The limits of motivational influence in ADHD: no evidence for an altered reaction to negative reinforcement

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Abstract

Functional magnetic resonance imaging studies have reported a diminished response in the brain's reward circuits to contingent cues predicting future monetary gain in adolescents with attention-deficit/hyperactivity disorder (ADHD). The situation with regard to monetary loss is less clear, despite recognition that both positive and negative consequences impact ADHD behaviour. Here, we employ a new Escape Monetary Loss Incentive task in an MRI scanner, which allows the differentiation of contingency and valence effects during loss avoidance, to examine ADHD-related alterations in monetary loss processing. There was no evidence of atypical processing of contingent or non-contingent monetary loss cues in ADHD — either in terms of ratings of emotional and motivational significance or brain responses. This suggests that the ability to process contingencies between performance and negative outcomes is intact in ADHD and that individuals with ADHD are no more (or less) sensitive to negative outcomes than controls. This latter finding stands in stark contrast to recent evidence from a similar task of atypical emotion network recruitment (e.g. amygdala) in ADHD individuals to cues predicting another negative event, the imposition of delay, suggesting marked specificity in the way they respond to negative events.

Key words: negative reinforcement; monetary loss; fMRI; ADHD; motivation; delay aversion

Introduction

Attention-deficit/hyperactivity disorder (ADHD) has been characterised as a motivational disorder caused by impaired processing of reinforcing events (Sonuga-Barke, 2003, 2005; Sagvolden et al., 2005; Tripp and Wickens, 2008; Sonuga-barke et al., 2010). Motivational models on ADHD are mainly supported by research showing an atypical response to positive reinforcement (administer a rewarding stimulus) in children with ADHD (for review, see Luman et al., 2005; Van der Oord and Tripp, 2020). One of the most consistent findings in this regard is that individuals with ADHD have a characteristic preference for small immediate over larger delayed rewards (Marco et al., 2009). Further evidence for altered reward processing deficits comes from functional magnetic resonance imaging (fMRI) studies that have demonstrated a reduced activation in the brain's reward circuit to cues predicting the delivery of future monetary rewards following successful performance on the monetary incentive delay (MID) task (for review,

see Plichta and Scheres, 2014). The questions as to whether these neural effects extend to negative reinforcement processes (the avoidance of negative outcomes, such as monetary loss) have not been answered definitively (Luman et al., 2010).

The small number of fMRI studies that have looked at brain activation to monetary loss in ADHD has been limited in a number of ways and produced inconsistent results. Most fMRI studies using the MID task have restricted their analysis to predetermined reward-related brain regions [e.g. ventral striatum (VS)] (Scheres et al., 2007; Ströhle et al., 2008; Hoogman et al., 2011; Edel et al., 2013; Carmona et al., 2012), leaving out some brain networks that one might predict would be activated by cues of negative events, such as the amygdala and anterior insula (AI) (Lemiere et al., 2012; Van Dessel et al., 2018, 2019b). Even where individuals with ADHD have been shown to display different activation patterns to cues of performance-contingent monetary gain and loss compared to controls, the meaning and significance

of these results have been hard to determine (Stoy *et al.*, 2011; Wilbertz *et al.*, 2017). This is because how the brain reacts to opportunities to avoid negative events depends on its ability to distinguish both contingent from non-contingent and positive from negative cues. In the MID task, the relative valence of the monetary loss cues is influenced by interspersed monetary gain cues during tasks — so that while relative to immediately preceding monetary gain or neutral cues they are likely to be regarded as negative, whereas in other situations they may be perceived as positive (e.g. if the alternative was certain loss) (Nieuwenhuis *et al.*, 2005).

We were recently able to distinguish brain networks activated by contingency-related and valence-related (positive and negative) cues in typically developing adolescents using a modified version of the MID task, the Escape Monetary Loss Incentive (EMLI) task, which contrasts cues predicting either certain monetary loss or certain loss avoidance (no contingency) with a cue predicting conditional loss where monetary loss was determined by performance (Van Dessel *et al.*, 2021). Contingency processing, revealed by contrasting the conditional loss condition with the certain loss and certain avoidance conditions, was associated with the activation of the salience [i.e. AI, midcingulate cortex (MCC), VS, inferior parietal cortex (IPC) and primary visual cortex (PVC)] and motor preparation regions [i.e. dorsolateral prefrontal cortex (DLPFC), posterior parietal cortex (PPC), thalamus (THA) and supplementary motor area (SMA)]. In contrast, valence processing (contrast between certain loss and certain loss avoidance conditions) was associated with activation in reward-related brain regions such as the VS, medial orbitofrontal cortex and temporal areas towards the end of sessions.

In the current paper, we used the EMLI task to compare negative reinforcement processing in ADHD and typically developing children and adolescents. We made a number of predictions. First, cues indicating that monetary loss could be avoided by fast responding (CONDITIONAL LOSS AVOIDANCE) will be (i) more motivational salient, (ii) increase mobilization of cognitive resources that prepare for responding and (iii) lead to faster reaction times than both conditions where there was no contingency between performance and outcome (CERTAIN LOSS or CERTAIN LOSS AVOIDANCE) irrespective of the valence of the cues (i.e. the negative reinforcement effect) (Van Dessel *et al.*, 2021). We expected these effects in the salience and motor preparation network to be smaller individuals with ADHD compared to typically developing controls based on their reward processing deficits (Luman *et al.*, 2005).

Our second prediction was that more positively valenced cues would activate the reward network (i.e. VS and medial orbitofrontal cortex) while negatively valenced cues would activate what has been called the punishment network (i.e. amygdala and insula (AI)). With rewards centres more activated in the CERTAIN LOSS AVOIDANCE *vs* CERTAIN LOSS contrast, while the punishment centres more activated in the CERTAIN LOSS *vs* CERTAIN LOSS AVOIDANCE contrast (Michel Chávez *et al.*, 2015). Based on ADHD fMRI studies showing a lower sensitivity to rewards (Plichta and Scheres, 2014) and heightened sensitivity to aversive events (Lemiere *et al.*, 2012; Wilbertz *et al.*, 2017; Van Dessel *et al.*, 2018; 2019b), we expected the effects of the positive-valence contrast to be smaller and those of the negative-valence contrast to be larger in individuals with ADHD compared to typically developing controls. We also expected these effects seen at a neural level to be mirrored in terms of participant's subjective ratings of the cues. With the certain loss cues being rated more negatively than the conditional loss and this being rated more negatively than the certain loss avoidance cues.

