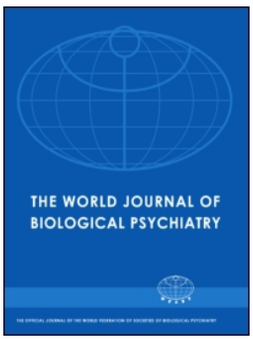

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ORIGINAL INVESTIGATION

Neural response during anticipation of monetary loss is elevated in adult attention deficit hyperactivity disorder

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ABSTRACT

Objectives: Risky behaviour seriously impacts the life of adult patients with attention deficit hyperactivity disorder (ADHD). Such behaviours have often been attributed to their exaggerated reward seeking, but dysfunctional anticipation of negative outcomes might also play a role. *Methods*: The present study compared adult patients with ADHD ($n = 28$) with matched healthy controls ($n = 28$) during anticipation of monetary losses versus gains while undergoing functional magnetic resonance imaging (fMRI) and skin conductance recording. *Results*: Skin conductance was higher during anticipation of losses compared to gains in both groups. Affective ratings of predictive cues did not differ between groups. ADHD patients showed increased activity in bilateral amygdalae, left anterior insula (region of interest analysis) and left temporal pole (whole brain analysis) compared to healthy controls during loss versus gain anticipation. In the ADHD group higher insula and temporal pole activations went along with more negative affective ratings. *Conclusions*: Neural correlates of loss anticipation are not blunted but rather increased in ADHD, possibly due to a life history of repeated failures and the respective environmental sanctions. Behavioural adaptations to such losses, however, might differentiate them from controls: future research should study whether negative affect might drive more risk seeking than risk avoidance.

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ADHD; fMRI; monetary loss; reward; anticipation

Introduction

Altered response to positive or negative outcomes in everyday life can promote risky and maladaptive decisions. Take the example of parking in a busy street when you are in a hurry. Some people may be willing to park illegally and risk the negative consequence of a fine, but others may be more sensitive to the potential negative outcome and decide to not take the risk. This simple example can extend to more difficult, complex decisions (e.g., drug-seeking behaviour) and has implications for clinical disorders where anticipation of positive and negative outcomes is affected.

Attention deficit hyperactivity disorder (ADHD) has frequently been associated with abnormalities in reward processing (Wender 1972; Haenlein and Caul 1987; Sagvolden et al. 2005; Tripp and Wickens 2008; Rubia et al. 2009; Wilbertz et al. 2012) and, consequently, with a number of maladaptive behaviours in adults, including drug abuse (Elkins et al. 2007), sexual risk taking (Flory et al. 2006), risky driving (Barkley and Cox 2007) and traffic violations (Fischer et al. 2007). Behaviourally, individuals with ADHD often show performance deficits compared to healthy controls in tasks without reward but tend to increase their performance to a greater extent than healthy controls when reward is provided (Konrad et al. 2000; Marx et al. 2013). Similar effects have been observed in response to negative outcomes, i.e., children with ADHD showed stronger improvements than healthy children in problem solving tasks after introduction of negative consequences (Carlson and Tamm 2000). Thus, behavioural evidence suggests a high sensitivity to both positive and negative outcomes in ADHD. Interestingly, neuroimaging research has focussed largely on positive outcomes and revealed diminished rather than enhanced neural response to

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reward cues in patients with ADHD (Scheres et al. 2007; Ströhle et al. 2008; Carmona et al. 2012) (see also Plichta and Scheres 2014, for review). Deficient signalling of delayed reward in dopaminergic neurons is considered as one potential explanation (Sagvolden et al. 2005; Tripp and Wickens 2008; Plichta et al. 2009) which could result in compensatory higher reward seeking (Blum et al. 2008).

However, less is known about neural representation of *negative outcomes* in ADHD. This is surprising, since maladaptive behaviour in ADHD results in an increased frequency of experiencing negative outcomes (like accidents, injuries, fines, and sanctions, Fischer et al. 2007; Mannuzza et al. 2008; Nigg 2013). Thus, besides deficient reward anticipation also the anticipation of negative outcomes might be altered in ADHD (Quay 1997). Empirical evidence, however, is scarce. Stoy et al. (2011), for example, used the monetary incentive delay task and did not find altered brain activations in adults with childhood ADHD during the anticipation of monetary loss. Likewise, Maier et al. (2014) found normal brain activations in differential fear conditioning using electrical shocks in adults with ADHD. However, during an instructed fear paradigm (no shock application) in another study by Maier et al. (2014) patients exhibited hypoactivation in the dorsal ACC and an inverse pattern in the amygdala. Our own previous work demonstrated increased responsiveness of the amygdala in adult patients compared to healthy controls during the anticipation of forced waiting times (Wilbertz et al. 2013), which are supposed to be particularly aversive to individuals with ADHD (Sonuga-Barke 2005). A number of other studies involved both gains and losses but confined their focus to reward related regions, making it difficult to evaluate responding to negative outcomes in ADHD (Scheres et al. 2007; Ströhle et al. 2008; Carmona et al. 2012). Thus, whereas abnormalities during reward processing in ADHD seem to be associated with neural hypoactivation, studies on negative outcomes have not revealed a consistent neural response pattern.

