

## Orbitofrontal reward sensitivity and impulsivity in adult attention deficit hyperactivity disorder

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### ARTICLE INFO

#### Article history:

Received 28 September 2011

Revised 25 November 2011

Accepted 8 December 2011

Available online 16 December 2011

#### Keywords:

ADHD

Reward

fMRI

OFC

Striatum

Impulsivity

### ABSTRACT

Impulsivity symptoms of adult attention deficit hyperactivity disorder (ADHD) such as increased risk taking have been linked with impaired reward processing. Previous studies have focused on reward anticipation or on rewarded executive functioning tasks and have described a striatal hypo-responsiveness and orbitofrontal alterations in adult and adolescent ADHD. Passive reward delivery and its link to behavioral impulsivity are less well understood. To study this crucial aspect of reward processing we used functional magnetic resonance imaging (fMRI) combined with electrodermal assessment in male and female adult ADHD patients (N=28) and matched healthy control participants (N=28) during delivery of monetary and non-monetary rewards. Further, two behavioral tasks assessed risky decision making (game of dice task) and delay discounting. Results indicated that both groups activated ventral and dorsal striatum and the medial orbitofrontal cortex (mOFC) in response to high-incentive (i.e. monetary) rewards. A similar, albeit less strong activation pattern was found for low-incentive (i.e. non-monetary) rewards. Group differences emerged when comparing high and low incentive rewards directly: activation in the mOFC coded for the motivational change in reward delivery in healthy controls, but not ADHD patients. Additionally, this dysfunctional mOFC activity in patients correlated with risky decision making and delay discounting and was paralleled by physiological arousal. Together, these results suggest that the mOFC codes reward value and type in healthy individuals whereas this function is deficient in ADHD. The brain-behavior correlations suggest that this deficit might be related to behavioral impulsivity. Reward value processing difficulties in ADHD should be considered when assessing reward anticipation and emotional learning in research and applied settings.

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### Introduction

Between 15 and 65% of children with attention deficit hyperactivity disorder (ADHD) continue to show symptoms during adulthood (prevalence rate: 2.5%) (Faraone and Biederman, 2005; Simon et al., 2009). Whereas hyperactivity symptoms remit over time, attentional deficits and impulsivity persist (Wender et al., 2001). In adult ADHD, impulsivity manifests in poor occupational performance (Mannuzza et al., 1997), drug abuse (Elkins et al., 2007), sexual risk taking (Flory et al., 2006), intimate partner violence (Fang et al., 2010), risky driving (Fischer et al., 2007), and other disadvantageous behaviors (Biederman et al., 1994; Eakin et al., 2004; Weafer et al., 2011). In

terms of gender ratio, ADHD in adulthood is more evenly distributed in men and women.

Impulsivity in ADHD has been explained primarily by deficits in executive functioning and inhibition (e.g. Barkley, 1997). Premature responses, e.g., might be related to timing disturbances (Rubia et al., 2009a). Another line of research has highlighted the role of emotional and motivational aspects for impulsivity in ADHD (e.g. Sonuga-Barke, 2005). One crucial motivational aspect of impulsive behavior is an altered reward sensitivity (see e.g. Luman et al., 2010 for review). Accordingly, ADHD patients prefer immediate over delayed rewards due to a steeper gradient for delay-of-gratification during learning (Sagvolden et al., 2005). Neurobiologically, this might reflect dysfunctions in tonic or phasic dopamine levels in response to reward (Tripp and Wickens, 2008).

Behavioral studies have indeed demonstrated altered responses to reinforcement in ADHD (Aase and Sagvolden, 2006; Douglas and Parry, 1994; Frank et al., 2007; Luman et al., 2009). Also a specific

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preference for immediate over delayed reward has been described in childhood and adolescent ADHD (Bitsakou et al., 2009; Paloyelis et al., 2010; Solanto et al., 2001) accompanied by an orbitofrontal hypoactivation (Rubia et al., 2009a). A brain imaging study in adult ADHD patients demonstrated a neural dissociation between decisions for immediate and delayed reward (Plichta et al., 2009) but no behavioral preference. ADHD patients exhibited a diminished response to immediate reward in the ventral striatum (VS) and an increased response to delayed reward in the dorsal striatum.

A related line of fMRI studies has focused on reward anticipation as studied in the Monetary Incentive Delay (MID) task (Knutson et al., 2001). In this task, distinct cues inform participants about the possibility to win or to avoid losing money by responding quickly to a target. During the presentation of these cues, i.e. during the reward anticipation phase, adolescents (Scheres et al., 2007) and adults (Carmona et al., 2011; Hoogman et al., 2011; Strohle et al., 2008) with ADHD showed decreased activation in the VS compared to controls. Strohle et al. (2008) also analyzed neural responses during the reward delivery phase and found increased activations in the dorsal striatum and lateral orbitofrontal cortex (OFC) in male ADHD patients.

Altered OFC functioning in ADHD has also been reported in studies investigating the effect of reward on executive functioning (Cubillo et al., 2011; Dibbets et al., 2009; Rubia et al., 2009b). However, in these study designs a specific attribution of OFC deficits to either anticipatory or consummatory processes is difficult since the focus is the effect of reward on inhibition or sustained attention rather than reward processing alone. Moreover, some uncertainties remain with regard to the direction of the OFC deficit (some studies found a hypoactivation whereas others a hyperactivation), its specificity to type of reward (positive feedback vs. monetary reward), its location within the OFC (medial, antero-lateral, postero-lateral) as well as its generalizability to female ADHD patients (cf. Valera et al., 2010) and interaction with comorbid disorders (e.g. conduct disorder, Cubillo et al., 2011; Rubia et al., 2009c).