Third, although our main focus was on cue processing, we also looked at how participants responded to positive and negative feedback. We predicted a diminished response in the brain's reward circuits (i.e. VS) during positive feedback (successful monetary loss avoidance) and an increased response in emotional brain networks (i.e. amygdala and AI) for negative feedback (monetary loss avoidance failure) when comparing ADHD subjects with typically developing controls. For all these effects we predicted that greater effects would be seen when cues signalled the loss or potential loss of larger amounts of money.

Finally, we explored the effect of age on these effects. Based on previous fMRI studies on age-related reward processing differences in ADHD (Von Rhein *et al.*, 2015) and monetary loss avoidance effects in typically developing adolescents (Van Dessel *et al.*, 2021), no age-related findings were anticipated.

Material and methods
Participants

Eighteen right-handed male children (8–12 years) and 20 adolescents (13–18 years) with a clinical diagnosis of ADHD based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders 5 were recruited through the Child and Adolescent Psychiatry department of UPC-KU Leuven (Table 1). The reassessment procedure of ADHD diagnosis consisted of a Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime (KSADS-PL; Kaufman *et al.*, 1997) interview with one of the parents. Twenty-nine participants met the ADHD combined criteria and nine met criteria for the inattentive presentation. Nine ADHD participants fulfilled the criteria for an additional diagnosis of a learning disorder, one had comorbid autism spectrum disorder and one comorbid oppositional defiant disorder. Twenty-four of the children and adolescents with ADHD were taking psychostimulant medication (methylphenidate). Medication was withheld 48 h prior to testing. The Dutch version of the Disruptive Behaviour Disorders Rating Scale (Pelham *et al.*, 1992; Dutch translation Oosterlaan *et al.*, 2008) was administered to the parent(s) to assess dimensional symptom severity. Fifteen right-handed male typically developing children (8–12 years) and 18 adolescents (13–18 years) were included and were free of any current or lifetime psychiatric disorder as determined by the KSADS-PL interview. Groups were matched based on age and parental monthly allowance (Table 1). The full-scale intelligence quotient (IQ) for each subject was estimated using four subtests [vocabulary, similarities, block design and picture arrangement (Sattler, 2001)] of the Dutch adaptation of the Wechsler Intelligence Scale for Children (version 3; Kort *et al.*, 2005) or adults (version 4; Wechsler, 2005), and participants were excluded if their total IQ was below 80. The IQ scores of participants with ADHD were significantly lower than those of matched controls (Table 1). Participants were excluded if parents reported drug or substance abuse, neurological abnormalities or MRI contraindications. Written informed consent was obtained from parents and participants after detailed explanation of the study protocol. The study was approved by the Ethics Committee of the University Hospital Leuven, Leuven, Belgium (S59637).

Experimental paradigm and training

Participants performed the EMLI task (Van Dessel *et al.*, 2021), while their brain responses were acquired under fMRI (Figure 1). At the start of each trial, one of three possible geometrical cues (2 s) predicted a contingent or non-contingent monetary outcome. Triangle-shaped cues signalled the possibility of avoiding

Table 1. Demographic data, group characteristics (Disruptive Behaviour Disorders Rating Scale, Quick Delay Questionnaire) and response speed on the EMLI task are presented as mean (s.d.)

	ADHD (*n* = 33)	Control (*n* = 33)	*P*-value
Background characteristics			
Age (years)	13.3 (2.9)	13.7 (2.6)	0.53
IQ	98.1 (9.9)	106.7 (11.7)	<0.001
Allowance (€ per week)	4.9 (6.5)	4.6 (5.1)	0.85
Questionnaire measures			
Disruptive Behaviour Disorder Rating Scale (parent-rated behaviour problems)			
DBDRS—Inattention	15.0 (1.7)	10.8 (1.7)	<0.001
DBDRS—Hyperactivity/impulsivity	14.3 (2.4)	10.5 (1.3)	<0.001
DBDRS—Oppositional defiant disorder	13.9 (2.6)	10.8 (1.4)	<0.001
DBDRS—Conduct disorder	12.4 (2.0)	10.7 (1.0)	<0.001
Quick Delay Questionnaire (self-rated delay aversion and discounting)			
Delay aversion	16.8 (5.0)	13.9 (3.1)	0.005
Delay discounting	12.5 (2.7)	11.7 (3.1)	0.32
Response speed (in milliseconds)			
EMLI Task			
CONDITIONAL LOSS AVOIDANCE	400.6 (123.9)	375.5 (110.5)	<0.001
CERTAIN LOSS AVOIDANCE	424.2 (146.7)	395.7 (121.7)	<0.001
CERTAIN LOSS	423.4 (151.8)	401.7 (134.6)	<0.001

monetary loss (CONDITIONAL LOSS AVOIDANCE) by responding fast during target presentation, circle-shaped cues signalled that monetary loss would be imposed regardless of performance (CERTAIN LOSS) and diamond-shaped cues signalled that monetary loss would always be avoided regardless of performance (CERTAIN LOSS AVOIDANCE). Triangle- and circle-shaped cues both had horizontal lines that indicated how much money was at stake: three lines corresponded to €5, two lines to €1 and one line to €0.20. After an anticipation interval of between 3 and 3.5 s, a square target was briefly presented on the screen (0.25 s). Participants were instructed to respond as quickly as possible via a button box. Feedback (3 s) was given after responses—a green tick for 'fast enough' and a red cross for 'too slow'. This paradigm used a trial-by-trial staircase tracking procedure (+20 ms at fail / −20 ms at success) that adjusts the response window to obtain 'fast enough' responses in 66% of all trials for each participant. This also ensured that all participants lost the same amount of money (±€25 per run). Participants started with a €150 stake and were told that they could take home what money remained on completion of the task. All participants, however, received €50 upon study completion irrespective of their performance and were debriefed on the study purpose. Before scanning, participants received extensive training on a desktop computer outside the fMRI scanner to ensure that they learned the cue-related contingencies. After successful training, a practice run of 27 trials under the fMRI scanner was completed to determine the initial response threshold and to confirm the association between each cue and experimental condition. Familiarity with the EMLI task and scan procedure was checked for each participant. Whereafter, the actual MRI procedure was conducted in 5 experimental runs of 27 trials with a short break between each run and with a total duration of 25 min. Real-time monitoring of in-scanner performance confirmed that all participants were engaged in the task.

