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Research Report

Waiting and working for rewards: Attention-Deficit/Hyperactivity Disorder is associated with steeper delay discounting linked to amygdala activation, but not with steeper effort discounting

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ABSTRACT

Objective: Children and adolescents with ADHD have a relatively strong preference for smaller immediate rewards over larger delayed rewards (steep delay discounting). It is unknown whether such steep discounting of rewards is specific for delayed rewards, i.e., supporting the delay aversion account of ADHD, or whether it is also present for effortful rewards, i.e., representing general reward insensitivity. Therefore, this study examined behavioral and BOLD responses during delay discounting (DD) and effort discounting (ED) in ADHD.

Method: Thirty adolescents with ADHD and 28 controls (12–17 years) were scanned while performing a DD-ED task (fMRI findings were based on 21 and 25 participants, respectively). During DD, participants were presented with a series of choices between a small reward delivered immediately and a larger reward delivered after 5–25s. During ED, participants were presented with choices between a small reward that was delivered after exerting 15% of their maximal hand grip strength and a larger reward delivered after exerting 30–90% of their strength.

Results: Analyses on the subjective values of delayed and effortful rewards and on the Area Under the discounting Curves (AUCs) indicated that adolescents with ADHD showed steeper discounting than controls for DD, but not for ED. This was accompanied by a slightly stronger delay dose–response relationship in the amygdala for adolescents with ADHD who reported to be more delay averse in daily life.

Conclusion: Together, these results–steeper DD in the ADHD group and a stronger delay dose–response relationship in the amygdala, while no evidence for group differences in ED was found–support the delay aversion account of ADHD.

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1. Introduction

Relatively strong preferences for small immediate rewards over larger delayed rewards (Jackson & MacKillop, 2016; Patros et al., 2016) are thought to be an important correlate of symptoms of Attention-Deficit/Hyperactivity Disorder (ADHD) (Sonuga-Barke, 2005). These preferences are frequently examined by delay discounting (DD) tasks in which people choose between large delayed rewards, and smaller immediate rewards. Preferences for the larger delayed reward typically decrease as the delay preceding this reward increases. This decrease of subjective value of the large reward as a function of increasing delay is referred to as DD (Critchfield & Kollins, 2001). Understanding the mechanism(s) of this impulsive behavior may contribute to development of interventions to reduce this behavior and associated unhealthy outcomes.

One theoretical model proposes that the main mechanism involved in steep DD in ADHD is delay aversion (Sonuga-Barke, Dalen, & Remington, 2003). Individuals with ADHD are thought to experience relatively strong negative emotions during waiting times, resulting in a preference to escape delay. Evidence for this theory, however, is still limited. There are only a few studies that have examined whether *subjective experiences* during waiting contribute to an immediate reward preference in ADHD. Scheres, Tontsch, and Thoeny (2013b), for example, showed that impulsive choices were more strongly correlated with difficulty waiting in youth with ADHD than in controls. In another study, self-reported delay aversion was associated with preferences for smaller sooner rewards in undergraduates (Mies, De Water, & Scheres, 2016). In addition, the neural correlates of delay aversion have not been clearly established yet. Some studies showed increased amygdala and insula activation in individuals with ADHD compared to controls in response to cues predicting delay (Lemiere et al., 2012; Van Dessel et al., 2018), and with increasing length of anticipated delays (Wilbertz et al., 2013). Increased amygdala activation was also found in adults with ADHD in response to anticipated delayed rewards (Plichta et al., 2009). Activation in these brain regions is thought to reflect emotional value and salience of delay-related stimuli, indirectly suggesting that steep DD in ADHD is associated with delay aversion. Competing alternative explanations for steep DD in ADHD have not yet been tested. Aberrant reward sensitivity (Luman, Tripp, & Scheres, 2010) could, for example, play a role. Therefore, we investigated the extent to which steep DD in ADHD was associated with delay aversion versus a relative insensitivity to reward magnitude.

One of the ways to examine this is by comparing behavioral and neural responses of adolescents with ADHD and controls during a *delay discounting (DD)* and an *effort discounting (ED)* task. In this latter task, participants chose between exerting more physical effort by squeezing a handgrip in order to gain a larger reward, or less effort to gain a smaller reward. Differences in the duration needed to exert more versus. less physical effort is negligible, making it an ideal 'control' condition to compare DD against. A recent study in young healthy men showed that rewards associated with physical effort were devalued in the same way as rewards associated with delays (Prevost, Pessiglione, Metereau, Clery-Melin, & Dreher, 2010). Clearly, both waiting and working for rewards are costly. Here, our aim was to examine whether altered discounting behavior in adolescents with ADHD is limited to *delayed* rewards, or whether it represents insensitivity to reward magnitude. If delay aversion is the primary factor involved in steep DD in ADHD, then group differences are expected for DD but not ED. If, however, reward insensitivity is an important factor, or if ADHD is associated with effort aversion, then we would expect to see steep discounting in ADHD also for ED.

Importantly, we chose to use *real* monetary rewards and *real* delays and efforts, as opposed to hypothetical designs used in previous fMRI studies on DD in ADHD (Carlisi et al., 2016; Chantiluke et al., 2014; Ortiz et al., 2015; Plichta et al., 2009; Rubia, Halari, Christakou, & Taylor, 2009). Real delays and rewards require less episodic prospection, which may not be fully developed in children and adolescents yet, and real delays are, intuitively, more likely to capture delay aversion. Examining ED will advance our understanding of discounting of different types of cost, and increase our knowledge of motivational mechanisms in ADHD. Additionally, subjective experiences during the task, and daily-life delay aversion and reward sensitivity were assessed to gain a better understanding of the mechanisms involved in DD and ED.