Taken together, there is clear evidence for a ventral striatal deficit (hypoactivation) during the *anticipation* of reward which has been replicated consistently in ADHD patients of different ages and sexes. In contrast, the role of the OFC and alterations in neural response to reward *delivery* in ADHD are less well understood. Yet, both issues are of great importance for several reasons: First, from a theoretical standpoint, the interpretation of altered reward anticipation implicitly relies on assumptions about a normal reward receipt, e.g. a normal subjective valuation of this reward. In other words, differences in reward valuation would effectuate similar differences during anticipation. Second, electrophysiological studies, which due to excellent temporal resolution can reliably characterize both anticipation and delivery of rewards, suggest altered processing of the latter, i.e. altered responses to feedback and monetary outcomes, in ADHD (Groen et al., 2008; Holroyd et al., 2008; van Meel et al., 2005, 2011). Third, together with observed abnormalities in the OFC of ADHD patients this altered processing of actual reward could refer to altered *reward coding* in ADHD (Kahnt et al., 2010; Kringelbach and Rolls, 2004; Sescousse et al., 2010). Fourth, a better understanding of reward delivery processing and the role of the OFC might help to clarify discrepant findings about the association of VS activity and impulsivity: findings in ADHD patients suggest VS *hypoactivation* as a neural correlate of impulsivity (Scheres et al., 2007; Strohle et al., 2008) whereas findings in healthy controls suggest that impulsivity is represented by VS *hyperactivation* (Hariri et al., 2006). Therefore, there has been a discussion about a missing link between VS hypoactivation and impulsivity in ADHD (Carmona et al., 2011; Hoogman et al., 2011; Strohle et al., 2008). Fifth, due to close interactions with the VS as well as impulsivity in ADHD the OFC should be considered as an important candidate (Konrad et al., 2010). Overall, a study with particular focus on reward delivery and the OFC, where

alterations from normal functioning can be expected, could help to clarify these issues.

One task that proved particularly useful for the study of 'pure' reward delivery (that is, reward delivery processing in the absence of performance or learning aspects) is the card guessing task (Delgado et al., 2004). In this task, participants guess the value of a card and receive feedback about the actual outcome. In high-incentive blocks, they receive monetary feedback (gain/loss of money), in low-incentive blocks they receive non-monetary feedback (correct, incorrect). Thus this task allows the independent modeling of outcome and motivational value/incentive. Increased striatal and lateral as well as medial OFC activations under high incentive conditions have been observed consistently in this task (Delgado et al., 2000, 2004; May et al., 2004).

Using this task we aimed to extend previous reports of altered reward processing in male and female adults with ADHD by focusing on striatal and orbitofrontal regions. We expected altered *reward sensitivity* – defined as differential neural responses to reward delivery – in ADHD compared to healthy controls (Luman et al., 2010). This could be evident in altered striatal or orbitofrontal responses to rewarding feedback on either low or high incentive level (pure feedback or monetary outcome, respectively). The *direction* of these group differences (i.e. hyper or hypo responding in ADHD on either incentive level) is hard to predict. In fact, the electrophysiological results introduced above suggest a more complex pattern where group differences in outcome processing depend on incentive level: ADHD patients showed normal responses to low incentive reinforcers but differed from controls in responding to high incentive outcomes (van Meel et al., 2005, 2011). In the present design, this might manifest in an incentive  $\times$  outcome interaction between groups.

Two types of complementary data were acquired to reinforce potential fMRI findings. First, we recorded electrodermal activity concurrently to the card guessing task since reward processing should affect autonomic arousal. Second, we administered two behavioral impulsivity tasks to test whether reward delivery processing indeed correlates with behavioral impulsivity as suggested by current theory (Luman et al., 2010). Furthermore we addressed some common limitations of this kind of research (predominantly small sample sizes and only male participants) by recruiting a large sample that would allow us to assess the role of gender and comorbidity (Biederman et al., 2004; de Zwaan et al., 2011).

## 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 (Association AP, 1994) were recruited from a specialized outpatient clinic for adult ADHD. Childhood diagnosis was assessed retrospectively by experienced clinicians on the basis of a clinical interview as well as additional informants and sources (e.g. school reports). According to DSM-IV 8 patients were classified as primarily inattentive and 20 as combined subtype. Seven patients had at least one current comorbid disorder (5 anxiety disorder, 1 substance abuse, 2 dysthymic disorder, 2 somatoform disorder), and 9 further patients had a comorbid lifetime diagnosis as determined by the Structured Clinical Interview for DSM-IV-TR interview (SCID, First and Pincus, 2002). Exclusion criteria were schizophrenia, bipolar depression, borderline or antisocial personality disorder and acute substance dependence. Regarding psychotropic medication history, 20 patients were drug-naïve, 4 had prior stimulant medication, 6 antidepressant, 2 sedative and 2 neuroleptic medication. At the time of study conduct, all patients were free of possible medication for at least 2 months. Twenty-eight 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. All participants gave informed written consent. The study was approved by the local ethic committee (see Table 1 for sample characteristics).

#### Brain imaging: card guessing task

##### Trial structure

In the scanner, participants completed two runs of 48 card guessing (Delgado et al., 2004) trials (see Fig. 1). Trials commenced with the presentation of a card displaying a question mark and prompting participants to guess whether the value on the back of the card was greater than 5 (i.e. 6–9 by pressing the left of two buttons) or smaller than 5 (1–4 by pressing the right button). Participants had 2 s to make their guess.<sup>1</sup> After a jittered interval (2 to 3.75 s) an animation of a turning card was shown and the back side of the card revealed the actual card value as well as a feedback regarding the participant's guess (correct guess, incorrect guess, 1 s). An inter-trial interval (9.25 to 10.75 s depending on the pre-feedback jitter) preceded the next trial. According to a predefined pseudo-randomized trial sequence the feedback was either positive (rewarding) or negative.