To gain more insight into the neural representation of anticipated negative outcomes and possible deficits in adult ADHD, the present study featured a probabilistic anticipation of monetary loss, representing one of the most frequent societal penalties in adulthood. Anticipation of loss was directly compared against anticipation of gains to mimic the trade-off of negative and positive outcomes characteristic of many real-life situations and to account for possibly abnormal responses of ADHD patients to no-outcome events (cf. delay aversion, Sonuga-Barke 2005; Wilbertz et al. 2013; Maier et al. 2014; also see below: data analysis). We focussed our analysis on regions of interest (ROIs) previously involved in anticipation of negative outcomes (i.e., striatum, amygdala, anterior insula, Phelps et al. 2001; Mechias et al. 2010; Delgado et al. 2011). With regard to the direction of our hypothesis, we built on evidence of a positive correlation between neural activity during loss anticipation and later avoidance of negative outcomes (Samanez-Larkin et al. 2008). Given the presence of risky behaviour in adult ADHD (Flory et al. 2006; Barkley and Cox 2007; Elkins et al. 2007; Fischer et al. 2007), we assumed the anticipation of negative outcomes to be deficient and therefore expected lower neural activation in ADHD than healthy controls during the anticipation of loss. We further explored relationships of neural responses with affective ratings of loss and gain predicting cues.

Methods

Participants

Twenty-eight right-handed adult patients with a clinical diagnosis according to the German guidelines for adult ADHD (Ebert et al. 2003) which correspond to the DSM-IV criteria (APA 1994) were recruited from a specialised outpatient clinic for adult ADHD. Seven patients had at least one current comorbid disorder (five anxiety disorder, one substance abuse, two dysthymic disorder, one major depression, two somatoform disorder), nine further patients had a comorbid lifetime diagnosis as determined by the Structured Clinical Interview for DSM-IV-TR interview (SCID, First and Pincus 2002; see supplementary material for analyses of pure ADHD and comorbid subgroups). Exclusion criteria were schizophrenia, bipolar, borderline or antisocial personality disorder and acute substance dependence. All patients were free of medication for at least 2 months. Twenty-eight right-handed control participants were recruited from general population via newspaper advertisement and were free of any current or lifetime mental disorders as determined by the SCID interview. Samples were matched with regard to age, gender, education and financial situation (i.e., amount of monthly spare money; see Table 1 for sample characteristics). All participants gave informed written consent. The study was approved by the local ethic committee. Most of the patients and participants were identical to a previous report from our group (Wilbertz et al. 2012). With regard to our analyses, however, all data reported here are original (with the exception of sample characteristics and psychopathological symptoms questionnaires).

Task procedure

The anticipation of monetary loss & gain task (see Figure 1) is a modified version of conditioning paradigms previously used by Delgado et al. (2006, 2011). Participants were

Table 1. Sample characteristics and descriptive variables.

Variable	ADHD Patients ($N = 28$)	Healthy Controls ($N = 28$)	P value
Age	38.25 (9.04)	37.11 (9.38)	0.644
Gender (m/f)*	15/13	15/13	n/a
Educational level (low/medium/high/college)*	5/9/8/6	3/12/8/5	0.797
Financial situation (20€ remain monthly)§	95 (237.02)	100 (278.71)	0.365
Satisfaction with financial situation (7 ratings 1–7)	4.14 (1.17)	4.65 (1.06)	0.094
Unemployed*	4	2	0.284
Smoker*	12	8	0.265
Hours sleep per night	6.61 (1.17)	7.21 (0.97)	0.041
Hours sleep during night before	6.55 (1.10)	7.80 (1.56)	0.001
Beck Depression Inventory (BDI-II)	15.26 (11.28)	4.59 (3.62)	<0.001
State Trait Anxiety Inventory (STAI) – State	43.58 (7.89)	33.64 (6.63)	<0.001
State Trait Anxiety Inventory (STAI) – Trait	48.37 (6.96)	33.91 (6.89)	<0.001
Conners'Adult ADHD Rating Scale (CAARS)	101.55 (24.13)	34.45 (14.55)	<0.001
Subscale hyperactivity	17.19 (5.61)	7.31 (3.67)	<0.001
Subscale impulsivity	18.36 (5.44)	6.14 (3.05)	<0.001
Subscale inattention	19.45 (7.21)	6.18 (3.92)	<0.001
Wender Utah Rating Scale short (WURS-k)	39.52 (10.55)	–	

Reported are mean and standard deviation (*SD*) as well as the *P* value of the two sample *t*-test unless specified differently.
*Reported are counts and the *P* value of the chi-square test.
§Reported are median and *SD* as well as the *P* value of the Mann–Whitney *U*-test (due to non-normal distribution of the variable). Financial situation ratings (Fahrenberg et al. 2000), BDI-II (Hautzinger et al. 2006), STAI (Spielberger et al. 1970), CAARS (Conners 1999; Christiansen et al. 2011,2012).

