolescent mental health clinics and all had a clinical diagnosis of ADHD. Controls were recruited from local schools.

2.2. Materials, inclusion and exclusion criteria

Participants undertook a comprehensive clinical research assessment as part of the South Hampshire ADHD Register (SHARe). This included the ADHD section of the parent version of the Diagnostic Interview Schedule for Children-NIMH-DISC-IV (Shaffer et al., 1993) and the self-report, parent and teacher versions of the Strengths and Difficulties Questionnaire-SDQ (Goodman, 1997). Participants completed the self-report Quick Delay Questionnaire (QDQ) including a five-item scale measuring subjective ratings of delay aversion in everyday life (e.g., 'I hate waiting for things'). The QDQ has good internal and test-retest reliability in older adolescents (Clare et al., 2010) and good internal reliability in children with and without ADHD (Hsu et al., 2015). Internal reliability of the delay aversion subscale in the current study was reasonable (Cronbach's alpha = 0.65). Full scale IQ was assessed using the Wechsler Intelligence Scale for Children; WISC-IV

(Wechsler, 2004). Adolescents with ADHD were only included if they met criteria for ADHD on the DISC-IV including manifestation of ADHD symptoms in multiple settings (home and school). Control adolescents completed the same measures as the participants with ADHD apart from the DISC-IV. They also only completed the Block Design and Vocabulary subtests of the WISC-IV. For both groups, WISC-IV Full Scale IQ was estimated based on the scores of the Block Design and Vocabulary subtests (Sattler, 2001). General exclusion criteria were IQ < 75 and diagnosis of autism spectrum disorder or a neurological condition. In addition, one control child was excluded as they scored above borderline thresholds on the hyperactivity subscales of the SDQ-parent report assessing hyperactivity and inattention. All participants with ADHD scored above borderline thresholds on the hyperactivity subscales of the SDQ-parent report and SDQ-teacher report. For teacher report-SDQ, data were available from 14 controls and 8 adolescents with ADHD only, therefore, only parent report-SDQ data were included in analyses. Two adolescents with ADHD also had a DISC-IV Conduct Disorder diagnosis and 8 were taking stimulant medication. Specifically, all 8 were taking different formulations of methylphenidate - five children were taking Ritalin, two children were taking Concerta and one child was taking Equasym. These participants were asked to withdraw their medication 24 h prior to testing (5 half-lives). The two groups were not matched on IQ, age and gender at the time of recruitment. The study was approved by the University of Southampton Ethics Committee and National Health Service (NHS) Research Ethics Committee.

2.3. Experimental paradigm and procedure

Participants performed the electrophysiological Escape Delay Incentive (EDI; Broyd et al., 2012a) task (see Fig. 1). At the start of each trial, participants saw one of three blue cue stimuli followed by the target (a white star). Participants were instructed to respond to the target as quickly as possible via a button box key. Feedback included a green tick for 'fast enough' response and a red cross for a 'too slow' response. The task included an algorithm which tracked each participant's response on a trial-by-trial basis and adjusted the response window for a 'fast enough' response so that all participants received positive feedback, based on their own performance, on 66% of trials. Three trial types were presented with equal probability and in random order. First, in the CERTAIN DELAY condition (signaled by a blue circle

cue) participants were told that although they would receive feedback about the speed of their response (positive feedback for a fast response and negative feedback for a slow response), they would experience a delay period after their response on every trial irrespective of the speed of their performance. In the CONDITIONAL DELAY condition (signaled by a blue triangle cue) participants were informed that a fast response would receive positive feedback and allow them to progress directly to the next trial and escape any post response delay, while a slow response would receive negative feedback and be followed by delay. The delay period was signaled by a bar presented centrally on the computer monitor that disappeared a little at a time. The delay stimulus appeared on screen for a variable duration of between 8 and 10 s with a 1 s inter-trial interval. Two practice blocks were completed prior to the experimental blocks to allow participants to learn the association between each cue and experimental condition. In the NO DELAY condition (signaled by a blue square cue) participants were informed that although they would receive feedback about the speed of their response (positive feedback for a fast response and negative feedback for a slow response), they would experience no delay after their response. There were 30 practice trials in total. Participants completed 3 blocks for the main task. Each experimental block consisted of 20 presentations of the three conditions.