##### Block structure

The motivational relevance of these trials was manipulated by alternating between blocks of high incentive in which a correct or incorrect guess resulted in a win of € 4 or a loss of € 2 (about \$ 5.2 and \$ 2.6, respectively) and blocks of low incentive in which a correct or incorrect guess resulted in positive or negative feedback (FB+, green checkmark; FB–, red cross). Thus, the task comprised six different events: guessing under low or high incentive (guess high, guess low), win, loss, FB+, and FB–. High and low incentive blocks were distinguished by preceding instructions (“money block” vs. “no money block”) and card color (golden vs. white). Blocks comprised 12 trials each. Four blocks of each type were presented in alternating order. A brief practice phase assured that participants understood the task. Before starting participants were instructed to maximize their balance and were shown the money they could win in cash (€ 30 to 60, about \$ 39 to 77 for the total experiment), depending on their performance.

#### Behavior: delay discounting

Before entering the scanner participants completed a computerized hypothetical delay discounting task (Richards et al., 1999). On each of 42 trials participants choose between € 200 (about \$ 270) that would be delayed by the time to delivery (t) and an immediate amount of money that was adaptively decreased or increased in order to reach a subjective indifference point. Every 7 trials t changed (1, 3, 9, 24, 60, 120, 240 months) and the immediate amount option was reset to 100 €. Indifferent points for the 7 delay periods were used to calculate the fitted parameter k which describes the rate of discounting (Rachlin et al., 1991). Higher ks indicate a stronger loss of the subjective value of money with delay. In order to minimize the impact of outliers in delay discounting the natural logarithms of k were computed before entering correlation analyses (Hariri et al., 2006; Mitchell, 1999).

#### Behavior: impulsive decision making (game of the dice task)

After exiting the scanner and reimbursement for the card guessing task, participants completed two runs of the game of dice task (GDT) (Brand et al., 2005) to capture impulsive decision making. They were told that they could win another € 5 if they made correct guesses

**Table 1**  
Sample characteristics and psychometry.

	ADHD patients	Healthy controls	p
Age	37.11 (9.13)	36.71 (9.31)	.874
Gender(male/female)	15/13	14/14	.789
Educational level (low/medium/high/college)	5/9/8/6	3/12/9/4	.708
Intelligence (MWT-B)	113.21 (16.39)	105.71 (11.20)	.051
Financial situation (€ remain monthly) (236.76)	164.11	214.11 (259.95)	.455
Satisfaction with financial situation (7 items)	4.22 (1.05)	4.65 (1.06)	.139
# unemployed	3	2	.514
# smoker	12	7	.158
Depression (Beck Depression Inventory, BDI)	16.14 (11.47)	4.77 (3.56)	<.001
State anxiety (State Trait Anxiety Inventory, STAI)	43.76 (8.00)	34.43 (7.10)	<.001
Trait anxiety (State Trait Anxiety Inventory, STAI)	48.56 (7.15)	34.22 (6.75)	<.001
Conner's adult ADHD Rating Scale (CAARS)	101.66 (24.17)	33.52 (13.38)	<.001
Subscale inattention	18.99 (6.92)	6.18 (3.92)	<.001
Subscale hyperactivity	17.37 (5.55)	6.93 (3.15)	<.001
Subscale impulsivity	18.86 (5.48)	6.07 (3.05)	<.001
Trait impulsivity (Barratt's Impulsivity Scale)	71.61 (9.33)	57.0 (8.37)	<.001

Note: psychometry explained below. Depicted are means (and standard deviations) or counts (#). P refers to t-test or  $\chi^2$ -test for group comparison.

about the value of a dice. On each of 24 trials (in 2 blocks) participants could bet on the value of the dice by choosing one of four options, each associated with different probabilities of guessing correctly and monetary outcomes: single number guess (probability 1/6, win/loss 1000 points [pts]), pair of numbers (probability 2/6, win/loss 500 pts), triple of numbers (probability 3/6, win/loss 200 pts) and quad of numbers (probability 4/6, win/loss 100 pts). After making a choice an animation of a rolling dice was shown before the final number and the monetary outcome (win/loss) was displayed. Choices of ‘single number’ or ‘pair’ are considered risky choices because losses are high and probabilities of winning are below 50%. In addition, the frequency of shifting from a risky to a more conservative choice after a loss trial was assessed as an indicator for negative feedback use.

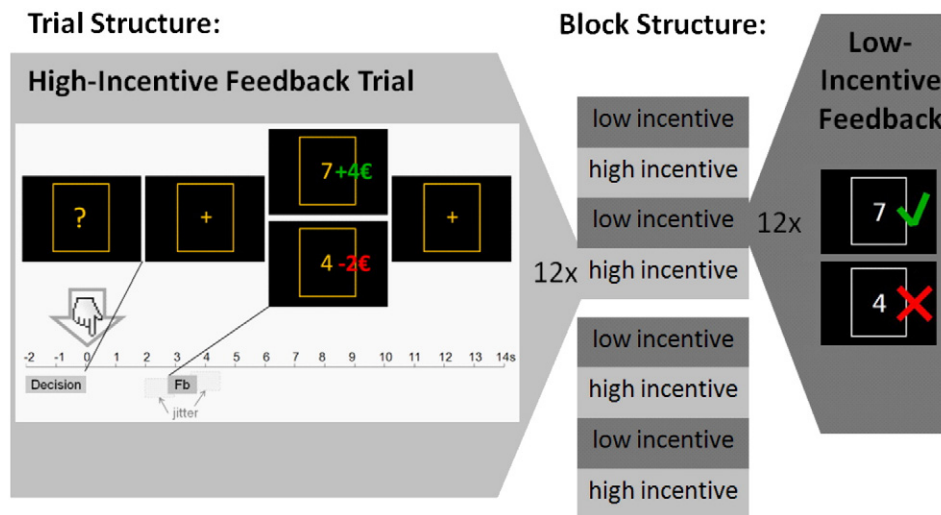
#### Psychometry

Psychometric Assessment of psychopathology and impulsivity comprised the following scales: Conners Adult ADHD Rating Scale (CAARS) (Christiansen et al., 2011a,b; Conners, 1999), Beck Depression Inventory (BDI-II) (Hautzinger et al., 2006), State Trait Anxiety Inventory (STAI) (Spielberger et al., 1970), Barratt's Impulsivity Scale (BIS-11) (Patton et al., 1995). Potential confounds such as participants' personal financial situation (amount of ‘spare’ money at the end of a month), financial satisfaction (7 items subscale from a German life satisfaction scale) (Fahrenberg et al., 2000) as well as intelligence (measured by a German vocabulary test, MWT-B) (Lehrl, 1977) were also assessed.