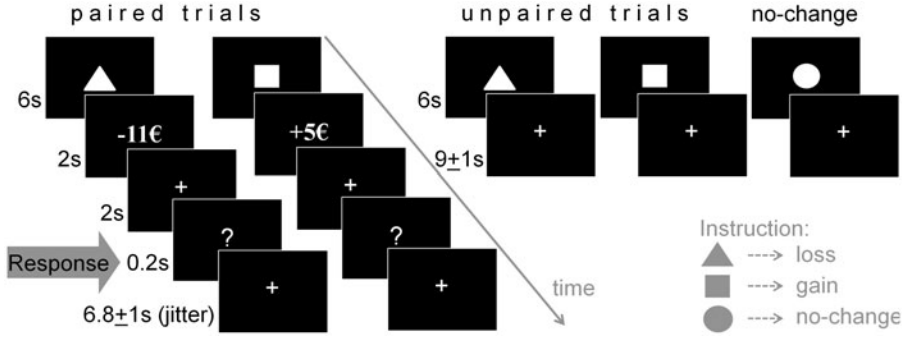

Figure 1. Task design. Trials of the anticipation of loss and gain task started with a presentation of a geometrical shape ("cue") that was either followed by a monetary loss or gain (25% paired trials), or no change in balance (75% unpaired trials). In addition, an explicit no-change cue was never followed by any loss or gain. Participants were informed about the specific meaning of each shape beforehand (i.e., its association with loss, gain or no-change) in order to trigger anticipatory responses from the very beginning of the task. Importantly, anticipation was purely passive since the outcome could not be influenced by participants (note, button presses after receipt of a gain or loss served to ensure continuous attention to the stimuli, only). Analyses of fMRI data focussed on unpaired trials.

presented with three different geometrical forms, each predicting a probabilistic monetary outcome (loss, gain, "no change"). Specifically, participants were informed that: stimulus A (e.g., a triangle) predicted a possible loss of €11 (about $15); stimulus B (e.g., a square) predicted a possible gain of €5 (about $7); and stimulus C (e.g., a circle) predicted a neutral outcome of €0 ("no change" in balance). Stimulus-condition assignment was counterbalanced across participants/groups. To ensure that participants were attentive to the task, they were asked to press a button in response to gain or loss outcomes (prompted by a question mark, see Figure 1) to indicate they acknowledged the outcome (response rates and times are reported in Supplemental Table S1 available online). Further, they were told that the outcome was not contingent on their response (unlike previous paradigms; e.g., Delgado et al. 2000; Tricomi et al. 2004), i.e., probabilistic anticipation was purely passive in this task. Participants were presented with 40 trials during the experimental session, broken down into 16 trials of loss and gain each (four of which were accompanied by a monetary gain or loss respectively, i.e., "paired", 12 were "unpaired") and eight "no change" trials. Each trial consisted of a cue presentation (stimulus A, B or C, 6 s), followed by a jittered inter-trial interval (8–10 s). During trials that were reinforced by a monetary loss or gain ("paired trials"), an outcome screen (2 s) immediately followed the cue presentation indicating the monetary reinforcer (€–11 or 5) along with a corresponding acoustical signal (buzzer or pling sound, respectively). Trials from all three conditions were displayed in a pseudo-random order. Participants rated the valence of each of the three cues on an 11-point Likert scale (–5 unpleasant to 5 pleasant) twice in the experiment: pre- (i.e., before

contingency instructions) and post-task. The anticipation task was preceded by a card-guessing task (Delgado et al. 2000) during which participants earned a monetary endowment of €48 (about $65, results reported in Wilbertz et al. 2012). This endowment was important for the current study as the participants were instructed that losses in the anticipation task were subtracted from this initial endowment (similar to Delgado et al. 2006,2011). At the conclusion of the experiment, participants were debriefed and compensated for their participation.

Physiological set-up and skin conductance analyses

Skin conductance was measured with two electrodes on the left hand middle and ring finger tip (BrainAmps ExG MR, BrainProducts). Data were preprocessed using an in-house software (Avg_q, https://github.com/berndf/avg_q). Skin conductance responses (SCRs) were assessed as base to peak difference, using the mean signal ±500 ms around cue onset as base and the maximum within 0.5–4.5 s after cue onset as peak. Base to peak differences <0.01 were set to zero. All SCRs were square root transformed.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) was performed on a 3-Tesla Siemens Trio MR scanner (Siemens AG, Erlangen, Germany) with a standard eight-channel ^{1}H head coil. Functional scans were acquired using a blood–oxygen-level dependence (BOLD) sensitive T2*-gradient echo planar imaging sequence (TR = 2.25 s, TE = 30 ms, flip angle = 90°, 36 axial slices with 3 mm thickness, field of view, FOV = 192 mm, spatial resolution = 3 × 3 × 3 mm). Structural images were acquired using a standard T1-weighted pulse sequence (TR = 2.2 s, TE = 4.11-ms, flip angle = 12°, FOV = 256 mm, spatial resolution = 1 × 1 × 1 mm).