Prevost et al. (2010) showed that the neural systems tracking rewards associated with delay and effort are different. They found, largely consistent with other imaging studies on DD (Scheres, de Water, & Mies, 2013a), involvement of the ventral striatum (VS), ventromedial prefrontal cortex (vmPFC) and lateral prefrontal cortex (LPFC) in DD. These brain regions were found to value larger delayed rewards. In the ED condition, however, the anterior cingulate cortex (ACC) and anterior insula appeared to track the devaluation of rewards that require more effort.

In the present study, we expected, in accordance with the delay aversion model 1) that adolescents with ADHD would show steeper DD than controls, but similar ED, and 2) to find group differences in the neural system underlying DD, but not underlying ED. Specifically, we expected aberrant activation of the VS, vmPFC, LPFC, posterior cingulate cortex (PCC) and posterior parietal cortex (PPC) in response to delay-related reward cues (*decision-making*) in the ADHD group compared to controls (Prevost et al., 2010; Scheres et al., 2013a). In response to effort-related reward cues, we expected activation of the ACC and anterior insula (Prevost et al., 2010), and no group differences, in line with our behavioral hypothesis. Additionally, we expected that adolescents with ADHD would show increased amygdala and insula activation during the *experience* of delay. During effort *exertion*, no group differences were expected.

2. Material and methods

2.1. Participants

Thirty-four adolescents (12–17 years) with ADHD (combined subtype) and 32 controls matched on age and gender were

enrolled. Participants and parents both gave written informed consent, and the study was approved by the local medical ethics committee.

ADHD participants had an ADHD-combined type diagnosis by a child psychiatrist/psychologist. We assessed current validity of the diagnosis, and screened for other disorders, with the Diagnostic Interview Schedule for Children (DISC-IV) (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000) ('behavioral disorders' and 'whole life' modules). Controls were screened for the same psychiatric disorders. Additionally, parents completed the Child Behavior Checklist (CBCL) (Achenbach & Rescorla, 2001) to assess emotional and behavioral problems, the Disruptive Behavior Disorders Rating Scale (DBDRS) (Oosterlaan, Scheres, Antrop, Roeyers, & Sergeant, 2000) to assess ADHD symptom severity, Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD), and the Social Responsiveness Scale (SRS) (Roeyers, Thys, Druart, De Schryver, & Schittekatte, 2011) to screen for Autism Spectrum Disorders. Four participants with ADHD included in the analyses were in partial remission for a current ADHD diagnosis on the basis of the DISC-IV, CBCL and DBDRS.

Exclusion criteria were neurological illness, contraindications for undergoing MRI, use of psychoactive medication that could not be discontinued, IQ < 70, and, for ADHD participants, current comorbid psychiatric disorders except for ODD/CD. Participants were excluded from the control group if they met clinical cutoff criteria for any current psychiatric disorder based on the DISC-IV, DBDRS and CBCL (see supplement for excluded individuals).

Thirty ADHD and 28 control participants (Table 1) were included in the behavioral analyses, and 21 ADHD and 25 control participants in the fMRI analyses. Excessive head movement was the main cause of drop-out. Participants who used medication (N = 22; all participants used methylphenidate except for one who used dexamphetamine) were asked to discontinue medication 24h prior to the experiment.

Table 1 – Participant characteristics (means, standard deviations, and group differences).

	ADHD (N = 30)	Control (N = 28)	
Females (number)	10 (33%)	11 (39%)	$p = .64$
Age (years)	15.1 ± 1.8	15.4 ± 1.7	$p = .44$
IQ estimate	98 ± 15	106 ± 13	$p = .025$
DBDRS			
Inattention	14.7 ± 1.8	10.5 ± 0.9	$p < .001$
Hyperactivity/ impulsivity	14.8 ± 2.2	10.3 ± 0.9	$p < .001$
ODD	12.4 ± 1.9	10.4 ± 1.0	$p < .001$
CD	12.5 ± 2.4	11.4 ± 1.4	$p = .034$
CBCL (DSM scales)[a]			
ADHD problems	67.2 ± 8.4	51.5 ± 2.8	$p < .001$
ODD problems	57.2 ± 7.1	50.5 ± 0.7	$p < .001$
CD problems	56.7 ± 6.0	50.5 ± 1.1	$p < .001$
Affective problems	59.0 ± 7.4	51.7 ± 2.5	$p < .001$
Anxiety problems	54.5 ± 4.8	51.4 ± 3.3	$p = .008$
Somatic problems	55.1 ± 6.4	53.0 ± 4.0	$p = .14$
SRS (total score)[b]	56.5 ± 12.5	45.0 ± 4.5	$p < .001$

DBDRS = Disruptive Behavior Disorders Rating Scale, standardized scores (range: 10–19): ≤14 normal range, 15 subclinical range, ≥16 clinical range for inattention and hyperactivity/impulsivity, ≤15 normal range, 16 subclinical range, ≥17 clinical range for ODD and CD; CBCL=Child Behavior Checklist, T-scores for DSM scales: 50–64 normal range, 65–69 borderline clinical range, 70–100 clinical range; SRS=Social Responsiveness Scale, T-scores: <40 high social responsiveness, 40–60 normal social responsiveness, 61–75 mild to moderate deficit in social responsiveness, ≥76 severe deficit in social responsiveness.