#### Magnetic resonance imaging

Imaging was performed on a 3 Tesla Siemens Trio MR scanner (Siemens AG, Erlangen, Germany) with a standard 8-channel <sup>1</sup>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

<sup>1</sup> Late responses were indicated as being invalid on the screen and excluded from analyses.



**Fig. 1.** Card-guessing task. The fMRI session consisted of 2 runs with 4 blocks each. In blocks of high incentive a monetary outcome (€ 4 win or € 2 loss) was provided after participants guessed a card value whereas in blocks of low incentive non-monetary outcome (feedback: correct, incorrect) was provided.

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).

#### Physiological set-up and analysis of skin conductance responses (SCRs)

Skin conductance level was continuously measured during the card-guessing task using two electrodes on the left hand middle and ring finger tip connected to a BrainAmps ExG MR device, BrainProducts, Gilching, Munich, Germany, with a sampling rate of 5000 Hz. Outcome-related SCRs were scored as difference between a 2 second pre-trial baseline and the maximum skin conductance within 5 to 11 s after trial onset (due to jittered inter-stimulus-intervals outcome was provided 2 to 5.75 s after trial onset). Artefactual trails defined as SCRs below 0.02  $\mu$ S or above a z-score of 2 were set to zero. SCRs were averaged by condition and square root transformed in order to reduce skewness of the frequency distribution. Skin conductance data were lost for one patient due to technical problems.

#### Data analysis

The fMRI data were analyzed with SPM8 (Wellcome Department of Cognitive Neurology, London, United Kingdom, <http://www.fil.ion.ucl.ac.uk/spm>) after an automatic online correction for motion and distortion artifacts (Zaitsev et al., 2004) and discharging the first 5 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 with the structural image, spatial normalization into the MNI reference system and smoothing (with a three-dimensional isotropic Gaussian kernel, 8 mm full-width at half maximum [FWHM]). A general linear model (GLM) included six event types for modeling neural responses to guess high, guess low, win, loss, FB+ and FB− (onsets were folded with the canonical hemodynamic response function for events with 1 s duration). Further included were 6 movement regressors and 4 regressors for slow signal drifts (linear, quadratic, cubic and 4th order spline). Three contrast images were computed based on beta values of task regressors modeling brain responses to high-incentive outcome (win > loss), low-incentive outcome (FB+ > FB−) as well as their interaction (outcome × incentive: [win > loss] > [FB+ > FB−]) for every participant. One sample t-tests and independent samples t-tests on these contrast images were used to estimate statistical

significance of activations in each group separately and between patients and controls, respectively.

Five types of analyses were performed: *First*, an exploratory whole brain (family wise error (FWE) corrected  $p < .05$ ) analysis served the purpose of unbiased assessment of brain activation in ADHD and controls as well as of differences between groups. *Second*, a more sensitive region-of-interest (ROI) analysis was performed for the striatum and OFC as indicated by prior applications of this task (Delgado et al., 2004; May et al., 2004), a meta-analysis on reward coding (Kringelbach and Rolls, 2004), as well as empirical findings on reward processing in ADHD (Cubillo et al., 2011; Dibbets et al., 2009; Plichta et al., 2009; Rubia et al., 2009b; Scheres et al., 2007; Strohle et al., 2008). ROI analyses were based on anatomical masks from the automatic anatomical labeling (AAL) (Tzourio-Mazoyer et al., 2002) for ventral and dorsal striatum, medial, anterolateral and posterolateral OFC (separate for left and right, each); a FWE small volume correction (SVC) was applied at  $p < .05$  for these ROIs. *Third*, possible confounding effects of gender and comorbid disorders were investigated in confirmatory analyses: Extracted beta values at group effect peak voxels<sup>2</sup> were entered in an ANCOVA including gender, depressive and anxious symptomatology (BDI, STAI) as covariates. Furthermore, all patients with comorbid disorders (current or lifetime) were excluded from a confirmatory SPM analysis on the relevant ROI and contrast. *Fourth*, gender specific group differences between ADHD patients and controls were explored in separate ROI analyses for men and women. Finally, correlation analyses aimed to validate group differences obtained in the main ROI analysis. Therefore we calculated within group Pearson correlations between beta values at the group effect peak voxel<sup>2</sup> with self-reported psychopathology (CAARS, BDI, STAI) behavioral impulsivity (GDT) self-reported impulsivity (BIS, SSS), and delay discounting (DD).

Behavioral data (i.e. decision times and number of missing in the card guessing task as well as relative number of risky decisions and relative number of used negative feedback in the GDT) were compared between groups in a 2 × 2 repeated measure analysis of variance (ANOVA; card guessing: periods of high incentive/low incentive × ADHD/Control; GDT: first session/second session × ADHD/Control).

<sup>2</sup> Sphere (6 mm radius) extraction was computed as well, leading to similar results.

## Results

### Self-report and behavioral results

ADHD patients scored significantly higher on measures of self-reported impulsivity (BIS) as well as on ADHD (CAARS), depression (BDI), and anxiety (STAI, see Table 1).