Data analysis

Functional imaging data were analysed with SPM8 (http://www.fil.ion.ucl.ac.uk/spm) after an automatic online correction for motion and distortion artefacts and discharging the first five scans. Pre-processing comprised manual rigid body transformation to match the MNI (Montreal Neurological Institute) standard brain's AC-PC orientation, slice timing correction, realignment to the first image, co-registration of the structural image, spatial normalisation into the MNI reference system and smoothing (6 mm full-width at half maximum). The general linear model included the following regressors for anticipation: loss cue paired, loss cue unpaired, gain cue paired, gain cue unpaired, "no change" cue. Anticipation was modelled by a 6-s boxcar function and convolved by the canonical hemodynamic response function. Additional regressors of no interest coded for actual losses, gains, and button presses (each modelled as an event with 1 s duration) as well as head movements (using realignment parameters). Slow signal changes were filtered at 1/128 Hz. fMRI analyses focussed on the non-reinforced (unpaired) trials to avoid response overlap with the outcome. As main outcome, one contrast image was computed based on beta values of task regressors modelling loss and gain anticipation for every participant ("loss > gain anticipation" contrast). Contrasts including the "no change" condition, presented with lower frequency, were used for secondary control analysis (reasons for the lower sampling of no-change conditions were practical concerns, i.e., total task duration constrains, as well as doubts on the "neutral character" of no-change conditions in ADHD, cf. delay aversion (Wilbertz et al. 2013; Maier et al. 2014) and altered responses to neutral pictures or missing gains and losses (Ströhle et al. 2008; Schlochtermeier et al. 2011; Stoy et al. 2011; van Meel et al. 2011)). One sample and independent samples *t*-tests were performed on the loss > gain anticipation contrast image. Anatomical masks from the automatic anatomical labelling project (Tzourio-Mazoyer et al. 2002) were used for definition of ROIs (left amygdala 36 voxels, right amygdala 49 voxels, left anterior [defined as $y > 0$] insula 355 voxels, right anterior insula 308 voxels, left striatum [defined as caudate + putamen] 553 voxels, right striatum 579 voxels). *P* values of voxels within these ROIs were family-wise error (FWE) corrected for the corresponding ROI using SPM's small volume correction. In an exploratory whole brain analysis *P* values of all voxels outside these ROIs were FWE corrected for voxels from the entire brain.

To aid the interpretation of group differences, contrast estimates were extracted at peak voxels of significantly activated clusters and correlated with cue ratings and measures of self-reported psychopathological symptoms (ADHD, depression, anxiety), separately for ADHD patients and healthy controls (Spearman's coefficients).

Results

Subjective ratings

A 2 × 2 × 2 ANOVA (group [ADHD/healthy control] × time [pre-/post-task] × condition [loss/gain]) on cue valence ratings yielded a significant interaction of condition and time ($F[1, 54] = 107.25$, $P < 0.001$), as well as a marginal group main effect ($F[1, 54] = 3.22$, $P = 0.078$). Further interaction or main effects were not significant (all $Ps > 0.141$). Post-hoc tests revealed significantly decreased (i.e., more negative) ratings of the

loss cue from pre- to post-task ($t[55] = -3.18$, $P = 0.002$) as well as significantly increased (i.e., more positive) ratings of the gain cue ($t[55] = 4.52$, $P < 0.001$). There was a statistical trend for more negative affective ratings of the loss cue after the experiment in ADHD patients compared to healthy controls ($t[54] = 1.74$, $P = 0.087$) but no difference for the gain cue or before the experiment (all $Ps > 0.29$, see Figure 2A).

Skin conductance responses

A 2×2 ANOVA (group $\times$ condition) of SCRs yielded a significant main effect for anticipation condition ($F[1, 54] = 7.32$, $P = 0.010$), but no interaction with group or group main effect (all $Ps > 0.76$). SCR was higher during loss than gain anticipation (see Figure 2B).

Imaging results

We used a priori ROIs in left and right amygdala, anterior insula, and striatum and tested for differences between groups in the main contrast "loss > gain anticipation". We observed significantly higher activation for ADHD patients compared to healthy controls in the left anterior insula and bilateral amygdala (all P values < 0.047, FWE corrected for small volume, see Table 2 and Figure 3). Other ROIs showed no differences between the two groups (all $Ps[FWE] > 0.178$). Post-hoc tests indicated significant activation within the ADHD group alone for these ROIs (left anterior insula $P[FWE] = 0.008$, left and right amygdala $P[FWE] = 0.016$ and 0.030, respectively; see Figure 3B). Within the healthy control group, there was no significant activation in these ROIs (marginal statistical trends rather pointed to a reverse pattern, i.e., higher activation for gain than loss anticipation, see Supplemental Table S3 available online).