2.4. EEG recording and pre-processing

We used an electrode cap (Easycap, Herrsching, Germany) containing 52 equidistantly spaced silver/silver chloride (Ag/AgCl) electrodes. EEG data was recorded using Neuroscan Synamps2 70 channel EEG system, DC-coupled recording equipment. The data were sampled at 500 Hz with a low pass filter at 70 Hz and referenced to an electrode on the nose. A ground electrode was fitted midway between the electrode at the vertex and frontal sites. Vertical electro-oculogram (vEOG) was recorded from four electrodes: two bipolar electrodes beneath the left and right eyes and two placed above the right and left eye. Impedances were kept below 5 k Ω . The data were high pass filtered at 0.2 Hz and lowpass filtered at 15 Hz offline. Data pre-processing was done in Neuroscan (Scan 4.5). For *cue-locked* ERP analyses, epochs were locked to the onset of the *cue stimuli* and were extracted from -200 to +1800 ms. Baselines were calculated in the -200 to 0 ms relative to the onset of the *cue stimuli*. Epochs locked to the *feedback* were also

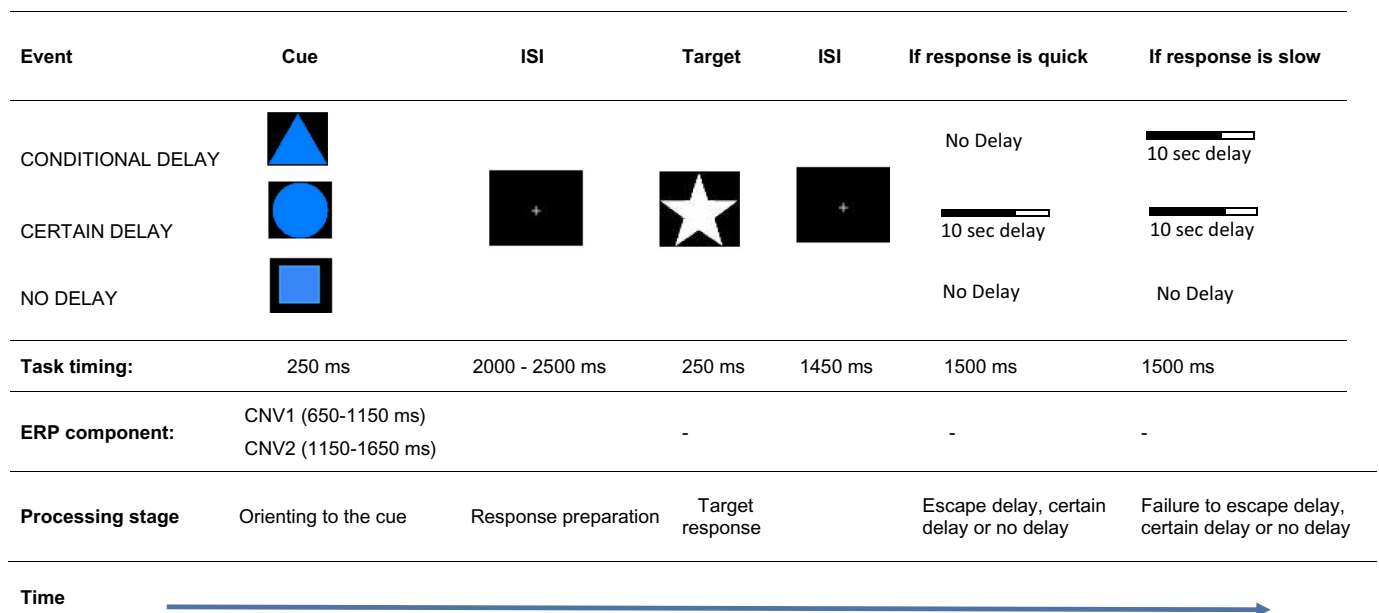


Fig. 1. Timing and ERP components of the Electrophysiological Delay Incentive (EDI) task. The cue and target were each presented for 250 ms. The ISI varied randomly between 2000 and 2500 ms. The feedback stimuli were presented for 1500 ms and appeared on screen 1450 ms following the offset of the target stimulus.

extracted – however, due to the low number of clean epochs per subject, the feedback trials were omitted from further analysis. Epochs containing data points above or below $\pm 150 \mu\text{V}$, or with eye-movements as determined based on vEOG channels, were rejected. An ocular artifact reduction procedure (Semlitsch et al., 1986) based on left eye vEOG activity was used to remove blink artifacts and other eye-movements from the ERP data. Individual ERP averages were based on a minimum of 20 trials per condition. The number of artifact-free trials was as follows: Cue: Controls: CONDITIONAL DELAY: $M = 50$, $SD = 9.38$, CERTAIN DELAY: $M = 51.30$, $SD = 0.8.00$, NO DELAY: $M = 51.30$, $SD = 8.08$, ADHD: CONDITIONAL DELAY: $M = 40.00$, $SD = 10.10$, CERTAIN DELAY: $M = 40.70$, $SD = 11.80$, NO DELAY: $M = 38.20$, $SD = 10.90$. There was no difference in the number of artifact-free trials between conditions ($p > .20$). There were fewer artifact-free epochs for adolescents with ADHD than controls ($p < .01$). Based on these criteria, five adolescents with ADHD and two controls were excluded, leaving 15 adolescents with ADHD and 28 controls in final analyses. A baseline-to-peak mean amplitude method was used to calculate the CNV (Handy, 2005). Peaks were confirmed by visual inspection and clearly visible in all individual waveforms. Following the cue, a CNV component was quantified in two separate time windows corresponding to the two CNV sub-components (CNV1: 650–1150 ms and CNV2: 1150–1650 ms at centro-parietal sites 1, 2, 3, 4, 5, 6, 7, 12, 13 and 14; see Fig. S1). These time windows were consistent with previous research (Goldstein et al., 2006). Although we observed a difference between 400 and 600 ms, which seemed to have larger amplitudes to certain delay compared to conditional and no delay, we purposefully focused on the CNV in the present study because this component was directly linked our theoretical predictions of the delay aversion hypothesis. Frontal sites were affected by extensive eye blinks and not included in analyses.