During card guessing both groups missed more responses during periods of low incentive (ADHD:  $M=2.26$ ,  $SD=2.12$ ; Control:  $M=1.68$ ,  $SD=1.63$ ) than during periods of high incentive (ADHD:  $M=1.15$ ,  $SD=1.88$ ; Control:  $M=1.21$ ,  $SD=1.93$ ,  $F(1,53)=7.55$ ,  $p=.008$ ), with no difference between groups ( $F<1.0$ ). Response times did not differ between groups ( $F(1,53)=1.50$ ,  $p=.23$ ) or incentive periods ( $F<1.0$ ; low incentive ADHD:  $M=657$ ,  $SD=184$ , Control:  $M=731$ ,  $SD=171$ ; high incentive ADHD:  $M=667$ ,  $SD=202$ , Control:  $M=711$ ,  $SD=177$  ms).

In the GDT participants of both groups chose from the risky options equally often ( $t<1.0$ ). Groups did not differ in use of negative feedback nor in regard to change between sessions. No significant group differences appeared for the delay discounting rate  $k$  ( $t<1.0$ ; see Tables 1 and 2 in the supplementary material online for more details).

### Neuroimaging results

During high-incentive outcome processing (win vs. loss) whole brain analyses revealed most robust activations in the striatum for both groups as well as in the thalamus and posterior cingulate cortex for ADHD patients and frontal activations for the control group (see Table 3 in the supplementary material online for a complete list of activations). ROI-analyses of striatal and orbitofrontal regions showed that both, patients and controls, significantly activated ventral and dorsal parts of the striatum as well as the medial, anterior and

posterior lateral OFC (for more detail see also Table 4 in the supplementary material online). No difference between groups emerged neither in any of the defined ROIs (all  $ps>.01$  uncorrected) nor in whole brain analysis (all  $ps>.05$  corrected) (see Fig. 2A).

The low-incentive outcome contrast (FB+ vs. FB−) revealed significant whole brain activations only in the ventral caudate of ADHD patients. However, using the more sensitive ROI approach significant effects were observed similar to the high-incentive contrast in dorsal and ventral striatum as well as lateral and medial OFC. In the control group, significant activations were consistently found only within the striatum and right mOFC in ROI analysis, whereas no activation passed the more conservative whole brain threshold. Group comparisons again revealed no differences neither in ROIs (all  $ps>.01$  corrected) nor whole brain analysis (all  $ps>.05$  corrected, see Fig. 2A).

Differential responding to high vs. low incentive outcomes (win vs. loss and FB+ vs. FB−, respectively) was assessed in the incentive  $\times$  outcome interaction contrast. Here, increased responses to high-incentive outcome compared to low-incentive outcome were found in the ventral striatum (bilaterally) as well as in the left dorsal striatum in the ADHD group (see Table 2). A similar effect in the striatum was found for the control group although only marginally significant (all  $ps<.081$  corrected). Interestingly, a strong modulation effect was found in the mOFC for the control group, which passed the whole brain analysis. Group comparison revealed significantly increased right mOFC activity (as well as a statistical trend for the left mOFC) to high-incentive outcome relative to low-incentive outcome in healthy participants compared to ADHD patients (Fig. 2B). Whole brain analysis revealed no significant activations for the ADHD group or the group comparison.

Since the main group difference was obtained in the mOFC in the incentive  $\times$  outcome contrast, this peak voxel was selected for additional confirmatory analyses. First, gender as well as depressive and anxious symptomatology (BDI, STAI) were entered into an ANCOVA with the extracted contrast estimates for outcome  $\times$  incentive in the mOFC. Besides the group factor only gender revealed a significant main effect ( $p=.013$ ) with no interaction between these two factors ( $p=.501$ ). Post-hoc investigation revealed that mOFC modulation in the outcome  $\times$  incentive contrast was generally weaker in females than in male participants. The group difference between patients and controls, however, appeared in both men and women ( $p=.015$  and  $.016$ , respectively). Next, all patients with comorbid disorders were excluded from an additional SPM analyses, revealing identical results in the mOFC for the outcome  $\times$  incentive contrast (peak voxel  $[x,y,z]$ :  $6,41,-14$ ;  $t=3.69$ ,  $p[FWE]=.030$  with exclusion of  $N=6$  patients with current comorbidity, and peak voxel  $[x,y,z]$ :  $6,41,-14$ ;  $t=3.45$ ,  $p[FWE]=.061$  with exclusion of  $N=14$  patients with lifetime comorbid disorders).