Subjective valence ratings of experimental cues

After task completion, subjects rated the valence they attached to the experimental cues used in the EMLI on a 7-point Likert scale (−3 negative, 0 neutral and +3 positive) and ranked the different cue types according to the extent they would be likely to invest effort on the upcoming reaction time task after their presentation. Participants were also asked to describe in words the emotions the different cue types elicited on four dimensions—negative (disappointed, frustrated, agitated), neutral (indifferent, normal), attentive (attentive, concentrated, focused) and positive (satisfied, I liked this, happy).

MRI acquisition and image pre-processing

Imaging was performed on a 3 T Philips Ingenia MR scanner (Philips Medical Systems, Best, The Netherlands) with a 32-channel head coil at the Department of Radiology of the University Hospital in Leuven. Functional scans were acquired using a blood-oxygen-level-dependent sensitive T2* echo imaging sequence with the following parameters: TR = 1100 ms, TE = 30 ms, flip angle = 90°, SENSE reduction factor = 2, field of view = 220 × 220 mm² without slice gap, 36 interleaved bottom-up slices with a spatial resolution of 2.75 × 2.75 × 3.75 mm. At the end of each scanning session, a high-resolution structural image was acquired using a standard T1-weighted pulse sequence with the following parameters: TR = 9.6 ms, TE = 4.6 ms, flip angle = 8°, field of view = 256 × 256 mm², spatial resolution of 1 × 1 × 1 mm. Stimuli were presented on a screen using Presentation (Neurobehavioral Systems, http://www.neurobs.com).

For pre-processing and statistical analyses, Statistical Parametric Mapping software (SPM12, Wellcome Trust Centre for Neuroimaging, London, UK) implemented in Matlab 7 (Math Works, Natick, Massachusetts, USA) was used. Children and adolescents with ADHD often struggle with lying still under the scanner and therefore their MRI images are more susceptible to motion artefacts. The ArtRepair SPM toolbox was used to prevent a decrease in data quality by detecting and removing scans with excessive motion. The recommended ArtRepair pre-processing steps were followed, which included slice-time correction of functional images, functional image realignment to the middle slice of each run, smoothing of functional images using a 3D Gaussian kernel of 4 mm full width at half maximum (FWHM), motion adjustment by removing volumes with >0.5 mm/TR, artefact repair, spatial normalization of all images to the Montreal Neurological Institute (MNI) space and smoothing of functional images using a 7 mm FWHM kernel (Mazaïka *et al.*, 2009). Runs with more than 25%

CONDITIONAL LOSS AVOIDANCE – slow response

CONDITIONAL LOSS AVOIDANCE – fast response

CERTAIN LOSS

CERTAIN LOSS AVOIDANCE

| Cue (2s) | Anticipation (3 - 3.5s) | Target (1.5 s) | Feedback (3 s) | Outcome (3 s) |

Fig. 1. EMLI task design. Cues indicate different money-related response consequences. The triangle (CONDITIONAL LOSS AVOIDANCE) signals monetary loss can be avoided (on 66% of trials) if reaction times meet performance thresholds (contingency). The circle (CERTAIN LOSS) demonstrates that monetary loss always occurs, regardless of reaction time (no contingency). The diamond (CERTAIN LOSS AVOIDANCE) indicates that monetary loss will not occur, regardless of the response speed (no contingency). Monetary amounts were €0.20, €1 or €5 and were indicated by one to three horizontal bars inside the cue. The analysis focused on cue presentation and feedback on performance.

of volumes repaired and participants with less than half of the runs remaining were excluded from image analyses. These criteria led to the removal of three children and two adolescents with ADHD, resulting in a final sample of 33 ADHD participants and 33 matched controls (each consisting of 15 children and 18 adolescents).

Statistical analyses
### Behavioural measurements
Two separate repeated-measures analysis of variance (ANOVA)s examined the effects of group (ADHD, control), condition (CONDITIONAL LOSS AVOIDANCE, CERTAIN LOSS, CERTAIN LOSS AVOIDANCE), age (8–12, 13–18 years) and run (1, 2, 3, 4, 5) on reaction time and subjective cue-valence ratings. To further investigate the effect of monetary amount (€0.20, €1, €5), additional ANOVAs were made with condition (CONDITIONAL LOSS AVOIDANCE, CERTAIN LOSS), group, monetary amount, run and age as within-subject factors. Post-hoc Bonferroni-corrected *t*-tests were used to explore significant interaction effects, when appropriate. Statistical analyses were conducted in SPSS (version 22, IBM, New York, USA) at a significance level of 0.05.

