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ADHD related behaviors are associated with brain activation in the reward system

R. Stark[a,*], E. Bauer[a,b], C.J. Merz[a,c], M. Zimmermann[a], M. Reuter[d], M.M. Plichta[e], P. Kirsch[f], K.P. Lesch[e], A.J. Fallgatter[g], D. Vaitl[a], M.J. Herrmann[e]

[a] Bender Institute of Neuroimaging, University of Giessen, Otto-Behaghel-Str. 10H, 35394 Giessen, Germany
[b] CognitiveNeuroScience at Centre for Psychiatry, University of Giessen, Germany
[c] Department of Cognitive Psychology, Ruhr-University Bochum, Germany
[d] Department of Psychology, University of Bonn, Germany
[e] Department of Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Germany
[f] Central Institute of Mental Health Mannheim, Germany
[g] Department of Psychiatry and Psychotherapy, University of Tuebingen, Germany

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ABSTRACT

Neuroimaging studies on attention-deficit/hyperactivity disorder (ADHD) suggest dysfunctional reward processing, with hypo-responsiveness during reward anticipation in the reward system including the nucleus accumbens (NAcc). In this study, we investigated the association between ADHD related behaviors and the reward system using functional magnetic resonance imaging in a non-clinical sample. Participants were 31 healthy, female undergraduate students with varying levels of self-reported ADHD related behaviors measured by the adult ADHD self-report scale. The anticipation of different types of reward was investigated: monetary reward, punishment avoidance, and verbal feedback.

All three reward anticipation conditions were found to be associated with increased brain activation in the reward system, with the highest activation in the monetary reward anticipation condition, followed by the punishment avoidance anticipation condition, and the lowest activation in the verbal feedback anticipation condition. Most interestingly, in all three conditions, NAcc activation was negatively correlated with ADHD related behaviors.

In conclusion, our results from a non-clinical sample are in accordance with reported deficits in the reward system in ADHD patients: the higher the number and severity of ADHD related behaviors, the lower the neural responses in the dopaminergic driven reward anticipation task. Thus, our data support current aetiological models of ADHD which assume that deficits in the reward system might be responsible for many of the ADHD related behaviors.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common behavioral disorder characterized by excessive inattention, hyperactivity, and increased impulsivity (American Psychiatric Association, 2000). Early aetiological models of ADHD mainly focused on the apparent cognitive deficits including attentional deficits (Douglas, 1972), motor hyperactivity (Porrino et al., 1983), working memory deficits (Barkley, 1997), and especially response inhibition deficits (Nigg, 2001; Schachar, Tannock, & Logan, 1993), which are considered the primary deficit of ADHD in the influential model of Barkley (1997). Since then, several reviews (Castellanos & Tannock, 2002; Doyle et al., 2005; Luman, Oosterlaan, & Sergeant, 2005; Nigg, 2001) and meta-analyses have been published (Schoechlin & Engel, 2005; van Mourik, Oosterlaan, & Sergeant, 2005; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005): integrating the literature, it becomes evident that alongside deficits particularly in prefrontal cognitive functions, impaired motivational processes seem to play a role in the aetiology of ADHD. Although previously discussed (e.g. Glow & Glow, 1979), research concerning ADHD have only in the last decade started to focus on motivational deficits (e.g. Martel, 2009).

In a recent review, Luman, Tripp, and Scheres (2010) identified at least seven different theories proposing altered reinforcement sensitivity in ADHD: the dynamic developmental theory (Sagvolden, Johansen, Aase, & Russell, 2005), the dopamine transfer deficit theory (Tripp & Wickens, 2008), the response modulation theory (Patterson & Newman, 1993), the Go/No-Go learning model (Frank, Santamaria, O'Reilly, & Willicutt, 2007), the extended temporal difference model (Williams & Dayan, 2005), the integrative

* Corresponding author. Tel.: +49 641 9926082; fax: +49 641 9926099.
E-mail address: rudolf.stark@psychol.uni-giessen.de (R. Stark).

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theory (Nigg & Casey, 2005), and the dual pathway model (Sonuga-Barke, 2002, 2003, 2005). Most of these models suggest alterations within the dopaminergic thalamo-cortico-striatal reward circuit (Breiter, Aharon, Kahneman, Dale, & Shizgal, 2001; Kirsch et al., 2003; Knutson & Cooper, 2005; Koepp et al., 1998; Schultz, Dayan, & Montague, 1997). This network encompasses the amygdala, the anterior cingulate cortex (ACC), the orbitofrontal cortex (OFC), the thalamus, and as a key structure, the ventral striatum with the nucleus accumbens (NAcc). Regarding the reported reward processing abnormalities in ADHD, most of the cited models assume a reduced phasic anticipatory dopamine release to reward cues in the ventral striatum. This is especially emphasized in the dynamic developmental theory of Sagvolden et al. (2005) and the dopamine transfer deficit model of Tripp and Wickens (2008). The latter authors hypothesize that there is a fundamental difference in the dopaminergic firing rate towards cues which signal delayed reward between normal children and children suffering from ADHD. In healthy children, the dopaminergic response first occurs with the reward delivery, but after few pairings with an anticipatory stimulus the main response already occurs with the anticipatory stimulus. In ADHD children, the theory assumes that this shift of the dopaminergic response from the actual reward to the anticipatory stimulus is diminished. Instead, the prominent dopaminergic response remains with the reward (Tripp & Wickens, 2009). This reduced anticipatory response is suggested to be responsible for most of the symptoms observed in ADHD; it leads to weaker conditioning, faster extinction of behavior, and a weaker influence of reinforcers on behavior. Thus, behavior is controlled mainly by proximal than by distal reinforcers, which eventually results in inattention and hyperactivity/impulsivity (Tripp & Wickens, 2008).