2.5. Data analysis

Repeated measures ANOVAs tested the effects of group as a between-subjects factor and condition (CONDITIONAL DELAY, CERTAIN DELAY, NO DELAY) as a within-subjects factor on mean reaction time (MRT), SD of RT and Cue CNV. As CNV mean amplitude was examined in two time windows, CNV1 and CNV2, we included these levels within a time window factor in analyses, based on prior research (Broyd et al., 2012a). Where time window interacted with condition, time window was retained as a factor in analyses. We conducted planned comparisons of the CONDITIONAL DELAY condition against the CERTAIN DELAY as this related to our main prediction. RT data were trimmed to remove responses, which were faster than 150 milliseconds and exceeded ± 2.5 SD around the mean response time. For consistency, the behavioural analyses included the same participants as the ERP analyses - 28 controls (11 girls) and 15 ADHD (3 girls) adolescents' data were included after excluding outliers. Pearson's correlations examined the relationship between the effects of cue type on CNV and both performance and QDQ delay aversion scores. We also calculated a difference score by subtracting performance (MRT and SDRT) and CNVs on NO DELAY trials from that on CONDITIONAL DELAY trials. As the groups differed in IQ, conduct problems and age we first examined whether these characteristics were correlated with task performance or CNV amplitude. Where they were we included them as covariates in analyses.

3. Results

3.1. Task performance

There was no correlation between IQ, conduct problems and age and either RT ($ps > 0.06$) or SDRT ($ps > 0.20$). These variables were therefore not entered as covariates into analyses. Table 2 presents RT and SD of RT data per group and condition. When MRT was the

Table 2

Mean reaction time (MRT) and SD of reaction time in the two groups.

	ADHD		Controls	
	Mean	S.D.	Mean	S.D.
MRT (ms)				
Conditional delay	343.40	65.70	325.30	56.00
Certain delay	347.15	67.90	331.60	55.40
No delay	357.90	68.64	329.60	55.00
SD of RT (ms)				
Conditional delay	113.60	44.80	92.00	54.70
Certain delay	113.90	59.60	97.90	46.90
No delay	128.70	66.60	98.30	47.80

dependent variable there was no overall significant effect of condition ($F(2, 80) = 2.10$, $p = .12$, $\eta_p^2 = 0.05$) or group ($F(1, 40) = 1.20$, $p = .27$, $\eta_p^2 = 0.03$) and no significant group \times condition interaction effect on RT ($F(2, 80) = 1.35$, $p = .26$, $\eta_p^2 = 0.03$). The same was true for SD of RT ($F^{condition}(2, 80) = 1.10$, $p = .30$, $\eta_p^2 = 0.02$; $F^{group}(1, 40) = 2.35$, $p = .13$, $\eta_p^2 = 0.06$; $F^{interaction}(2, 80) = 0.48$, $p = .60$, $\eta_p^2 = 0.01$).