fMRI
A general linear model (GLM) was made with eight regressors of interest for each session: cue type (CONDITIONAL LOSS AVOIDANCE, CERTAIN LOSS, CERTAIN LOSS AVOIDANCE), monetary loss amount (€0.20, €1, €5) and performance outcome (success, fail). Realignment parameters and reaction times were included as regressors of no interest to account for variability in movement and response speed. Regressors were modelled at cue onset for the anticipation phase and feedback onset for performance outcome with a duration of 2 and 3 s, respectively. First, six t-contrast images were calculated for each subject to investigate the effects of contingency (CONDITIONAL LOSS AVOIDANCE > CERTAIN LOSS, CONDITIONAL LOSS AVOIDANCE > CERTAIN LOSS AVOIDANCE), valence (CERTAIN LOSS > CERTAIN LOSS AVOIDANCE, CERTAIN LOSS AVOIDANCE > CERTAIN LOSS), and feedback (CONDITIONAL LOSS AVOIDANCE success > CONDITIONAL LOSS AVOIDANCE fail, CERTAIN LOSS success > CERTAIN LOSS fail). Secondly, three supplementary contrast images were created to examine the influence of monetary loss amounts on contingency (CONDITIONAL LOSS AVOIDANCE €0.20 > CERTAIN LOSS AVOIDANCE, CONDITIONAL LOSS AVOIDANCE €1 > CERTAIN LOSS AVOIDANCE, CONDITIONAL LOSS AVOIDANCE €5 > CERTAIN LOSS AVOIDANCE). These specific monetary level contrasts were not created for the contingent CONDITIONAL LOSS AVOIDANCE > CERTAIN LOSS contrast, as CERTAIN LOSS also contains separate monetary levels and is therefore underpowered to explore dose–response influences. Finally, to check the potential influence of
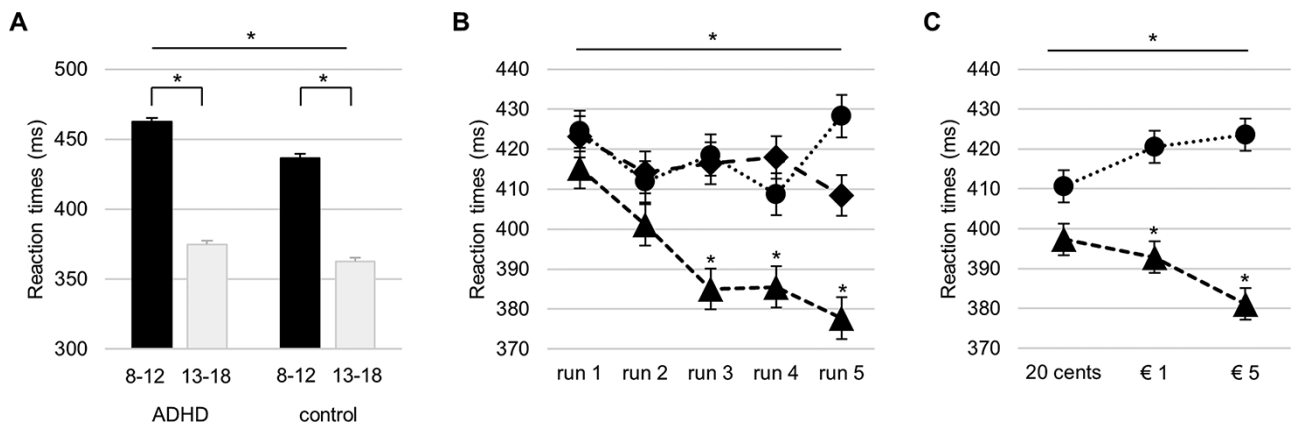
Fig. 2. Performance on the EMLI task. (A) For children (8–12 years) and adolescents (13–18 years) with ADHD and typically developing controls. (B) For the contingent CONDITIONAL LOSS AVOIDANCE cue (triangle), and non-contingent CERTAIN LOSS (circle) and CERTAIN LOSS AVOIDANCE (diamond) cues for each task session. (C) For CONDITIONAL LOSS AVOIDANCE (triangle) and CERTAIN LOSS (circle) for different monetary amounts. Depicted are the means and standard error of the mean in milliseconds. Asterisks (*) indicate $P < 0.05$.

time-on-task, the brain activity during runs 4–5 (only €50 remaining) was directly contrasted with runs 1–3 for the main contingency and valence contrasts. All individual t-contrast images were then used in second-level analysis. We first conducted a 2×2 factorial ANOVA with group (ADHD, control) and age (8–12 years, 13–18 years) as factors to test the main effects of group and age as well as the potential interaction of the two factors on whole-brain activation for contingency, valence and feedback contrasts. Parameter estimates were extracted at peak voxels of significant activated clusters to facilitate the interpretation of the feedback effects. In all whole-brain analyses, statistical tests were considered significant having a voxel level P-value of <0.05 family wise error (FWE) corrected and a cluster size of >5 voxels based on the peak beta-value and labelled using the automated anatomical labelling atlas (Tzourio-Mazoyer et al., 2002).

Results
Behavioural results
Performance EMLI task

In accordance with the hypothesis participants responded significantly faster ($F = 36.8$; $P < 0.001$; $\eta_p^2 = 0.008$) on CONDITIONAL LOSS AVOIDANCE trials compared to both CERTAIN LOSS and CERTAIN LOSS AVOIDANCE trials. Individuals with ADHD were significantly slower ($F = 50.496$; $P < 0.001$; $\eta_p^2 = 0.006$) compared to typically developing controls. No interaction between condition and group was found ($F = 0.7$; $P = 0.51$; $\eta_p^2 < 0.001$). A secondary age-analysis showed that children responded slower ($F = 50.496$; $P < 0.001$; $\eta_p^2 = 0.006$) than adolescents. There was an interaction between group and age ($F = 6.2$; $P = 0.001$; $\eta_p^2 = 0.001$) with the largest group difference occurring for children (Figure 2A).

A time-on task analysis indicated significantly ($F = 5.4$; $P < 0.001$; $\eta_p^2 = 0.002$) shorter reaction times towards the end of a session. An interaction between condition and time-on-task was found ($F = 3.3$; $P < 0.001$; $\eta_p^2 = 0.003$; Figure 2B) with shorter reaction times for the CONDITIONAL LOSS AVOIDANCE condition towards task end relative to the CERTAIN conditions.

There was no overall effect of monetary amount ($F = 0.7$; $P = 0.52$; $\eta_p^2 < 0.0001$), but an interaction between monetary amount and condition ($F = 4.8$; $P < 0.01$; $\eta_p^2 = 0.002$) was seen. Shorter reaction times were recorded with increasing monetary amounts in the CONDITIONAL LOSS AVOIDANCE condition relative to the CERTAIN LOSS condition (Figure 2C). No interaction

between the monetary amount and group was seen ($F = 2.8$; $P = 0.06$; $\eta_p^2 = 0.001$).