The empirical foundation of this model is mainly based on functional magnetic resonance imaging (fMRI) studies, which report hypo-responsiveness of the ventral striatum in ADHD patients during reward anticipation. Scheres, Milham, Knutson, and Castellanos (2007) found reduced ventral striatal activation in adolescents with ADHD in comparison to healthy controls in a monetary incentive delay task developed by Knutson, Westdorp, Kaiser, and Hommer (2000). Interestingly, ventral striatal activity was negatively correlated with parent-rated ADHD symptoms across the entire sample. Similarly, Ströhle et al. (2008) found reduced ventral striatal activation during reward anticipation in a comparable task in adult ADHD patients. Using a temporal delay discounting paradigm (which refers to the observation that the subjective value of a reward decreases the longer one has to wait for it), Plichta et al. (2009) also found a hypo-responsiveness of the ventral striatum in adult ADHD patients during reward anticipation.

Further, the crucial role of the dopaminergic system in ADHD has been confirmed in several studies. Reduced levels of both tonic and phasic dopamine have been found (Madras, Miller, & Fischman, 2005; Sagvolden et al., 2005). An abnormally high density of dopamine transporters has been reported to cause an accelerated removal of dopamine from the synapse (Dougherty et al., 1999; Krause, Dresel, Krause, Kung, & Tatsch, 2000; Larisch et al., 2006; Volkow et al., 2009). Further, treatment of ADHD with methylphenidate leads to an increased dopamine concentration in the synaptic cleft and results in a reduction of ADHD symptoms (see Pietrzak, Mollica, Maruff, & Snyder, 2006 for a review).

Based on the suggested idea that a reduced dopaminergic anticipatory response is related to ADHD symptomatology, e.g. inattention and hyperactivity/impulsivity, the question arises whether this relationship can also be found in a healthy sample. To our knowledge, no study has so far been conducted exploring the impact of ADHD related behaviors (inattention, hyperactivity/impulsivity) on reward anticipation in a non-clinical sample. In alcoholics, Beck et al. (2009) reported a negative correlation between impulsivity and ventral striatum activity during reward anticipation. Therefore, we decided to investigate healthy subjects covering a wide range of scores on the adult ADHD self report scale (ASRS, Kessler et al., 2005). Since the scale consists of an inattention and a hyperactivity/impulsivity subscale, it allows to investigate the association of each of these ADHD related behavior-clusters with reward anticipation processes separately.

Further, we were interested in whether the hypothesized association of ADHD related behaviors and the diminished reward anticipation response is independent of the type of the expected reward. We used three different reward conditions: in the first condition subjects could receive a monetary reward, in the second they could avoid a loss of money, and in the third they received only a neutral verbal feedback. It was previously shown (Kirsch et al., 2003, 2006) that all these experimental conditions can produce reliable increase in the reward circuit during reward anticipation, but to a different extent. Due to these results, we expected the greatest reward circuit activation when anticipating a monetary reward, lower activation anticipating a possible loss of money, and the lowest activation when anticipating verbal feedback. As no differential effects of positive and negative reinforcement in ADHD patients are known, we expected negative correlations between ADHD related behaviors and the neural responses to reward anticipation for all three types of reward (monetary reward, punishment avoidance, verbal feedback) in our healthy sample.

Despite the fact that the male-to-female ratio is around 5:1 in ADHD (Staller & Faraone, 2006), we examined only healthy females with varying degrees of ADHD related behaviors. Studies comparing the symptomatology of girls and boys with ADHD (Gaub & Carlson, 1997; Mahone & Wodka, 2008) revealed hardly any gender differences (Biederman, Faraone, Monuteaux, Bober, & Cadogen, 2004) or only minor differences, e.g. in lower ratings on hyperactivity, inattention, impulsivity, and externalizing problems but greater intellectual impairments and internalizing in girls than in boys (see e.g. the meta-analysis by Gershon, 2002). We investigated only females because firstly, we wanted to investigate a homogenous sample, secondly, there is a bias towards research on males, and thirdly, no systematic gender differences concerning motivational processes have so far been reported.

2. Materials and methods

2.1. Participants

Our sample consisted of 33 healthy, right-handed females, who were all students of psychology at the University of Giessen, except one. All participants were enlisted in the genetic data bank of the *Giessen Gene Brain Behavior Project* (*GGBBP*). The GGBBP research program aims to identify the biological basis of cognitive, motivational, and emotional processes inherent in normal and psychopathological individuals.

Two subjects had to be excluded from the study, one because of very strong movement-artifacts, and one because of high score in the Beck-Depression-Inventory (Hautzinger, Bailer, Worall, & Keller, 1993). Data of 31 subjects (mean age: 23.0 years, $SD = 2.9$) were analyzed. All subjects were paid 25 € for participating in this fMRI study. They could increase this amount by earning additional money over the course of the experiment.

To ensure that the healthy participants spread widely on ADHD related behaviors, we chose subjects according to their score on the adult ADHD self-report scale (ASRS, see below) from a total data pool of 600 healthy subjects. Participants were randomly and evenly selected from the lower, the middle and the higher part of the distribution in the data pool. 11 subjects with a sum ASRS score <20, 11 subjects with a score ranging from 28 to 30, and 9 subjects with a score >34 were invited. None of the participants reported to have been treated for ADHD in the past. The project was in accordance with the latest version of the Declaration of Helsinki and was approved by the ethics commission of the German Psychological Association. All subjects were informed about the nature of the experiment in detail before giving written informed consent.Assessment of ADHD related behaviors with the ASRS

The ASRS is an 18 item scale (Kessler et al., 2005) and is based on the criteria of ADHD from the DSM-IV-TR (American Psychiatric Association, 2000). It measures the frequency of symptoms, i.e., how often ADHD symptoms occur (0 = never, 1 = rarely, 2 = sometimes, 3 = often, 4 = very often). The ASRS has a two-factorial structure with an inattention scale and a hyperactivity/impulsivity scale. The reliabilities (Cronbach's alpha) for the two subscales of inattention (.75) and impulsivity