[a] Data from 1 ADHD participant missing.

[b] Data from 1 control and 4 ADHD participants missing.

2.2. DD-ED task

The DD-ED task (Fig. 1) was based on Prevost et al. (2010). A control condition was added to compare neural responses against. In the delay condition, participants repeatedly chose between a small sooner reward (e.g., 2 cents after 1.5s) and a larger fixed delayed reward (e.g., 10 cents after 25s). In the effort condition, participants repeatedly chose between a small reward that requires little physical effort (e.g., 2 cents for exerting 15% of their maximal effort) and a larger fixed reward that requires more effort (e.g., 10 cents for exerting 90% of maximal effort). The reward associated with the delayed/effortful options was 10 cents, while the rewards associated with the sooner/less effortful options were 2, 4, 6, and 8 cents. Delays were 1.5 (immediate/sooner option), 5, 10, 15, 20 and 25s, and efforts were 15 (less effortful option), 30, 45, 60, 75, and 90% of an individual's maximal strength. Participants were not informed about the exact delay durations and efforts, but experienced all delays/efforts before the task. In the control condition, participants had to choose the larger one of two carts, aided by the arrow pointing at that cart. No delay, effort, or reward was involved in this condition, but visual input and the required motor response were similar to the other conditions. Delay and effort trials were pseudo-randomly presented with a maximum of three effort trials in a row.

Participants completed four sessions of 49 trials (total: 88 delay, 88 effort, 20 control trials). In both task conditions, 8 'catch' trials were included to check potential response strategies (supplement). Each session lasted ~5–10 min, depending on participants' choices. Participants were informed that there was a fixed number of trials. It was emphasized that they should choose whatever they preferred. Participants held an MRI-compatible hand grip (Current Designs, Inc., Philadelphia, USA) that measured force in their right (dominant) hand, and a button box (to indicate choices) in their left hand. On effort trials, participants had to squeeze the hand grip until a thermometer was filled up to the required level of effort, while the thermometer remained fixed during delay trials.

2.3. Self-report measures

Groups were compared on *trait impulsivity* ($\alpha = .80$) (Barratt Impulsiveness Scale; Patton, Stanford, & Barratt, 1995), *reward sensitivity* ($\alpha = .82$) (subscale from Behavioral Inhibition/Approach System Scales; Carver & White, 1994), *anhedonia* ($\alpha = .89$) (Snaith-Hamilton Pleasure Scale; Snaith et al., 1995), *delay aversion* ($\alpha = .77$) and *delay discounting* ($\alpha = .59$) (Quick Delay Questionnaire, QDQ; Clare, Helps, & Sonuga-Barke, 2010), and *mood* (αs>.80) (shortened Profile of Mood States, POMS; McNair, Lorr, & Droppleman, 1971).

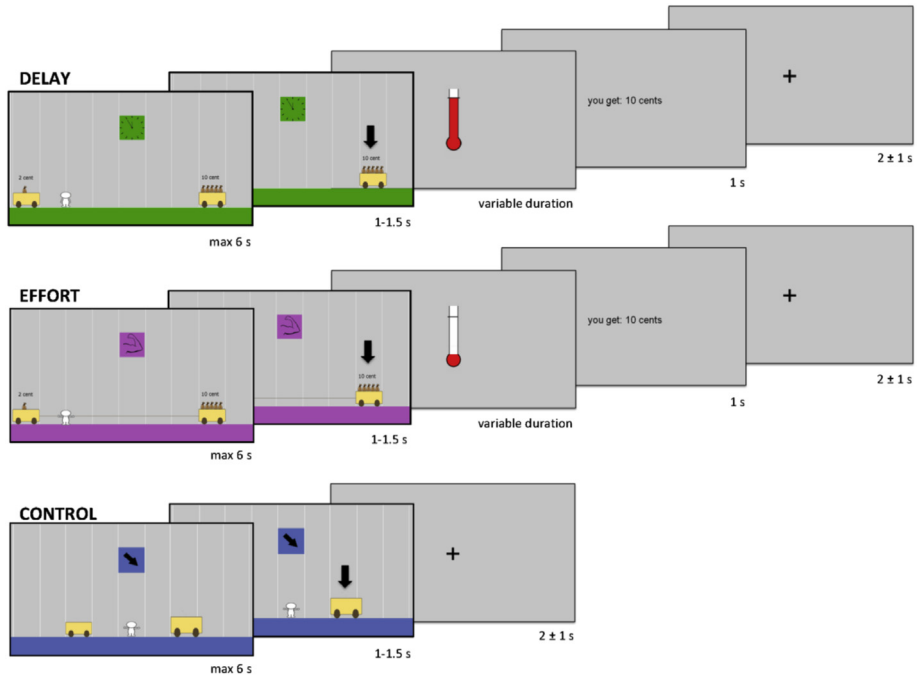

Fig. 1 – Task design, programmed in Presentation® (Neurobehavioral Systems, Inc.). The three task conditions–delay, effort, control–were indicated by a clock, biceps and arrow (decision phase), respectively. Colors (green/purple) were counterbalanced across participants. Participants were instructed to choose one of two carts, one cart was always close to the character (participant), and the other further away. The position (left/right) of the cart further away was balanced over trials. Vertical lines indicated the delay/effort level. Participants were informed that they had to wait longer when they chose the cart/reward further away in the delay condition, and that they had to pull the rope (squeeze) harder when they chose the cart/reward further away in the effort condition. During the cost-enduring phase a thermometer was shown and participants either had to wait or squeeze. After the cost-enduring phase, the reward associated with their choice was shown (outcome phase).