3.2. CNV

IQ, conduct problems and age were not correlated with CNV amplitude ($ps > 0.05$). Therefore, these variables were not included as covariates in the analysis. Grand mean averages are displayed in Fig. 2 alongside bar charts showing the group and condition effects on Cue-CNV1 and Cue-CNV2. The effect of group was not significant ($F(1, 41) = 1.06$, $p = .30$, $\eta_p^2 = 0.02$). There was a significant effect of time window on CNV amplitude ($F(1, 41) = 5.10$, $p = .03$, $\eta_p^2 = 0.11$), with larger CNV amplitude in the second compared to the first time window. Although the overall effect of condition was not significant ($F(2, 82) = 0.60$, $p = .54$, $\eta_p^2 = 0.01$), there was a significant condition \times time window interaction effect on CNV amplitude ($F(2, 82) = 3.80$, $p = .026$, $\eta_p^2 = 0.08$), with larger CNV amplitude for CONDITIONAL DELAY compared to NO DELAY in the second time window ($F(1, 41) = 8.05$, $p = .007$, $\eta_p^2 = 0.16$). There was no overall effect of group ($F(1, 41) = 1.06$, $p = .30$, $\eta_p^2 = 0.02$) and no two-way interaction between group and condition overall ($F(2, 82) = 0.47$, $p = .62$, $\eta_p^2 = 0.01$). There was, however, a significant group \times condition \times time window interaction ($F(2, 82) = 3.70$, $p = .028$, $\eta_p^2 = 0.08$). The planned contrasts revealed a larger CNV to the CONDITIONAL DELAY than the CERTAIN DELAY cues ($F(1, 41) = 5.60$, $p = .020$, $\eta_p^2 = 0.12$) in the ADHD but not the control group for CNV2. When a Bonferroni correction was applied with an alpha level of $0.05/2 = 0.02$ adopted, this effect remained significant. When we conducted a one-way ANOVA comparing the effect of condition on the CNV2 separately for the ADHD group and controls, effects were not significant (all $ps > 0.05$). A similar effect was seen for CNV1, but this did not reach significance ($F(1, 41) = 3.47$, $p = .070$, $\eta_p^2 = 0.07$).

3.3. Correlations between CNV and performance

MRT across conditions was correlated with CNV2 across conditions in the whole sample ($r = 0.34$, $p = .027$). This correlation was significant in the control ($r = 0.38$, $p = .048$) but not the ADHD group ($r = 0.24$; $p = .38$). Further, the overall effect was significant in the CONDITIONAL DELAY condition ($r = 0.40$, $p = .01$) but not in the CERTAIN DELAY ($r = 0.24$, $p = .12$) or the NO DELAY ($r = 0.22$, $p = .15$) condition in the whole sample. Correlations between MRT and CNV2 for each condition separately were not significant for the ADHD ($r < 0.40$, $p > .10$) or control ($r < 0.35$, $p > .07$) group. There was no relationship between CNV2 and SD of RT except for an overall significant correlation with CNV2 in the CERTAIN DELAY condition ($r = 0.44$, $p = .03$).