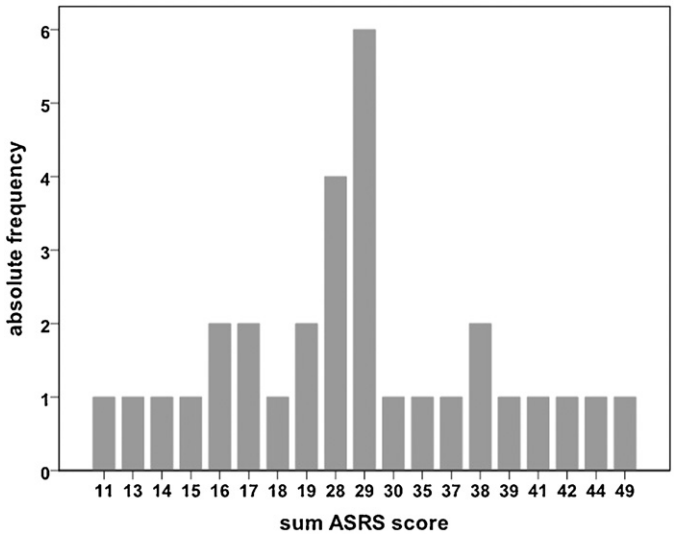

Fig. 1. Distribution of the subjects on the sum ASRS score.

(.77) as well as for the total ASRS (.82) are satisfactory (Reuter, Kirsch, & Hennig, 2006).

If the sum score of both scales is <34, a subject is unlikely to have ADHD, if the score is between 34 and 46 the subject is likely to suffer from ADHD and a score greater or equal to 48 indicates that the subject is most likely to have ADHD. The sum ASRS scores of our sample ranged from 11 to 49 ($M = 27.55$; $SD = 10.31$, see Fig. 1). A median of 29 indicates that most of the subjects had only subclinically relevant ADHD behaviors. For the subscale inattention, the scores ranged from 6 to 26 ($M = 13.58$; $SD = 5.48$) and for the subscale hyperactivity/impulsivity from 2 to 27 ($M = 13.97$; $SD = 6.19$). In the present sample, the two ASRS subscales are positively correlated ($r = .557$; $p = .001$). This is similar to the results of Caci, Bouchez, and Baylé (2009) and Reuter et al. (2006) who reported an intercorrelation of the two scales of .40 and .61, respectively.

2.3. Experimental paradigm

The experimental design was adopted from a study by Kirsch et al. (2006). Before scanning, subjects were informed about the different stimulus types used in the experiment. They were asked to respond to a bright flash of light as fast as they could by pressing a button mounted on a grip held in their right hand. During scanning, subjects were presented four different conditions (Fig. 2). The first condition, the so-called "monetary reward anticipation" condition, was initiated by a vertically oriented arrow pointing upwards. It was presented for 6 s and immediately followed by the imperative stimulus (flash, 100 ms) without an inter-stimulus-interval. After subjects had responded to the flash, a verbal feedback was given whether they had responded fast enough to earn money ("fast: +1 €" or "slow: +0 €"). In the second condition, the so-called "punishment avoidance anticipation" condition, the initial stimulus was a vertically oriented arrow pointing downwards. Again, the task was presented 6 s after trial onset. However, in this case, a slow response was punished by the loss of money while a fast response was rewarded by the avoidance of that loss (feedback: "fast: −0 €" or "slow: −1 €"). Thus, the maximum win or loss per trial was 1 € instead of 2 € in the study by Kirsch et al. (2006). The third condition, the "verbal feedback anticipation" condition, consisted of a vertically oriented double-sided arrow. The only difference to the two monetary conditions was that the feedback contained no information about a monetary gain or loss, only information on the speed, i.e., "fast" or "slow", was given. In all three conditions, the feedback screen was displayed for 1.5 s. For all of the three experimental conditions, the threshold of the "fast"/"slow" feedback varied trial by trial depending on the individual reaction time of the preceding trial. For the first trial, the threshold between fast and slow reaction was set to 300 ms. The adaptive algorithm was a simple increase of 5% of the threshold after a slow response and a decrease of 5% after a fast response in the last trial. This way, we ensured that all subjects were able to win money and work on their maximum performance level. Trials with fast responses were considered as successful trials.

In an additional "control condition", a horizontally oriented double-sided arrow was presented for 6 s, followed by a black screen for 3 s. This condition was used to include a condition without anticipation of a consequence.

After the feedback, the actual account balance was displayed for 1.5 s. The inter-trial interval was randomly varied between 6.001 and 9.000 s (i.e., jitter between 0 and 3 s on a millisecond basis). Each of the four conditions was presented 20 times in a pseudo random trial order with no more than two equal conditions in succession. In total, each subject underwent 80 trials, with an entire duration of approximately 22 min. Reaction times falling below 100 ms and exceeding 1000 ms were labelled as missing.

The experiment was realized with the Presentation software package (Neurobehavioral Systems, Albany, CA). The stimuli were presented with an LCD projector on a screen at the back of the scanner. The subjects were able to see the screen by use of a mirror located approximately 20 cm above their eyes.

2.4. fMRI data acquisition

Imaging data were acquired by a 1.5 T whole-body tomograph (Siemens Symphony) with a Quantum gradient system (Siemens, Erlangen, Germany). Structural image acquisition consisted of 160 T1-weighted sagittal images (MPRage, 1 mm slice thickness). To measure the blood oxygen level dependent (BOLD) contrast, a T2*-weighted single shot gradient echo EPI sequence (TR = 3 s, TE = 55 ms, flip angle = 90°, FOV = 192 mm × 192 mm, 64 × 64 matrix) was used. One volume contained 30 slices with a 4 mm slice thickness. The gaps in between these slices were of 1 mm thickness. The slices were acquired in descending order.