Prior to the task, participants underwent an experience session in the scanner, and estimated the duration of each delay in seconds (*time estimation*), indicated on 9-point scales how long each delay felt to them (*time perception*), and how effortful each exerted effort was (*effort perception*). Post-scanning, participants were asked to indicate on a visual analogue scale how much they liked receiving the different rewards (*reward valuation*), how much difficulty they experienced with waiting during the delays (*difficulty waiting*), and with reaching the different levels of effort (*difficulty squeezing*). To assess how participants felt during waiting and squeezing, they completed the *valence* and *arousal* Self-Assessment Manikin dimensions (Bradley & Lang, 1994).

2.4. Procedure

During visit 1, participants completed the above-mentioned questionnaires, two subtests of the Wechsler Intelligence Scale for Children (Kort et al., 2002) (vocabulary, block design), and got acquainted with the scanning environment in a mock scanner, while parents were interviewed (DISC-IV) and completed the CBCL, DBDRS, and SRS. During visit 2, we determined maximal hand grip strength by having the participant squeeze five times in a hand grip as forcefully as possible, in the mock scanner. Then, participants were instructed on the DD-ED task, and asked to explain the task to the experimenter to confirm that they understood instructions. In the scanner, participants squeezed the hand grip again five times. The average of the two highest levels of effort reached was used as maximum force level for the ED condition. Then, participants experienced each level of delay and effort, and performed a short practice session, followed by two task blocks. After a short break outside the scanner, during which participants completed the POMS, they again performed two task blocks, and an anatomical scan was made. After scanning, participants completed subjective rating scales, and received the money they earned in cash. This procedure took 2–2.5h.

2.5. MRI acquisition and preprocessing

BOLD-fMRI data were acquired on a 1.5T Siemens Avanto scanner with a 32-channel head coil. For the functional scans, a multi-echo GRAPPA EPI sequence was used. The T2*-weighted images were acquired in 32 ascending slices (thickness = 3 mm, interslice gap = .51 mm) with a TR of 2010 ms, five TE's (9.2, 20.9, 33, 44, and 56 ms), FOV of 224 mm, voxels of 3.5 × 3.5 × 3.0 mm and flip angle of 90°. Multi-echo fMRI causes better coverage of activation in different brain regions, less signal drop-out and less distortion than single-

echo fMRI (Poser, Versluis, Hoogduin, & Norris, 2006). For anatomical reference, a whole-brain T1-weighted scan was acquired in 176 slices (thickness = 1 mm, interslice gap = 0.5 mm, voxel size = 1 × 1x1mm, FOV = 256 mm, TR = 2250 ms, TE = 2.95 ms, flip angle = 15°). Before the first and third task sessions started, 30 volumes were collected that were used to calculate the weighting parameters of the five TE's (Poser et al., 2006). To minimize head movement, foam inserts were placed around the head of the participant and a piece of tape was used across the forehead.

For preprocessing and statistical analyses, SPM8 (Wellcome Trust Centre for Neuroimaging, University College London, UK) was used. Preprocessing of the structural data included segmentation using the MNI T1 templates for gray matter, white matter and CSF, and normalization. Preprocessing of the functional data included combination of the five TE's on the basis of optimal weighting parameters into one image per volume (Poser et al., 2006), realignment using a rigid body transformation, slice time correction (reference = middle slice), coregistration to the gray matter image derived from segmentation, normalization to the MNI template, and smoothing using a Gaussian kernel of 6 mm FWHM. ICA-AROMA (Pruim, Mennes, Buitelaar, & Beckmann, 2015) was used to identify motion-related noise and denoise functional images.

2.6. Statistical analyses

2.6.1. Behavior

Subjective values (SV's) were calculated for the delayed and effortful reward based on the proportion costly choices (supplement). Two repeated-measures ANOVA's (RM-ANOVA's) were conducted using SV as dependent variable with cost (delay/effort level) as within-subject factor and group (ADHD, control) as between-subjects factor to examine (group differences in) discounting behavior. To directly compare DD with ED we calculated the area under the discounting curve (AUC) (Myerson, Green, & Warusawitharana, 2001), and compared groups using RM-ANOVA with condition (delay, effort) as within-subject factor. Analyses were repeated with age as covariate, and with only participants that were included in the fMRI analyses.

2.6.2. fMRI

2.6.2.1. Decision phase. A general linear model (GLM) was made with three regressors of interest for each task session[4]: delay, effort, control. These were modeled as boxcars starting at cue onset with response time (including response confirmation) as duration, convolved with a hemodynamic response function (HRF) and its temporal derivative. The proposed level of delay and effort, and amount of the less costly option were included as parametric modulations on the first two regressors. Four additional regressors were included to account for the experienced delay period and the effort investment period (modeled as boxcars with event duration), and for the reward outcome phase (modeled as zero-duration events). A high-pass filter of 128s was used. Computed t-contrasts were: delay > control, effort > control, delay > effort, effort > delay. We additionally computed three t-contrasts for the parametric modulators. The individual contrast images were used in second-level analysis.