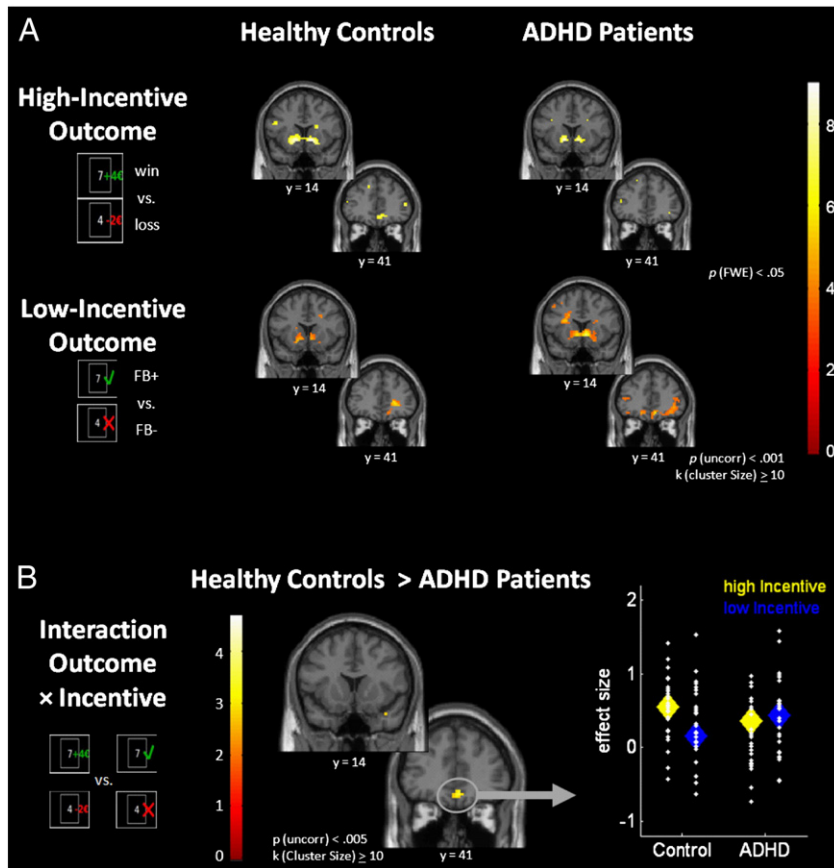
### Gender specific ADHD effects

To account for possible gender specific differences between ADHD patients and healthy controls in the lateral OFC or striatum, male and female participants were analyzed separately in ROI analyses. Results indicate a right anterior lateral OFC hyperactivation in male patients during low-incentive outcome (FB+ vs. FB−: peak voxel  $[x,y,z]$ :  $33,41,-11$ ,  $t=3.42$ ,  $p[FWE]=.046$ ) as well as a statistical trend on the left side during high-incentive reward outcome processing (win > loss: peak voxel  $[x,y,z]$ :  $-30,47,-2$ ,  $t=3.6$ ,  $p[FWE]=.054$ ). These effects were driven by increased responses to both high incentive reward outcome and low incentive positive feedback compared to controls. In contrast, female ADHD patients exhibited a hypoactivation in the left mOFC during negative feedback processing (peak voxel  $[x,y,z]$ :  $-12,47,-8$ ,  $t=3.8$ ,  $p[FWE]=.036$ ) as well as a trend for reduced activity in the right posterior-lateral OFC during positive feedback (peak voxel  $[x,y,z]$ :  $36,35,-8$ ,  $t=3.74$ ,  $p[FWE]=.085$ ) compared to female controls.

**Table 2**

Significant voxels within regions of interest (ROIs) for the outcome  $\times$  incentive contrast in both groups. Depicted are all activations with uncorrected  $p<.01$ . Note: FWE = family wise error correction for small volume, MNI = Montreal Neurological Institute.

Contrast	ROI	MNI coordinates			$t$	$p$ (FWE)	$p$ (uncorrected)	
		$x$	$y$	$z$				
<i>Outcome <math>\times</math> incentive contrast</i>								
ADHD	Ventral striatum L	−15	14	−5	4.20	.017	<.001	
	Ventral striatum R	15	11	−5	4.14	.020	<.001	
	Dorsal striatum L	−24	−4	4	4.49	.017	<.001	
	Dorsal striatum R	18	2	19	3.05	.286	.003	
	Control	Ventral striatum L	−6	20	−5	3.64	.053	.001
		Ventral striatum R	9	20	−5	3.52	.070	.001
		Dorsal striatum L	−33	−7	1	3.72	.081	<.001
		Dorsal striatum R	24	−7	7	3.59	.108	.001
		mOFC L	0	38	−14	5.77	<.001	<.001
		mOFC R	6	41	−11	6.29	<.001	<.001
ADHD > Control	Antero-lateral OFC R	36	38	−14	2.96	.107	.003	
	Postero-lateral OFC L	−45	26	−14	3.33	.173	.001	
	Postero-lateral OFC R	45	26	−14	4.15	.025	<.001	
	Control > ADHD	mOFC L	0	49	−14	3.20	.078	.001
		mOFC R	6	41	−14	3.46	.049	.001
	ADHD > Control	No suprathreshold activations						



**Fig. 2.** Neural responses to reward in ADHD patients and healthy controls. A: Activations during high-incentive outcome (win > loss of money) and low-incentive outcome (FB+ > FB-) separate for both groups. Patients and control participants did not differ significantly on either of these main contrasts in striatal or orbitofrontal regions B: Group comparison for the interaction outcome × incentive ((win > loss) > [FB+ > FB-]). Healthy controls exhibited a significantly higher interaction effect in the mOFC. Note: FB+ = non-monetary positive feedback, FB- = negative feedback, mOFC = medial orbitofrontal Cortex, and FWE = family wise error.

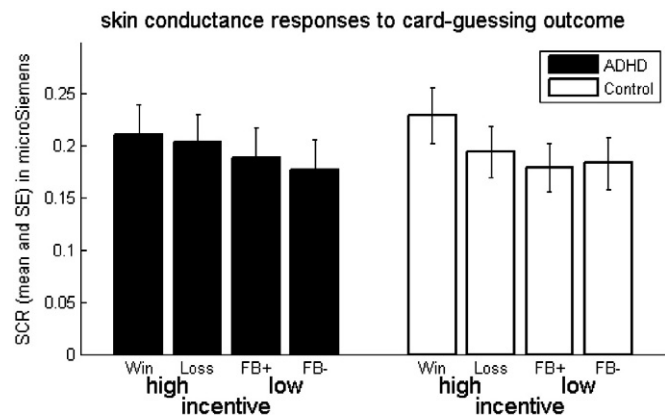
*Skin conductance response data*

An ANOVA including the two within factors outcome (positive/negative) and incentive level (high/low) as well as the between factor group (ADHD/Controls) revealed a weak trend for a 3-way interaction effect ( $F(1,53) = 2.16, p = .147$ ). Separate group analyses revealed a significant interaction between incentive and outcome only in the control group ( $F(1,27) = 5.13, p = .032$ ) whereas patients failed ( $p = .858$ , see Fig. 3). The incentive main effect (higher SCR)

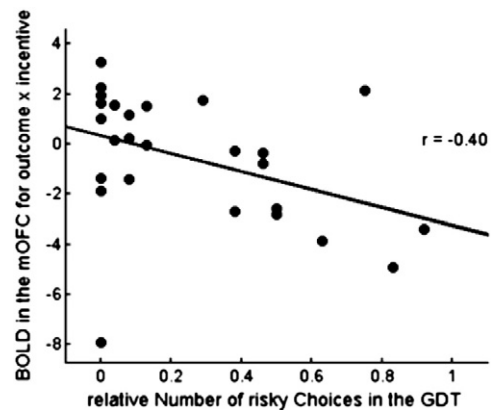
was significant in the control group ( $F(1,27) = 4.21, p = .050$ ) and as a trend in the ADHD group ( $F(1,26) = 3.28, p = .082$ ).