Subjective cue ratings

There was a main effect of condition ($F = 149.2$; $P < 0.001$; $\eta_p^2 = 0.57$). CERTAIN LOSS cues were rated significantly negatively (-1.9 ± 0.9), CONDITIONAL LOSS AVOIDANCE cues were rated as neutral (-0.2 ± 0.9) and CERTAIN LOSS AVOIDANCE cues were rated significantly positively ($+2.7 \pm 0.2$). There were no significant interactions between the condition and group ($F = 2.63$; $P = 0.07$; $\eta_p^2 = 0.01$), and age ($F = 0.67$; $P = 0.51$; $\eta_p^2 = 0.003$). Individuals with ADHD did not rate the cues significantly differently compared to controls ($F = 50.496$; $P < 0.001$; $\eta_p^2 = 0.006$) nor did children compared to adolescents ($F = 0.67$; $P = 0.51$; $\eta_p^2 = 0.003$).

There was a significant effect of amount of money ($F = 98.8$; $P < 0.001$; $\eta_p^2 = 0.33$). The higher the amount of money that could be lost, the more negatively the symbols were rated. The interactions between the monetary amount and condition ($F = 0.7$; $P = 0.50$; $\eta_p^2 = 0.003$) and the group ($F = 0.2$; $P = 0.84$; $\eta_p^2 = 0.001$) were not significant.

No significant group differences were found for the frequency of words used to describe the emotions attached to each condition. Participants used predominantly positive words to describe CERTAIN LOSS AVOIDANCE (89% ADHD, 92% controls) and negative words for CERTAIN LOSS cues (84% ADHD, 91% controls). For CONDITIONAL LOSS AVOIDANCE, the control group used words suggesting attentiveness to cues (88% attentive; 9% negative; 3% neutral), while for the ADHD group, it was slightly more negative (70% attentive; 24% negative; 6% neutral). All ADHD participants and controls indicated they wanted to put most effort in the CONDITIONAL LOSS AVOIDANCE condition. Participants reported CERTAIN LOSS was especially aversive from €50 downwards (run 4).

Functional imaging
Contingency effects

No significant group differences [P(FWE) > 0.05] were found at the whole-brain level for the two contingency contrasts CONDITIONAL LOSS AVOIDANCE > CERTAIN LOSS and CONDITIONAL LOSS AVOIDANCE > CERTAIN LOSS AVOIDANCE. However, similar brain activation patterns were observed for each group individually for both contrasts (for ADHD see Supplementary Table S1 and
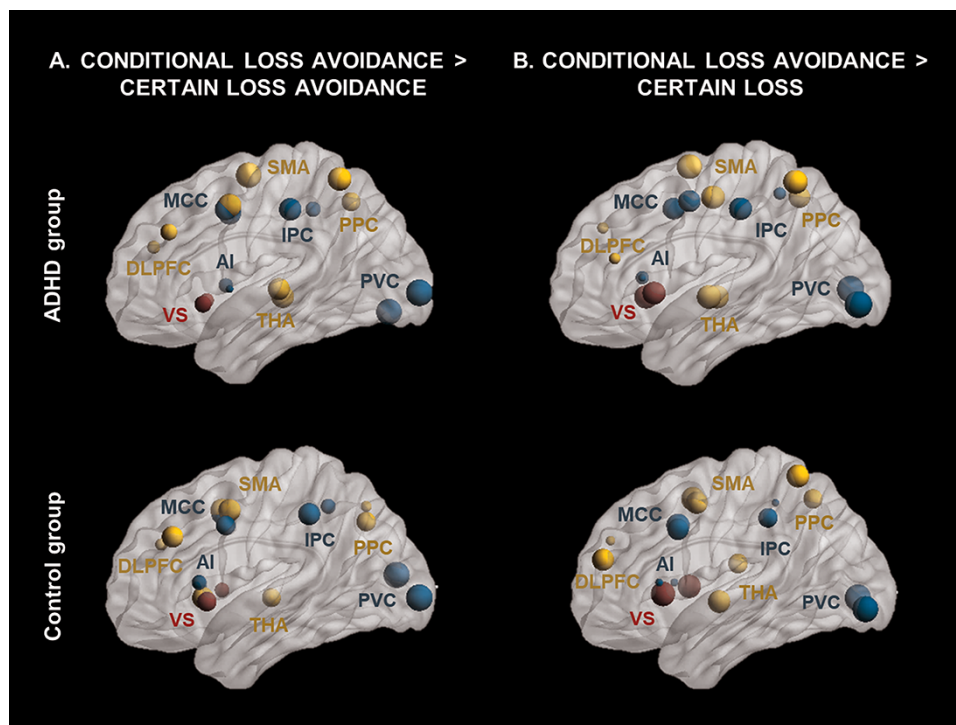
Fig. 3. Location of significant [P(FWE) < 0.05] whole-brain activation clusters for the contingent CONDITIONAL LOSS AVOIDANCE cue compared to non-contingent (A) CERTAIN LOSS AVOIDANCE and (B) CERTAIN LOSS cues between participants with ADHD and typically developing controls. Similar regions of the salience (AI, MCC, IPC, PVC), motor preparation network (DLPFC, PPC, THA, SMA) and VS were activated for each contingency contrast. The size of the dot corresponds with the cluster size.

for typically developing controls see Supplementary Table S2). CONDITIONAL LOSS AVOIDANCE cues elicited significant whole-brain activation [P(FWE) < 0.05] in the salience network (bilateral AI, mid-cingulate cortex, IPC, primary visual area), motor preparation network (bilateral THA, PPC, DLPFC, SMA) and VS compared to both CERTAIN LOSS and CERTAIN LOSS AVOIDANCE cues in both the ADHD and the typically developing control group (Figure 3).

Time-on task analysis indicated that the activation within these brain regions remained constant across the runs. There was a significant interaction (P < 0.05) between monetary amount and brain response in all activated brain regions for each group (Figure 4).

Valence effects

The ADHD group showed no significant differences [P(FWE) > 0.05] in whole-brain activation for positive (CERTAIN LOSS AVOID-ANCE > CERTAIN LOSS) and negative valence (CERTAIN LOSS > CERTAIN LOSS AVOIDANCE) in comparison with controls.

Feedback processing

Feedback indicating successful avoidance of loss in the CON-DITIONAL LOSS AVOIDANCE condition resulted in a significant hypoactivation of the bilateral VS for the ADHD group compared to controls (Table 2). This effect resulted mainly from an increased activation in the control group and decreased activation in the ADHD group during success feedback (Figure 5A). Fail-ure feedback in the CERTAIN LOSS condition led to a significant hyperactivation of the bilateral AI in ADHD participants compared to controls (Table 2). This effect is primarily due to increase activation in the ADHD group during failure feedback (Figure 5B).