Whole-brain analyses were performed on all contrasts comparing the two groups (two-sample t-tests). Only clusters that survived a family-wise-error (FWE) corrected threshold of $p < .05$ (based on an initial cluster-forming threshold of $p < .001$ uncorrected) are reported.

Region-of-interest (ROI) analyses were performed using MarsBaR (Brett, Anton, Valabregue, & Poline, 2002) on the following seven regions (coordinates adopted from Prevost et al. (2010) and McClure, Laibson, Loewenstein, and Cohen (2004)): VS (8-mm-radius sphere around MNI coordinates ±10 10−12), vmPFC (±10 24−12), LPFC (±34 34 8), posterior parietal cortex (PPC, ±40−60 44), posterior cingulate cortex (PCC, ±8−28 32), ACC (±6 24 28) and anterior insula (±30 22 10), for the contrasts delay > control and effort > control. RM-ANOVAs were conducted on the beta values extracted for these ROIs with condition (delay, effort) and hemisphere as within-subjects factors, and group as between-subject factor. False Discovery Rate (FDR) correction (Benjamini & Hochberg, 1995) was applied.

2.6.2.2. Cost-enduring phase. A GLM was made with two regressors of interest, modeled as stick functions: delay cost and effort cost. Delay duration and exerted effort were included as parametric modulations. Five additional regressors were included to account for the decision phase (delay, effort, control), modeled as boxcars with event duration, and the outcome phase (delay, effort), modeled as stick functions. Whole-brain (group) analyses were performed on the following t-contrasts: delay cost > implicit baseline, effort cost > implicit baseline, delay modulator, effort modulator. ROI analyses were performed on the amygdala and insula (Tzourio-Mazoyer et al., 2002) for all four contrasts in a similar fashion as reported above.

3. Results

3.1. Behavior

DD was reflected by a large main (linear) effect of delay on SV [$F(4,53) = 24.0$, $p < .001$, $\eta^2_p = .30$]. The ADHD group discounted delayed rewards more than controls [main effect of group: $F(1,56) = 5.3$, $p = .025$, $\eta^2_p = .087$; Fig. 2A]. The interaction between group and delay did not reach statistical significance [$F(4,53) = 2.6$, $p = .09$, $\eta^2_p = .045$], suggesting that the group effect did not depend on delay level. Physical effort was also discounted [$F(4,53) = 14.9$, $p < .001$, $\eta^2_p = .21$],[5] but no main group effect was found [$F(1,56) = .8$, $p = .37$, $\eta^2_p = .015$], nor an interaction with effort level [$F(4,53) = 1.6$, $p = .21$, $\eta^2_p = .028$] (Fig. 2B). No age effects were found.

The AUC analysis showed a strong effect of condition on discounting [$F(1,56) = 15.9$, $p < .001$, $\eta^2_p = .22$]: delayed rewards were discounted more than effortful rewards. Additionally, there was a group-by-condition interaction [$F(1,56) = 4.9$, $p = .031$, $\eta^2_p = .08$], and a main effect of group [$F(1,56) = 4.6$,

[4] For four participants (1 control, 3 ADHD) one of the four sessions was excluded from further analysis due to excessive head motion (>4 mm).

[5] There was both a linear and a quadratic effect of effort on SV.

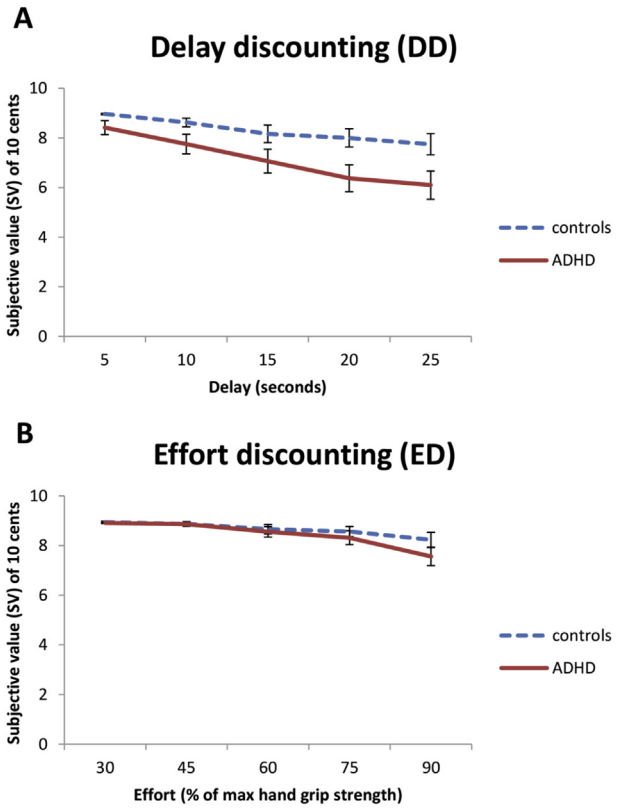

Fig. 2 – Average subjective values of the costly reward (10 cents) per group for each level of delay (A) and effort (B). Error bars represent SEM. In both DD and ED, a subgroup of participants always chose the costly option: 29 out of 58 individuals (11 ADHD, 18 control) showed no ED, and 24 individuals (8 ADHD, 16 control) showed no DD.

$p = .037$, $\eta^2_p = .075$]. Follow-up Mann–Whitney *U* Tests showed that the ADHD group showed steeper discounting than controls during DD only (delay: $p = .014$; effort: $p = .10$). See supplementary figure S2 for AUC values per group and condition.