*Correlations between behavioral and brain data*

In ADHD, mOFC activity in the outcome × incentive contrast correlated negatively with number of risky choices and the frequency of unused feedback in the GDT ( $r = -.40, p = .038$ , see Fig. 4, and  $r = -.50, p = .031$ , respectively). Similar correlations were observed for mOFC activity in the win > loss contrast ( $r = -.47, p = .013$  and  $r = -.61,$



**Fig. 3.** Skin conductance responses (SCR) to high incentive (monetary win or loss) and low incentive outcome (positive [FB+] or negative [FB-] feedback) during card guessing averaged by group. Only healthy control subjects showed a differential response pattern to high vs. low incentive outcomes. However, group differences were not significant. Note: SCR is square root transformed, SE: standard error.



**Fig. 4.** Correlation between number of risky choices in the game of dice task (GDT), representing impulsive behavior, and neural activity in the medial orbitofrontal cortex (mOFC) during card guessing in ADHD patients. Depicted are beta values for the interaction outcome × incentive. BOLD = Blood Oxygen Level Dependent.

$p = .006$ , respectively). Thus, the lesser ADHD patients recruited their mOFC during the coding of high incentive outcomes the more risky and inflexible was their decision making. Further, the delay discounting rate  $k$  correlated positively with mOFC activation to low incentive outcome (FB+ vs. FB-;  $r = .45$ ,  $p = .018$ ). Thus, the more ADHD patients recruited their mOFC during low incentive outcomes the stronger was their delay discounting, i.e. the stronger was the subjective devaluation of money with delay. Significant correlations between brain activation and severity of self-rated ADHD symptoms were not found. In the control group no significant correlation was found (all  $ps > .144$ ).

Intelligence, as a possible confounding factor, was not correlated with mOFC activity in the outcome  $\times$  incentive contrast ( $r = -.16$ ,  $p = .24$  for the whole sample,  $r = -.03$ ,  $p = .89$  and  $r = -.12$ ,  $p = .54$  for the ADHD and control group, respectively).<sup>3</sup>

## Discussion

Based on current theories assuming deficient reward processing and impulsivity in adult ADHD the present study assessed neural and electrodermal responses to monetary and non-monetary reward delivery as well as behavioral delay discounting and impulsive decision making. Our hypothesis focused on altered striatal or orbitofrontal responses to rewarding feedback on either low incentive level (correct vs. incorrect feedback), high incentive levels (monetary gain versus monetary loss) or their interaction (outcome  $\times$  incentive). However, no group differences emerged in the striatum or the OFC for either the low or high incentive contrasts separately. Instead, group differences emerged when comparing outcome processing during condition of high (monetary gain versus monetary loss) and low (correct vs. incorrect feedback) incentive. Specifically, activation in the mOFC was found to code for the motivational change in reward value in healthy controls, but not ADHD patients. This points to a possible mOFC deficit in ADHD, representing an insensitivity to the motivational value of outcomes. The relevance of this mOFC deficit for behavior and autonomic arousal is underscored by a consistent correlational pattern with two behavioral impulsivity tasks and a parallel finding in concurrently recorded skin conductance. Specifically, weaker neural incentive modulation as well as decreased neural response to high-incentive (monetary) outcome was accompanied by more risky decisions and insufficient feedback processing on the GDT, possibly reflecting insensitivity to the negative consequences of risky behavior. In addition, stronger neural response in the mOFC to low-incentive outcome (pure feedback) was associated with increased delay discounting in the ADHD group. Thus, both response patterns contributing to an insufficient modulation of neural activity by incentive level, i.e. a relatively decreased response to monetary outcome and a relatively increased response to non-monetary outcome, are positively correlated with impulsivity in ADHD. Finally, electrodermal activity measures paralleled the neural findings on autonomic level suggesting less specific arousal to reward and feedback in ADHD. Together, these results support our hypothesis of altered reward sensitivity in adult ADHD and its relation to impulsive behavior.

The present results are generally in line with previous findings of altered OFC functioning in ADHD (Cubillo et al., 2011; Rubia et al., 2009a,b; Strohle et al., 2008); but see also (Rubia et al., 2009c). The locus of group differences in the mOFC (Kringelbach and Rolls, 2004) and its correlations with GDT and DD is consistent with research linking the mOFC with symptoms of impulsivity in ADHD (Konrad et al., 2010), as well as with impulsive behavior (Bechara et al., 2000) and delay discounting (Roesch et al., 2007) in general. Whereas prior studies with male ADHD patients have localized altered responding to reward in more lateral parts of the OFC (Cubillo et al., 2011; Dibbets et al., 2009; Rubia et al., 2009b; Strohle et al.,

2008), the present results suggest that this pertains mainly to male participants. Moreover, this effect seems to be driven by generally increased responses to high-incentive and low-incentive reward in the lateral OFC of male ADHD patients. In contrast, female patients alone exhibited an increased sensitivity to negative feedback as well as reduced sensitivity to positive feedback in the lateral and mOFC. It is likely that these effects reflect gender specific traits for impulsivity (Cross et al., 2011) which could be augmented in ADHD. The deficient response modulation in the medial OFC, however, did not interact with gender.