2.5. Behavioral data analyses

The behavioral data, i.e., the amount of earned money, rates of successful trials, and response times, were analyzed using the statistical software package SPSS for Windows (Version 17.0, SPSS Inc., IL, USA). We conducted correlation analyses for

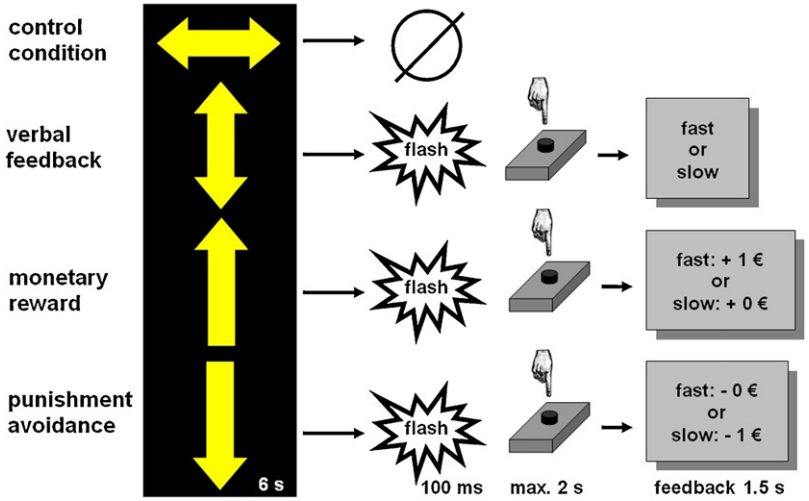

Fig. 2. Exemplary illustration of the four experimental conditions. A yellow arrow indicated which experimental condition was displayed for 6 s. Responding fast enough to the following flash (100 ms), subjects could either win 1 € (monetary reward), avoid a loss of 1 € (punishment avoidance), or gain positive feedback (verbal feedback, "fast"). Responding too slowly, they did not win 1 €, lost 1 €, or gained negative feedback ("slow"). In the control condition, no flash was displayed and therefore no response was necessary. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

the overall rate of successful trials and the successful trials for each experimental condition separately with the sum ASRS score and the subscales inattention and hyperactivity/impulsivity. The success rate was calculated by dividing the number of successful trials by the number of considered trials (i.e., 20 for each condition). For the overall success rate, we divided the number of successful trials by 60, not distinguishing between the conditions monetary reward anticipation, punishment avoidance anticipation, and verbal feedback anticipation. Differences between success rates between the three experimental conditions were tested with paired *t*-tests. For response times, we also calculated paired *t*-tests between all three experimental conditions. Additionally, we analyzed correlations of response times with the sum ASRS scores as well as with the subscales inattention and hyperactivity/impulsivity. For all statistical analyses α was set to .05.

2.6. fMRI data analyses

FMRI data were analyzed using statistical parametric mapping methods with the SPM8 software package (Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks Inc., Sherborn, MA, USA). The first three volumes were discarded due to an incomplete steady state of magnetization.

During preprocessing, realignment (2nd degree b-spline interpolation to the first image), slice time correction (reference slice: 15), coregistration of functional data to each participant's anatomic image, and normalization to the standard space of the Montreal Neurological Institute (MNI) brain were performed. Spatial smoothing was executed with an isotropic three-dimensional Gaussian filter with a full width at half maximum (FWHM) of 9 mm to allow for corrected statistical inference.

The evoked BOLD responses were modelled for the four conditions (monetary reward anticipation, punishment avoidance anticipation, verbal feedback anticipation, control condition). We also modelled the bright flash (which was followed by a button press) and the black screen following the control condition (without button press). We used stick functions convolved with a hemodynamic response function for modelling these regressors. In order to account for movement related variance, the six movement parameters derived from the realignment preprocessing step were included as covariates into the analysis. A high pass filter (time constant = 128 s) was implemented by using cosine functions in the design matrix. Group analyses were based on a random effects analysis.

For explorative whole brain analyses, the significance threshold was set to $\alpha = .05$ on voxel-level corrected for multiple testing (family-wise error (FWE) correction) and a minimum cluster size $k = 20$ voxels. Significant peak voxels of the whole brain analyses were labelled with the software-program MARINA (http://www.bion.de/Marina.htm), which is based on the anatomical parcellation of the brain (Tzourio-Mazoyer et al., 2002). Region of interest (ROI) analyses were conducted with brain regions known to be part of the reward network and which were reported in comparable previous studies (Kirsch et al., 2003, 2006). We created structural ROI according to the results of these studies by designing masks using MARINA. The ROI were the amygdala, the ACC, the NAcc, the OFC, and the thalamus. All these analyses were conducted separately for each hemisphere. The resulting *p*-values of the *F*- and *t*-statistics were adjusted for multiple comparisons (family-wise-error (FWE) corrected) within the ROI, using small volume correction (threshold $p_{corr} < .05$, cluster size $k = 0$). Trends up to a threshold of $p_{corr} < .10$ are also reported.

To check if all conditions provoked activation in the reward system, we tested the contrasts [monetary reward anticipation – control condition], [punishment avoidance anticipation – control condition], and [verbal feedback anticipation – control condition] separately. For all following analyses, we contrasted the respective condition with the control condition. In an *F*-test including all three reward conditions, we tested for general differences between these conditions. In post hoc paired *t*-tests, we determined the underlying differences comparing each condition with the others.

In order to test the proposed hypothesis that monetary reward anticipation provokes higher BOLD responses than punishment avoidance anticipation, which in turn provokes higher BOLD responses than verbal feedback anticipation (i.e., assumption of a parametric modulation), we conducted the conjunction analysis [monetary reward anticipation – punishment avoidance anticipation] ∩ [punishment avoidance anticipation – verbal feedback anticipation]. In a second conjunction analysis, we tested for joint activations during all three reward anticipation conditions (monetary reward anticipation ∩ punishment avoidance anticipation ∩ verbal feedback anticipation).