When repeating the main analyses only for participants included in the fMRI analyses, main effects of delay and effort on SV remained [delay: $F(4,41) = 19.7$, $p < .001$, $\eta^2_p = .31$; effort: $F(4,41) = 13.0$, $p < .001$, $\eta^2_p = .23$], as well as the main group effect during DD [$F(1,44) = 4.6$, $p = .038$, $\eta^2_p = .09$]. See supplement for additional analyses (e.g., catch trials, response times).

3.2. *Self-report measures*

As expected, the ADHD group scored higher on delay aversion than controls [$t(56) = 3.52$, $p = .001$, $d = .9$]. Reward sensitivity did not differ between groups [$t(56) = .86$, $p = .39$, $d = .2$]. See supplement for other questionnaires and associations between delay aversion, reward sensitivity and DD.

3.3. *fMRI*

3.3.1. *Decision phase*

Whole-brain general task effects (supplement) were largely the same for the ADHD and control group, except for an interaction between group and condition in the delay > effort contrast: the ADHD group showed more activation close to the posterior part of the corpus callosum/PCC, and the anterior corona radiata/middle frontal gyrus (MFG) during delay choices than effort choices, while the control group showed the opposite, i.e., more activation in these regions during effort than delay choices (Fig. 3; Table S2). None of the other contrasts (delay > control, effort > control, parametric modulators for proposed level of delay, effort, and amount of less costly option) showed group differences surviving correction for multiple comparisons. Also, no effects of age were found. The ROI analyses showed no significant group differences.

3.3.2. *Cost-enduring phase*

No significant group differences were found during the experience of delay and effort at the whole-brain level (see supplement for general task effects). ROI analyses, however, showed that with increasing delay and effort levels, the amygdala was more active in the ADHD group than in controls [$F(1,43) = 4.89$, $p = .032$, $\eta^2_p = .10$],[6] especially in the delay condition [$F(1,43) = 4.31$, $p = .04$, $\eta^2_p = .09$]. Although these effects did not survive correction for multiple comparisons ($p_{FDR} < .0125$), they suggest a somewhat stronger dose–response relationship of delay in the amygdala for the ADHD group than controls (Fig. 4A). We examined whether this was associated with self-reported delay aversion and/or difficulty waiting. Delay aversion was associated with an increased delay dose–response relationship in the amygdala [$F(1,41) = 7.01$, $p = .011$, $\eta^2_p = .15$, Fig. 4B]. This relationship was only significant for the ADHD group, reflected by an interaction between group and delay aversion [$F(1,41) = 5.75$, $p = .021$, $\eta^2_p = .12$], and by a significant main effect of delay aversion in the ADHD [$F(1,18) = 6.39$, $p = .021$, $\eta^2_p = .26$], but not in the control group [$F(1,23) = .10$, $p = .75$, $\eta^2_p = .004$], when examined separately.

4. Discussion

This study aimed to dissociate the contribution of delay aversion and altered reward sensitivity to steep DD often found in ADHD. ED was included to examine whether steep discounting in adolescents with ADHD is limited to DD, or also occurs during ED, which would suggest that not only delay aversion, but also altered sensitivity to reward magnitude might play a role in DD. We replicated earlier findings by showing steeper DD in ADHD than control participants, using a task with real delays and rewards. The results suggest that delay aversion, rather than altered reward sensitivity, is associated with steeper discounting in ADHD. First, a group difference occurred for DD, but not for ED. Second, the ADHD group scored higher on daily-life delay aversion than the control group. Third, groups did not differ on reward sensitivity, further indicating that steeper discounting was unrelated to altered reward sensitivity in ADHD. Finally, in the ADHD group, a somewhat stronger delay dose–response

[6] One ADHD participant was excluded from this analysis because of extremely high beta-values associated with amygdala and insula activation during DD.