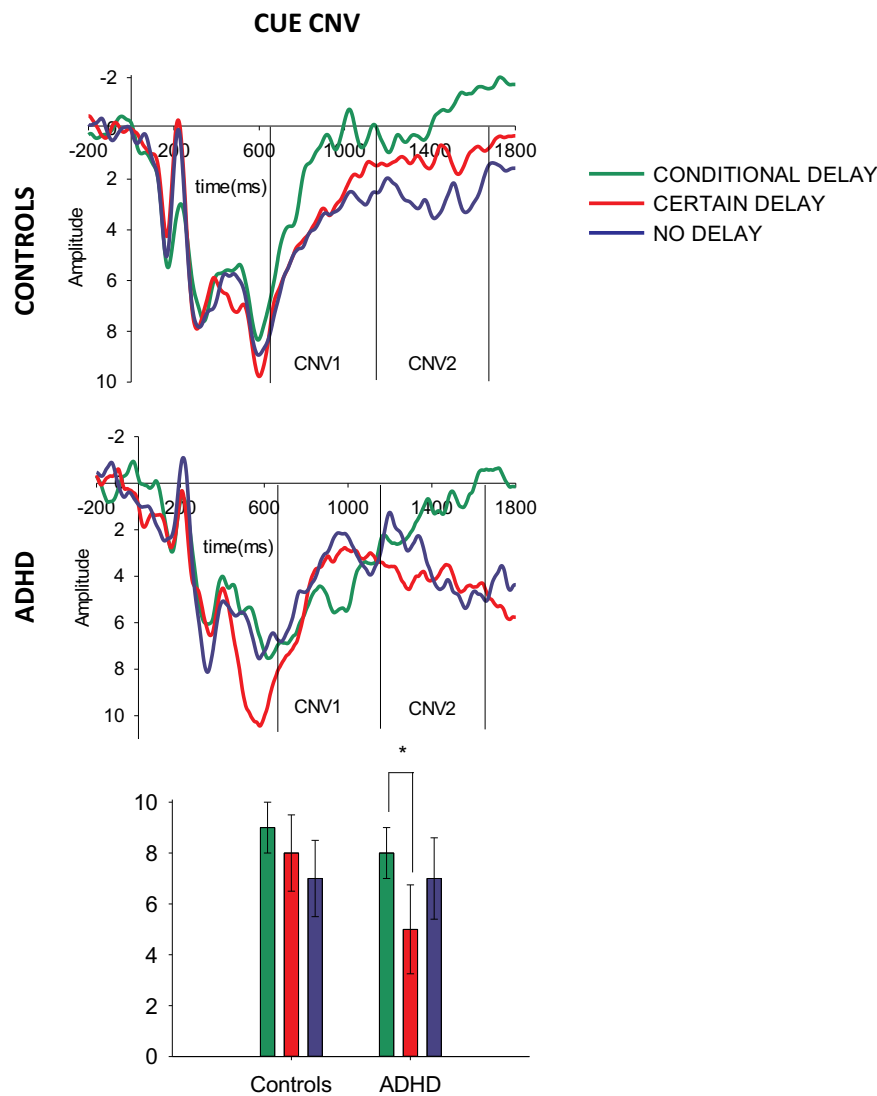


Fig. 2. Grand mean averages and bar graphs with error bars for the CNV per condition in the ADHD and controls group. Amplitude (μV) is shown on the y axis and time (ms) on the x-axis. The bar graphs plot the ERPs in an adjusted positive scale to capture the amount of the amplitude change. Error bars represent standard error of the mean. Group \times Condition interaction with larger amplitude to conditional delay vs. certain delay in ADHD relative to controls for the CNV2 ($p < .05$). The bar graphs show the conditional delay in green, the certain delay in red and the no delay condition in blue.

3.4. Correlations between CNV and delay aversion

Individuals with ADHD rated themselves significantly more delay averse than controls on the QDQ delay aversion scale (see Table 1). In the whole sample there was a trend for delay aversion scores to be correlated with the amplitude difference score (NO DELAY minus CONDITIONAL DELAY) for CNV1 ($r = 0.30$, $p = .058$) but not CNV2 ($p = .12$, $p = .45$). When running these correlations separately for the ADHD and control group, correlations were not significant in the ADHD group ($p > .45$) and delay aversion tended to correlate with CNV1 in the control group ($r = 0.38$, $p = .056$).

4. Discussion

We used electrophysiology to test a prediction from the delay aversion hypothesis: That cues signaling a contingency between task performance and escape from delay would differentially activate neural components known to be associated with response preparation (i.e. cue CNV) in individuals with ADHD. There were several findings of note.

First, the CNV was sensitive to experimental manipulation. As predicted, and previously found, amplitudes were larger to CONDITIONAL

DELAY compared to NO DELAY cues. This finding supports the notion that in general delay escape negatively reinforces adolescent response preparation at the neural level in adolescents (Broyd et al., 2012a). More generally the findings add to recent evidence of enhanced CNV amplitude in response to monetary reinforcement in adolescents using a similar paradigm (Chronaki et al., 2017)- supporting cue-CNV amplitude as a marker of the motivational salience on performance contingent outcomes. They also highlight the value of combining the spatial resolution of fMRI analyses and the temporal resolution of EEG in studies of the neural basis of reinforcement. While previous fMRI studies using variants of Monetary Incentive Delay (MID) tasks have been successful in linking reward cues to ventral striatal activity (Plichta and Scheres, 2014; van Hulst et al., 2015) and delay cues to amygdala activity (Van Dessel et al., 2018) - these studies have failed to link these effects to increased engagement of attentional networks during motivated task engagement.

Second, consistent with the predictions of the delay aversion hypothesis, we found that this enhancement of CNV amplitude in the CONDITIONAL DELAY condition was greater for individuals with ADHD than controls. This provides some of the first evidence showing that, at the neural level at least, escape from delay has greater power as

a negative reinforcer in ADHD compared to controls. Although the effect of group was not significant, there was a significant three-way interaction in our study, suggesting that the interaction among group and condition was different across the two time windows of the CNV. Interestingly, this effect was specific to the second-time window of the CNV. Previous work has suggested an alerting role for the early subcomponent of the CNV and a stronger preparatory role for the later subcomponent (Loveless and Sanford, 1974; Van Boxtel and Böcker, 2004). This finding is consistent with previous research showing that ADHD symptoms measured in a non-clinical sample were associated with larger CNV differences to CONDITIONAL DELAY cues in a community sample of 15-year-olds (Broyd et al., 2012a). Most importantly, it helps resolve the conundrum that ADHD individuals find the imposition of delay aversive - but don't seem to find escape from delay reinforcing. In this way it complements the Van Dessel et al. (2018) finding that amygdala is differentially hyperactivated to CERTAIN DELAY cues in ADHD - but with no evidence of activation to cues indicating the possible escape delay in attention networks, known to be associated with the CNV (Gómez et al., 2007). This is presumably because of the limited methodology as dynamic changes in brain activity in the millisecond range involved in response preparation cannot be measured with fMRI.