Further, we correlated the three reward anticipation conditions with the respective sum ASRS scores as well as with the two subscales in order to investigate the specific relationship between neural activations in all three conditions and ADHD related behaviors. Therefore, the sum ASRS scores were included as regressor in a simple regression model. Significant *t*-values indicate brain regions in which the functional activation significantly correlates with the reported ADHD related behaviors. To gain a quantitative measure for the magnitude of the correlations, we calculated the correlation coefficients *r* for the resulting brain regions using the *t*-values at the peak voxels of the respective analysis (Rosenthal, 1994). We also conducted the same analyses for the two ASRS subscales separately and calculated the correlation coefficients at the respective peak voxels corresponding to the correlation analysis with the sum ASRS scores. Differences in correlation coefficients between the subscales and between the reward conditions were tested for the respective peak voxels with the adequate *t*-statistic (Chen & Popovich, 2002). Finally, we conducted the same analysis for all subjects with a sum ASRS score lower than 34 to assure that the results are not exclusively based upon persons with high ADHD related behaviors.

3. Results

3.1. Behavioral data

All subjects, except one, won additional money; on average 5.81 € (range: 0–9 €; $SD = 2.27$). The subjects made 2.5 omission errors (range: 0–13 omissions; $SD = 3.13$) on average.

Correlation analyses of the overall success rate (58% of the 60 experimental trials) as well as the success rates of the three experimental conditions separately with the sum ASRS scores as well as with both subscales did not reveal any significant results (all $p > .10$). The success rate in the monetary reward anticipation condition (62.75% of the 20 trials) did not differ from the punishment avoidance anticipation condition (66.75%; $t(30) = 1.42$; n.s.). Yet, the verbal feedback anticipation condition (44,5%) had a lower success rate than the monetary reward anticipation ($t(30) = 5.54$; $p < .001$) and the punishment avoidance anticipation ($t(30) = 7.24$; $p < .001$) condition.

Reaction times for the two monetary anticipation conditions did not differ significantly (monetary reward anticipation: 191.72 ms; punishment avoidance anticipation: 185.36 ms; $t(30) = 1.52$, n.s.). Reaction times for the condition verbal feedback anticipation ($M = 208.91$ ms) were significantly longer than for the condition monetary reward anticipation ($t(30) = 3.81$; $p = .001$) and for the condition punishment avoidance anticipation ($t(30) = 4.80$; $p < .001$).

To assess a possible relation between the behavioral data and ADHD related behaviors, we correlated reaction times and standard deviations of the reaction times of the three conditions with the sum ASRS scores as well as with both scales (inattention and hyperactivity/impulsivity) of the ASRS. No significant correlations could be found (all $p > .20$).

3.2. Functional imaging data

At the neural level, we compared the effects of monetary reward anticipation, punishment avoidance anticipation, and verbal feedback anticipation with the control condition to identify brain regions activated during the presentation of a motivating stimulus. For the contrast [monetary reward anticipation – control condition] we found significant activations in the whole brain analyses in the left posterior central gyrus, the left pallidum, the left supplementary motor area, and the vermis as well as in all ROI (amygdala, ACC, NAcc, OFC, thalamus). For the contrast [punishment avoidance anticipation – control condition], we found a less pronounced activation pattern with neural activations in the left supplementary motor area and the left precentral gyrus (whole brain analyses) as well as in the left amygdala, the left OFC, and the bilateral NAcc and thalamus (ROI analyses). The condition verbal feedback anticipation in comparison to the control condition revealed no significant neural activation in the whole brain analyses, and a significant ROI analyses activation in the left NAcc only (see Table 1).

For all following analyses, exploratory whole brain analyses did not reveal any significant effects. To reveal more detailed information about reward processing, we conducted an *F*-test including the three reward anticipation conditions. There were significant differences in all ROI ($p \leq .005$). Post hoc *t*-tests revealed that these activations were due to significant differences in the contrast [monetary reward anticipation – verbal feedback anticipation] as well as [monetary reward anticipation – punishment avoidance anticipation] for all ROI ($p \leq .010$). The contrast [punishment avoidance

Table 1
Localization and statistics of the peak voxels activated during the three reward anticipation conditions resulting from the ROI and the exploratory whole brain analyses (WB).

Contrast	Brain structure	*x*	*y*	*z*	T_{max}	p_{corr}
Monetary reward anticipation – control condition	L amygdala	−15	−1	−14	3.90	.005
	R amygdala	21	2	−14	3.44	.015
	L ACC	−3	38	−8	4.91	.002
	R ACC	15	29	19	4.60	.004
	L OFC	−21	11	−17	5.22	.003
	R OFC	12	14	−14	4.13	.035
	L NAcc	−12	8	−5	7.15	<.001
	R NAcc	12	8	−2	7.06	<.001
	L thalamus	−12	−16	−2	6.75	<.001
	R thalamus	6	−19	10	6.46	<.001
	Vermis (WB)	6	−58	−11	6.40	.009
	L supplementary motor area (WB)	−9	−4	55	7.06	.002
	L pallidum (WB)	−12	8	−2	7.18	.001
	L postcentral gyrus (WB)	−42	−22	55	7.89	<.001
Punishment avoidance anticipation – control condition	L amygdala	−15	2	−17	3.86	.006
	L OFC	−18	11	−20	4.34	.024
	L NAcc	−12	5	−5	5.69	<.001
	R NAcc	15	5	−2	5.74	<.001
	L thalamus	−12	−7	−2	4.22	.009
	R thalamus	6	−16	13	3.39	.047
	L supplementary motor area (WB)	−6	−1	56	6.91	.003
	L precentral gyrus (WB)	−42	−19	55	6.83	.004
Verbal feedback anticipation – control condition	L NAcc	−12	11	−20	3.99	.008

The threshold was $p_{corr} < .05$ (FWE-corrected; small volume correction). All coordinates (*x*, *y*, *z*) are given in MNI space. L: left, R: right.

anticipation – verbal feedback anticipation] yielded significant neural activation in all ROI ($ps \leq .010$) except the right amygdala and right OFC ($ps = .054$). No inverse contrasts resulted in significant results.