To test whether it was actually loss or gain that drove group differences in the "loss > gain anticipation" contrast we compared loss and gain separately against the putative neutral ("no change") condition. Differences between groups were generally more prominent during loss anticipation (e.g., left amygdala at trend level, $P[FWE] = 0.055$, left striatum $P[FWE] = 0.029$) than during gain anticipation (all P values$[FWE] > 0.428$; see Supplemental Table S3 available online for more details).

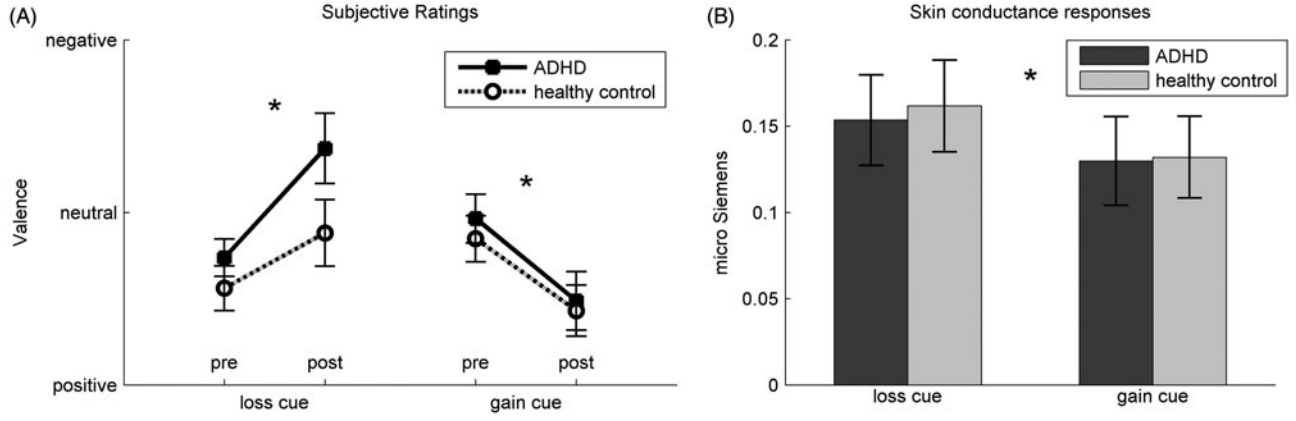

Figure 2. Behavioural results. Valence ratings of loss and gain cues before ("pre") and after ("post") the experiment (A) as well as SCRs to these cues during the experiment (B). *Indicates significant main effects ($P < 0.05$), the group differences for post-rating of the loss cue was only marginally significant ($P < 0.10$), depicted are means and standard errors.

Table 2. Region of interest (ROI)-based analyses of estimated brain activations in the predefined contrast "loss > gain anticipation" for healthy controls vs. ADHD patients.

		MNI Coordinates					
Contrast	ROI	*x*	*y*	*z*	*t*	*P* (FWE)	*P* (uncorrected)
Loss > gain anticipation							
Control > ADHD	*No suprathreshold activations*						
ADHD > Control	Anterior Insula L	−33	8	16	3.72	0.047	<0.001
	Anterior Insula R	33	17	−8	2.57	0.444	0.007
	Striatum L	−24	−4	−8	3.03	0.321	0.002
	Striatum R	15	−19	22	3.35	0.178	0.001
	Amygdala L	−27	−7	−14	3.59	0.013	<0.001
	Amygdala R	30	−1	−26	4.17	0.003	<0.001

Depicted are peak voxels within ROIs thresholded at $P < 0.05$ uncorrected.
MNI, Montreal Neurological Institute; FWE, family-wise error corrected; ROIs significant at $P[FWE] < 0.05$ are depicted in bold.