Our findings are also in agreement with current neurobiological models on ADHD which relate altered reward processing in ADHD to impulsive behavior and delay aversion/discounting (Sagvolden et al., 2005; Sonuga-Barke, 2005; Tripp and Wickens, 2008). It is noteworthy, however, that most current neurobiological ADHD models assume a deficient anticipation of rewards in these patients without making specific predictions about the neural processing of reward delivery. Only Tripp and Wickens (2008) explicitly target delivery and propose a normal dopamine response to established reinforcers in ADHD. Assuming that mOFC activation partially reflects dopaminergic activity (Lodge, 2011; Winstanley et al., 2010) our finding would challenge this account. However, the altered mOFC activity in ADHD could also reflect an unspecific hedonic reward coding (Kahnt et al., 2010; Kringelbach and Rolls, 2004; Sescousse et al., 2010) and be related to another neurotransmitter system (Berridge and Kringelbach, 2008). One could speculate that the altered mOFC activity in ADHD reflects malfunctions in the opioid system. Animal research has revealed opioid hot spots for hedonic pleasure coding in the nucleus accumbens (Pecina et al., 2006). Since the mOFC is supposed to fulfill similar functions in humans (Berridge and Kringelbach, 2008) and also receives opioid projections (Kringelbach et al., 2007; Mansour et al., 1987; Mena et al., 2011) future research might consider the role of this system as a potential explanation of mOFC alterations during reward processing in ADHD (cf. Prossin et al., 2010).

In contrast to studies focusing on the anticipation of reward (Carmona et al., 2011; Hoogman et al., 2011; Scheres et al., 2007; Strohle et al., 2008) the present results suggest that during the delivery of reward striatal ADHD-abnormalities are not apparent, with deficits observed primarily in the mOFC. The work of Berridge and coworkers (Berridge and Kringelbach, 2008; Berridge et al., 2009) might provide a framework for understanding this functional and anatomical dissociation along the striatal-orbitofrontal axis: they distinguish between motivational 'wanting', the incentive salience that promotes approach towards the reward, and 'liking', which reflects the hedonic pleasure. Accordingly, anticipatory striatal deficits might map on 'wanting', mOFC deficits on hedonic 'liking'. Applied to ADHD, impulsive behavior would not only be interpreted as an exaggerated reward seeking behavior (in order to compensate for reduced reward anticipation) (Robbins and Everitt, 1999; Scheres et al., 2007; Strohle et al., 2008) but as a problem of 'liking' or hedonic pleasure during reward delivery. Phenomenologically, this interpretation of ADHD as an emotional (and motivational) disorder would bring ADHD conceptionally closer to anhedonic depression (Diler et al., 2007; Ferguson and Boctor, 2010) than to addiction (characterized by exaggerated reward seeking, Robbins and Everitt, 1999). The notion of deficient hedonic reward processing is generally consistent with studies on emotional processing in ADHD. Two event related potential studies demonstrated diminished emotional responses to pleasant (Herrmann et al., 2009) as well as unpleasant stimuli (Conzelmann et al., 2009) pointing to a more general deficit in the processing of affective stimuli. However, these interpretations remain speculative and should be considered as inspiring future research on ADHD.

Our results bear implications for behavioral studies and the long standing debate of whether reward sensitivity is reduced (Haenlein and Caul, 1987; Wender, 1972) or increased (Douglas and Parry,

<sup>3</sup> Significant correlations with some of the mentioned variables were also found for the striatum but groups did not differ. Results can be obtained from the authors on request.

1994; Strohle et al., 2008) in ADHD. We suggest that reward magnitude and type (i.e. monetary, non-monetary) might moderate reward sensitivity: due to a reward value insensitivity, ADHD patients might be underresponsive (as shown here for high-incentive, monetary rewards) or overresponsive (low-incentive, none-monetary rewards)

The following potential limitations need to be considered: First, ADHD diagnosis in childhood was assessed retrospectively which can produce false classifications if the interviewer relies completely on the patients' self-report (Mannuzza et al., 2002). However, given the presence of persistent ADHD symptomatology during adulthood as well as the use of additional informants and sources (e.g. school reports) during our diagnostic process, probabilities for false positive cases in the present study should be relatively low. Second, about half of the patients suffered from comorbid disorders which might complicate the attribution of findings to ADHD specifically. However, subgroup analyses confirmed the main findings in patients with 'pure' ADHD. Furthermore, comorbid disorders in adult ADHD are very common (Biederman et al., 2006) making the present sample selection representative for this phenotype. Third, anticipatory reward processing was not assessed in this study. This precludes any conclusions about the association between anticipatory and reward delivery deficits and calls for tasks that assess both aspects. Fourth, the present task compared non-monetary with monetary reinforcers and therefore outcomes that differ not only in incentive level but also in reinforcer type. Future studies should also use parametric manipulations of reward magnitude within outcome type (e.g. different amounts of monetary gains/losses) to verify the present interpretation of an abnormal reward coding in ADHD. Fifth, although comparable in educational level, groups tended to differ in the administered intelligence test. However, intelligence was not associated with mOFC activity in any way, making an intelligence interpretation of this finding unlikely. Finally, although only a few patients reported on the prior use of psychoactive medication a replication of the present study in medication naïve participants would be desirable on the background of known long-term medication effects (Bledsoe et al., 2009; Shaw et al., 2009).

## Conclusions

Whereas neural response in the mOFC of healthy controls corresponds well with actual reward values, this is not the case for ADHD patients. Neural signals in the mOFC suggest an overvaluing of low incentive reinforcers (non-monetary rewards) and an undervaluing of high incentive reinforcers (monetary rewards) in adult ADHD. This deficit has implications for impulsive behavior and autonomic arousal and therefore for crucial aspects of emotional and motivational functioning in everyday life of individuals suffering from ADHD. Future research on psychological and pharmacological treatments could probe the causality and sensitivity to change of the mOFC deficit identified here.

## Acknowledgments

This work was supported by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG, BL 1009/2-1) and in part by the German Federal Ministry of Education and Research (BMBF, 01GV0606). The authors would like to thank all participants for their cooperation and Amalie Trüg for assistance in data collection.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at [doi:10.1016/j.neuroimage.2011.12.011](https://doi.org/10.1016/j.neuroimage.2011.12.011).

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