Third, experimental effects at the neural levels were not mirrored at performance level. First, individuals with ADHD did not display longer reaction times and greater reaction time variability. This appears to contradict a large body of ADHD literature showing deficits in RT studies. Second, there was no evidence that performance was enhanced in the CONDITIONAL DELAY condition in ADHD as would be expected given enhanced CNV activation in that condition. In prior studies using MID-based protocols little attention is paid to performance data - partly because the task itself is not sufficiently demanding to probe the boundaries of an individual's competence (Broyd et al., 2012b; Chronaki et al., 2017). This also possibly explains the lack of group effects as in prior studies. ADHD RT deficits are increased under demanding and effortful task conditions (Carte et al., 1996; Nigg, 2011). We did find a link between CNV amplitude and performance for CONDITIONAL DELAY - with faster RTs linked to the size of CNV increase across groups - however, against expectation this effect was greater in the control compared to the ADHD group. In future it would be interesting to examine the impact of varying cognitive load on EDI task performance.

Finally, there was no evidence that the differentially greater CNV to CONDITIONAL DELAY cues seen in ADHD was related to individual differences in self-reported delay aversion. In line with the general pathophysiological heterogeneity of ADHD - not all individuals with ADHD are delay averse. We examined variations in this trait by using the QDQ. Our prediction was that the CONDITIONAL DELAY versus CERTAIN DELAY difference in CNV would be related directly to delay aversion. One possibility is that our manipulation of the contingency between performance and delay outcomes was, in fact, picking up a more general reinforcement related effect on neural activity - rather than one specific to ADHD. This will need to be explored in subsequent experiments using negative outcomes other than delay imposition (e.g., monetary loss).

Our study provided the first ERP evidence that delay escape differentially reinforces neural activation of attention preparation in carefully diagnosed ADHD cases. However, there were some limitations to consider when interpreting the results. First, the sample size was relatively small, and the findings need to be replicated in larger samples. Second, the task was not optimized to study feedback-related processes because of insufficient numbers of artifact-free trials. Third, we were not able to test the impact of different amount of delay in the neural responses to certain delay cues. Finally, we had to exclude some cases because of movement and other artifacts. This is inevitable, but it is possible that the severe cases were lost to analysis. The number of cases excluded from analyses is consistent with other ERP studies in

children with ADHD (Baijot et al., 2017; Chronaki et al., 2015; Chronaki et al., 2017).

In summary, we provide the first electrophysiological evidence supporting the motivational power of delay escape in ADHD - consistent with the delay aversion hypothesis (Sonuga-Barke, 1994). More specifically the CNV was differentially enhanced to cues indicating a contingency between performance and whether delay can be escaped or not. EEG paradigms can complement fMRI studies of the neural basis of reinforcement generally and delay aversion more specifically.

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Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.nicl.2019.101917>.

References

- Baijot, S., Cevallos, C., Zarka, D., Leroy, A., Slama, H., Colin, C., ... Cheron, G., 2017. EEG dynamics of a go/nogo task in children with ADHD. *Brain Sci.* 7 (12), 167. <https://doi.org/10.3390/brainsci7120167>.
- Broyd, S.J., Richards, H.J., Helps, S.K., Chronaki, G., Bamford, S., Sonuga-Barke, E.J.S., 2012a. Electrophysiological markers of the motivational salience of delay imposition and escape. *Neuropsychologia* 50 (5), 965–972. <https://doi.org/10.1016/j.neuropsychologia.2012.02.003>.
- Broyd, S.J., Richards, H.J., Helps, S.K., Chronaki, G., Bamford, S., Sonuga-Barke, E.J.S., 2012b. An electrophysiological monetary incentive delay (e-MID) task: a way to decompose the different components of neural response to positive and negative monetary reinforcement. *J. Neurosci. Methods* 209 (1), 40–49. <https://doi.org/10.1016/j.jneumeth.2012.05.015>.
- Brunia, C., van Boxtel, G., Böcker, K., 2012. Negative slow waves as indices of anticipation: the Bereitschaftspotential, the contingent negative variation, and the stimulus-preceding negativity. In: *The Oxford Handbook of Event-related Potential Components*. Oxford University Press, Oxford, pp. 189–207.
- Carte, E.T., Nigg, J.T., Hinshaw, S.P., 1996. Neuropsychological functioning, motor speed, and language processing in boys with and without ADHD. *J. Abnorm. Child Psychol.* 24 (4), 481–498. <https://doi.org/10.1007/BF01441570>.
- Chronaki, G., Benikos, N., Fairchild, G., Sonuga-Barke, E.J.S., 2015. Atypical neural responses to vocal anger in attention-deficit/hyperactivity disorder. *J. Child Psychol. Psychiatry* 56 (4), 477–487. <https://doi.org/10.1111/jcpp.12312>.
- Chronaki, G., Soltesz, F., Benikos, N., Sonuga-Barke, E.J.S., 2017. An electrophysiological investigation of reinforcement effects in attention deficit/hyperactivity disorder: dissociating cue sensitivity from down-stream effects on target engagement and performance. *Dev. Cogn. Neurosci.* 28, 12–20. <https://doi.org/10.1016/j.dcn.2017.10.003>.
- Clare, S., Helps, S., Sonuga-Barke, E.J.S., 2010. The quick delay questionnaire: a measure of delay aversion and discounting in adults. *ADHD Attent. Deficit Hyperact. Disord.* 2 (1), 43–48. <https://doi.org/10.1007/s12402-010-0020-4>.
- Goldstein, R.Z., Cottone, L.A., Jia, Z., Maloney, T., Volkow, N.D., Squires, N.K., 2006. The