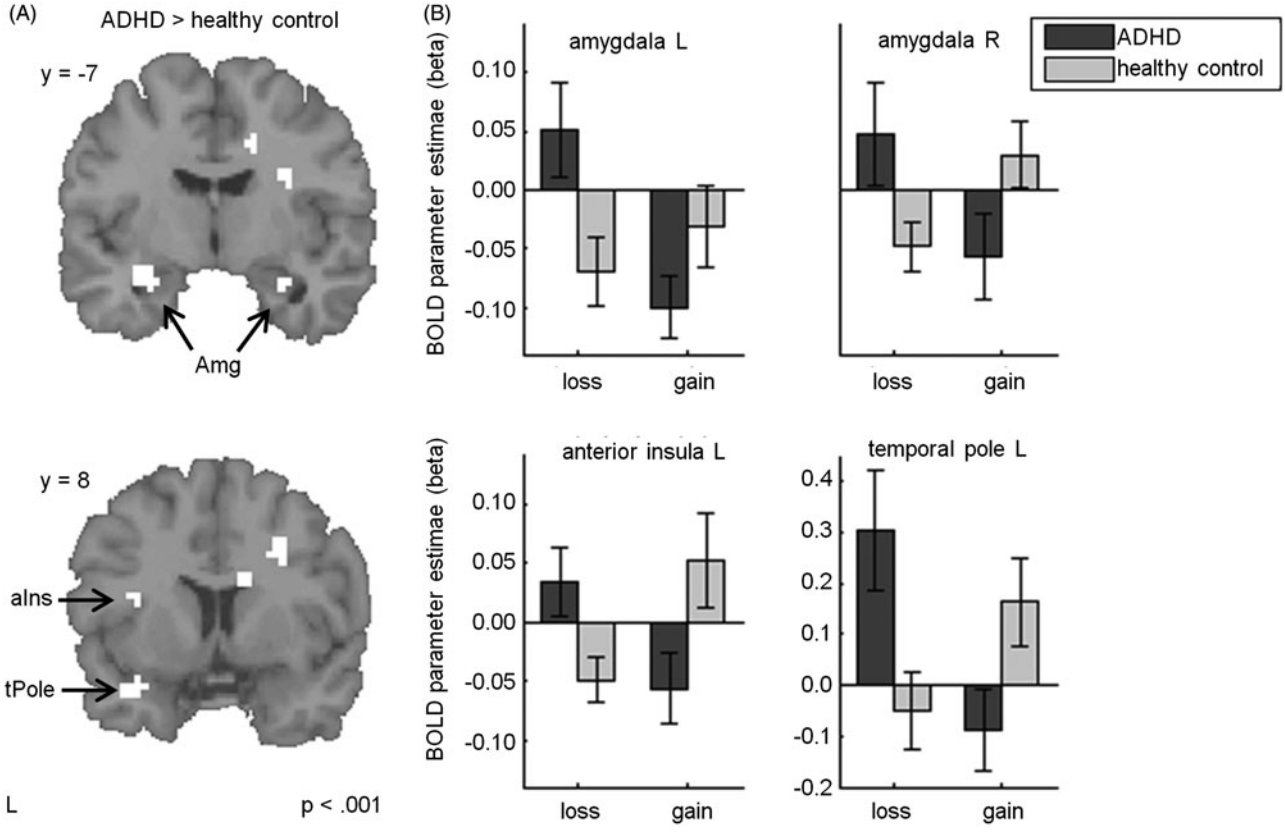

Figure 3. Functional imaging results. Statistical T-maps (A) for the comparison of brain activation between ADHD patients and healthy controls during "loss > gain anticipation" (thresholded at $P < 0.001$, uncorrected, for illustrative purpose only). Corresponding parameter estimates (B) for significant, i.e., $P[\text{FWE}] < 0.05$, peak voxels in the region of interest analyses (amygdala [Amg], anterior insula [aIns]) and exploratory whole brain analysis (temporal pole [tPole]). Note: BOLD, blood–oxygen-level dependent; FWE, family-wise error corrected; L, left; R, right.

Auxiliary analyses tested the robustness of group differences in several analyses of covariance. All described group effects remained significant after adding lifetime comorbidity as covariate to the SPM two sample *t*-test model (left insula $P[\text{FWE}] = 0.007$, left and right amygdala $P[\text{FWE}] < 0.001$ and 0.008, respectively). Covariance control analyses were also performed for financial satisfaction, hours of sleep, depressive and anxiety symptoms since these variables differed between groups (see Table 1). Results were almost the same with or without these covariates for the left amygdala (all *P* values$[\text{FWE}] < 0.049$, reduced to trend level when covarying for anxiety symptoms $P[\text{FWE}] = 0.088$) and right amygdala (all *P* values$[\text{FWE}] < 0.031$, trend level when covarying for anxiety $P[\text{FWE}] = 0.051$ or depression symptoms $P[\text{FWE}] = 0.115$), whereas the left anterior insula group effect did not survive statistical correction when covarying for several variables (see Supplemental material available online for more details).

An *Exploratory whole brain analysis* investigated group differences during "loss > gain anticipation" outside predefined ROIs. ADHD patients exhibited higher activation than healthy controls in the left temporal pole ($x, y, z = [-36,11,-26]$, $t = 5.28$, $P[\text{FWE}] = 0.045$, corrected for whole brain; see Figure 2). Examination of parameter estimates indicated opposite patterns for loss and gain anticipation in the two groups (see Figure 3B). However, the group effect in the temporal pole did not survive whole brain correction when covarying for any possible confounding variable (e.g., lifetime comorbidity $P[\text{FWE}] = 0.252$; see Supplemental material available online for more details). No further activations appearing in the whole brain analysis survived statistical correction in either single group analyses or group comparisons.