The resulting activation pattern from these post hoc *t*-tests suggests a parametric modulation of the three reward anticipation conditions; more precisely, monetary reward anticipation provokes greater activation than punishment avoidance anticipation, which in turn provokes greater activation than verbal feedback anticipation. The conjunction analysis [monetary reward anticipation – punishment avoidance anticipation] ∩ [punishment avoidance anticipation – verbal feedback anticipation] confirmed this assumption in all ROI except the OFC and the right ACC (see Table 2). For an illustration of this parametric modulation effect, see Fig. 3.

In all three reward anticipation conditions (conjunction monetary reward anticipation ∩ punishment avoidance anticipation ∩ verbal feedback anticipation), we found joint neural activations in the bilateral OFC and the NAcc (all $p \leq .010$) as well as a trend in the right ACC ($p = .061$).

To analyse the relation between brain activation during the respective reward anticipation condition and ADHD related behaviors, we correlated sum ASRS scores with the three reward anticipation contrasts [monetary reward anticipation – control condition], [punishment avoidance anticipation – control condition], and [verbal feedback anticipation – control condition]. We found significant negative correlations between ADHD related behaviors and activation for the contrast [monetary reward anticipation – control condition] in the left amygdala, the left thalamus, and bilaterally in the NAcc. In the contrast [punishment avoidance anticipation – control condition], neural activation in the bilateral ACC and the NAcc were negatively correlated with ADHD related behaviors. We also found the same negative correlation in the contrast [verbal feedback – control condition] in the left amygdala, the left ACC, the right thalamus, and bilaterally in the NAcc (cf. Table 3).

Correlation analyses of the inattention and hyperactivity/impulsivity scales at the respective peak voxels revealed that both scales were negatively correlated with the neural activation in the three reward anticipation conditions. Correlation coefficients of the two subscales were not significantly different from each other (all $T_{diff} < 1.9$; n.s.). The same holds for the comparisons of the correlation coefficients of the three reward anticipation conditions (all $T_{diff} < 1.7$; n.s.). For an illustration of the left NAcc results, see Fig. 4.

To prove whether these results were caused by the subjects with high ASRS scores we conducted a further analysis: including only participants with a sum ASRS score lower than 34 led to similar

Table 2
Localization and statistics of the peak voxels resulting from the parametric modulation of the three reward anticipation conditions (conjunction [monetary reward anticipation – punishment avoidance anticipation] ∩ [punishment avoidance anticipation – verbal feedback anticipation]) within the respective ROI.

Brain structure	*x*	*y*	*z*	T_{max}	p_{corr}
L amygdala	−24	−1	−14	3.28	.016
R amygdala	*21*	*2*	*−14*	*2.81*	*.052*
R ACC	15	29	19	3.89	.014
L NAcc	−12	11	−5	3.58	.011
R NAcc	15	11	−2	4.76	<.001
L thalamus	−12	−19	−2	3.84	.012
R thalamus	6	−19	10	4.17	.005

The threshold was $p_{corr} < .05$ (FWE-corrected; small volume correction). All coordinates (*x*, *y*, *z*) are given in MNI space. L: left, R: right. Trends up to a threshold of $p_{corr} < .10$ are written in italics.

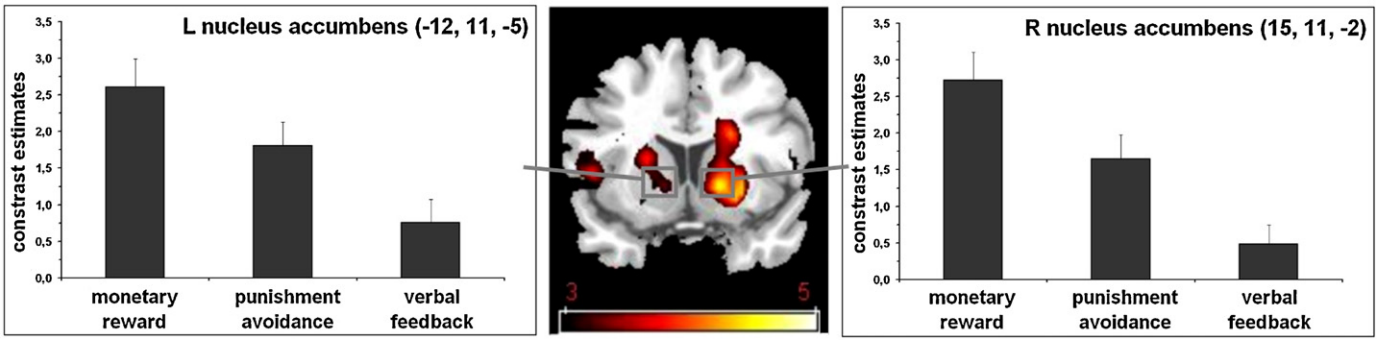

Fig. 3. Neural activation for the conjunction analysis [monetary reward anticipation – punishment avoidance anticipation] ∩ [punishment avoidance anticipation – verbal feedback anticipation] in the brain slice with $y = 11$. For illustration reasons, data were thresholded with a $T \geq 3.0$ (see color bar for exact t-values). Mean (SE) contrast estimates for the parametric modulated activity in the left and right NAcc in the respective peak voxels are illustrated for the three reward anticipation conditions (minus control condition) in the bar graphs. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Table 3
Localization and statistics of the peak voxels for the correlation analyses in the three reward anticipation conditions within the respective ROI. Correlation coefficients of the ASRS scores with the neural activity and the sum ASRS scores (sum) and the subscales inattention (inatt) and hyperactivity/impulsivity (hyp) are inserted at the right side. All correlation coefficients were calculated for the peak voxels resulting from the correlation analysis with the sum ASRS score.