Age-related differences

Relative to children, in adolescents there was a significant whole-brain hyperactivation [P(FWE) < 0.05] of the salience network (bilateral AI, MCC, IPC and PVC), motor response network (SMA, PPC, THA and DLPFC), and bilateral VS for CONDITIONAL LOSS AVOIDANCE cues relative to both CERTAIN LOSS AVOIDANCE and in less extent to CERTAIN LOSS cues (Figure 6 and Supplementary Table S3). No age-related differences were found for valence contrasts nor for feedback processing.

Discussion

Theoretical models on ADHD suggest that altered processing of reinforcement contingencies contribute to the disorder's symp-toms (Luman *et al.*, 2010). Evidence for these motivational deficits in ADHD comes mainly from fMRI studies that have demonstrated a diminished ventral-striatal response during reward anticipation and feedback (Plichta and Scheres, 2014). The question of whether these neural effects extend to negative reinforcement processes (such as monetary loss avoidance) is still unclear, despite recognition that both positive and negative consequences impact ADHD behaviour (Luman *et al.*, 2005; Furukawa *et al.*, 2017).

This fMRI study investigated ADHD-related alterations in the brain during the processing of monetary loss using a new EMLI task design where pre-target cues predicted either no contin-gency (CERTAIN LOSS, CERTAIN LOSS AVOIDANCE) or a contin-gency between performance and outcome (CONDITIONAL LOSS AVOIDANCE). We made three core predictions. First, that contin-gent stimuli (CONDITIONAL LOSS AVOIDANCE) would increase the performance and would enhance the salience and motor response preparation networks when being contrasted with the non-contingent conditions (CERTAIN LOSS, CERTAIN LOSS
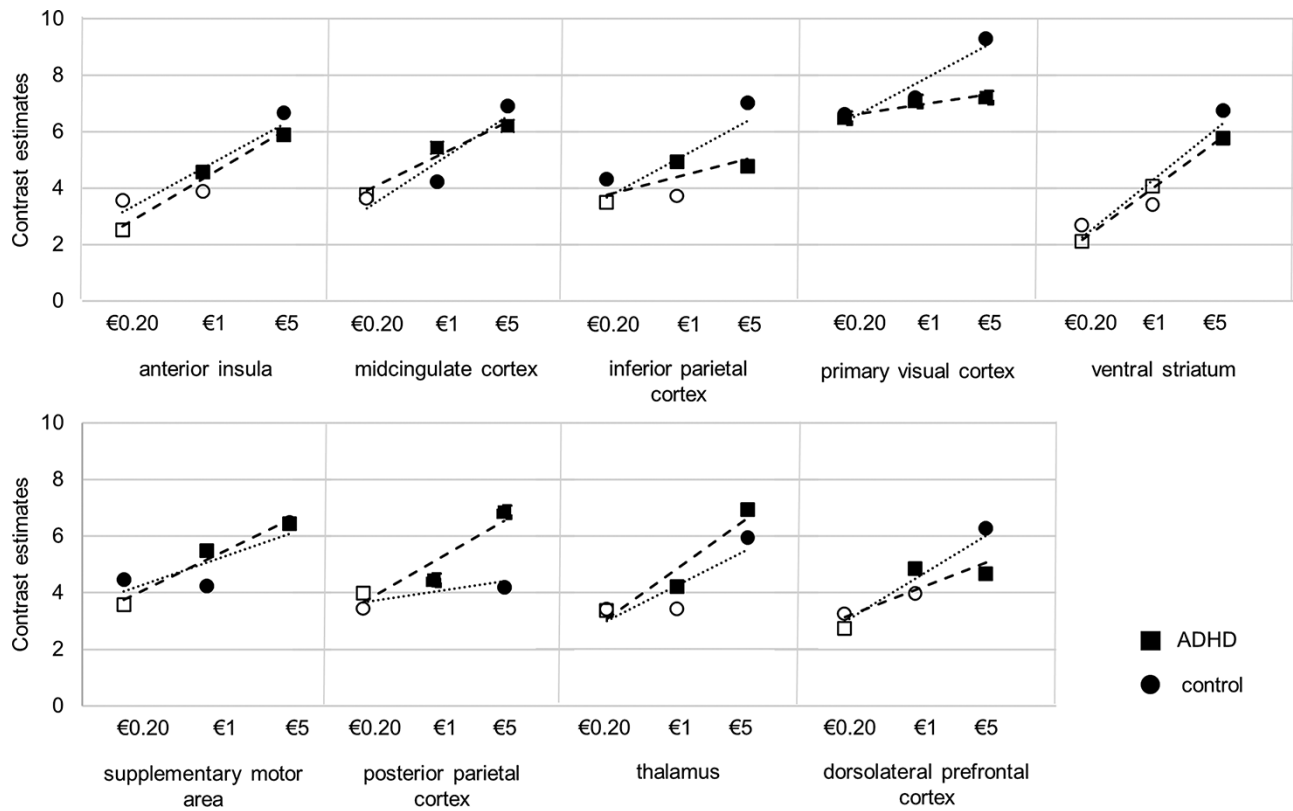
Fig. 4. Dose–response relationships for brain regions within the salience and motor preparation network for ADHD (square) and control (circle) participants. Contrast estimates were extracted at peak activation clusters for CONDITIONAL LOSS AVOIDANCE *vs* CERTAIN LOSS AVOIDANCE. Neural activation was averaged across both hemispheres. Filled dots indicated significant brain activation (P < 0.05) for a given monetary amount.