- effect of graded monetary reward on cognitive event-related potentials and behavior in young healthy adults. *Int. J. Psychophysiol.* 62 (2), 272–279. <https://doi.org/10.1016/j.ijpsycho.2006.05.006>.
- Gómez, C.M., Flores, A., Ledesma, A., 2007. Fronto-parietal networks activation during the contingent negative variation period. *Brain Res. Bull.* 73 (1), 40–47. <https://doi.org/10.1016/j.brainresbull.2007.01.015>.
- Goodman, R., 1997. The strengths and difficulties questionnaire: a research note. *J. Child Psychol. Psychiatry* 38 (5), 581–586. <https://doi.org/10.1111/j.1469-7610.1997.tb01545.x>.
- Handy, T., 2005. Basic principles of ERP quantification. In: *Event-related Potentials: A Methods Handbook*, pp. 33–55.
- Holroyd, C.B., Yeung, N., 2012. Motivation of extended behaviors by anterior cingulate cortex. *Trends Cogn. Sci.* 16 (2), 122–128. <https://doi.org/10.1016/j.tics.2011.12.008>.
- Hsu, C.-F., Benikos, N., Sonuga-Barke, E.J.S., 2015. Spontaneous activity in the waiting brain: a marker of impulsive choice in attention-deficit/hyperactivity disorder? *Dev. Cogn. Neurosci.* 12, 114–122. <https://doi.org/10.1016/j.dcn.2015.01.007>.
- Knutson, B., Greer, S.M., 2008. Anticipatory affect: neural correlates and consequences for choice. *Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci.* 363 (1511), 3771–3786. <https://doi.org/10.1098/rstb.2008.0155>.
- Lemiere, J., Danckaerts, M., Van Hecke, W., Mehta, M.A., Peeters, R., Sunaert, S., Sonuga-Barke, E., 2012. Brain activation to cues predicting inescapable delay in adolescent Attention Deficit/Hyperactivity Disorder: an fMRI pilot study. *Brain Res.* 1450, 57–66. <https://doi.org/10.1016/j.brainres.2012.02.027>.
- Loveless, N.E., Sanford, A.J., 1974. Slow potential correlates of preparatory set. *Biol. Psychol.* 1 (4), 303–314.
- Marco, R., Miranda, A., Schlotz, W., Melia, A., Mulligan, A., Müller, U., ... Sonuga-Barke, E.J.S., 2009. Delay and reward choice in ADHD: an experimental test of the role of delay aversion. *Neuropsychology* 23 (3), 367–380. <https://doi.org/10.1037/a0014914>.
- Marx, I., Hacker, T., Yu, X., Cortese, S., Sonuga-Barke, E., 2018. ADHD and the choice of small immediate over larger delayed rewards: a comparative meta-analysis of performance on simple choice-delay and temporal discounting paradigms. *J. Atten. Disord.* <https://doi.org/10.1177/1087054718772138>.
- Nigg, J.T., 2011. Attention, task difficulty, and ADHD. *Br. J. Dev. Psychol.* 23 (4), 513–516. <https://doi.org/10.1348/026151005X55848>.
- Novak, K.D., Foti, D., 2015. Teasing apart the anticipatory and consummatory processing of monetary incentives: an event-related potential study of reward dynamics. *Psychophysiology* 52 (11), 1470–1482. <https://doi.org/10.1111/psyp.12504>.
- Olson, E.A., Hooper, C.J., Collins, P., Luciana, M., 2007. Adolescents' performance on delay and probability discounting tasks: contributions of age, intelligence, executive functioning, and self-reported externalizing behavior. *Personal. Individ. Differ.* 43 (7), 1886–1897. <https://doi.org/10.1016/j.paid.2007.06.016>.
- Ortega, R., López, V., Carrasco, X., Anllo-Vento, L., Aboitiz, F., 2013. Exogenous orienting of visual-spatial attention in ADHD children. *Brain Res.* 1493, 68–79. <https://doi.org/10.1016/j.brainres.2012.11.036>.
- Plichta, M.M., Scheres, A., 2014. Ventral–striatal responsiveness during reward anticipation in ADHD and its relation to trait impulsivity in the healthy population: a meta-analytic review of the fMRI literature. *Neurosci. Biobehav. Rev.* 38, 125–134. <https://doi.org/10.1016/j.neubiorev.2013.07.012>.