Contrast	Brain structure	x	y	z	T_{max}	p_{corr}	Correlation coefficient r		
							Sum	Inatt	Hyp
Monetary reward anticipation – control condition	L amygdala	−18	2	−17	3.18	.025	−.51	−.40	−.50
	L NAcc	−3	2	−8	3.81	.010	−.58	−.45	−.56
	R NAcc	9	2	−8	3.27	.032	−.52	−.47	−.45
	L thalamus	*−6*	*−7*	*−2*	*3.14*	*.075*	*−.50*	*−.45*	*−.44*
Punishment avoidance anticipation – control condition	L ACC	−9	47	10	3.36	.084	−.53	−.50	−.44
	R ACC	9	29	−8	3.92	.023	−.59	−.55	−.49
	L NAcc	−9	2	−11	3.94	.008	−.59	−.57	−.48
	R NAcc	15	8	−11	2.76	.089	−.46	−.38	−.43
Verbal feedback anticipation – control condition	L amygdala	−21	2	−17	3.13	.034	−.50	−.34	−.53
	L ACC	−12	41	10	3.88	.034	−.58	−.65	−.39
	L NAcc	−9	14	−8	3.54	.022	−.55	−.44	−.53
	R NAcc	9	2	−8	4.93	.009	−.60	−.47	−.58
	R thalamus	12	−7	−2	3.80	.027	−.58	−.41	−.59

The threshold was $p_{corr} < .05$ (FWE-corrected; small volume correction). All coordinates (x, y, z) are given in MNI space. L: left, R: right. Trends up to a threshold of $p_{corr} < .10$ are written in italics.

correlation coefficients ($r \geq .53$) to those including all participants in all ROI. All p-values of the correlation coefficients ranged from $p = .003$ to $p = .11$.

4. Discussion

In this fMRI study, we investigated subjects with varying degrees of ADHD related behaviors in a reward anticipation task. As expected, we found that the anticipation of reward was associated with activation of the reward circuit including the NAcc. Further, our assumption that the different reward anticipation conditions (monetary reward anticipation, punishment avoidance anticipation, verbal feedback anticipation) activate the reward network differentially was confirmed: monetary reward anticipation was most effective in activating the NAcc, the thalamus, the ACC, the OFC, and the amygdala followed by the punishment

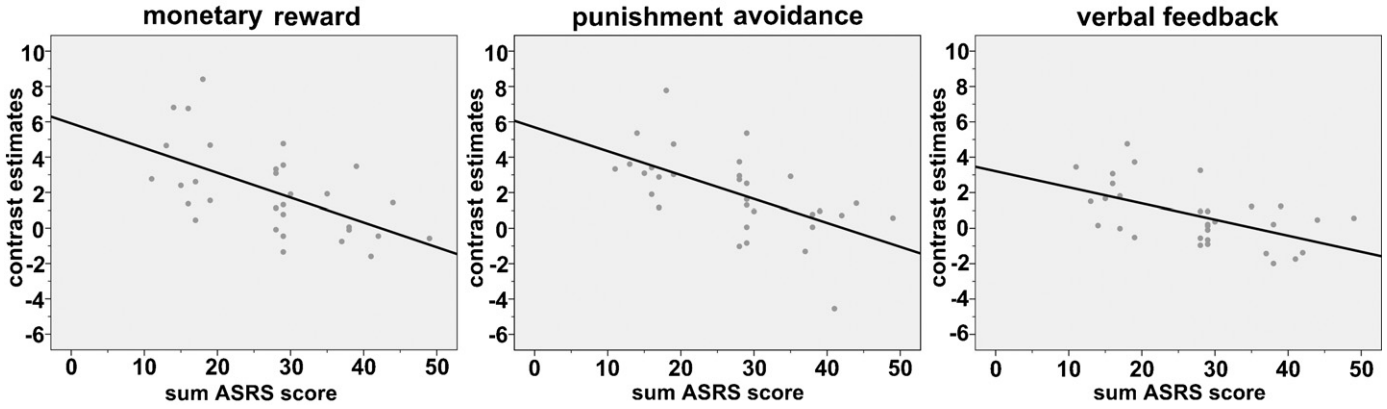

Fig. 4. Scatterplots for the negative correlations of the neural activity in the peak voxel of the left NAcc and the sum ASRS score. The left column represents the condition monetary reward anticipation (peak voxel $x = -3$, $y = 2$, $z = -8$), the middle column punishment avoidance anticipation (peak voxel $x = -9$, $y = 2$, $z = -11$), and the right column verbal feedback anticipation (peak voxel $x = -9$, $y = 14$, $z = -8$).

avoidance anticipation condition and then the verbal feedback anticipation condition. For all ROI, except the right and the left OFC and the right ACC, the ranking of the conditions (monetary reward anticipation > punishment avoidance anticipation > verbal feedback anticipation) was statistically significant. A possible explanation for this dissociation lies in the different functions of these structures within the reward system as reviewed for example by Martin-Soelch et al. (2007): the OFC is meant to encode outcome expectations and is meant to be involved in facilitating associative learning in the basolateral amygdala. The ACC has been repeatedly implicated in situations of conflict and discriminative learning. Maybe these functions are less dependent of the type of reward anticipation and do therefore not result in significantly different activations during the three anticipation conditions. Why the left and the right ACC react differentially must be a question of further research. The motivational differences between the two monetary conditions (monetary reward anticipation, punishment avoidance anticipation) and the verbal feedback anticipation condition were mirrored in the behavioral data: success rates were higher in the monetary conditions than in the verbal feedback anticipation condition and reaction times in the monetary conditions were significantly faster than in the verbal feedback anticipation condition. Therefore, the experimental design allowed us to activate the reward system in a wide range of intensities as suggested by the experiments of Kirsch et al. (2003, 2006).