Brain-behaviour correlations

Individual parameter estimates were extracted from peak voxels of significant group differences and correlated with cue ratings and symptom severity. Higher neural activity during loss > gain anticipation in ADHD went along with more negative valence of the loss cue (defined as change in valence rating from pre- to post task, left anterior insula $r[26] = -0.38$, $P = 0.046$, left temporal pole $r[26] = -0.42$, $P = 0.027$; no similar correlation for the gain cue: left anterior insula $r[26] = 0.16$, $P = 0.403$, left temporal pole

$r[26] = 0.16$, $P = 0.403$). In healthy participants, by contrast, higher anterior insula activity in the same contrast went along with more positive valence of the gain cue ($r[26] = 0.38$, $P = 0.044$; no similar correlation for the loss cue, $r[26] = -0.31$, $P = 0.107$). No correlations were found with symptom severity (ADHD, depression, anxiety) in either group (all P values > 0.10).

Discussion

To test a previously neglected hypothesis of deficient signalling of negative cues in adult ADHD, the present study investigated anticipation of probabilistic negative outcomes relative to gains in patients and matched healthy controls. In contrast to our hypothesis of reduced neural activation in ADHD, results demonstrate an *increased* neural activation in patients compared to controls, as found in bilateral amygdala, as well as in left anterior insula and left temporal pole. Moreover, higher neural activation during loss anticipation was correlated with an increase in negative valence to these cues. Thus, it is unlikely that maladaptive behaviours in adult ADHD derive from reduced neural response to cues signalling potential negative outcomes. Several lines of possible interpretation emerge. In the following we discuss our results in the context of cue salience, behavioural compensation, and neural dysregulation.

One possible interpretation of stronger responses to loss than gain cues in ADHD patients is increased *salience* of cues predicting negative outcomes in these individuals. Anterior insula, amygdala and temporal pole are central parts of a ''salience network'' (Seeley et al. 2007; Barrett and Satpute 2013). Increased salience of cues predicting negative outcomes in ADHD patients might be the result of a learning history characterised by repeated exposition to negative outcomes. Investigations on the social environment of children with ADHD have revealed enhanced negative feedback from peers, teachers and parents (Whalen et al. 1980; Mash and Johnston 1982; Cunningham et al. 1985; Barkley 1989). Adults with ADHD are known to retrospect a life replete with failure and underachievement (Frazier et al. 2007; Mannuzza et al. 1997; Biederman et al. 2009; Klein et al. 2012), as well as accidents and physical injuries (Nigg 2013). Prominent theories of ADHD emphasise the role of bio-psycho-social interactions during the development of the disorder (Wender 1972; Sagvolden et al. 2005; Sonuga-Barke 2005), and affected individuals might adapt to these experiences by evolving an increased sensitivity to any predictors of possible negative outcomes.

The co-existence of such increased sensitivity to negative outcomes in ADHD on the one hand and generally higher risk-taking on the other, however, seems counterintuitive. A potentially mediating factor, *compensatory behaviour*, might help to understand this paradox. Individuals with a gambling disorder (cf. DSM-5) are known to exhibit a behavioural paradox termed "chasing one's losses" – the continued and sometimes increasingly risky gambling in the face of previous losses (Lesieur 1979). It has been hypothesised that this pattern of increased risk-taking is motivated by the hope for the ultimate gain (Ariyabuddhiphongs and Chanchalermporn 2007). Empirically, however, it is less related to gain but rather to the experience of loss and failure (as suggested by experimental findings of more risk taking after losses than gains (Barkan and Busemeyer 1999; Nicolle et al. 2011) or increased gambling when the own perceived income is lower compared to others (Haisley et al. 2008)). By analogy, ADHD adults might lack confidence in a steady strategy which takes small steps to overcome their problems but rather go for all-or-nothing decisions and, moreover, continue to risk negative outcomes to compensate for experienced frustration. However, these interpretations are obviously speculative at present and call for more research on neural loss sensitivity in relation to a range of behavioural outcomes in adult ADHD.

With regard to *neural dysregulation*, several parallels of our findings with previous ADHD neuroimaging findings emerge. Regarding *amygdala* activity, Delgado et al. (2011), in a similar anticipation task reported that primary reinforcers such as electric shocks activated the amygdala in healthy controls, but secondary reinforcers such as monetary losses fail to do so. This finding represents an interesting reference frame for the amygdalar hyperresponding in the present study, implicating a lower threshold for amygdala responding in ADHD. Similarly, abnormal amygdala responses in ADHD have been reported in response to cues signalling delays (Wilbertz et al. 2013) or cues signalling safety vs. threat of shock (Maier et al. 2014).

Another key emotion processing region, the *anterior insula*, showed enhance activity in ADHD. In the previously mentioned study involving anticipation of electric shock (Maier et al. 2014), ADHD patients also showed increased activation of the anterior insula compared to healthy controls when residualizing for anxiety differences between groups. Theories of the anterior insula emphasise its role for interoception, i.e., the sensing and mapping of body states (Craig 2002) and generating subjective feelings (Damasio and Carvalho 2013). This interpretation fits well with the observed correlation in our study between insular activity and affective rating of the stimuli. In fact, insular hyperactivity in ADHD has also been reported in response to actual loss outcomes (Stoy et al. 2011). Together, these results are in line with an interpretation of altered salience of negative

outcomes (and possibly more negative affect during their anticipation) in ADHD.