Table 2. Whole-brain-based differences of estimated brain activations between ADHD and control group for feedback contrasts

|		MNI			T	P	Cluster
	Side	X	Y	Z	Score	(FWE)	size
Control > ADHD							
CONDITIONAL LOSS AVOIDANCE success > failure							
Ventral striatum	L	−28	−18	6	3.86	0.02	185
	R	28	44	6	3.45	0.04	42
CONDITIONAL LOSS AVOIDANCE failure > success							
No suprathreshold voxels							
ADHD > control							
CERTAIN LOSS success > failure							
No suprathreshold voxels							
CERTAIN LOSS failure > success							
Anterior insula	L	−30	14	6	4.01	0.007	25
	R	44	0	4	4.07	0.006	50

AVOIDANCE). We expected these effects to be smaller children and adolescents with ADHD compared to their peers based on their reward processing deficits. Second, those children and adolescents with ADHD would show an exaggerated response to CERTAIN LOSS relative to CERTAIN LOSS AVOIDANCE cues based on the idea that they are more sensitive to the aversive properties of stimuli. Third, that positive feedback (successful monetary loss avoidance) would have a diminished response in the brain's reward circuits (i.e. VS), and negative feedback (monetary loss avoidance failure) would lead to an increased response in emotional brain networks (i.e. amygdala and AI) when comparing ADHD subjects with controls.

With regard to the first prediction, contrary to fMRI findings for positive reinforcements (Plichta and Scheres, 2014), there was

no evidence of an altered response to anticipation of contingent or non-contingent monetary loss at any level. At a behavioural level, cues signalling the opportunity to avoid monetary loss were found equally reinforcing by speeding up responses to the target for ADHD and typically developing controls. Reaction times were faster on CONDITIONAL LOSS AVOIDANCE trials than the two 'certain' types. This is in line with behavioural studies that showed that motivational contingencies do not differentially affect the performance of children and adolescence with ADHD when compared to typically developing controls (Solanto, 1990; Uebel *et al.*, 2010; Liddle *et al.*, 2011). Both groups showed a clear distinction of cues in terms of valence and motivation ratings, with CERTAIN LOSS being rated negatively, CERTAIN LOSS AVOIDANCE being rated positively and CONDITIONAL LOSS

A **CONDITIONAL LOSS AVOIDANCE: Ventral Striatum**
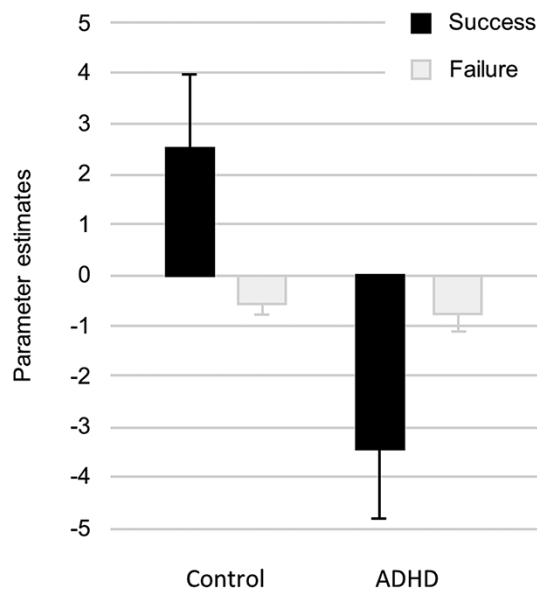
B **CERTAIN LOSS: Anterior Insula**
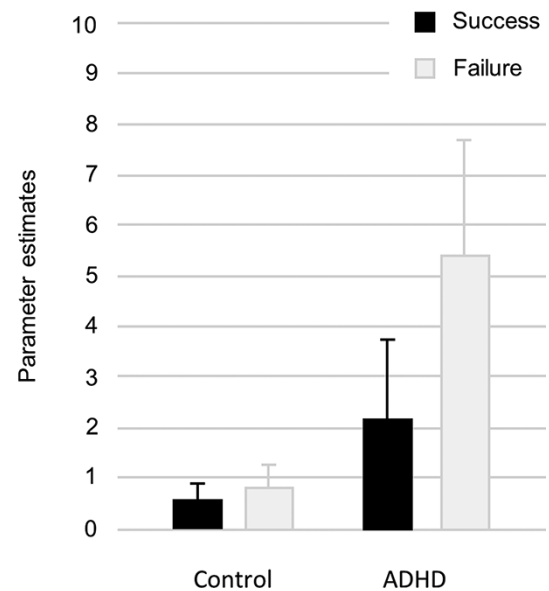
Fig. 5. Parameter estimates extracted at the significant peak voxels and averaged over both hemispheres for the conditions (A) CONDITIONAL LOSS AVOIDANCE and (B) CERTAIN LOSS to successful and failure feedback for the ADHD and control group.
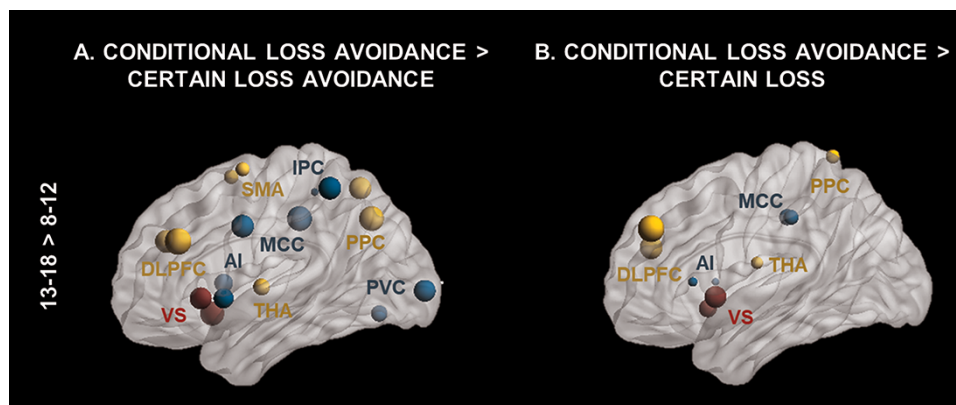
Fig. 6. Location of significant [$P(FWE) < 0.05$] whole-brain activation clusters for the contingent CONDITIONAL LOSS AVOIDANCE cue compared to non-contingent (A) CERTAIN LOSS AVOIDANCE and (B) CERTAIN LOSS cues between adolescents (13–18 years old) and children (8–12 years old). Similar regions of the salience (AI, MCC, IPC, PVC), motor preparation network (DLPFC, PPC, THA, SMA) and VS were activated for each contingency contrast. The size of the dot corresponds with the cluster size.