Our main question of interest was whether and how inattention and hyperactivity/impulsivity, typical ADHD related behaviors, are correlated with deficits in the reward circuit regarding reward anticipation in a non-clinical sample. This question arose from the observation of a hypo-responsiveness of the reward anticipating system (Scheres et al., 2007; Ströhle et al., 2008) in ADHD patients and recent models of ADHD proposing this hypo-responsiveness to be one of the major underlying factors leading to ADHD symptoms (Sagvolden et al., 2005; Tripp & Wickens, 2008). We expected that the reported amount of indices of inattention and/or hyperactivity/impulsivity is negatively correlated with the activation of the reward anticipation network in a non-clinical sample.

The present results clearly show that there was a significant negative correlation in the NAcc independent of the type of reward anticipation (exception: for the right NAcc there is only a trend). For the amygdala, the ACC, and the thalamus, the results are more heterogeneous: in some reward anticipation conditions there are significant negative correlations between the ASRS scores and the corresponding contrast estimates while in other conditions no significant correlations were observed. Whether poor statistical power or the different functions of these structures within the reward system are responsible for this outcome must be investigated in future research. For the NAcc, this means that the higher the scores on the inattention and hyperactivity/impulsivity scales in the self-report questionnaire, the lower the BOLD response in the NAcc during reward anticipation. This was also the case when subjects with high questionnaire scores were excluded from the correlation analysis ensuring that this effect is not due to subjects who perhaps suffer from an undiagnosed ADHD. Importantly, the main result of the negative correlation between anticipatory responses and ADHD related behaviors cannot simply be explained by different actual earnings or success rates, because we did not find a significant correlation between the ASRS scores and these outcome measures.

The observed reduced neuronal responses in the nucleus accumbens in subjects with more pronounced ADHD related behaviors could potentially be due to a diminished dopaminergic response. It is generally accepted that dopamine is the most important transmitter in reward anticipation processes (e.g. Knutson et al., 2001; Schultz, 2002) and further the BOLD response in the NAcc indeed reflects the dopamine release in this structure (see e.g. review by Knutson & Gibbs, 2007).

Can deficits in reward anticipation system directly explain symptoms like inattention and hyperactivity/impulsivity? Modern theories of reward learning like the incentive-sensitization theory of addiction (Robinson & Berridge, 1993) or the theory of the dopamine reward prediction error (Schultz et al., 1997) assume that dopaminergic transmitted responses in the ventral striatum move from the delivery of a reward to cues which announce a reward. In our study, we found that the lower the anticipatory neural responses (measured by the BOLD response), the higher the scores on the inattention and hyperactivity/impulsivity scales. Although correlations cannot be causally interpreted, it is allowed to speculate about possible relations. Modern theories of ADHD try to explain how a deficient anticipatory response can lead to ADHD typical behaviors: for example, Sagvolden et al. (2005) assume in their dynamic developmental theory that altered reinforcement of novel behavior and deficient extinction of previously reinforced behavior due to a hypo-functioning mesolimbic dopamine system are responsible for some of the ADHD behaviors. As a consequence, they suggest that the time window for associating behavior with its consequences is narrower; new upcoming stimuli strongly control behavior resulting in attention problems. They explain behaviors like motor impulsivity, hyperactivity, and impulsivity accordingly. Comparable hypotheses are put forward by the dopamine deficit theory of Tripp and Wickens (2008).

Our data indicate in a non-clinical sample that, in the dopamine system, a reduced processing of cues signalling reward is by some means related to inattention and hyperactivity/impulsivity. The fact, that the correlation coefficients were similar in the three reward anticipation conditions suggests that this phenomenon is rather robust.

Interestingly, we found similar negative correlation coefficients between the reward anticipation response and both subscales of the ASRS (inattention and hyperactivity/impulsivity) in the NAcc. Although the two scales are positively correlated in our study, they co-varied with different aspects in recent studies: in a study by Herrmann et al. (2009) only the inattention scale was negatively correlated with the neural correlate of error processing. Further, Plichta et al. (2009) and Scheres et al. (2007) found a significant correlation with neural responses to reward expectations only for the hyperactivity/impulsivity subscale. From our data, one can conclude that inattention as well as hyperactivity/impulsivity are connected to reduced reward anticipating neural responses.

Possible limitations of the present study should be mentioned: first of all, we investigated a healthy, female student sample who reported no ADHD history. Thus, the question arises whether it is adequate to link the present results to clinical studies with ADHD patients. Traditionally, psychiatric diagnoses like ADHD are seen as categorical entities. However, there is an ongoing debate whether dimensional approaches can substantially improve psychiatric diagnoses (e.g. Moeller, 2009). Further, we investigated females only. Thus it is questionable whether the results can be generalized to both sexes. We decided for an exclusively female sample because ADHD is more often investigated in males so far than in females. Therefore, there is a lack of studies on females in this field. Additionally, we did not expect fundamental gender differences in the processing of reward anticipations from previous research (Biederman et al., 2004; Spreckelmeyer et al., 2009). However, follow-up studies should attempt to show the same relationship between neural responses towards reward anticipation and ADHD related behaviors in males for a sex independent generalization.

5. Conclusion

In conclusion, our study highlights that deficits in the reward system measured by neural responses to reward signalling cues are by some means related to inattention and hyperactivity/impulsivity, which are ADHD related behaviors. Furthermore, this effect was independent of the reward condition used.

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