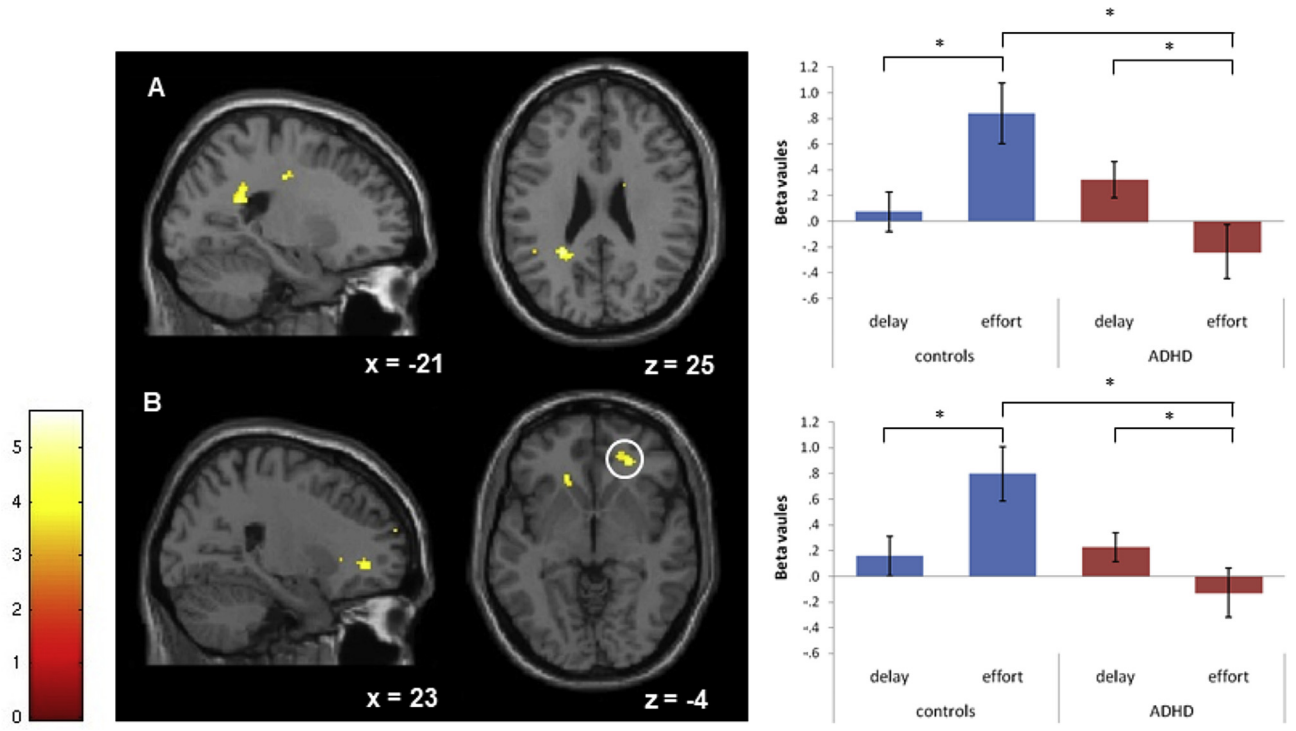

Fig. 3 – Group (ADHD, control) x condition (delay, effort) interaction during decision phase in white matter close to the splenium of the corpus callosum/posterior cingulate cortex (A), and white matter close to the anterior corona radiate/middle frontal gyrus (B), and the corresponding mean beta values extracted for 8 mm-radius spheres surrounding the peak coordinates of these regions (on the basis of the contrasts delay > control and effort > control). In the ADHD group, these two regions were more active during delay decisions, whereas in the control group they were more active during effort decisions, reflected by significant interactions in post-hoc repeated-measures ANOVAs and subsequent t-tests (* = $p < .05$).

relationship was found in the amygdala with increasing delay aversion scores.

Groups differed on the DD-task, daily-life delay aversion and discounting, and trait impulsivity. This confirms that our ADHD sample was more impulsive and delay averse than our controls. We found no support for decreased motivation to wait or work for rewards due to decreased sensitivity to reward magnitude in ADHD. Furthermore, adolescents with ADHD were not effort averse, since they were just as willing to exert physical effort as controls. Our behavioral, and to lesser extent, neural results are in line with the delay aversion model. However, the ADHD group did not report more sadness or arousal during waiting than controls. This suggests that the measured states are not the ones underlying the hypothesized negative emotional response associated with waiting, or individuals with ADHD might, for example, have poorer emotional self-awareness (Factor, Rosen, & Reyes, 2013). They reported that they found waiting slightly more difficult, and the question arises whether this is purely affective in nature, as suggested by the delay aversion model, or reflects something else, e.g., a lack of mental strategies to deal with (the boredom of) waiting or more difficulty with having to put actions on hold. More research on what causes delay aversion is required.

The behavioral group effect in DD was less apparent at the neurophysiological level during the decision phase: no group effects were found in brain activation during delay choices, neither was there a relationship between brain activation and delay aversion or choice behavior across groups. Other fMRI studies on DD in individuals with ADHD versus controls have generally found decreased activation in fronto-striatal and fronto-cerebellar networks in ADHD (Carlisi et al., 2016; Chantiluke et al., 2014; Norman et al., 2017; Ortiz et al., 2015; Plichta et al., 2009; Rubia et al., 2009). These studies used hypothetical designs, and most used an algorithm to obtain an approximately equal number of delayed and immediate choices, and then contrasted these choices. Our design did not result in such balanced choices. We contrasted choices in the delay condition—whether delayed or immediate—with choices in the control condition (and effort condition). This makes it difficult to directly compare our findings with the results of these previous studies. By contrasting delay and effort trials with control trials, effects may have been diminished. Although control trials did not involve self-control or temporal foresight, they may have been rewarding for participants because there was no delay or effort involved. This could perhaps have obscured general task effects in fronto-striatal areas as well as potential group differences (see supplement for a more elaborate discussion on general task effects). We did, however, find a group-by-condition interaction close to the PCC and MFG. Both regions are part of an attention network (Pliszka, McCracken, & Maas, 1996), and associated with DD, either as a self-control region (MFG), or as a reward valuation region (PCC) (Scheres, de Water & Mies 2013a). Our