- Plichta, M.M., Vasic, N., Wolf, R.C., Lesch, K.-P., Brummer, D., Jacob, C., ... Grön, G., 2009. Neural hypo-responsiveness and hyper-responsiveness during immediate and delayed reward processing in adult attention-deficit/hyperactivity disorder. *Biol. Psychiatry* 65 (1), 7–14. <https://doi.org/10.1016/j.biopsych.2008.07.008>.
- Polanczyk, G.V., Salum, G.A., Sugaya, L.S., Caye, A., Rohde, L.A., 2015. Annual research review: a meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. *J. Child Psychol. Psychiatry* 56 (3), 345–365. <https://doi.org/10.1111/jcpp.12381>.
- Rossi, A.F., Pessoa, L., Desimone, R., Ungerleider, L.G., 2009. The prefrontal cortex and the executive control of attention. *Exp. Brain Res.* 192 (3), 489–497. <https://doi.org/10.1007/s00221-008-1642-z>.
- Sattler, J.M., 2001. *Assessment of Children: Cognitive Applications*. 4th ed. ed. Author, San Diego, CA.
- Semlitsch, H.V., Anderer, P., Schuster, P., Presslich, O., 1986. A solution for reliable and valid reduction of ocular artifacts, applied to the P300 ERP. *Psychophysiology* 23 (6), 695–703. <https://doi.org/10.1111/j.1469-8986.1986.tb00696.x>.
- Shaffer, D., Schwab-Stone, M., Fisher, P., Cohen, P., Placentini, J., Davies, M., ... Regier, D., 1993. The diagnostic interview schedule for children-revised version (DISC-R): I. preparation, field testing, interrater reliability, and acceptability. *J. Am. Acad. Child Adolesc. Psychiatry* 32 (3), 643–650.
- Sonuga-Barke, E.J., 1994. On dysfunction and function in psychological theories of childhood disorder. *Journal of Child Psychology and Psychiatry* 35, 801–815.
- Sonuga-Barke, E.J.S., Cortese, S., Fairchild, G., Stringaris, A., 2016. Annual research review: Transdiagnostic neuroscience of child and adolescent mental disorders—differentiating decision making in attention-deficit/hyperactivity disorder, conduct disorder, depression, and anxiety. *J. Child Psychol. Psychiat.* *Allied Discip.* 57 (3), 321–349. <https://doi.org/10.1111/jcpp.12496>.
- Toplak, M.E., Jain, U., Tannock, R., 2005. Executive and motivational processes in adolescents with Attention-Deficit-Hyperactivity Disorder (ADHD). *Behav. Brain Funct.* 1 (1), 8. <https://doi.org/10.1186/1744-9081-1-8>.
- Van Boxtel, G., Böcker, K., 2004. Cortical measures of anticipation. *J. Psychophysiol.* 18 (2–3), 61. <https://doi.org/10.1027/0269-8803.18.23.61>.
- Van Dessel, J., Sonuga-Barke, E., Mies, G., Lemiere, J., Van der Oord, S., Morsink, S., Danckaerts, M., 2018. Delay aversion in attention deficit/hyperactivity disorder is mediated by amygdala and prefrontal cortex hyper-activation. *J. Child Psychol. Psychiatry* 59 (8), 888–899. <https://doi.org/10.1111/jcpp.12868>.
- van Hulst, B.M., de Zeeuw, P., Lupas, K., Bos, D.J., Neggers, S.F.W., Durston, S., 2015. Reward anticipation in ventral striatum and individual sensitivity to reward: a pilot study of a child-friendly fMRI task. *PLoS One* 10 (11), e0142413. <https://doi.org/10.1371/journal.pone.0142413>.
- Walter, W.G., Cooper, R., Aldridge, V.J., McCallum, W.C., Winter, A.L., 1964. Contingent negative variation: an electric sign of sensori-motor association and expectancy in the human brain. *Nature* 203 (4943), 380–384. <https://doi.org/10.1038/203380a0>.
- Wechsler, D., 2004. *The Wechsler Intelligence Scale for Children*, 4th ed. Pearson Assessment, London.
- Wilbertz, G., Trueg, A., Sonuga-Barke, E.J., Blechert, J., Philippen, A., Tebartz van Elst, L., 2013. Neural and psychophysiological markers of delay aversion in attention-deficit hyperactivity disorder. *J. Abnorm. Psychol.* 122 (2), 566–572. <https://doi.org/10.1037/a0031924>.