A surprising finding in this study was an abnormal response in the *temporal pole* of ADHD, i.e., hyperactivation during loss vs. gain anticipation in ADHD patients compared to healthy controls. In general, the temporal pole seems to play a crucial role in emotion processing (Olson et al. 2007) and has primary functional connectivity to amygdala, OFC, NAcc and hypothalamus (Pascual et al. 2013). The temporal pole is activated during the experience of negative emotions like sadness (Lane et al. 1997; Blair et al. 1999; Aalto et al. 2002), disgust (Lane et al. 1997), guilt (Shin et al. 2000), and – in direct comparison – more so during negative than positive emotions (Aalto et al. 2002; but see also Lane et al. 1997; Maddock et al. 2003). Interestingly, a genetic and brain imaging study with healthy participants used a similar task as we did and found temporal pole activity during the anticipation of monetary losses to be associated with a genetic polymorphism of the dopamine degrading enzyme catechol-*O*-methyltransferase (COMT, Schmack et al. 2008). Dysfunctions in the dopamine pathway could be involved in temporal pole hyperactivity of ADHD patients given significant amounts of dopamine in the temporal cortex on the one hand (Hall et al. 1996; Moore et al. 2003) and evidence for an association between dopamine receptor genes and ADHD on the other hand (Wu et al. 2012). Emphasising the relevance of the reported findings, a 33-year follow-up study on children with and without ADHD identified not only insular but also the temporal pole cortical thickness as significant predictors for persisting ADHD (Proal et al. 2011). Taken together, the present study adds to the existing evidence for a role of the temporal pole in ADHD psychopathology.

The following *limitations* apply. First, the present study did not provide behavioural measures of impulsivity and problem behaviour in ADHD. The potential role of increased neural response to negative outcomes in the context of behavioural adaptation or maladaptation, thus, has to remain hypothetical. Future studies would profit from including a wide range of behavioural impulsivity tasks as well as from acquiring actual real-life data. Secondly, and related to this, our task involved passive anticipation and did not require actual decision making. While this was simplifying the task and analyses, higher brain-behaviour correlation could result from active decision making tasks during scanning. The passive anticipation might also have been one reason why we could not replicate prior reports of reward related striatal hypofunction in ADHD patients using this paradigm (please note, a numerically decreased striatal response of ADHD patients compared to controls during gain vs. no-change anticipation did not survive correction for multiple comparisons, see Supplemental Table S3 available online). Another reason for the absence of group differences during gain anticipation might be reward habituation during the preceding gambling task (Wilbertz et al. 2012). Third, neural activations in this fMRI task were generally weak when considering groups separately (e.g., see Supplemental Figure S2 available online), which might be the result of a low number of trials, hence low statistical power. The analyses, however, focussed on specific hypotheses in a two-group design, where all effects survived correction for multiple comparisons. Furthermore, while lack of statistical power is usually associated with increasing risk for type II error, the present study revealed several significant results that clearly contradict the a priori hypothesis of deficient negative anticipation in ADHD. Fourthly, group effects might have been confounded by other group differences, e.g., comorbid disorder, sleep alterations, etc. Importantly, covariance analyses confirmed that some of our key findings (e.g., the left amygdala group difference) were unaffected by these confounds. However, despite these auxiliary analyses we cannot completely exclude that comorbid depression contributed to the observed group effect (which could be interpreted as a negative bias) and future studies with larger subgroups of depressed vs. non-depressed ADHD samples should follow up on this result. Fifth, an alternative explanation for the SCR and BOLD findings would relate to the magnitude of outcomes: not only is €–11 a loss (vs. gain of €+5), it is also higher in magnitude than the respective gain, thus possibly shifting autonomous and neural response readiness to a higher level (see e.g., Camara et al. 2010; Stillman et al. 2015 for magnitude effects in amygdala and insula). Future studies on reward and/or loss processing in ADHD should include a range of monetary outcomes from different levels to parametrically map the value response functions of these patients.

Bearing these limitations in mind we draw the following conclusions: adult ADHD patients respond with enhanced sensitivity to anticipated losses, based on a neural network involving amygdala, anterior insula and temporal pole. This neural hyperactivation is proportional to experienced negative affect. Thus, dysregulated behaviour in ADHD is unlikely to be a direct consequence of failures during anticipation of negative outcomes. Future research should explore whether dysregulated behaviour might be related to dysfunctional translation of such affect into action. Neural hyperactivity during loss anticipation also adds to the existing literature on reward deficits in ADHD and suggests more research considering both positive and negative outcomes (i.e., gains and losses) in ADHD.

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Statement of interest

LTvE received fees from Lilly, EISAI, Unimed, and UCB. AP from advisory boards, lectures, phase-III studies or travel grants within the last 2 years: Eli Lilly, Medice Arzneimittel Pütter GmbH, Novartis and Shire; she is author of books and articles on treatment of adult ADHD published by Elsevier, Hogrefe, Schattauer, Kohlhammer and Karger. All other authors report no potential conflicts of interest.

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