AVAIDANCE being rated motivational. This suggested that all participants were aware of the distinctive valence and salience properties of the cues, confirming that the EMLI behaviourally engaged participants' negative reinforcement processes.

Crucially, for the aims of the current paper, the EMLI task also effectively differentiated the specific brain responses associated with contingency and valence (Van Dessel *et al.*, 2021). In line with our predictions and behavioural findings, CONDITIONAL LOSS AVOIDANCE cues activated brain regions previously associated with the salience network anchored in the MCC, AI and IPC and PVC (Jensen *et al.*, 2007; Kahnt *et al.*, 2014). It has been frequently shown that when a directed action is required, the salience network co-activates with a distinct motor preparation network that consists of the SMA, PPC, THA and DLPFC (Lau *et al.*, 2004; Seeley *et al.*, 2007). In line with previous investigations, we found that higher monetary amounts seemed to induce larger brain activity

within these brain regions of the salience and motor preparation network (Lallement *et al.*, 2014).

Our results demonstrate that the brain processes underpinning contingency-related actions are intact in ADHD—at least with regard to monetary loss. This finding is in accordance with electrophysiological research in which event-related potentials associated with attention allocation (cue P3) and cognitive preparation (contingent negative variation) were only attenuated in ADHD on non-incentive trials (Albrecht *et al.*, 2013). Heinrich and colleagues (2017) found no differential effects on reward contingent cues on either cue component between ADHD and controls. This was further confirmed by Chronaki and colleagues (2017) who found that cue P3 and CNV were not differently modulated by contingency between ADHD and controls. Previous fMRI studies using MID tasks were not able to isolate the neural activity specifically associated with motivational salience

towards avoidance of monetary loss, as they were not able to distinguish contingency from valence effects (Maunsell, 2004; Litt *et al.*, 2011). This is because MID tasks typically rely on the direct contrast between monetary gain and monetary loss cues, therefore indistinguishably mixing up the relative contribution of each valence outcome. Differential brain responses have been found for the same monetary amount during 'gain' conditions ($0 is the worst possible outcome) and 'lose' conditions ($0 is the best possible outcome) (Nieuwenhuis *et al.*, 2005).

With regard to the second prediction, there was no evidence of a heightened neural sensitivity to the aversiveness of monetary loss anticipation. This despite that one of the certain cues CERTAIN LOSS AVOIDANCE was designed and clearly experienced by participants as positively valenced and the other CERTAIN LOSS experienced and recognized as negatively valanced. This seems to stand in stark contrast to previous fMRI research using a very similar paradigm in which children and adolescents with ADHD displayed amygdala hyperactivation in response to cues predicting the imposition of delay (Lemiere *et al.*, 2012; Wilbertz *et al.*, 2013; Van Dessel *et al.*, 2018, 2019b). This indicates that individuals with ADHD are not more sensitive to aversive stimuli in general but rather to specific aversive stimuli such as delay (Sonuga-Barke, 2005; Van Dessel *et al.*, 2019a). In contrast to the models predicting neural hypoactivation during reward processing in ADHD, the delay aversion theory postulates hyperactivation in the emotional network towards delayed reward. Future studies testing delayed monetary loss can result in another neural activation pattern.

Despite the fact that the processing of reinforcement contingencies seems to be intact, children and adolescents with ADHD show a different response to performance feedback compared to typically developing controls. A diminished brain response to successful and an increased response to failure feedback was found. This is consistent with the neuroimaging literature on feedback processing, where children and adolescents with ADHD show a hypoactivation of the VS to positive feedback (Plichta and Scheres, 2014) and hyperactivity of the AI to negative feedback (Wilbertz *et al.*, 2017). Several neuropsychological studies have indicated a dysfunctional processing of positive and negative feedback in ADHD (Van Meel *et al.*, 2005; Groen *et al.*, 2008, 2013; Rosch and Hawk, 2013). The present findings indicate that subjects with ADHD do not simply show blunted responses to all stimuli but overreact to aversive outcomes.

Of more general interest, there was an age-specific increase in activation of the salience and motor preparation network towards contingent monetary loss cues. Both age groups, however, reported to perform their utmost best when they had the opportunity to avoid monetary loss and no differential brain response was seen for valence-related and feedback-related contrasts. Since the neurocognitive level automatically increases with age, it is difficult to say how specific the age-related effects are for negative reinforcement (Reed *et al.*, 2014). A staircase tracking algorithm of the EMLI ensured that brain responses were not linked to differences in performance. Reaction times were included in the GLM to account for variability in response speed. Evidence from neurodevelopmental studies has solely focused on positive reinforcing brain effects and consistently reported increased activation in the VS to monetary gain during adolescence (Bjork *et al.*, 2004; Galvan *et al.*, 2006; Van Leijenhorst *et al.*, 2010). Future studies are needed to replicate these findings not only for monetary loss avoidance but for other aversive stimuli in general.

Despite clear evidence that the task itself worked well in distinguishing contingency effects since these were mirrored in terms of performance and subjective ratings of cue valence, there are some limitations that need to be taken into account. First, these results focus on a specific subgroup of ADHD, more specifically right-handed boys with ADHD. Although ADHD is more common in males, these findings may not be generalised to the overall ADHD population. Second, studying age-related changes is challenging, as there is a large heterogeneity of aging processes especially during puberty. Individual differences in the rate of development might also result in variable functional patterns of activation in children and adolescents (Casey *et al.*, 2000), which could reduce group activation maps. Slower cortical thinning during adolescence has been linked with the presence of ADHD symptoms (Shaw *et al.*, 2011). Unfortunately, we did not control for precise pubertal development using any standardized measures. Third, to guarantee equal performance of participants, the significance of each cue symbol was trained before the start of the experiment. This meant that the process of learning could not be studied. Future research should examine the effects of contingency during learning.

Conclusion

The current results were clear cut in finding no evidence that children and adolescents with ADHD react to anticipation of monetary loss differently from controls in terms of either contingency-related or valence-related effects. Motivational models of ADHD need to explain the specificity of motivation effects—why they show *a general* hyposensitivity to the positive reinforcement (monetary gain) but not negative reinforcement (monetary loss avoidance).

Conflict of interest

The authors declare no competing financial interests.

Supplementary data

Supplementary data are available at SCAN online.

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