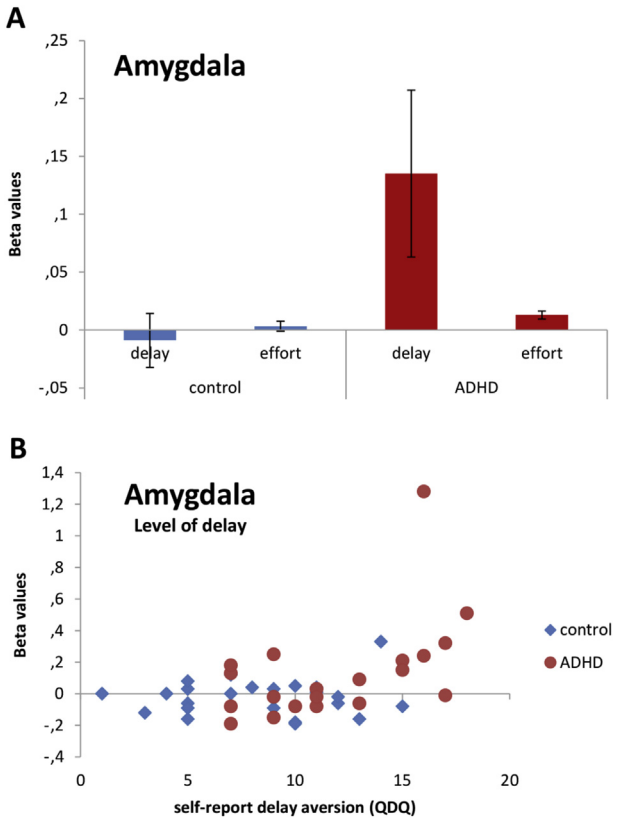

Fig. 4 – (A) Mean beta values extracted for the amygdala on the delay and effort modulator contrasts (cost-enduring phase) averaged across both hemispheres, reflecting steeper positive slopes in the ADHD group than the control group with increasing level of delay (note that this effect did not survive FDR-correction). Error bars represent SEM. (B) Association between self-reported delay aversion and the extracted beta values for the amygdala on the delay modulator contrast, reflecting steeper positive slopes in individuals who report higher delay aversion. This effect was present for the ADHD group but not for the control group. The outlier (ADHD participant with a beta value approximately +7 SD) did not drive the effect.

findings may suggest that controls are more attentive to effort cues, while ADHD participants are more attentive to delay cues, consistent with the idea that delays are highly salient for adolescents with ADHD, which is reflected in less delayed reward choices.

The behavioral results might be better explained in the context of the cost-enduring phase. The ADHD group showed a slightly stronger delay dose–response relationship than controls in the amygdala. This finding is in line with previous studies that have reported increased amygdala activation in response to delay-related cues in ADHD (Lemiere et al., 2012; Plichta et al., 2009; Van Dessel et al., 2018; Wilbertz et al., 2013). Our finding that this dose–response relationship is somewhat stronger in ADHD individuals who reported higher levels of delay aversion supports the delay aversion account, by suggesting a stronger emotional response in delay-averse adolescents with ADHD *during* waiting times. This is the first study that reported brain activation during actual delay in ADHD, rather than to cues of impending delay.

The remaining questions are: what *causes* delay aversion, and why is it more likely to occur in ADHD? Qualitative studies that ask participants *why* they find waiting aversive, and which mental strategies they use to cope with waiting, may be able to answer these questions, as well as longitudinal studies examining whether children with ADHD develop negative emotions associated with delay over time. This knowledge can then be used to develop interventions aimed at decreasing impulsive behavior in ADHD.

Several limitations should be addressed. First, half of participants did not show ED, leading to a ceiling effect which may have contributed to the lack of a group effect. This ceiling effect suggests that the effort condition might not have been aversive enough for many participants. However, sadness, arousal and difficulty ratings increased with increasing level of effort (see supplement), also in those who did not show ED. To be able to draw stronger conclusions about whether individuals with ADHD differ from controls in effort discounting, future studies should use an effort task that is more aversive. Second, there were group differences in IQ. Wilson, Mitchell, Musser, Schmitt, and Nigg (2011) found that group differences in DD disappeared when IQ was taken into account. In our study, however, IQ was not associated with DD, and covarying for IQ had no effect on the group difference (see supplement for this additional exploratory analysis). There were also group differences in comorbid symptoms and medication history. Power issues and their inherently strong associations with ADHD complicated controlling for comorbid symptoms such as anxiety and affective problems, and medication use. Two-thirds of our ADHD sample used medication. From recent studies it is known that long-term stimulant use is associated with higher striatal dopamine transporter levels (Fusar-Poli, Rubia, Rossi, Sartori, & Balottin, 2012), and increased activation in, for example, the anterior insula (Norman et al., 2016). A wash-out period of 24h cannot prevent such long-term effects. Medication use may thus have contributed to the lack of group differences in these brain regions specifically, and in smaller group differences in general. It should be noted though that including only individuals with ADHD who are medication-naïve is not only a practical challenge, but can also bias the results, as it is likely that these individuals are less severely affected by the disorder. Finally, although not uncommon and reflective of the representativeness of our ADHD sample, there was a relatively large motion-related drop-out in the ADHD group. Since the behavioral results were similar with or without inclusion of these individuals, its effect on the neural results is likely to be limited.

5. Conclusion

In sum, this study shows that adolescents with ADHD discount rewards associated with delay–but not with effort–more than controls. This effect was accompanied by a stronger delay dose–response relationship in the amygdala during waiting for those who reported to be more delay averse in daily life. This study therefore provides evidence for delay aversion in adolescents with ADHD.

Conflict of interest

Jan K Buitelaar has been in the past 3 years a consultant to / member of advisory board of / and/or speaker for Janssen Cilag BV, Eli Lilly, Lundbeck, Shire, Roche, Medice, Novartis, and Servier. He has received research support from Roche and Vifor. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, royalties. Gabry W Mies, Ili Ma, Erik de Water and Anouk Scheres report no financial interest or potential conflicts of interest.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.cortex.2018.05.018.

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